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**Jubilee Conference
“The Medicine of the Future”**

**75th Anniversary of
Medical University of Plovdiv**

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Jubilee Scientific Conference “Medicine of the Future”

**29-31 October 2020
on the occasion of the 75th Anniversary of
Medical University of Plovdiv**

The Conference is held under the auspices of the Rector of
Medical University of Plovdiv

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The authors are entirely responsible for the content of their abstracts.

WELCOME ADDRESS

Dear colleagues,

On behalf of the Academic Board of the Medical University of Plovdiv, I would like to invite you to the Jubilee Scientific Conference dedicated to the 75th Anniversary of the foundation of our Alma Mater.

Thanks to the knowledge, professionalism and dedication of our teaching staff, we have been successfully building our Temple of Education and Science for decades.

The Jubilee Science Conference is another opportunity to share our success and experience in all areas of medical science, education and practice.

I do believe that sharing our achievements and challenges is an expression of our mission to be humane!

Good luck to the forum!

Prof. Marianna Murdjeva, MD, PhD, MHM

Rector

Medical University of Plovdiv

Contents

PLENARY LECTURES	7
ORAL PRESENTATIONS.....	32
- BIOMEDICINE	32
- BIOPHARMACY.....	46
- CONTEMPORARY SURGICAL TECHNIQUES	51
- INNOVATIVE METHODS OF DIAGNOSIS AND TREATMENT	58
- DENTAL MEDICINE.....	61
- PUBLIC HEALTH/HEALTHCARE.....	67
POSTER SESSIONS.....	74
- POSTER SESSION I.....	74
• BIOMEDICINE	74
• BIOPHARMACY	90
• CONTEMPORARY SURGICAL TECHNIQUES.....	94
• INNOVATIVE METHODS OF DIAGNOSIS AND TREATMENT	96
• DENTAL MEDICINE.....	99
• PUBLIC HEALTH-HEALTHCARE.....	103
- POSTER SESSION II.....	116
• PROJECTS WITH NATIONAL/INTERNATIONAL FUNDING.....	116
INTRA-UNIVERSITY PROJECT SESSION	120
- INTRA-UNIVERSITY PROJECTS 2016-2018	120
- DOCTORAL PROJECTS 2015-2017	142
- POST-DOCTORAL PROJECTS 2018.....	150
INDEX	162

PLENARY LECTURES**COVID-19, Cytokine Storms and Natural Inhibitors****Theoharis C. Theoharides, BA, MS, MPhil, PhD, MD, FAAAAI**Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Immunology,
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Increasing reports indicate that inflammation is a critical component of the pathogenesis of many diseases. We first proposed that the unique immune cells, mast cells, originally thought to participate only in allergic reactions, play a key role in the pathogenesis of inflammatory diseases including (alphabetically): autism spectrum disorder, chronic inflammatory response syndrome, environmental disease, fibromyalgia, interstitial cystitis, mast cell activation syndrome, multiple chemical sensitivity syndrome, and myalgic encephalomyelitis/chronic fatigue syndrome. COVID-19 derives from infection with Coronavirus [severe acute respiratory syndrome (SARS)-CoV-2] and is associated with high morbidity and mortality due to release of a storm of pro-inflammatory cytokines and thrombogenic agents resulting in destruction of the lungs. Moreover, many reports indicate that many patients who are positive for SARS-CoV-2 and have mild symptoms develop diffuse multiorgan symptoms months after the infection. These symptoms include brain fog, chest tightness, dermatologic manifestations, gastrointestinal problems, headaches, malaise, and myalgias, originally reported in children and named Multisystem Inflammatory Syndrome (MIS-C). The US Center for Disease Control (CDC) recently announced the recognition of a similar condition in adults, named Multisystem Inflammatory Syndrome (MIS-A). The symptoms characterizing MIS, especially what has been called "COVID-Brain Fog," worsen with stress and are very similar to those associated with Mast Cell Activation Syndrome (MCAS). Mast cells can be triggered by neuropeptides, stress, toxins and viruses leading to release of pro-inflammatory cytokines, as well as thrombogenic and vasoactive molecules. This process can be inhibited by two natural anti-inflammatory cytokines, IL-37 and IL-38, as well as the natural flavonoids luteolin and methoxyluteolin. We should be focusing on treating the whole patient and not an infection.

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Surgical treatment of the early onset scoliosis

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Introduction: Surgical treatment of early onset scoliosis (EOS) is one of the most challenging problems of spine surgery and includes staged distraction and final fusion at the end of skeletal maturity that remains debatable.

The **objective** of the review is to evaluate efficacy of final fusion following staged distraction with VEPTR instrumentation in patients with EOS.

Materials and methods: Outcomes of multi-staged operative treatment of 37 patients with EOS of different etiology were reviewed. Medical records and radiographs of the patients were retrospectively analyzed. Standing postero-anterior and lateral spine radiographs were used for the spinal radiologic assessment before and after each stage of distraction-based treatment, before and after final fusion and at the last follow-up.

Results: The mean age at the beginning of treatment was 5.2 years and the mean age at final fusion was 13.9 years. All patients demonstrated decrease in the angle of primary (from 81.5° to 51.6°) and secondary (from 59.3° to 37.8°) curves, increase of the height and normalized body balance. The mean height increased from 104.8 cm to 141.0 cm, and the mean weight increased from 15 kg to 35 kg throughout the treatment period. The height of the thoracic and lumbar vertebra (Th1-S1) increased from 245 mm to 340 mm, and the thoracic vertebra, from 136 mm to 193 mm. There were a mean of 2.3 complications per patient during distraction performed in a staged manner, and they were arrested during elective procedures. There were 7 (19%) complications after final fusion that required 6 (16%) unplanned revisions.

Conclusion: Multi-staged pediatric surgeries performed in the first decade of life facilitate radical changes in the natural history of progressive scoliosis and ensure satisfactory functional and cosmetic results despite multiple difficulties and complications. The VEPTR instrumentation used for the thoracic curve is unlikely to result in the spinal fusion of the major arch and this is the cause for the use of *third-generation* instrumented final *spinal fusion* in the patients.

EPOS2020 new classification, new treatments

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The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 is the update of similar evidence based position papers published in 2005, 2007, and 2012. The core objective of the EPOS2020 guideline is to provide revised, up-to-date and clear evidence-based recommendations and integrated care pathways in ARS and CRS. EPOS2020 provides an update on the literature published and studies undertaken in the eight years since the EPOS2012 position paper was published and addresses areas not extensively covered in EPOS2012 like paediatric CRS and sinus surgery. EPOS2020 also involved new stakeholders, like pharmacists and patients and addressed new target users who have become more involved in the management and treatment of rhinosinusitis since the publication of the last EPOS document, including pharmacists, nurses, specialised care givers and indeed patients themselves, who employ increasing self-management of their condition using over-the-counter treatments. The document provides suggestion for future research in this area and offer updated guidance for definitions and outcome measurements in research in different settings.

The document contains chapters on definitions and classification, we defined large number of terms and indicated preferred terms. A new classification of CRS into primary and secondary CRS and further division into localized and diffuse disease based on anatomic distribution is proposed. The new classification has large implications on the understanding of the management of the disease.

Research and educational projects funded by the Francophonie University Agency: overview and perspectives

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The Agence universitaire de la Francophonie AUF (Francophonie University Agency) is the largest university network in the world, bringing together 1007 academic networks and scientific research centers that fully or partially employ French language in education and/or research, in 119 countries. As an operator of institutional Francophonie in the academic space, AUF develops and supports project activities within its strategic focus areas: research, education, university governance and quality of training. Throughout the period spanning from 2011 to 2019, MU-Plovdiv participated as a leading or associated partner in six projects involving academic teams from France (Marseille and Nantes Universities), Romania (13 medical and general universities) and Moldova (Medical University of Chisinau): two scientific projects concerning unhealthy eating habits and the related morbidity, two educational ones (including a project for a doctoral course with international participation within the Doctoral School of MU-Plovdiv), and two projects for external expertise on French language training programs. The comparative analysis of staged implementation of the diverse projects within the AUF development strategy reveals prospects for expanding both the opportunities for partnerships within this university network and the thematic scope of future project intentions.

Keywords: projects, francophonie, AUF

3D-bioprinting – the unexpected present and the unpredictable future

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3D-bioprinting is a modern technology which by combining cells, growth and nutritional factors and biomaterials creates spatially organized tissues and organs with similar structure and function like the normal ones. It is used to produce organoids and spheroids. Organoids are clusters of organ-specific cell types that develop from stem or progenitor cells and self-organize spatially (when given a scaffolding extracellular environment) in a manner similar to that in vivo. Their applications include personalized medicine (disease modeling, drug discovery, regenerative medicine) and research (gene editing, mutational signatures of selected cancers). Spheroids are simple clusters of broad-ranging cells which do not require a scaffolding. Their applications are in oncology (understanding the in vivo microenvironment of tumors, predicting drug efficacy in cancer patients, studying the impact of radiotherapy) and in research (development of structures from induced pluripotent stem cells to study diseases and treatments). 3D-bioprinted tissue chips use an in vitro platform of human cells and tissues and microfluids to assess efficiency, safety and toxicity while screening new drugs. 3D-bioprinting is a useful approach in personalized medicine to individualize therapy. It also provides biomaterials for transplantation. The future perspectives of 3D-bioprinting include wound dressing, implants, models for surgical planning and training, phantoms and prostheses, organs-on-chips, 4th dimension of printing and biorobotics. The unpredictable future which this promising technology tackles depends on ethical and legal issues, control of 3D printed drugs, training of physicians and pharmacists. It is worth facing the challenge.

Acknowledgement: To Amgen Project № 25-05-58/2018 and MU-Plovdiv Project DPDP-1/2020.

Keywords: 3D-bioprinting, personalized medicine, regenerative medicine

PI3K inhibitors curtail MYC-dependent mutant p53 gain-of-function in head and neck squamous cell carcinoma

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Head and neck squamous cell carcinoma (HNSCC) is typically characterized by mutation of TP53 gene, associated with therapy resistance and high incidence of local recurrences. However, drugs specifically targeting mutant p53 proteins, frequently presenting gain-of-function activity associated with radioresistance, are not available. We then set out to identify mutant p53-associated functions that might be targeted with drugs currently used in HNSCC trials. This study identifies MYC as a crucial mediator of mutant p53 activity in HNSCC and PI3K inhibitors as compounds able to impinge on mutant p53-MYC dependent gene expression.

Specifically, we identified a signature of transcripts directly controlled by gain-of-function mutant p53 protein and prognostic in HNSCC, which is highly enriched of MYC targets.

Interestingly, both in patient-derived xenografts (PDX) and cell lines of HNSCC treated with the PI3K α -selective inhibitor BYL719 (Alpelisib) the down-regulation of mutant p53/MYC-dependent signature correlates with the response to this compound. Mechanistically, a complex comprising mutant p53, YAP, and MYC-p(Ser62) proteins interacts with MYC target promoters and treatment with BYL719 disrupts this interaction. Of note, depletion of MYC, mutant p53 or YAP potentiates the effectiveness of BYL719 treatment. Importantly, upon treatment with BYL719 depletion of mutant p53 also leads to decreased MYC protein stability. Collectively, the blocking of this transcriptional network is an important determinant for the response to BYL719 in HNSCC.

Evaluating the contemporary scientific aetiology of cerebral palsy and its influence in the jurisprudence of alleged obstetric negligence

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Cerebral palsy often involves multi-systemic physical incapacitating symptoms which necessitate a multitude of major familial and socio-economic supportive elements. The ravaging individual, familial and societal effects and cost are paralleled by the often incapacitating compensatory quanta awarded by the Courts where obstetric negligence is claimed and proven. Quoting one example, in the UK case *Montgomery v. Lanarkshire Health Board*, UKSC 11 (2015) the plaintiff was awarded £5.25 million.

This paper seeks to evaluate the Achilles' heel of just and fair cerebral palsy jurisprudence. It commences by examining the 'Great Cerebral Palsy Myth' originating in the USA of the 1960's but spreading far and wide and which held that the great bulk of such cases are the result of peri-partum hypoxia. Much of the original "science" underlying cerebral palsy causation was clearly disproven even by the end of the 20th century. Yet, its evil effects are not entirely demolished.

Similar and far more medico-legally and jurisprudentially active are a significant number of misconceptions involving intra-partum cardiotocography (I-P CTG). This indispensable method of monitoring intra-partum fetal well-being is associated with a number of drawbacks including often changing criteria for classification

of abnormal tracings. These and other drawbacks are not rarely contributory to questionable jurisprudential decisions.

On a separate stage and also evaluated in some detail is Hypoxic Ischaemic Encephalopathy (HIE). This concept, indispensable to deciphering the underlying aetiological pathophysiology of cerebral palsy unfortunately at times contributes to confusion and challengeable jurisprudential rulings. One such basic problem involved the criteria for the very establishing of the diagnosis of HIE. Fortunately this aspect has been greatly mitigated by the American College of Obstetricians and Gynaecologists in conjunction with the American Academy of Pediatrics in the form of two task forces in 2003 and in 2014.

The paper quotes a number of contemporary jurisprudential decisions and challenges the scientific principles by which obstetric liability was ruled on.

Keywords: Cerebral palsy, neonate, encephalopathy, multi-systemic effects, Court, cost, liability, quanta, medico-legal challenge, jurisprudence, myth, intra-partum, CTG monitoring, ACOG, AAP, task force, diagnostic criteria, challenge

Achilles curse and remedy: tendon diseases from pathophysiology to novel therapeutic approaches

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In Greek mythology, Achilles is almost invulnerable - except for his heel. How could a tendon injury take such a prominent place in the legendary Iliad of Homer? Presumably, the ancient Greeks have already wondered how can the greatest tendon of man suddenly break, even in young athletes?

Tendons are dense connective tissues connecting bone to muscle and thus critical for the integrity and function of the musculoskeletal system. Tendons are hierarchically organized, matrix-rich tissues containing resident stem cells. Due to the increasing age of our society and a rise in extreme sports, tendon diseases present major challenges in modern medicine. Hence, the first part of the lecture will focus on the clinical burden of tendon diseases and on our current understanding of the pathomechanisms leading to tendon degeneration and rupture. Furthermore, phenotypic changes in the tendon stem cells during age-associated tendon degeneration will be presented.

So far, only few treatments for tendon degeneration have been approved, but there is little evidence of effectiveness. Regarding tendon rupture, patients undergo surgical or conservative therapy, as both require long periods for rehabilitation. Therefore, the second part of the lecture will discuss an alternative strategy for tendon repair, namely tissue engineering and how innovative biomaterials can reconstruct the tendon cell niche, counter degeneration and rejuvenate aged tendon stem cells.

Gender disparity in academic otolaryngology

Jean Anderson Eloy

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Academic rank and leadership positions are measures of career progression in academic medicine. Research productivity plays an integral role in evaluation for advancement and promotion in academic medicine. There are known gender, race, and ethnicity disparities in Otolaryngology, specifically with regards to research and grant funding. Female academic otolaryngologists have been shown to lag in scholarly productivity, repre-

sentation at national meetings, leadership positions on journal editorial boards, and National Institutes of Health and industry funding. This presentation aims to discuss gender disparities in academic medicine with a focus on Otolaryngology and other surgical specialties, their professional implications, and the approaches by which our specialty can make concerted efforts to promote equity. Directed approaches, such as research funding for women and minorities or targeted promotion and retention of under-represented faculty may move our field toward parity.

Diagnosis of different types of bradykinin-mediated angioedema

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The diagnosis of angioedema as a distinct disease entity is often a challenge to the clinician in everyday practice.

Of the eleven known types of bradykinin-mediated disease forms, only type I and type II of hereditary angioedema (HAE) resulting from C1-inhibitor (C1-INH) deficiency, as well as acquired angioedema due to C1-INH deficiency can be diagnosed by laboratory methods, by performing complement tests. The results of the latter may be influenced by a number of factors, such as blood sampling, the handling of blood samples, the method applied for the measurement of complement components, as well as the age and sex of patients. Accordingly, these must be taken into account when interpreting complement values.

The differential diagnosis of the other types of angioedema is aided by the family history, inadequate response to conventional therapy, and molecular genetics testing. Hereditary angioedema due to a mutation in the *Factor F12/Plasminogen/Angiopoietin1* or in the *Kininogen1* gene can be diagnosed by mutation analysis exclusively. In the hereditary form of angioedema, family screening is essential, because early diagnosis – optimally before the onset of symptoms – makes it possible that patients are supplied with appropriate medicines, which allow prompt management of the HAE attacks of unpredictable onset.

Idiopathic, non-histaminergic, acquired angioedema (InH-AAE), acquired angioedema related to angiotensin-converting enzyme inhibitor (ACEI-AAE), and hereditary angioedema of unknown origin (U-HAE) can be diagnosed by evaluating the medical and family history, the clinical symptoms, and the therapeutic response, as well as by excluding C1-INH deficiency and mutations in the genes mentioned above. A variety of assignments is forecasted for the future, making available blood test for the diagnosis of InH-AAE, ACEI-AAE, and U-HAE and establishing angioedema registries and biorepositories.

It is to be hoped that the elaboration of state-of-the-art diagnostic methods and the introduction of early diagnosis will make it possible to avoid both life-threatening complications and unnecessary surgical interventions.

Diode laser thermal effect on the paranasal sinus osteoma

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In the 21st century, laser medicine made a rapid step forward; over the past decade it has gained rich experience in laser technologies.

Studies of the effects of optical quantum generators' beams on biological tissues and systems were started in 1960s. Laser technologies were widely used in ophthalmology and otorhinolaryngology. Later - in dentistry and dermatology. In the beginning of 1970s the surgeons started using laser scalpel and physicians tested low-energy laser radiation in cardiological practice. Laser energy is characterized by monochromaticity, coherence and collimation. Monochromaticity means that it generates radiation with a certain wavelength, which helps to concentrate all the radiation energy in an extremely narrow spectral range, which determines a selective effect on biological tissues and also has a clear color - blue, green, red or invisible to the eye, ultraviolet or infrared. Coherence means that light vibrations at different points of space occur synchronously, it means coincidence of the wave phases in space and in time. Collimation helps to form high density of the radiation power, thereby, to provide higher concentration of radiation energy in a small spot. Biological effects of the laser energy on the tissues depend on physical parameters of radiation (power, exposure, wavelength), geometrical parameters of the laser beam, optical and thermal properties of the tissues.

At the retrospective analysis of the literature we have found a lot of information on the application of CO₂, erbium, holmium lasers with the purpose of destruction of the bone tissue in otorhinolaryngology. However, there is very little data about the effects of diode lasers on bone tissues.

When the bone is exposed to lasers, whose maximum absorption corresponds to the absorption by the water of biological tissues, surface damage takes place. On the damaged surface from the center to the periphery there are several standard zones. The ablation zone is a crater where there is no bone substance, the vaporization zone where the organic component of the bone evaporates, and the remaining mineral substances look like a whitish coating; then there is a zone of charring - photocarbonization. Next is a zone of photocoagulation - thermal necrosis and a zone of photohyperthermia, where membrane vaporization and denaturation of proteins takes place. During the contact action the following processes occur: carbon formed between the end of the optical fiber and the biological tissue leads to a multiple, in comparison with the slightly pigmented tissue, increase in absorption of the laser radiation in the carbonization zone. This leads to burning out of tissues. Additional carbon release during burning helps to limit the tissue damage area. Therefore, the contact method of influence on the bone tissue helps to limit the damage area due to combined action of the concentrated laser beam and the heated end of the fiber.

Osteoma is a benign slow-growing encapsulated tumor which is usually asymptomatic. Only surgical treatment is indicated. Type of the surgery depends on the size, anatomic localization and dimension of the tumor and includes different approaches (open, endoscopic and combined). In case of osteoma growing on the agger nasi or frontal bulla, frontal sinus can't be opened endoscopically without osteoma mobilization. Mobilized tumor can be removed only after wide sinus opening endoscopically, with Draf III procedure or with open approach. In both cases all pathological bone tissues should be removed. Another possibility for successful resolution of this difficult situation is to destroy the mobile bone tumor inside the sinus. Diamond drill or punch forceps can't be applied, because neoplasm with smooth surface "runaway" from that instrument. After translocation of the neoplasm to the sinus cavity, it is necessary to remove it transnasally through the formed expanded ostium. In order to reduce the dimensions of the osteoma down to the size required for its removal, we use diode laser. In the literature, we did not find any information on the application of a laser to achieve this result.

Based on the literature, we invented a design of experimental research. We decided to research the thermal effects of a diode laser with a wavelength of 980 nm and to determine the modes for the safe and effective application of this laser for the mobilized osteoma reduction. Fragments of the corpse ilium and removed osteomas measuring 1 cm³ in size were used in the experiment. We used the diode laser in contact continuous mode with time exposure 10 to 30 seconds at a power of 6 W to 15 W. At the same time, the bone fragments were heated at a different rate to a temperature of 47°C and cooled with saline solution. We also conducted a series of experiments using diode laser in distant continuous mode at each tested power of 10, 20, 30 watts. The tip of the light guide was located at a standard distance of 10 mm. The next series of experiments was performed in a pulsed mode with a pulse duration from 30 ms to 200 ms at a distance of 10 mm and contact with quartz fiber, with a duration of applying radiation for 30 seconds.

After a series of experiments, we have found a safe mode of diode laser application for bone tissue reduction in mobilized osteoma cases. Thus, as a result of our experiment, the following conclusions were obtained: the optimal laser mode for bone mass reduction is contact mode with a power of 10 W with a wavelength of 980 nm. Use of the contact mode of the laser surgical treatment helps to avoid undesirable biological effects, observed at distant laser radiation, it significantly reduces the coagulation necrosis zone.

This mode provides predictable results, which makes them safe, and helps to control thermal effects and damage to surrounding tissues.

Safe and effective approach in endoscopic sinus surgery

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Endoscopic Sinus Surgery (ESS) is a common surgical procedure in otolaryngology. The endoscopic technique of approaching the ethmoid and sphenoid sinuses from an anterior to posterior direction is commonly taught in dissection courses and is excellent for initial learning of paranasal sinus anatomy. However, in a bleeding surgical field obscured by nasal polyps, a novice surgeon using this technique might cause inadvertent damage to the orbit and skull base resulting in intra-orbital injury or intra-cranial damage and cerebrospinal fluid leak. Injury most commonly occurs during attempts to enter the posterior ethmoids, as the landmark for entry is not well defined.

A safe technique to enter the posterior ethmoid is to first identify the sphenoid ostium posteriorly and to proceed with removal of the anterior wall of the sphenoid identifying the skull base and orbital wall safely from a posterior to anterior and from medial to lateral direction. The sphenoid sinus is identified as a constant landmark.

Similarly, the sinus ostium is opened widely as a landmark to identify the orbital floor for the safe removal of the anterior ethmoid cells using the classical anterior to posterior direction.

The neuro-immune and neuro-oxidative pathophysiology of mood disorders

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There is now evidence that mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD) are neuro-immune and neuro-oxidative diseases. Both MDD and BD, especially type 1 (BP1) are accompanied by activation of the immune-inflammatory response system (IRS) as indicated by increased M1 macrophage, T helper 1 (Th1), Th2, and Th17 with increased levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-17, and tumor necrosis factor- α (TNF- α). Both mood disorders are also accompanied by activation of the compensatory immune regulatory system (CIRS), conceptualized as the aggregate of anti-inflammatory mediators including T regulatory (Treg) and Th2 cells. Nevertheless, the acute phase of illness (either MDD or BD) is characterized by an increased IRS/CIRS ratio, indicating a pro-inflammatory state. In addition, both MDD and BD are accompanied by multiple signs of increased reactive oxygen and nitrogen species (RONS) as well as nitro-oxidative stress toxicity (NOSTOX), as indicated by increased levels of superoxide dismutase activity, peroxides, nitric oxide, lipid hydroperoxides, malondialdehyde, and advanced oxidation protein products, indicating increased aldehyde formation and chlorinative stress. In addition, the levels of antioxidant and anti-inflammatory enzymes/products are significantly decreased in both mood disorders, including paraoxonase 1 (PON1), high-density lipoprotein cholesterol (HDL), glutathione (GSH), and GSX peroxidase. Both disorders are also accompanied by increased autoimmune IgM responses to oxidatively specific epitopes (OSEs) and NO-adducts, indicating increased hypernitrosylation, and increased IgG directed against oxidized low-density lipoprotein cholesterol. The combination of the paraoxonase 1 (PON1) gene and its en-

zymatic activity, coupled with early lifetime trauma (ELT) is probably a key phenomenon in both disorders which predicts increased RONS and NOSTOX as well as activation of the IRS. Staging of illness is associated with changes in the Teffector/Treg ratio and with nitro-oxidative stress whereby the number of episodes may prime the immune system to increased IRS/CIRS responses upon immune injuries. Based on these results, we computed nomothetic networks using machine learning techniques to construct new data-driven models of mood disorders by ensembling risk-resilience, adverse outcome pathways, and phenome data.

How oral infections link to cancer?

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Cancer is the number two killer in industrialized countries, second to cardiovascular diseases. It has been estimated that inflammation plays a role in 15% -20% of all malignancies. The cellular pathways include genetic events leading to malignant transformation. Tumor-infiltrating leukocytes are the principal regulators of inflammation associated with cancer. The mouth harbors a magnitude of bacteria, both aerobic and anaerobic that form the oral microbiome. From the mouth, bacteria get easily an access to blood circulation with subsequent spread all over the body. Oral bacterial spread increases if there are infections in the mouth. Epidemiological and cohort studies have shown that dental diseases indeed link statistically to the prevalence and incidence of cancer. For example, if a person suffers from long-term periodontitis, then he/she has an increased risk for many kinds of malignancies. A recent meta-analysis showed that infection with periodontal bacteria increased the incidence of cancer with Odds ratio 1.25 (95% CI 1.03 – 1.52) and it also linked to mortality. The association is not causal, however, and there can be common background factors, which need to be controlled. Evident ethical reasons prevent conducting case control studies in this area.

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A European perspective on inequalities: Long-term outcomes for individuals with orofacial clefts

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In Europe, about 23% of our population is at risk for poverty or social exclusion and those that are affected by a condition, disease or disability are even more at risk. For example, it is estimated that there are over 1,000,000 individuals (babies, children and adults) with orofacial clefts in Europe - a significant figure, especially when one considers that not only the patients but also their families are affected in terms of psychosocial adjustment and having to endure the burden of a long treatment pathway.

At the same time, there have been significant improvements in health in Europe due to advancing health-care systems; however, access to healthcare remains uneven across countries and social groups, according to

socioeconomic status, place of residence, ethnic group, and gender. This lecture will focus upon educational and mental health outcomes for individuals with an orofacial cleft in relation to the variation of health, social, educational and economic resources between European countries. The audience will gain an understanding of the challenges an individual with an orofacial cleft can experience concerning long-term outcomes and that it is not only related to their condition but also very dependent in which European country they reside.

Innovative therapies against atopic dermatitis benefit from *in vitro* research

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Atopic dermatitis (AD) is a common cutaneous inflammatory condition that is associated with dryness, itching, and redness of the skin areas where AD lesions appear. The etiology of AD is still unclear although likely associated with allergic responses and includes increased epidermal hyperplasia and upregulated epidermal expression of antimicrobial proteins. Several approaches devoted to the understanding of the pathological steps that characterize AD or designed in order to identify potential triggering events have recently brought new light on this disease. Indeed, investigation of the Th2 immune response at skin level identified a major role played by the activated immunity in the alteration of properties of the epidermal barrier. Lesions to the skin of AD patients develop with rather precise and limited localization, but interestingly, the non-lesional skin areas nonetheless exhibit close properties with their lesional skin, and differ both together from normal skin. The immune response observed in AD corresponds to some release of cytokines, like interleukin (IL)-4 and IL-13, from activated lymphocytes near epidermal keratinocytes. Because these cells constitutively express receptors made of IL-4 receptor α (IL-4R α) and IL13R α 1 and which become activated by IL-4 and/or IL-13, keratinocytes are sensitive to the Th2 immune response in a way that affects their differentiation program through a perturbed gene expression of proteins involved in epidermal keratinization. Simultaneously, Th2 conditions deeply alter the properties of the epidermal barrier, rendering it loose and permeable to foreign substances, including potential allergens, which might consequently initiate a vicious circle by triggering additional Th2 immune response in the epidermis. Humanized antibody to IL-4R α (dupilumab), designed and purified to block this receptor's function in organs affected by type 2-centered pathogenesis. When administered to diseased tissues, like AD skin, dupilumab can break the vicious circle and robustly bring quick and intense relief from such diseases. Among foreign substances that might trigger Th2 response and AD lesions, one may suspect molecules produced by a dysregulated microbiota over the pathological skin. Indeed, whereas *Staphylococcus aureus* is present but usually remains marginal on human skin, this bacterium may predominate over other microorganisms in AD skin lesions. Interestingly, treatment with dupilumab can restore equilibrated microbiota on AD skin, most likely through its preservation of an efficient epidermal barrier. Simultaneous proliferation of opportunistic *Malassezia* yeasts on AD lesions reinforces attention on the critical role played by cutaneous microbiota in order to maintain a healthy human skin. To lower the cost of AD treatment and limit the pharmacological use of potentially immunizing drugs, it remains highly expected to better identify mechanisms of action triggered in AD in order to select small molecules as potential drugs for AD. Besides presenting pathological mechanisms, this lecture will emphasize how much basic investigation using reconstructed skin models can help to identify and validate AD treatments.

PhotoBioModulation Therapy in Neuropathic Pain Management

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Neuropathic pain (NP) is an unpleasant sensation caused by a lesion or disease of the somato-sensory nervous system, which could be central or peripheral pain. It is caused by damage to the nervous system due to increase in the reactive oxygen species (ROS), antioxidants reduction, adenosine triphosphate (ATP) production imbalance and induction of apoptosis. Photobiomodulation therapy (PBMT) is a positive treatment modality to restore these chemical and biological changes. The use of low level of intensity of visible or near infrared light for reducing pain, inflammation and oedema, promoting healing of wounds, deeper tissues and nerves, and preventing cell death and tissue damage.

This lecture will give a scope of the evidence-based practice, evaluating the effect of PBM in the management of neuropathic pain in primary burning mouth syndrome and post-traumatic neuropathy patients based on a long-term follow-up.

Transcriptome profiling in molecular endocrinology studies

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Microarray together with RNA sequencing (RNA-seq) are innovative, high-throughput methods for transcriptomic profiling. The microarray technique involves the hybridization of labelled cRNA to oligonucleotide probes mounted in the surface in a high-density array format. The current technology allows to use the probes complementary to all of the genes identified in the examined genome. The information obtained from the global gene expression profile has several applications and can provide a good background for studies concerning the effect of newly discovered proteins/peptides on the physiological function of the examined organs, tissues or cells. Therefore, they are widely used in molecular endocrinology studies. As an example, we will present the results of a study concerning transcriptome regulation by newly discovered peptide called adropin. Adropin is a multifunctional peptide hormone encoded by the ENHO (energy homeostasis associated) gene. It plays a role in mechanisms related to increased adiposity, insulin resistance, as well as glucose and lipid metabolism. The multidirectional, adropin-related effects associated with the regulation of metabolism in humans also appear to be attributable to the effects of this peptide on the activity of various elements of the endocrine system, including adrenal cortex. Therefore, the main purpose of the present study was to investigate the effect of adropin on physiological activity and transcriptome regulation of HAC15 adrenal carcinoma cell line. Adropin led to significant inhibition of cortisol and aldosterone biosynthesis. Based on whole transcriptome study we demonstrated that attenuation of steroidogenesis caused by adropin is mediated by the TGF- β signalling pathway. These findings were confirmed in studies using a specific transforming growth factor (TGF)- β type I receptor kinase inhibitor. The obtained results will also be used to present methods for the analysis of microarray data by the R programming language together with the bioconductor package.

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Stem cell based tissue engineering in the cranio-maxillofacial skeleton: the few who made it

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Tissue engineering efforts involve multidisciplinary collaborations between groups of cell biologists, biochemists, biomaterial scientists, engineers, and clinicians. In order to understand the complex role of the various components of tissue engineering, one can consider the paradigm of an equilateral triangle where stem cells, resorbable scaffolds and bioactive molecules such as growth factors continuously interact with each other. The science of Tissue Engineering has been built on the understanding of the nature of the interactions between these three key components.

Mesenchymal stem cells (MSCs) are capable of multiple lineage differentiation including changing to adipocytes, chondrocytes and osteoblastic pathways. MSC clones can sequentially differentiate into adipocytes, dedifferentiate and subsequently transdifferentiate into osteoblasts *in vitro*. Using the tissue engineering model, it is possible to harvest autogenous adipose stem cells (ASCs) from patients to seed a resorbable scaffold manufactured using CAD/CAM technology to the precise dimensions of a missing segment of bone due to congenital deformity such as cleft lip and palate or following tumor resection or trauma. Three-dimensional bioprinting is another area to explore with printed cells to reconstruct a bony defect. Finally, in order to provide a more off the shelf approach the tissue engineering of bone using cell therapy with either autologous or allogeneic adult MSCs could provide adipose derived stem cells needed in this therapeutic approach.

Controversies in Surgical Management of Olfactory Neuroblastoma

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Olfactory neuroblastoma (ONB) or esthesioneuroblastoma is a rare malignancy that develops from the olfactory neuroepithelium which usually lies in the superior nasal vault. Because of the character and location, early cranial invasion is often encountered. The traditional approach for ONB with sinonasal and intracranial invasion has been via craniofacial resection (CFR), a combined open approach involving a lateral rhinotomy and bifrontal craniotomy. With the recent advances in endoscopic skull base surgery, an exclusive transnasal endoscopic approach without open craniotomy is being increasingly adopted in selective cases. Although the follow-up is limited and selection bias to a smaller tumor cannot be excluded, early results are encouraging showing comparable or even better disease control rates. However, due to the favourable nature of the tumor and concomitant advances in adjuvant therapy, an extended follow-up is needed to affirmatively give credit to the endoscopic resection. The extent of resection of earlier stage disease is a matter of controversy and ranges from unilateral extradural resection of the skull base to complete transdural resection including bilateral olfactory bulbs. In this presentation, surgical management of ONB will be presented focused on these issues.

Importance of particle engineering in traditional and alternative drug formulation

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Introduction: Nanoparticle engineering has been developed and reported for pharmaceutical applications. In this approach, poorly water-soluble compounds are formulated as nanometer-sized (100-1000 nm) drug particles. During our work the prepared nanosized systems (as pre-dispersions) were applied in drug formulation (to reach local or systemic effect) to get effective therapies in different diseases. Therefore, we should find cost-effective production by new technological processes containing the most important technological and material parameters.

Materials and methods: Different drugs were applied for preparation of nanosuspension using different kind of polymer as stabilizer. Pre-suspension were produced by wet-dispersion technologies (planetary ball milling, laser ablation, high pressure homogenization, and high intensity ultrasound). The particle size distribution and morphology were determined with laser diffraction (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd.) and scanning electron microscopy (Hitachi S4700, Hitachi Scientific Ltd.). The surface adhesion was analyzed using contact angle system (OCA, Dataphysics Inc). Physico-chemical properties analyzed with differential scanning calorimetry (Mettler Inc.) and X-ray powder diffraction (Bruker D8 Advance). In vitro drug release and permeability were carried out by modified methods in different media. Aerodynamic properties have been tested in vitro using Andersen Cascade Impactor (Copley Scientific Ltd.) for pulmonary formulations.

Results and discussion: The presentation will introduce our applied material and technological parameters during the preformulation of nanosuspension containing model drugs. Per os, intranasal and pulmonary formulation aspects of prepared systems will be also summarized focusing on structural, micrometric and in vitro, ex vivo, in silico and in vivo investigations.

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The role of autophagy and mitochondrial dynamics in neurodegenerative diseases: a study in an Alzheimer disease model

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Autophagy is an essential, highly conserved intracellular pathway involved in preserving cellular homeostasis by degradation of proteins, lipids, and organelles. Under normal conditions, autophagy occurs at basal levels, but it is induced by several stress conditions, including nutrient starvation, damaged organelles, aggregated proteins, DNA damage and infection.

Cytidine-5'-diphosphocholine (CDP-Ch), an intermediate in the biosynthesis of membrane phospholipids, is known to have neuroprotective effects in several diseases but the underlying precise mechanism remains elusive. The fact that choline is also involved in programmed cell death and apoptosis suggests that its protective actions may be associated with autophagy.

Recent studies suggest that autophagy may have a crucial role in Alzheimer's disease (AD). Phosphatidylcholine (PC), one of the essential membrane components synthesized by cytidine 5'-diphosphocholine, may play a role in the formation of autophagic vesicle membranes. In this study, we aimed to understand the effect of CDP-Ch treatment on autophagy and mitochondrial dynamics during amyloid-beta ($A\beta_{1-42}$) mediated neuronal injury.

To this end, nerve growth factor (NGF)-differentiated PC12 cells were treated with $A\beta_{1-42}$ in the presence and absence of CDP-Ch. We examined the levels of several autophagic markers, including LC3B, p62, Beclin-1 and also Mitofusin-2 (Mfn-2), an outer mitochondrial membrane GTPase involved in mitochondrial fusion by immunoblotting. Mitochondrial membrane potential (MMP) and mitochondrial mass were evaluated by flow cytometry and confocal imaging after probing with mitochondria-specific dyes. Oxygen consumption rate (OCR) was measured using Agilent Seahorse XFP Cell Mito Stress Kit.

We observed increases in LC3B and Mfn-2 levels of NGF-differentiated PC12 cells upon CDP-Ch treatment. $A\beta_{1-42}$ treatment of NGF-differentiated cells resulted in increased levels of autophagic markers, LC3B and Beclin-1. Beta-amyloid injury changed mitochondrial membrane potential and MitoSOX levels. CDP-Ch pretreatment of injured cells reduced MitoSox levels. The increases observed in Mfn-2 and mitochondrial mass of untreated cells suggested that CDP-Ch may be involved in mitochondrial dynamics.

Our data indicate that CDP-Ch treatment and amyloid beta injury affect autophagy and mitochondrial function in NGF-differentiated PC12 cells and that CDP-Ch may elicit different effects depending on the degree of damage in the cell. An understanding of the role of CDP-Ch in autophagy and mitochondrial dynamics may shed light into its neuroprotective effects.

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Medical education in(for) the future

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It is known that the aim of medical schools is to prepare the next generations of medical doctors that will respond to the health needs of the populations. Preparing doctors to work anywhere in the world through internationalization of higher education and international programs, in the field of medicine, is only part of the issue. Preparing a global or even universal doctor requires preparing him to deal successfully with differences in races, culture, pathologies, environments etc.

Globalization, emerging diseases, new technologies, and changes in practical methodologies are just some of the biggest challenges facing medical education in a global world.

Nutrigenomics and nutri-epigenetics in the programming of human health

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Maternal and neonatal nutrition, during the first 1000 days of life, can modulate offspring's epigenome leading to tissue specific epigenetic marks that influence organ development (i.e. brain, heart, lung) promoting a healthy/unhealthy phenotype in adulthood.¹⁻³

Malnutrition due to low or high protein or fat intake, alcohol, stress, smoking, xenobiotics and drugs during pregnancy and/or lactation increases the individual risk associated with the development of several diseases in adulthood (i.e. metabolic disorders, obesity, asthma, neurodegeneration, etc).⁴⁻⁶

Appropriate dietary nutrients, as well as dietary flavonoids and other bioactive compounds, can modulate chromatin structure and DNA methylation switching on/off genes properly. Selected foods can control inflammation and maintain a balanced redox state by modulating gene expression and gut microbiota responses toward specific metabolites that affect the epigenome. Therefore, early dietary interventions can modulate nutri-epigenetics towards a healthy status: the "epigenetic memory" of healthy food choices can confer cellular resilience to metabolic perturbations in adult age.

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Orthoplastic approach in complex traumatic tissue defects of the lower leg and foot

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Reconstruction of lower leg and foot is very challenging due to the anatomical characteristics of these organs. In the last half century, we assisted to a dramatical change in thinking and approaching the lower leg and foot complex tissue defects. This became possible due to the new knowledge in vascular anatomy and advances in microsurgical techniques and instrumentation.

The main way to well treat this kind of lesions is to ensure a multidisciplinary approach by collaboration between the specialists involved in approaching them. That's why, in the later part of the last millennium, a new specialty appeared - Orthoplastic Surgery. Orthoplastic extremity reconstructive surgery may be addressed to the treatment of traumatic, oncologic and septic conditions

This paper will discuss the timing of tissue transfer and the armamentarium of tissue reconstructive techniques for surgery of the lower leg and foot, from traditional flaps to the modern perforator flaps.

A cognitive neuroscience approach to auditory verbal hallucinations in schizophrenia: from cognition to neurotransmitters

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Auditory verbal hallucinations (AVHs) is not only a distressing symptom in schizophrenia and related disorders, but occurs also in individuals in the general population without a psychiatric or neurological diagnosis. As such, AVHs can be seen as an altered state of consciousness, in the sense of experiencing hearing «voices» that are not physically present, with perceptual, cognitive and emotional characteristics. This has led to much research over the last decade regarding brain correlates of AVHs, as they obviously must have some kind of intrinsic origin. Another characteristic is that AVHs manifest themselves at different levels of explanation, which means that AVHs can be studied from a cultural and a molecular level, with corresponding explanations. In this chapter I will review the research in our laboratory on how AVHs can be studied from a cognitive to a neurochemical perspective, using data from different MR imaging modalities, from structural MR to functional MR to MR spectroscopy, with the aim to elucidate underlying neuronal mechanisms for this remarkable state of the mind.

Nanocomponents in osteochondral defects engineering

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Introduction: Taking into consideration the significant economic losses among the working-age population due to pathology of the dentofacial system and joints (including both bone and cartilaginous tissues), the development of new treatment strategies is a current medical, social and economic challenge. Recent studies indicate the emergence of technology for additive production of implants based on selective laser sintering with the possibility of manufacturing of porous materials with precise mechanical properties, topological architecture of surface porosity and patient-specific design. The obtained structures should function as supporting scaffolds for osteogenic and chondrogenic cells in accordance with the subsequent replacement of damaged tissues, as well as to demonstrate mechanical properties similar to healthy tissue during rehabilitation. In addition to metals, Ca-P-based ceramics and polymers (natural or synthetic) can be used to make scaffolds. Also promising are the methods of introducing micro and nanoparticles into the surface of the implant. However, these coatings have limited mechanical resistance. Therefore, titanium-based scaffolds must be modified to improve their osteogenic properties.

The aim of osteochondral tissue engineering is to create hard bone substitutes that are tightly bound to bone, soft and cartilaginous tissue in order to develop an alternative to total replacement of bone or joint.

Materials and methods: With the help of X-ray diffraction analysis, a qualitative and quantitative study of the phase composition of the implant material obtained by the method of selective sintering was performed. Surface modification was performed using plasma electrolytic oxidation (PEO) with addition of silver and copper nanoparticles. The structural and chemical parameters of PEO coating were studied using TEM / SEM (transmission electron microscopy / scanning electron microscopy), EDX (energy-dispersive X-ray spectroscopy) and XRD (X-ray diffraction) methods. Tests for cellular toxicity and bacterial adhesion were used to confirm surface safety and antibacterial properties.

Results: Plasma electrolytic oxidation (PEO) is an advanced electrochemical method of surface modification of titanium implants, which is considered to be one of the most effective method because it can create homogeneous, porous and well-bonded ceramic layers of TiO₂. We believe that the functional properties of the PEO surface layers can be altered by the recently discovered MXenes, graphene-like 2D nanolaminates. We have demonstrated that silver and copper nanoparticles do not change their properties during PEO, so they can be used in coatings. Therefore, we suggested that MXenes should also not undergo any changes during the plasma electrolytic oxidation process.

Structuring the surface at the nanoscale can provide additional potential for bone development within metal templates. Preliminary data have shown that specific nano-topographies (60 - 80 nm, but not 15 - 25 nm or more than 100 nm), containing calcium ions as well as silver and copper nanoparticles increased the adhesion, proliferation and osteoblastic differentiation of mesenchymal stem cells. Therefore, PEO with the addition of nanocomponents can be used to obtain modified surfaces of scaffolds with controlled topography.

Conclusion: Based on the analysis of the composition, structure and mechanical properties, a technological scheme was developed for the manufacture of grafts, suitable for use in standard production processes. Creation of individualized jaw implants using titanium alloys, made according to the parameters of the patient's preoperative computed tomography, is a new level of high technology in Ukrainian medicine. The method, being implemented in Zaporizhzhia, allows full restoring the natural shape and function of the jaw.

Keywords: dentofacial system, plasma electrolytic oxidation, individualized jaw implants.

Tailored Approach to Saddle Nose Deformity

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Saddle nose affects mainly the lower two-thirds of the nose due to the loss of septal height and tip support. Because it compromises the integrity of the cartilaginous septum, the patients may show middle vault depression and widening, retraction of the columella, short nose deformity, and over-rotation of the nasal tip. Complex deformities of the nasal septum can result in both an aesthetic and functional impacts on a patient's nose.

Saddling of the nose is essentially caused by the loss of nasal septal support for the dorsum of the nose. Support of the nasal dorsum is provided by the cartilaginous and bony structures involved in nasal projection. Saddle nose can be divided into 4 categories: 1) good cartilaginous septal support with a minor supra-tip depression. This could be easily corrected by cosmetic dorsal camouflage; 2) moderate loss of septal cartilaginous support with moderate dorsal depression, which could be managed by septal reconstruction; 3) severe loss of septal cartilaginous support with a moderate to severe dorsal depression needs subtotal septal reconstruction; 4) severe loss of cartilaginous support with both bony and cartilaginous dorsal depression, in which case dorsal onlay graft and extended columellar strut are needed to total reconstruction of dorsum with costal cartilage.

The classification of saddle nose is important because the repair for a mild case of saddling differs greatly from a case of severe saddling. Understanding and having a mental map of the nasal deformity involved is the first step to planning for a successful outcome.

MU-Plovdiv and University Campus Bio-Medico of Rome + CNR-Institute of Translational Pharmacology: a story of friendship and fruitful scientific collaboration

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Since 2006, time of the first visit of MU-Plovdiv delegates in Rome, a long story of collaboration has started, with mutual scientific and cultural impact. Lecturing, mentoring PhD students and working on joint projects was a challenge that both sides faced with enthusiasm and professionalism. In this lecture, the important stages of this relationship will be re-traced, highlighting the scientific progress and advancements in studies on the mechanisms of onset and development of colorectal cancer (CRC) – a topic within the scope of research of all partners.

Colorectal cancer (CRC) represents the third most common neoplastic disease worldwide and the second leading cause of cancer death in the western world. Appropriate *in vivo* models are becoming of utmost importance to clarify the molecular pathways involved in occurrence and progression of CRC, and we propose the AOM/DSS mouse model as a valid translational platform for these studies. Our first investigations were focused to identify potential novel genes related to CRC progression. We performed a genome-wide expression profiling of AOM/DSS induced tumors. We found 2036 differentially expressed genes, 1092 upregulated and 944 downregulated genes, by comparing the colon mucosa in affected and control mice. The most altered genes were significantly involved in the activation of the Wnt/ β -catenin pathway. Particularly, we demonstrated significant changes, in NOTUM, GLYPICAN-1 and GLYPICAN-3 gene expression during CRC development. We are continuing in this line by investigating a member of the chitinase protein family for its role in regulating the epithelial mesenchymal transition in colon cancer. Furthermore, a new research field has been recently open to elucidate the role of diet-dependent Gut Microbiome (MB) composition on the presence and onset of CRC. Objective of this project is to identify novel microbial biomarkers related to diet and characterize the link between MB composition, diet and CRC risk for integrated prevention strategies. In this aim, following the ethical committee approval, the Department of Medical Biology at MU-Plovdiv in collaboration with the University Hospital "Eurohospital", has a leading role in organizing a bio-bank through the collection of blood and tissue samples from patients affected by colorectal adenomatous polyps or metastatic CRC. The samples will be analyzed in Italy by metagenomic approach.

Er:YAG Laser Supported Endodontic Treatment, Endodontic Retreatment and Endodontic Surgery

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Laser technology is being developed very quickly and new lasers applications are available today and are being used in the various fields of dentistry. The search for new laser applications for dental procedures was always challenging and more experience and knowledge was gained.

The laser principle will be explained using animations and the rationale in using laser irradiation in root canal therapy will be discussed.

The new Endo side firing spiral tip for use in root canal treatments was developed at the Hebrew University – Hadassah School of Dental Medicine and its use in endodontics will be presented.

SEM photographs following its use with Er:YAG laser irradiation in the root canal system showed clean root canal walls with open dentinal tubules.

The presence of biofilm in the contaminated root canal system calls for effective means to enable its removal. It will be shown that the laser irradiation could play a paramount role in the fulfilment of this objective.

The advantage of the Er:YAG laser to sterilize the bony walls of the crypt following the surgical removal of a periapical lesion will be also discussed.

Clinical cases of endodontic treatment, endodontic retreatment and endodontic surgery with follow-ups, using the Er:YAG laser will be presented.

OSA: the End of CPAP?

Nico de Vries

ENT, Head and Neck Surgeon

Obstructive sleep apnea (OSA) is traditionally treated by Continuous Positive Airway Pressure (CPAP). It was introduced in 1981 and has changed and saved numerous lives. In 2020, CPAP in many places in the world is still regarded as the only treatment available. In this talk we will highlight the new developments that have taken place in the diagnosis and treatment of OSA.

Presently, in addition to CPAP, oral devices, positional therapy, sleep surgery by ENTs and maxillofacial surgeons, bariatric surgery and neuromodulation are to our disposal. We can conclude that treatment of OAS is moving away from “one size fits all” CPAP therapy to personalized medicine.

After meticulous diagnostic work up, by way of shared decision making, the patient and doctor, based on careful consideration of the available treatment options, together decide on the best treatment plan in an individual case.

Tumor-associated thrombosis - the search for the new predictive biomarkers continues

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Cancer patients have an increased risk of developing venous thromboembolism (VTE), a condition that is associated with increased morbidity and mortality. Classical risk factors that contribute to VTE cannot explain the increased tendency for thromboembolism in neoplasms. Plasma hypercoagulability, genetic predisposition, tumor biology and mutation profile are of greater importance. Tumors of the brain, ovaries and pancreas have the highest risk of VTE, colon and lung cancers are with moderate risk, prostate and breast cancer - with low risk. In addition, cancer treatment such as surgery and chemotherapy further increases the risk of VTE. The main reason for the slow progress in understanding tumor-associated thrombosis and the validation of

new biomarkers is the extrapolation of classical hemostasis markers in VTE to patients with malignancies. A number of studies in cancer proteomics have confirmed that tumors leave a «unique protein imprint» on human plasma. Tissue factor, β -selectin, and the proinflammatory mediators IL-6 and IL-8 are thought to play a role in both tumor progression and the development of VTE. Mutations in K-ras, PTEN and p53 genes in tumors of different origin show a high risk of VTE, but the association has not been conclusively confirmed in EGFR mutations. Despite ongoing extensive research, developed algorithms can predict VTE only in 37% of cases. In the era of personalized medicine, we have to turn our attention to modern molecular techniques for genetic profiling and detection of circulating tumour cells in order to validate new predictive biomarkers in tumor-associated thrombosis.

Laboratory models for pulp regeneration

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Laboratory models for pulp regeneration based on stem cells, growth factors and natural or artificial scaffolds applied in sterile conditions have been highly developed in the last decade. These *in vitro* and *in vivo* models demonstrated the formation of novel, vital and functional pulp-like tissue in experimental conditions. Large range of factors like juridical difficulties of stem cell banking and autologous stem cell transplantation, difficulties to maintain sterile clinical conditions in the root canal, impossibility to follow the histological changes during the healing period etc. slow down the application of these laboratory models in the clinic. The modern clinical approach, named "regenerative endodontic procedure/treatment" (REP/RET), regroups the direct pulp capping on vital teeth and the revitalization/revascularization treatment in case of pulp necrosis of immature teeth. The RET allows repair of the dental organ and healing of the periodontium, but not the regeneration of the dental pulp tissue *ad integrum*. Recently, autologous transplantation of dental pulp stem cells in clinical cases of direct pulp capping and clinical application of "plasma rich in platelets" and "plasma rich in fibrin" in case of RET of immature necrotic teeth shows promising results. These new treatments are one step near, about to apply the laboratory models into the clinic. However, adopting the clinical approach for the development of a new laboratory model, could be the next important step to find his feasible clinical application.

Keywords: Pulp regeneration, Laboratory models, Regenerative endodontic treatment

New application of dermatoscopy in daily dermatological practice

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Dermatoscopy is a non-invasive diagnostic method in which the morphological features of the skin surface structures, invisible to the naked eye, are visualized with the help of hand-held dermatoscopes or video dermatoscopes. Originally introduced to assess pigmented skin lesions, dermatoscopy is now increasingly used to examine a variety of non-pigmented skin tumors, inflammatory dermatoses (inflammoscopy), infectious

dermatoses and parasitoses (entodermatoscopy), hair and scalp diseases (trichoscopy), and nail diseases (onychocopy). This presentation aims to illustrate the new applications of the dermatoscopy in daily practice. In the hands of a trained dermatologist, the dermatoscope is becoming nowadays a means equivalent to a headset in the hands of an internist.

Joint education and training programs - from the project to the practice

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Contemporary digital world is constantly changing the medical communities and the Medical Universities in particular. The novel information and communication technologies have been implemented into the medical research programs for decades, but nowadays these technologies are providing excellent means and capabilities for medical information exchange on all levels of the medical science - research, teaching, training, practice. The unprecedented real-time connectivity between scientists, researchers, practitioners and academics from different countries and continents is providing opportunities beyond imagination for novel educational and training medical practices.

The **aim** of this study is to present the opportunities provided by the joint educational and training programs for the Medical university Plovdiv students and academics.

Materials and Methods: By the means of descriptive and comparative methods the some of the ongoing project activities related to building joint medical educational and training programs are analysed.

Results and Discussion: Two Medical University initiatives are close to establishing joint educational programs with overseas medical teaching installations. The first one flourished by the fruitful Erasmus cooperation with the State Medical University in Aktobe, Kazakhstan. It is related to Joint Master program in Public Health Management for bachelors from both the countries. The second one is Joint education in Public Health for students in Chinese Medical Colleges.

Conclusion: Based on information exchange capabilities the best practices into Medical education could be shared as joint sophisticated educational and training medical programs.

Keywords: Medical education, Joint Training programs, Projects

Ageing of human dentin and dental pulp – structural, physico-chemical and molecular characteristics

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Age-related changes in human dentin and dental pulp odontoblast cells are in the area of interest regarding the morphology, ultrastructure, physico-chemistry and molecular biology of tissues. Fundamental biomarkers in autophagy (COX2, LAMP2, MAP LC3II) and intracellular signal paths and regulation of apoptosis (BID-Caspasa-8, JAK1-STAT3 and NFkB) in cells are observed in the perspective of the life span of long-lasting

post-mitotic fully differentiated pulp odontoblasts. The link between the pulp cells ageing and the crystallographic, and non-collagen protein components of dentin (SIBLINGs family) is clarified enlightening the association between the ageing and pulp-dentin homeostasis including the angiogenesis and vascularization (CD34) in time. The hypothesis for cell-independent non-secreted mechanism of dentinogenesis is presented. The molecular chart of senescent odontoblasts is done supporting the lysosomal-mitochondrial theory of ageing in pulp-dentin complex.

Challenges and perspectives in diabetes mellitus management

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Challenges in diabetes mellitus (DM) management include optimizing the use of current therapies to ensure adequate glycemic, blood pressure, and lipid control and to reduce the risk of micro- and macrovascular complications and disease progression. The various lines of research aimed at covering the unmet needs in DM management can be grouped into three categories: technological, biological, and pharmacological. The last century was a time of change and innovation of insulin therapy, starting with the isolation of insulin, the purification of animal pancreatic extracts, the development of various formulations, and the progression to human insulin and insulin analogues made with recombinant DNA technology. In type 1 DM, the complete lack of endogenous insulin has focused research on ever-more sophisticated ways to deliver insulin, with the goal of developing an 'artificial pancreas'. Advances in technology such as continuous glucose monitoring systems and continuous subcutaneous insulin infusion therapy provides new opportunities. In type 2 DM, a range of pharmacologic treatments has been developed, toward safer and more effective drugs, which can also reduce the cardiovascular and renal outcomes. Evidence from studies of dietary restriction and bariatric surgery suggests it may be possible to reset metabolism to effectively cure the disease and research into pharmacological agents that could selectively restore energy balance is currently the most exciting perspective for treatment of type 2 DM. Digital health technology has developed at a rapid pace and becomes an increasingly common aspect of care and self management to improve quality of life of diabetic people.

PCOS – a neverending story

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This year marks the 85th anniversary since Irving Stain and Michel Leventhal first described the polycystic ovary syndrome (PCOS). It has now become clear that the polycystic ovary syndrome is one of the most common endocrinopathies among women of reproductive age. It is a heterogenic collection of symptoms with genetic predisposition which, combined in different ways, determine the variety of clinical manifestations. The aetiology of this syndrome remains largely unknown, but mounting evidence suggests that PCOS might be a complex multigenic disorder with strong epigenetic and environmental influences. PCOS is characterized by reproductive, endocrine, metabolic, and psychological features. There is no cure and its management remains suboptimal as it only relies on the empirical management of symptoms. Despite significant progress in the understanding of the pathophysiology and diagnosis of the disorder, it remains underdiagnosed and misunderstood by many practitioners. Obviously, PCOS is a lifelong condition with long-term morbidity and significant deterioration in the quality of life.

Current understanding of the nature of the syndrome, diagnosis and future perspectives are discussed.

Enhancing precision medicine through clinical mass spectrometry platform

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There is an extraordinary flood of new technologies in medicine nowadays - sophisticated diagnostics based on genome assays, mass spectrometry and cell sorting platforms are driving the technological transfer and promote the entrance of individualized patient management in clinical practice. Mass spectrometry (MS) could be viewed as one of the major tools that promote the development of precision medicine, which employs patient's genotype and phenotype investigation to establish individually tailored drug treatment. While genetic testing allows the physician to choose appropriate medicine, the performance of MS assays provides the patient's actual phenotype, with all of the environmental, pharmacological and pathological variables. Therefore, MS is essential technology for personalized patient management. LC-MS/MS (QQQ) is the today's most utilized analytical platform, but high-resolution MS systems are also employed to resolve challenging analytical demands. The great technological advance of LC-MS/MS resulted in the introduction of methods with extreme sensitivity, specificity and extended linearity range, which are simpler to use in the medical laboratories, and are based on the current reference analytical principles. Further, the ability to perform panel profiling with simultaneous measurement of bioactive compounds, their precursors and metabolites in a single sample, enormously amplifies the informative value of results, with ultimate improvement of patient care. Typical examples include new born screening, TDM, toxicology, endocrinology, microbiology and others. It should be specially emphasized that clinical MS integrates chemical and anatomical pathology: MS imaging and I-knife-MS guidance in surgery, although still in research phase, open new horizons for personalized treatment and individualized patient care.

The incredible human brain. A journey beyond frontiers of knowledge

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Until late 19th century human brain attributes were considered to be 'mysteries'. And despite some remarkable advances, the brain remains largely incomprehensible. It continues to confuse, shock, stun with its incredible abilities and structural brilliance. Much has been discovered, but we are still largely unaware about brain. We know it is made up of about 100 billion neurons, each connecting possibly 10,000 other neurons in intricate network of 1,000 trillion connections that are beyond the capacity of any existing technology to trace. We know messages travel as electrical spikes and jump between neurons by release of neurotransmitter chemicals. We know the location of different brain functions, such as vision, hearing, smell, memory. But we are far behind the comprehension how these electrical and chemical signals lead to such amazing properties as consciousness, intelligence, and ingenuity. Scientists have yet to unravel the function of the intricate network that trigger countless electrical and chemical signals, giving us such amazing things as perception, intelligence, sensitivity, imagination. The ravenous strive to understand how thoughts, dreams, memories and other mental images are generated and stored is a vital force in neuroscience. Recent advances in nanotechnology, microelectronics, optics, data processing, information theory, and quantum computing could help make possible investigations that were unimaginable before. The knowledge achieved could contribute to understanding and treatment of major disorders like depression, schizophrenia, autism, Alzheimer's, Parkinson's and other brain illnesses.

Sources of hematopoietic stem cells for transplantation

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Hematopoiesis is the process of forming blood cell components. The proliferation, differentiation and maturation of hematopoietic and lymphoid cells is an intensive process that continues throughout life of the organism. The hematopoietic system originates from a bone marrow pluripotent stem cell from which the individual hematopoietic lines develop under the influence of specific factors. It is one of the systems with the highest degree of continuous replication with limited lifespan of its individual components and has both reserves, which are included immediately under stress, and regenerative potential in the presence of sufficient response time. The system is regulated by a complex network of control, humoral and cell-mediated mechanisms

Hematopoietic stem cells (HSCs) are defined as undifferentiated cells capable of dividing indefinitely by self-renewing and producing progeny from highly specialized cells. HSC transplantation is an established method for the treatment of benign and malignant hematological diseases, which expands its indications and is used in more and more elderly patients. Every year, the number of autologous and allogeneic HSC transplants in Europe and in the world increases.

Bone marrow, peripheral blood, or venous blood from the umbilical cord are used as sources of hematopoietic stem cells. When stem cells are obtained from the patient himself, they are called autologous, and when cells from a healthy donor (related or unrelated) are used, they are called allogeneic. Initially, bone marrow was used for hematopoietic stem cell transplantation. Still in certain diseases (e.g., aplastic anemia due to stromal cells in the aspirate), and with less donor-recipient compatibility, bone marrow is the preferred source of stem cells. Peripheral blood is increasingly being used as a source of hematopoietic stem cells for autologous and allogeneic transplants. The reason for this is the less invasiveness of the procedure, the faster capture of the graft, and in some cases, in allogeneic transplants, the desire of the donor himself or medical indications related to his health condition. Another alternative source of stem cells for allogeneic transplantation is umbilical cord blood. Extensive research over the past 20 years has established the safety and efficacy of umbilical cord blood transplantation in both children and adults with various malignancies and non-malignancies.

Five years autologous hemopoetic stem cells transplantation in St George University Hospital, MU - Plovdiv

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Patients and methods: Between October 2015 and July 2020, 107 patients underwent autologous transplantation of peripheral hematopoietic stem cells (PBSC) [68 (63.6%) males and 39 (36.4%) females]. Distribution by diagnosis: multiple myeloma (MM) - 56.1% (60), Hodgkin's lymphoma (HL) - 28.0% (30) and aggressive non-Hodgkin's lymphomas (NHL) - 15.9% (17).

Results: In the MM group, the mean age was 58.75 ± 5.96 years, four patients had a second auto-PBSC transplant. After the transplant, complete response (CR) was recorded in 28 (47.5%) patients, very good partial response (VGPR) in 23 (38.2%), partial response (PR) in 7 (11.9%) and progressive disease within the first 3 months after PBSCT in 2 (3.4%) patients. Maintenance treatment was received by 39 (65.0%) patients. The median progression-free survival was 46 months and the overall survival rate was 78% at 3 years. In patients with Hodgkin's lymphoma, mean age was 40.59 ± 13.15 years. After auto-PBSCT, CR was found in 17 (65.4%) patients, PR in 6 (23.1%), stable disease (SD) in one (3.8%) patient, and progressive disease in two (7.7%)

patients. The median progression-free survival was 36 months, at 3 years the overall survival was 71%. In the NHL group, the mean age was 40.8 ± 12.16 years. After PBSCT, CR was registered in nine (52.9%) patients, PR in three (17.6%), and progressive disease before month 3 - in three (17.6%) patients. The median progression-free survival was 44 months, and overall survival at 3 years was 70%. The reported side effects during myelosuppression were gastrointestinal, hepatic and renal toxicity grade 1 and 2, as well as inflammatory complications.

Discussion and conclusion: Autologous PBSCT is an established effective treatment method in patients with MM and in relapsed patients with lymphomas. It improves their therapeutic response and prolongs their overall survival.

Conditioning regimens for allogeneic hematopoietic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a treatment of choice for managing patients with different malignant and non-malignant diseases. The success of allo-HSCT depends on many factors the most fundamental among them being the conditioning regimen. The goal of conditioning is to prepare the host to accept the graft and, when used to treat malignant disorders, to eradicate or reduce the tumor burden as much as possible. In order to achieve this, different regimens combining chemo-, radio-, and immunotherapy have been developed. Choosing the best conditioning for every individual case is challenging due to the different patient- and disease-specific variables. According to their intensity, regimens are classified as myeloablative (MAC), reduced-intensity conditioning (RIC) and non-myeloablative (NMA). In recent years there has been growing interest in so-called myeloablative, reduced-toxicity regimens. The great variety of different conditioning regimens makes it possible to choose the most appropriate therapy in real-life clinical scenarios and also makes allo-HSCT a feasible treatment option in older patients or in those with comorbidities.

Indications, specificity and complications in hematopoietic stem cell transplantation in children and adolescents. Practical aspects of EBV post-transplant lymphoproliferative disorder in 2 cases after allogeneic bone marrow transplantation

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It has been estimated that more than 2000 allogeneic HSCT annually are performed in recipients younger than 20 years. These transplantations are mainly indicated in patients with malignant hematological diseases, inherited and acquired bone marrow failure syndromes, hemoglobinopathies and some metabolic diseases. The graft-versus-host disease remains the main complication but there are other immune-based conditions that are exclusively connected with the application of HSCT. Current knowledge about the EBV post-transplant lymphoproliferative disorder based on two cases is presented.

ORAL PRESENTATIONS

Biomedicine

Advantages of ddPCR in the diagnosis and follow-up of patients with chronic myeloproliferative diseases

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Digital PCR (ddPCR) is a new, advanced technology for molecular research. Its improved accuracy and precision help to diagnose at an earlier stage the genetic disorders in various oncohematological diseases and to monitor the effect of treatment with higher resolution.

Objective: To establish the advantages of ddPCR over real-time PCR (RT-PCR) by studying, quantifying and analyzing the T315I mutation in the ABL1 gene in patients with chronic myeloid leukemia (CML) after failure of first-line tyrosine kinase inhibitors and the V617F mutation in the JAK2 gene in patients with Philadelphia chromosome-negative myeloproliferative neoplasia (Ph (-)).

Materials and methods: 90 patients with CML and 37 patients with MPN – Ph(-) were studied. Both methods were used in all patients: allele-specific RT-PCR and ddPCR. Results: In the group of patients with CML, in the RT-PCR study, the T315i mutation was detected in 5.55% (5/90) and in ddPCR – in 11.1% (10/90). In patients with MPN – Ph (-), by RT-PCR, mutation of V617F in the JAK2 gene was detected in 59.5% (22/37) of the patients, and by ddPCR in 64.8% (24/37) of the patients.

Discussion: A comparative analysis of the results of the two methods showed that the ddPCR method was extremely sensitive (detects very low levels of target DNA -1/100,000 copies) and accuracy (measured the absolute concentration of nucleic acids without calibration curves).

Conclusion: ddPCR has enormous potential and is becoming the preferred method over the allele-specific real-time PCR in the diagnosis and follow-up of patients with CML and MPN Ph(-).

Keywords: Digital PCR (ddPCR), T315I mutation in the ABL1 gene, mutation of V617F in the JAK2 gene

Anterior-segment OCT indices and their diagnostic value in differentiating ectatic from normal corneas

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Purpose: To determine the diagnostic value of the AS-OCT indices in the diagnostics of ectatic corneas.

Material and methods: The study included two groups and each of them contained 80 eyes of 43 patients. Each patient underwent examination with Keratograph – OCULUS 5M and anterior segment - OCT RTVue-100. For the purpose of the study we evaluated the following indices: the mean thickness of corneal segments, the minimal corneal thickness (Min), the Min-Med, Min-Max, SN-IT, and S-N indices. Statistical analysis was performed using SPSS version 15 and the following test: Mann-Whitney U test, independent-samples T-test, ROC (Receiver Operating Characteristic Analysis).

Results: Significant difference was found for all of the examined indices (95% confidence Interval). The ROC analysis determined the minimal corneal thickness (Min) to be the best performing index with area under the curve (AOC) of 0.976. The rest of the examined indices showed good performance with AOC in the range from 0.973 to 0.814.

Conclusion: The examined AS-OCT indices show excellent diagnostic capability in differentiating ectatic from normal corneas.

Keywords: corneal ectasia, keratoconus, anterior-segment OCT, ophthalmology

Combination of primary hyperparathyroidism and ectopic thyroid gland – diagnostic and therapeutic options

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Introduction: The co-existence of various endocrine diseases is common in daily clinical practice. The development of an individualized therapeutic approach with respect to the age and comorbidities of the patient is essential for the prognosis and outcome of the treatment.

Clinical case: We present an 81-year-old patient after subtotal thyroidectomy for Graves' disease in the past and recurrent nephrolithiasis complicated by mild renal failure, with concomitant arterial hypertension and coronary heart disease. Hormonal assessment showed an euthyroid state being on replacement therapy and laboratory findings consistent with primary hyperparathyroidism. Subsequent ultrasound examination of the neck revealed a formation in the left thyroid lobe bed suspicious for parathyroid adenoma, confirmed by fine-needle aspiration biopsy (FNAB) and measuring parathyroid hormone (PTH) levels in the needle wash-out. In addition, a solid 3-cm mass bearing ultrasound characteristics of thyroid parenchyma was visualized in the retroclavicular area. FNAB with cytological evaluation and thyroglobulin testing in fine-needle aspirate was done and confirmed the presence of ectopic thyroid tissue. Considering the high operative risk the patient underwent serial percutaneous ethanol ablation of the parathyroid adenoma. After the third procedure normalization of serum calcium together with significant decrease in PTH levels were achieved.

Conclusion: Contemporary minimally invasive techniques significantly expand the diagnostic scope of ultrasound examination of the neck area. Ultrasound-guided percutaneous procedures provide the opportunity for precise application of therapeutic agents with minimal risk to surrounding structures and can be an effective and safe alternative to surgical treatment in patients at high operative risk.

Keywords: parathyroid adenoma, ectopic thyroid tissue, fine-needle aspiration biopsy, percutaneous ethanol ablation

Molecular cytogenetics of renal cell carcinoma – literature review

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Kidney tumors account for 3% of all cancers in adults. More than 85% of them originate from the renal parenchyma, predominantly represented by different subtypes of renal cell carcinoma (RCC), while the rest affect the renal pelvis or are of mesenchymal origin. Recently, attention has been focused on the genetic risks of increased susceptibility to the occurrence and development of RCC. It was found that the different subtypes

are characterized by different chromosomal rearrangements, which supports the idea of their nosological specificity and different tumor biology (clinical aggressiveness). However, molecular diagnostics and biomarkers have not yet reached the "clinical stage" for this tumor. It is absolutely necessary to validate all these findings, which will justify the introduction of genetic markers in the approaches to RCC. All this will lead to improved diagnosis, prognosis and personalized therapy of this heterogeneous enigmatic malignancy. This review presents the genetic aberrations in the literature related with RCC and the most commonly used techniques for their detection.

Keywords: Renal cell carcinoma, subtypes, molecular cytogenetics, personalized medicine

Clinical characteristics, disease evolution and median survival in patients with chronic myeloid leukemia, BCR-ABL +, carrying the T315I mutation

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Background: The T315i mutation in patients with chronic myeloid leukemia (CML) has been associated with therapeutic resistance and an unfavorable prognosis.

Aim: To study the frequency of T315i mutation in patients with CML, BCR-ABL +, their clinical characteristics, disease evolution and median survival

Material and methods: We studied 73 patients with CML, BCR-ABL1 +. T315i mutation was detected by digital droplet PCR and BCR – ABL 1 was analyzed by RT-PCR. A comparative analysis was performed by sex, age, disease phase, risk group, treatment, molecular response (MR) and median survival in T315i (+) and T315i (-) patients

Results: T315i mutation was detected in 11 (14.7%) patients. The m/f ratio in the T315i (+) group was 2/3, mean age 46±14.5 years, with no statistical difference in the whole cohort. No difference was found in phase, risk group, and first-line therapy. A significantly higher proportion of T315i + did not achieve MR: 7 (63.6%) vs 14 (26.4%), $p = 0.023$. The lowest mean BCR-ABL -1 levels were significantly higher in the T315i (+) group: 12.1±6.0 vs 3.77±1.28 ($p = 0.009$). The median survival of T315i + patients was significantly shorter 73 months vs 175 months ($p < 0.0001$, CI 95%).

Discussion and conclusion: Our data confirm the world experience on the frequency of T315i mutation, including the unfavorable evolution, resistance to TKI treatment and short survival. ddPCR is a highly sensitive method for early detection of genetic mutations which gives the chance for effective treatment.

Keywords: chronic myeloid leukemia, mutation T315i, digital droplet PCR

The study was conducted as part of project BG05M2OP001-1.002-0005-C01 - Competence Center "Personalized Innovative Medicine" (PERIMED), work package – 2.

Choroidal neovascularization secondary to wet age-related macular degeneration – frequency distribution and morphological types according to optical coherence tomography-angiography

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Introduction: Age-related macular degeneration (AMD) is the leading cause of visual impairment in individuals over the age of 55 years worldwide. Choroidal neovascularization (CNV) is the hallmark of neovascular AMD.

Aims: To investigate the frequency distribution and morphological types of the different CNV secondary to wet AMD using OCT-A. **Method:** A total of 43 patients (43 eyes, mean age 72 ± 6 years, 53.5% females) with wet AMD were enrolled. They underwent a complete ophthalmologic examination, including also fluorescein angiography (FA), and OCT-A (Cirrus HD-OCT, Angioplex, Carl Zeiss Meditec, Dublin, CA).

Results: In 36 eyes (83.7%) there was late leakage from an undetermined source on FA and a pathologic vascular complex under the retinal pigment epithelium (RPE) on OCT-A correlating with CNV 1. In 2 eyes (4.7%) there was leakage with a classic pattern on FA and a neovascular membrane into the avascular retina on OCT-A suspected for CNV 2. In 5 eyes (11.6%) we found CNV 4 (mixed CNV). CNV 3 (RAP) was not established in the examined group of patients. Three different morphological subtypes of CNV were visualized – “medusa-like” in 18 eyes (41.8%), “seafan-like” in 15 eyes (35.0%), and CNV with indistinct form in the rest 10 eyes (23.2%).

Conclusions: The results confirmed the higher incidence of CNV 1 than other CNV subtypes. “Medusa-like” and “seafan-like” CNV present an active subtype, while CNV with indistinct form – inactive subtype. OCT-A could be considered a reliable technique for easily visualizing different subtypes of CNV in patients with neovascular AMD.

Keywords: age-related macular degeneration, choroidal neovascularization, fluorescein angiography, optical coherence tomography-angiography

3D bioprinted cell models of colorectal cancer

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Introduction: Colorectal cancer (CRC) is the third most common and the fourth deadliest cancer in Western countries. Better in situ carcinoma-like predictive models for pre-clinical pharmacological trials of new therapies are urgently needed for more successful treatment of CRC. 3D bioprinting, as the latest method for creating tissues in vitro, offers a controlled spatial configuration of cells in supporting materials.

Aims: Development and validation of 3D bioprinted cell models of CRC for personalisation of the therapeutic treatment.

Materials and methods: Primary tumor cells from patient samples with CRC obtained after surgical resection and the Caco-2 cell line were cultured under standard conditions. Bioprinting was performed with a BioX

(Cellink, Sweden) bioprinter and commercial bioinks. Histo-morphological validation was conducted by H&E staining. Standard epithelial markers, CK7 and CK20, were used for immunohistochemical evaluation. Cell viability was examined by fluorescence live/dead staining and by MTT assay.

Results: We have developed 3D bioprinted models of CRC from an established colorectal cell line-Caco 2 and from patient samples. The created models were validated histologically and immunohistochemically. Printed cells have good viability for up to two weeks after printing. Clusters of cells with morphology resembling tumor structures in situ were observed. The models were also validated to assess the cellular response against 5-fluorouracil, irinotecan and oxaliplatin. 3D bioprinted organoids showed increased resistance to these chemotherapeutics compared to the 2D cell monolayer cultures. The mechanisms of this resistance are yet to be investigated.

Conclusion: We have successfully established a 3D bioprinted cell model of CRC, which may serve for studying oncogenesis, for pre-clinical drug testing and for personalised medicine.

Keywords: bioprinting, colorectal cancer

Reversal of age-related remodeling of tunica media of rat coronary arteries after supplementation with aronia melanocarpa juices

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Vascular dysfunction is a key characteristic of age-related cardiovascular and cerebrovascular diseases. The use of natural antioxidants is a strategy with huge prophylactic potential. Aronia melanocarpa (AM), in addition to being among the most antioxidant-rich natural remedies, has proven anti-inflammatory and immunomodulatory properties. The aim of the study was to investigate the effect of AM juices (AMJ) on age-related connective tissue remodeling in tunica media of coronary arteries in rats. Male Wistar rats (n=24) were divided in 4 groups: 1) Young controls (CY) – at the age of 2 months; 2) Old controls (CO) – 24 months old, without AMJ supplementation; and 3) AMJ A20 group (A20) – 24 months old, supplemented orally with AMJ, produced at 20°C (10 ml·kg⁻¹) and 4) AMJ group (A60) – 24 months old, supplemented orally with AMJ, produced at 60°C (10 ml·kg⁻¹) for 105 days. Paraffin sections of hearts were stained with Azan and coronary arteries were examined morphometrically with subsequent statistical analysis. The Kernoghan index of the coronary arteries in old rats was not affected by AMJ supplementation. The amount of collagen fibers in the tunica media of the coronary arteries in the old controls was significantly increased compared to CY as a manifestation of the age process. AMJ supplementation resulted in a significant reduction in the amount of collagen fibers in the tunica media of the coronary arteries compared to CO. Administration of AMJ affects age-related connective tissue remodeling in coronary arteries in rats and supports the beneficial potential of antioxidant dietary supplementation in age-related diseases.

Keywords: aging, Aronia melanocarpa, coronary arteries, rat

Bioenergetics in the response and resistance to glucocorticoids in childhood acute lymphoblastic leukaemia (cALL) cells

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Introduction: Resistance to chemotherapy, and in particular resistance to glucocorticoids (GCs), is considered to be the leading cause of relapse of childhood acute lymphoblastic leukaemia (cALL). The poor response to prednisolone of blast cells (in patients and in vitro) correlates with high values for minimal residual disease (MDR), increased risk of relapse, poor treatment outcome and low survival. Nevertheless, very little is known about the underlying causes for the lack of efficacy of prednisolone as well as for the cellular response to this glucocorticoid and the functional biology of resistant cells.

Aims: Study cALL cell metabolism and the immediate and long-term changes in the bioenergetics of cALL cells in response to prednisolone.

Materials and methods: Cell culture of commercial cALL cell lines; development of prednisolone-resistant sub-clones. Cellular metabolic analysis with Seahorse cell analyser (Agilent, USA).

Results: We developed subpopulations of cALL cell lines that are resistant to GCs. When comparing prednisolone-sensitive cells to the newly developed resistant subpopulations, we found changes at several levels: resistant cells showed increased proliferation, altered mitochondrial function profile with immediate response to prednisolone, increased ATP production and altered basal cell metabolism with the use of anaplerotic energy sources.

Conclusion: Leukemic cells have metabolic flexibility that allows them to readjust their energy phenotype by adapting to GCs through altering energy pathways and biosynthesis precursors.

Keywords: Leukaemia, resistance, cell metabolism

Capillaroscopic and clinical and chemical data for young people with high normal blood pressure (HNBP)

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High normal blood pressure (HNBP) according to the classification of European cardiologists from 2013, which is a systolic blood (SBP) 130-139 mmHg and diastolic blood pressure (DBP) 85-89 mmHg, presupposes an increased cardiovascular risk (CVR). Microcirculation and endothelial reactivity markers are new target areas for CVR assessment. The aim of our study is search of microcirculatory and matching them clinico-chemical changes, prior to clinical manifestations of arterial hypertension (AH) and CVR in young people with HNBP. Sixty-six healthy young people were studied: 32 with HNBP and 34 controls with normal blood pressure (NBP). We performed quantitative and qualitative analyses of microcirculation by capillaroscopy in vivo and study of serum adhesion molecules iCAM, vCAM and ADMA. The results of our studies show qualitative changes in the microcirculation in HNBP in the direction of vasospasm and increased values above the reference limits of iCAM in HNBP (366.07 ± 93.49) compared to controls (323.18 ± 72.82).

Keywords: high-normal blood pressure, capillaroscopy, serum adhesion molecules

Monocyte chemotactic protein-1 (MCP-1) / CCL2 levels in patients with rheumatic diseases

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Chemokine homeostasis imbalance plays a role in the clinical deterioration of patients with systemic lupus erythematosus (SLE). The aim of the study was to compare the serum concentrations of monocyte chemotactic protein-1 (MCP-1) / CCL2 in the serum of patients with SLE (with and without pancytopenic syndrome) and patients with rheumatoid arthritis.

Ninety patients with SLE, 30 patients with RA, and 10 controls were studied. Patients with SLE were divided into group A (59 patients, 65.5%) – no change in blood cell levels, and group B (31 patients, 34.44%) – patients with pancytopenia treated at the Clinic of Rheumatology, St George University Hospital, Plovdiv. MCP-1 / CCL2 concentrations were measured by ELISA, Diaclone, France. The statistical analysis was carried out using SPSS.

Results: The mean MCP-1 / CCL2 concentration in patients with SLE without pancytopenia was 54.77 ± 36.85 (Sx±SD) pg/ml, and in patients with pancytopenia - 271.22 ± 41.81 pg/ml. The mean value of MCP-1/CCL2 in patients with RA was 22.34 ± 14.98 pg/ml, and in healthy controls - 11.67 ± 4.18 pg/ml. The mean concentration of MCP-1/CCL2 was significantly higher in the group with pancytopenia than in the group with no change in blood cells ($p < 0.01$). The conclusions we drew from this study were that MCP-1/CCL2 levels are higher in patients with SLE and haematological syndrome than in patients without pancytopenia.

Conclusion: MCP-1/CCL2 reflects the inflammatory activity of SLE, suggesting that it may be used as a diagnostic marker and for monitoring the therapeutic response in patients with SLE, which distinguishes it from patients with RA.

Keywords: Monocyte chemotactic protein-1, lupus, rheumatoid arthritis

Correlations between monocyte chemotactic protein-1 (MCP-1)/ CCL2, human interferon alpha (h-INF-a) and disease activity in patients with systemic lupus

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Correlations between monocyte chemotactic protein-1 (MCP-1) / CCL2, human interferon alpha (hINF-a) and disease activity in patients with systemic lupus have not been studied in a Bulgarian population. The aim of the study was to evaluate the correlations between MCP-1/CCL2, hINF-a and disease activity in patients with systemic lupus.

Ninety patients with SLE and 10 control subjects recruited from the Clinic of Rheumatology, St George University Hospital, Plovdiv were studied. MCP-1/CCL2 concentrations were measured by ELISA, Diaclone, France.

Disease activity was assessed by SLEDAI-2K and BILAG2004. The statistical analysis was conducted using SPSS.

Results: The mean concentration of MCP-1/CCL2 in patients with SLE was 121.27 ± 23.29 (Sx \pm SD) pg/ml, and in healthy controls - 11.67 ± 4.18 pg/ml, the difference between the two groups was significant ($p < 0.01$). The mean hINF- α concentration in patients with SLE was 8.98 ± 13.2 (Sx \pm SD) pg/ml, and in healthy controls 1.67 ± 1.18 pg/ml, the difference between the two groups was significant ($p < 0.01$). of disease activity and chemokine levels, there is a strong correlation ($r_{x,y} = 0.81$, $p < 0.01$).

Conclusion: MCP-1/CCL2 and hINF- α reflect the disease activity of SLE and can be used to monitor the therapeutic response in patients with SLE.

Keywords: MCP-1 / CCL2, lupus, rheumatic diseases

Do prebiotics improve the condition of patients with diabetes mellitus?

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Type I diabetes mellitus (T1DM) is an autoimmune disease characterized by changes in the composition of the intestinal microflora and dysbiosis, leading to changes in the intestinal permeability, inflammation and insulin resistance. Functional oligosaccharides (xylooligosaccharides, galactooligosaccharides, fructooligosaccharides, etc.) are potential prebiotics with proven antidiabetic properties. Prebiotics are low molecular weight, indigestible carbohydrates, which improve the glucose and lipid homeostasis as well as insulin sensitivity in patients with T1DM. Oligosaccharides exert their antidiabetic activity by improving pancreatic function through inhibiting lymphocyte infiltration in the Langerhans islets and increasing insulin secretion. Some oligosaccharides inhibit the intestinal α -glucosidase, the pancreatic α -amylase, and the glucose transporters and thus lower postprandial glucose levels. Prebiotics also reduce leptin resistance, regulate the intestinal microbiome, and exhibit anti-inflammatory and antioxidant properties. The improvement of the diabetic dysbiosis by different prebiotics is associated with a decreased autoimmune response and intestinal permeability. The fermentation of oligosaccharides produces short-chain fatty acids, which reduce the levels of circulating inflammatory mediators, especially bacterial lipopolysaccharides. Prebiotic treatment induces a dose-dependent increase in bifidobacteria, which lowers the intestinal integrity and endotoxemia, and improves the glucose tolerance. It has been proven that prebiotics have a positive effect on oxidative stress by reducing serum malondialdehyde levels. Oligosaccharides also affect the lipid profile by lowering the serum levels of total cholesterol, triglycerides, LDL- and VLDL-cholesterol, and by raising HDL-cholesterol levels. In conclusion, prebiotics are a cheap and low-risk supplement that improves the glucose homeostasis, the lipid and the antioxidant profile in type I diabetic patients.

Keywords: intestinal microflora, microbiome, oligosaccharides, prebiotics, type I diabetes mellitus

Investigation of new target molecules for the treatment of premature aging and aging-related diseases

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Introduction: Cellular aging is a physiological process that has recently raised many questions about its inevitability, genetic programming, and potential reversibility. Many internal and external factors influence the epigenetic mechanisms that determine the rate of aging. The study of these factors through various biological models allows the discovery of cellular and molecular mechanisms controlling the process.

Objective: investigation and comparison of the molecular mechanisms of chronological aging in lower and higher eukaryotic cell models in optimal and stressful conditions.

Materials and methods: Different model systems (the yeast *Saccharomyces cerevisiae* and human fibroblasts) were cultured in optimal and stressful conditions. The vitality and morphology, mitochondrial metabolism, and chromatin organization in the course of the chronological aging were determined. The relationship between the way of aging in response to different cultivation conditions and the underlying chromatin organization was studied. A comparative analysis of the results obtained from the transcriptomic analysis of specific genes responsible for cell adaptation and aging was performed. The 3D organization of the genome in the course of aging has been studied.

Results: it has been proven that changes in the dynamics of chromatin organization are the main element through which the cell ages chronologically. The stress-influenced dynamics manifests in the expression of molecular markers reflecting premature aging, especially in cells with compromised 3D genome organization.

Conclusion: The relationship between the spatial stability of the genome and the way cells age under stress has been proven. A model of aging based on changes in chromatin organization has been developed.

Keywords: aging, chromatin, premature aging

The role of chest CT in early diagnosis of COVID-19

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The COVID-19 pandemic has rapidly spread around the world since the end of 2019, affecting first China and later on most European countries, USA, Asia, and South America. The variety of COVID-19 symptoms can range from very mild to severe and may include fever, cough, tiredness, shortness of breath or difficulty breathing, muscle aches, sore throat, headache, chest pain, also in some cases loss of taste or smell. In a few studies, chest CT has proved to be more sensitive and accurate than the standard method of RT-PCR testing among high-risk individuals. This is the reason why radiologists are on a front line in a healthcare chain and help clinicians by identifying and characterising pulmonary involvement of the virus infection. The key points in the chest CT include: bilateral ground glass opacities; crazy paving and organising pneumonia patterns

and extensive consolidation which is associated with a bad prognosis. We present 35 cases of COVID19 positive patients, who underwent X-ray and CT study in the early and later phase of the disease at the Department of Radiology at St George University Hospital in Plovdiv. In one-third of the cases, the RT-PCR was negative, but the chest CT showed typical findings consistent with the virus infection. CT is the modality of choice in patients with mild symptoms after clinical evaluation, also in patients with respiratory symptoms such as dyspnoea and by those who have co-morbidities, such as diabetes, obesity, chronic respiratory disease, etc.

Keywords: CT, chest CT, COVID-19, diagnosis

Time is brain: CT perfusion – our experience

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Acute stroke is the second most common cause of death and long-term disability in adults after cancer worldwide. Early detection of this emergency condition can reduce brain damage and other complications. That is why prompt diagnosis and treatment are crucial. Imaging plays a key role in the evaluation of acute stroke, in the early management and current guidelines for thrombolysis. According to them, head CT should be performed within 15-20 minutes after the patient arrives at the hospital and it is used to exclude hemorrhage, to assess the degree of brain injury and to detect the vascular lesion responsible for the ischemic condition. The advanced CT techniques, which include CT perfusion, are able to distinguish between brain tissue in risk, which is potentially salvageable and the infarcted core – the death tissue. The CT protocol for acute stroke used in our department include nonenhanced CT, perfusion CT (CTP) and in some cases CT angiography. We present 10 cases with suspected acute stroke, candidates for thrombolysis, who underwent unenhanced CT and CTP. A complete CT protocol was established with a focus on radiation dose, data acquisition, postprocessing, map quality and a whole-brain analysis. The CT findings were evaluated and included in a standardized stroke report, which helps neurologists in the treatment management and follow-up of patients.

Keywords: CT, CT perfusion, acute ischemic stroke

Mir-376a-3p suppresses the proliferation and colony formation in cell lines from head and neck squamous cell carcinoma through STK3, NETO2, PVR and HOXA1

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Background: One of the earliest events in cancer development is the loss of function of the tumor suppressor miRNAs. The resultant dysfunction can lead to tumorigenesis through changes in the regulation of key

cellular processes such as cell proliferation, survival, and apoptosis.

Aim: The aim of the present study was to functionally characterize the role of mir-376a-3p in HNSCC cell lines with identification of possible target genes.

Methods: Transfections of CAL27, FaDu, A253 and HNO91 HNSCC cell lines with mir-376a-3p-mimic and mimic control were performed using Lipofectamine RNAiMax (Life Technologies). After treatment with cisplatin, cell viability was assessed using an ATPlite assay (Perkin Elmer, Massachusetts, USA). Colony formation was investigated by staining colonies with crystal violet and counting them. Specific primer pairs were designed for STK3, NETO2, PVR and HOXA1 and their transcription levels were measured in CAL27, FaDu, A253 and HNO91 cells after transfection.

Results: The functional studies of mir-376a-3p in HNSCC cell lines clearly demonstrated its tumor-suppressor role by the ability to decrease cell proliferation, reduce the number of colonies of CaL27, FaDu, A253 and HNO91 cells, as well as to sensitize CaL27 to cisplatin. Further, target prediction and validation identified STK3, NETO2, PVR and HOXA1 as possible targets, indicating that miR-376a-3p most probably performs its tumor-suppressor role through these genes.

Conclusion: The present study have shown for the first time the tumor suppressor role of mir-376a-3p in HNSCC, which can be used as a basis for the development of new therapeutic strategies for this type of malignancy.

Keywords: HNSCC, miRNA, cell lines

Pharyngeal cancer: key points for the radiologist

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Pharyngeal cancer commonly present in adults over the age of 45 and show a strong male predominance (3-5:1). About 85%-90% are squamous cell carcinomas (SCC) and 10%-15% are minor salivary gland tumors, adenocarcinoma, lymphoma and various mesenchymal malignancies. The risk factors are long-term overuse of tobacco and alcohol and in the last few years HPVirus type 16, which occurs more often in younger, healthier individuals with little or no tobacco exposure. **Learning objectives:** to study normal radiological anatomy of the pharynx; to become familiar with the most common neoplasms affecting pharynx; to recognize key imaging features of pharyngeal cancer and understand the role of CT, MRI, and PET in diagnosis, staging and management of pharyngeal malignancies. Knowledge of the normal anatomy and anatomical topography is a fundamental basis for the evaluation of any pathological process. Beside the clinical examination and endoscopy performed by ENT specialists, imaging techniques play a crucial role in the diagnostic process and follow-up of patients with pharyngeal cancer. The contrast-enhanced CT, as well as MRI and PET-CT/ PET-MRI are required to determine the malignancy site, submucosal extension and invasion of adjacent structures. The combined information helps to define the general radiological criteria for tumor involvement and allows the tumor to be classified according to the relevant TNM staging - nodal metastasis, systemic metastasis, presence of synchronous masses, and recurrent disease. The clinical and endoscopic outcomes together with the diagnostic imaging evaluation improve the pre-therapeutic staging, post-therapeutic surveillance and follow-up of patients with pharyngeal cancers.

Keywords: pharyngeal cancer, anatomy, imaging modalities, CT, MRI

Clipping of aneurysm of the intracranial segment of the right vertebral artery by far lateral paracondylar approach

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Surgical approaches to lesions located near the foramen magnum, the caudal clivus, anteriorly or antero-laterally to the brainstem are challenging for neurosurgeons. They require detailed knowledge of the complex relations of the neurovascular structures in this region and careful preoperative planning. The pathology in this area includes tumors, tumor-like formations, aneurysms of the vertebro-basilar vascular complex. The term "far lateral approach" originates from the surgical trajectory used to address lesions in this area. Taking the maximum advantage of this surgical approach depends on the precise positioning of the patient and skin incision, followed by layer-by-layer dissection of the muscles below the sternocleidomastoid muscle while preserving adjacent neurovascular structures. There are three options to extend the approach in relation to the atlanto-occipital joint: A) Transcondylar approach - it is used to reach lesions of the anterior clivus and the anterior brainstem surface; B) Supracondylar approach - to access lesions located medially to the jugular tubercle; C) Paracondylar approach - to treat lesions located posteriorly and laterally to the jugular foramen. In order to demonstrate the clinical application of the approach, we present a case of a 71-year-old female who suffered from subarachnoid hemorrhage due to ruptured aneurysm that originated from the junction of the vertebral artery and the posterior inferior cerebellar artery. The aneurysm neck was clipped via far lateral paracondylar approach using meticulous microsurgical technique. In this presentation we discuss the indications for employment of the far lateral approach, illustrate the technique of the approach and present the regional microscopic anatomy by intraoperative images from the surgical intervention.

Keywords: far-lateral approach, aneurysm, vertebral artery, foramen magnum

COVID-19 pandemic and the marathon that lies ahead

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The COVID-19 pandemic, also known as coronavirus pandemic, is the biggest ever pandemic recognized by WHO. It has caused a worldwide sudden and substantial increase in hospitalization for pneumonia with multiorgan diseases. The offending pathogen, SARS-CoV-2 with animal origin is spread primarily via respiratory droplets during close face-to-face contact. The average time from exposure to symptoms onset is 5 days and almost all people who develop symptoms do so within 11 days. The most common symptoms are fever, dry cough and shortness of breath. Radiographic and laboratory abnormalities are common but nonspecific. Diagnosis is made by detection of SARS-CoV-2 via PCR from respiratory samples is the standard of diagnosis but the sensitivity depends on the quality and timing of testing. About 80% of the infections are mild or asymptomatic, 15% are severe, requiring oxygen, and 5% are critical. More than 75% of hospitalized patients require supplemental oxygen therapy. For those requiring invasive mechanical ventilation protective ventilation is recommended. Emerging data indicate that dexamethasone therapy reduces 28-day mortality in patients requiring supplemental oxygen and that remdesivir improves time to recovery from 15 to 11 days. The case fatality rate for patients in the intensive care units is up to 40%. The only way to curb the pandemic is vaccination yet there are no guarantees that an effective vaccine will be available soon and have high community uptake. Thus prevention of transmission is key. The primary methods to reduce spread are social distancing, face masks and contact tracing.

Keywords: COVID-19 pandemic, social distancing, face masks, contact tracing

Study of Anti-LL37 antibodies in patients with psoriatic arthritis

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Introduction and aim: The autoimmune etiology of psoriatic arthritis (PsA) is unclear, so the study of new antibodies may identify new pathogenic autoantigens related to the pathogenesis and therapy of the disease.

Methods: We examined 168 patients (of which 68 sera of patients with PsA with high disease activity before starting biological therapy, 32 sera of patients with psoriatic arthritis, treatment with anti-TNF- α blockers for more than 6 months and low disease activity, 30 sera from patients with osteoarthritis, 22 samples of synovial fluid from one knee in patients with PsA, 16 samples from synovial fluid from one knee in patients with gonarthrosis). Anti-LL37 antibodies were tested with ELISA, in the Department of Immunobiology of Reproduction, IBIR-BAS, Sofia.

Results: Anti-LL37 antibodies were significantly elevated in patients with active serum and synovial fluid psoriatic arthritis compared with patients with PsA with low disease activity, gonarthrosis, and healthy controls ($p < 0.001$).

Conclusion: Our results indicate that anti-LL37 antibodies may be useful biomarkers for diagnosis and may serve as therapeutic targets in psoriasis and PsA.

Keywords: anti-LL37-antibody, psoriatic arthritis, gonarthrosis

Expression of CD68-positive cells in the synovial tissue in a patient with psoriatic arthritis

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CD68 (macrosialin) is a glycoprotein of the LAMP family which is expressed on blood monocytes, tissue macrophages, lymphocytes, fibroblasts and endothelial cells and is important for the phagocytic activity of tissue macrophages.

The **aim** of the study was to evaluate CD68 positive cells in synovial tissue and their correlation with the presence of monosodium urate crystals in the synovial fluid of patients with active psoriatic arthritis.

Patients and methods: Eight arthrocentesis of one knee joint was performed in 8 patients with active psoriatic arthritis (DAPSA > 14) and 15 patients with gonarthrosis (Kelgren-Lawrence stage IV) used as a control group after signing an informed consent and synovial fluid tested for uric acid crystals. All patients during alloplasty surgery of the same knee joint had synovial tissue taken and immunohistochemical examination performed in the Department of Immunobiology of Reproduction, IBIR-BAS, Sofia

Results: Monosodium urate crystals were found in the synovial fluid of canine patients with PsA. In the preparations obtained from the control group, the expression of CD68 was 0.23 ± 0.44 positive cells, in the preparations of patients with 2.46 ± 0.28 ($p < 0.01$).

Conclusion: The presence of monosodium urate in the synovial fluid of patients with PsA correlates with a high percentage of CD68 positive cells, which seems to be associated with a more severe course of the disease, the need for aggressive treatment and is a prognostic factor for adverse disease progression.

Keywords: CD68-positive cells, synovial tissue, psoriatic arthritis

Treatment of children with acute lymphoblastic leukemia assisted by flow cytometric evaluation of minimal residual disease – a single centre experience

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Introduction: The prognosis of childhood acute lymphoblastic leukemia (ALL) is substantially improved and early identification of minimal residual disease (MRD) is the basis for treatment optimization.

Objective: To evaluate the treatment of children with ALL by the event-free (EFS) and overall survival (OS) and to analyze the 8-color flow cytometric (FCM) follow-up of MRD during induction.

Design: A retrospective analysis for the period from 2011 to 2018 in one pediatric oncohematology center in Bulgaria. PATIENTS: 63 children (33 boys and 30 girls), mean age 6.3 years, divided into standard (SR), intermediate (IR) and high-risk (HR) groups and treated according to a BFM-type therapeutic protocol. A standardized 8-color FCM MRD assay was used. Early therapeutic response was measured at D15 in BM and was used to stratify patients. Survival was calculated using the Kaplan-Meier method. No randomization was performed and all patients with SR and IR were included in the SR therapeutic arm of the protocol, and patients with HR- in the HR arm.

Results: Fifty-two (82.5%) patients had precursor B-ALL and 11 (17.5%) had T-ALL. Distribution: SR: 11 (17.5%); IR: 34 (54%); HR: 18 (28.5%). Fifty-seven (90.5%) children achieved complete remission on D33. EFS is: 90.9% for SR, 85.8% for IR and 69.3% for HR groups. The OS of the whole group is 90%. CONCLUSION: The EFS and OS of our cohort are comparable to those of other European centers. Measurement of the MRD during the induction therapy, using a standardized 8-color FCM, can improve disease monitoring, leading to better therapeutic outcomes.

Keywords: acute lymphoblastic leukemia, children, minimal residual disease

ORAL PRESENTATIONS

Biopharmacy

Investigation of complement-fixing compounds in immunologically active polysaccharide complexes from traditional medicinal plants

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Synergistic and/or antagonistic interactions between natural compounds are interesting for the discovery of therapeutic regulators of the complement system. Therefore, the aim of the study was to investigate the influence of small molecules in polysaccharide complexes (PSCs) from the flowers of linden (*Tilia tomentosa* L.), lavender (*Lavandula angustifolia* Mill.) and aerial parts of purslane (*Portulaca oleracea* L.) on the total *in vitro* complement-fixing activity of the complexes and their mixtures. Polysaccharides (PSC2) were separated from PSCs and smaller molecules were fractionated with petroleum ether, *n*-butanol and water. Hydrocarbons, fatty acids, sugars, phytosterols, triterpene acids, phenolic acids, flavonoids, phenylpropanoids, etc. were found in PSCs. Fatty acid-rich ether extracts expressed minor complement-fixing activity via the classical pathway (CP) and were inactive between 156 and 2500 µg/mL through the alternative pathway (AP). Aqueous extracts, rich in polyphenols, exhibited better activity via CP (IC_{50} =200.7-441.6 µg/mL) than AP. PSC2 were more effective on both pathways than initial PSCs. PSC2 showed higher activity through AP (IC_{50} <60 µg/mL), similarly to PSCs (IC_{50} <77 µg/mL). The butanol fractions of linden and purslane were more potent through AP (IC_{50} =471.7 and 115.9 µg/mL), and lavender one, rich in polyphenols, through CP (IC_{50} =201.1 µg/mL). The results from the study suggested that some polyphenols (especially phenylpropanoids) contribute positively and fatty acids, like butyric acid, negatively to the manifestation of activity via CP by PSCs. The high activity of PSCs through AP is mainly associated with polysaccharides. Combinations of polysaccharides and other compounds from the complexes can be tested as complement regulators under pathological conditions.

Keywords: linden, lavender, purslane, polysaccharides, complement

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Influence of *Silybum marianum* (milk thistle) on biochemical markers involved in lipid metabolism and glucose homeostasis

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Lipid metabolism and glucose homeostasis are regulated by multiple processes and signaling pathways. Dysfunction in these metabolisms leads to the development of insulin resistance and is a risk factor for a number of diseases such as diabetes, atherosclerosis, steatosis, obesity and others. Silymarin, extracted from the plant *Silybum marianum* (milk thistle), has great potential as a supplement in the treatment of these diseases. It has a lot of beneficial effects - antioxidant, anti-inflammatory, hepatoprotective, antifibrotic, immunomodulatory and others. Improves lipid metabolism by enhancing lipolysis, inhibits TAG synthesis, inhibits hepatic de novo lipogenesis, lowers levels of the "bad" cholesterol and increases those of the "good" cholesterol. This effect is manifested by silymarin, affecting a number of enzymes - phosphatidate phosphatase (PAP), AMP-activated protein kinase (AMPK), HMG-CoA reductase and others and transcription factors such as SREBP-1c (sterol regulatory element binding protein-1c). Silymarin regulates cholesterol levels through a double mechanism - suppression of its synthesis and the effect of resin in the entero-hepatic circulation. Regarding glucose homeostasis, milk thistle normalizes blood sugar levels, lowers glycated hemoglobin (HbA1c) levels and improves glucose tolerance. Affects hyperglycemia and insulin resistance through various mechanisms - supports the regeneration of β -cells of the pancreas and protects it from various agents, regulates the signaling pathway of phosphatidylinositol-3-kinase (PI3K), inhibits gluconeogenesis (GNG). The numerous beneficial properties of silymarin make it the focus of alternative medicine and a means of adjunctive therapy to statin therapy. However, more studies and clinical trials are needed to clarify its full potential and mechanism of action.

Keywords: *Silybum marianum*, silymarin, lipid metabolism, cholesterol, insulin resistance

Application of 32 experimental design in the preparation of casein nanoparticles as potential drug carriers

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The production of nanoparticles by nanospray drying is strongly influenced by the process parameters - polymer concentration, solubilizing agent concentration, inlet temperature, pumping speed, spray rate, as well as the spray mesh size. The aim of the present study is to establish the optimal process parameters - polymer concentration and crosslinking agent concentration required to produce casein nanoparticles with optimal structural and morphological characteristics for use as drug carriers. A full 32 factorial design was used to study the influence of process parameters. Three different concentrations of casein solution were varied: low concentration 0.05%, medium concentration 0.1% and high concentration 0.15%. The influence of the crosslinking agent concentration (CaCl_2 , $M_w = 110.98 \text{ g/mol}$) was also investigated: low concentration 0.5 M, medium concentration 1.0 M and high concentration 1.5 M. A spray membrane with a mesh size of $4.0 \mu\text{m}$ was used and the following spray conditions were applied: inlet temperature 40°C , solution feed rate 50%, spray intensity 70%, drying gas speed 120 L/min, pressure 30 nbar. Using the nanospray drying method, nine models of nanoparticles were obtained, which were characterized based on shape, size and size distribution,

surface morphology and yield. Optimal conditions to produce casein nanoparticles were derived and promising models were selected to be studied as potential drug-delivery systems.

Keywords: casein nanoparticles, nanospray drying, drug-delivery systems

Formulation of tablets with essential oil from *lavandula angustifolia*

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Lavender oil is one of the most well-known and widely exploited essential oils (EO) in perfumery, aromatherapy and alternative health therapy. EOs are very sensitive and easily undergo degradation when exposed to oxygen, light and even moderate temperatures. The stability of EO can be significantly enhanced after microencapsulation and incorporation into a solid dosage form. The aim of this study was to formulate Lavender essential oil tablets with optimal physicochemical characteristics and high EO stability. Lavender oil microcapsules (LOM) were obtained by a spray-drying method. Aqueous dispersions of *Boswellia serrata* resin were used as a coating agent. The obtained microcapsules were formulated into tablets by direct compression, using microcrystalline cellulose (MC) as a binder/filler excipient. The ratio LOM:MC (2:1 and 1:1) and the compression force (1.5 and 2.0 ton) were varied. The obtained tablets were characterized in terms of their hardness and disintegration. The results showed that increasing the LOM content in the tablets led to decreasing the tablet hardness. At the same time only the tablet models with higher microcrystalline cellulose content showed acceptable disintegration time within 15 min. The increase of the compression force from 1.5 to 2.0 ton led to a significant increase of the tablets hardness without hampering the disintegration time. The tablet model, formulated at ratio 1:1 LOM:MC and compressed with force 2.0 ton, was outlined as the most promising one. It showed the highest hardness (2.15 MPa), acceptable disintegration (9.8 min) and a relatively low EO loss after compression (0.5 %).

Keywords: microcapsules, direct compression, essential oil

Prevention and management of osteoporosis - role of the pharmacist

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Osteoporosis is a socially significant chronic disease with an increasing prevalence as a result of the aging population. Its name means "porous bones" and is due to an impaired balance between the processes of bone formation and bone resorption. It is called the "silent thief" because the bone loss occurs without any obvious symptoms and is found after a minimal trauma or a serious fracture. Osteoporosis is a common cause of decreased quality of life and place a major economic burden on healthcare systems. Osteoporosis can be successfully prevented, diagnosed and treated before fractures occur. Prevention of osteoporosis includes timely identification of risk factors and their modification, if applicable. Treatment of osteoporosis includes

non-pharmacological measures such as appropriate diet, physical activity and smoking cessation, prescription medications and dietary supplements containing calcium and vitamin D. Pharmacists as the most accessible healthcare providers can play an important role in the prevention and management of osteoporosis: ensuring proper use of prescription medications, providing information about the disease and adherence to therapy, identifying patients at risk, conducting screening with an ultrasound osteodensitometer, advising for appropriate supplementation and supporting patients about lifestyle changes.

Keywords: osteoporosis, prevention, pharmacists

New pharmacovigilance paradigm in cases of controlled ovarian hyperstimulation (COH) examples from real-life clinical practice

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Forty years after the first in vitro-baby, assisted reproduction treatment should result in a healthy newborn after minimal physical and mental suffering of treated couple.

Aim: to analyze safety surveillance system for medicines used for COH.

Materials and methods: The final analysis is based on two following studies, performed in a specialized OB/Gyn hospital. Type, incidence and severity of suspected adverse drug reactions (ADR) during COH have been evaluated in a study among 660 women, treated by COH. In addition, main target endpoints for evaluating clinical effectiveness of COH have been assessed from a safety perspective, investigating 4762 stimulation cycles. Following statistical methods have been used: descriptive statistics, Mann-Whitney U test, Kruskal-Wallis test, Pearson chi-square test, binary logistic regression.

Results: Mean number of suspected ADRs per patient is 1.27. Only 1.1% of participants have evaluated an experienced ADR as severe, while 90% of adverse effects are mild. Suspected ADRs have led to cycle cancellation in 3.8% of cases. More than 2/3 of experienced ADR are injection site reactions (63.1%), followed by headache (9.8%), gastrointestinal disorders (5.8%) and nausea (4.7%). Suffering of treated couples is not associated only with ADRs. Some markers for clinical effectiveness as cycle cancellation rate, induced follicle count, oocyte yield, mean values of estradiol, luteinizing hormone and progesterone and also valid indicator for patient safety.

Conclusion: Safety surveillance of medicines for COH exaggerates ADR detection. Unnecessary suffering of treated couples may be prevented by ensuring optimal efficacy of COH treatment.

Keywords: pharmacovigilance, controlled ovarian hyperstimulation, clinical effectiveness

Orodispersible tablets for pediatric practice

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The aim of the study was to develop and characterize orodispersible tablets (ODTs) with enalapril maleate (ENA) with improved taste for use in pediatric practice. ODTs were prepared by the direct tableting method (diameter 9 mm and weight 200 mg). Each tablet contains spray-dried polymer microspheres equivalent to 1 mg of ENA. Eight models of ODTs were developed and the concentration of the disintegrants was varied

(pre-prepared dry extracts of flax and quince seeds). The models were characterized by uniformity of weight, mechanical strength, friability, disintegration, wetting time and water absorption ratio. The biopharmaceutical behavior of the tablets was studied and their taste qualities were evaluated using a four-point scale. The mechanical strength was satisfactory and varied from 61 N to 79 N and the friability - in the range of 0.5% to 1.3%, was considered as optimal. The disintegration of the tablets varied from 50 s to 6.50 min, the wetting time from 20 to 180 s, and the water absorption ratio was between 9.1% and 24%. The tablets released 90% of the included ENA in the first 60 minutes and showed differences in the masking of the ENA's bitter taste. Optimal taste masking, technological and biopharmaceutical characteristics have been achieved by ODT1, which has been developed as a perspective model of orodispersible tablets for pediatric practice.

Keywords: orodispersible tablets, taste masking, enalapril maleate, pediatric practice

ORAL PRESENTATIONS

Contemporary surgical techniques

Comparative analysis of the methods for induction of anesthesia in paediatric and neonatal surgery

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Broadly speaking, pediatric anesthesia uses the same pharmacological agents and technique as are used in adults. The differences stem from the anatomical and physiological features of the child's body, as well as the different pharmacological response to the medications. The narrow airways, immaturity of the compensatory mechanisms, as well as the increased reactivity and propensity to laryngospasm, are the reason why anesthesia in children has its essential characteristics that distinguish it from that in adulthood. The choice of technique for induction of anesthesia stems from many factors - age and general condition of the child, type of surgery, family history of increased risk of malignant hyperthermia, presence or absence of a permanent venous source, and last but not least - the degree of cooperation on the part of the parents and patient. Inhalation with Sevoflurane is routinely used in pediatric surgery, except in cases of full stomach. It has its advantages that make it a preferred choice for young and non-cooperative children. However, intravenous administration of propofol finds its place, mainly in older patients. An alternative available is muscle induction, which is used in some special cases in severely anxious or mentally disabled children. The following article presents a comparative characteristic of the main methods of induction to anesthesia in the pediatric practice, as well as important pharmacological features of the general anesthetics used in pediatric patients.

Keywords: anesthesiology, paediatric anesthesiology, induction of anesthesia, paediatric surgery

Mini-invasive techniques in the overall treatment of complicated diverticulosis

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Introduction: The colonic diverticulosis is a condition met much more often nowadays with frequency increasing with the age. Surgical treatment is recommended for complicated forms and in cases with recurring diverticulitis. The most often used surgical procedure is the Hartmann's procedure. Mini-invasive techniques

are becoming more preferred. For a large part of the patients with formed stoma, restitution won't be performed for different reasons. Restitution, after Hartmann's procedure, remains a challenge associated with significant morbidity (up to 54.8%) and mortality (up to 4%). Laparoscopic restitution can lead to better results with reduction of these rates. Purpose of our research is to analyze the indications for laparoscopic approach and to consider the methods to perform these procedures.

Materials and methods: We explored and analyzed retrospectively all patients that received a mini-invasive surgical treatment for complicated diverticulosis in the Surgery Department at Eurohospital University Hospital in Plovdiv between May 2014 and December 2019.

Results: For this period, 128 patients were treated for complicated diverticulosis and for 21 we applied a surgical treatment. We used mini-invasive approach in 12 of the cases. Hartmann's procedure was performed in 10 cases. We restituted the passage in 8 of the patients, and used laparoscopic approach for 5 patients. We had 1 conversion.

Conclusion: In the contemporary emergency surgery, the mini-invasive methods are finding wider application in the treatment of various conditions. Analogically, they have a place in the treatment of the colonic diverticulosis. We consider that the laparoscopic techniques are reliable and technically feasible.

Keywords: laparoscopic surgery, diverticulosis of the colon, Hartmann's

Laparoscopic treatment of iatrogenic perforations of the colon

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Introduction: Throughout the years, the colonoscopy has affirmed itself as the best method for screening, diagnostics, treatment and follow-up care for patients with colorectal conditions. As an invasive procedure, it is accompanied with major risk of bleeding, perforation and even death. One of the most serious complications is the endoscopic perforation. The frequency, reported in literature, varies between 0.2-0.4% for diagnostic colonoscopy, and 0.3-1.0% after polypectomy. Even though the frequency of these complications is low, the continuous growth of usage of these procedures, suggests an increase in the cases with complications. In cases with diagnosed iatrogenic perforation that requires a surgical treatment, the contemporary recommendations are for laparoscopic approach. The purpose of our research is to consider and evaluate the methods of treatment and complications after iatrogenic perforations.

Materials: For the period from 06.2012 to 06.2019 we examined and analyzed retrospectively all patients treated for iatrogenic colonoscopic perforation in the Surgery Department at Eurohospital University Hospital, Plovdiv.

Results: For this period, there were 12 patients diagnosed and treated with this diagnosis. In 10 of the cases we performed an operation. We used minimally invasive techniques in 8 patients. We had 2 conversions. Average hospital stay after laparoscopic surgery was 5 days, with no postoperative complications observed.

Conclusion: In the era of the laparoscopic surgery, mini-invasive methods have their place in the treatment of iatrogenic perforations during colonoscopy. Performed by experienced surgeons, this type of procedures have good postoperative results comparable with the ones after conventional surgery.

Keywords: colonoscopy, iatrogenic colonoscopic perforation, laparoscopic surgery

One stage image-guided spinal navigation surgery in a patient with degenerative lumbar spinal stenosis and L5 nerve root myxoid neurofibroma

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O-arm based spinal navigation is a modern technology for three-dimensional intraoperative real-time guidance of spinal procedures. It can be used both for precise implantation of various spinal instrumentation systems and for navigated resection of spinal extra-axial tumors. We present a case of a 51-year-old female with complaints of severe, drug-resistant low back pain irradiating bilaterally to the legs for 3 months. Upon admission, the neurological status revealed severe lumbar vertebral syndrome, bilateral L4 and L5 radiculopathy and neurogenic claudication at 50 meters. The magnetic resonance imaging of the lumbar segment demonstrated a combination of multi-level degenerative stenosis of the spinal canal in L4-L5-S1 segment and oval tumor formation originating from the L5 nerve root on the left. The patient underwent one-stage surgery including O-arm based, image-guided pedicle screw fixation in the L3-L4-L5-S1-S2 segment, followed by L4 and L5 laminectomy and navigated microsurgical resection of the tumor. The histological examination of the tumor confirmed myxoid neurofibroma originating from the sheath of the left L5 nerve root. We observed complete resolution of the preoperative clinical complaints during the postoperative follow-up of the patient. O-arm based three-dimensional spinal navigation enables surgeons to perform spinal surgical interventions with increased precision and accuracy, reducing the risk of intraoperative iatrogenic damage to nerve structures and significantly reduces the radiation exposure of the medical staff compared to conventional techniques.

Keywords: spinal tumor, O arm, spinal navigation, lumbar spinal stenosis, surgery

Surgical treatment of complex inguinal hernias

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Introduction: Complex forms of inguinal hernias represent a heterogeneous and diverse group of clinical cases in which there are large or complicate in structure hernial defects, with frequent difficulties in their surgical treatment. This is a reason for frequent complications and unsatisfactory postoperative results, and according to some authors recurrences can reach 28 to 50%.

Aim: To analyze the surgical treatment of various complex forms of inguinal hernias.

Patients and methods: For the period 2015-2019, 369 patients were operated, of which 162 (43.9%) had complex inguinal hernias. Cases were divided into recurrent – 39 patients (10.6%), irreparable – 34 patients (9.2%), giant – 29 patients (7.9%), inguinoscrotal – 25 patients (6.8%), sliding – 22 patients (6.0%), combined – 9 patients (2.4%) and with bilateral hernias – with 4 patients (1.1%). Intraoperatively, attention must be paid to the structural condition of the transverse fascia, the degree of its destruction and the size of the defect in the inner opening of the groin canal.

Results: The following surgeries were performed: inguinohernioplasty with synthetic mesh in 91 patients (56.2%) and plastic with own tissues in 71 patients (43.8%). The following operations with polymeric endoprotheses were performed: Lichtenstein technique in 47 patients (29.0%), Rutkow-Robbins technique in 25 patients (15.4%) and Trabucco technique in 19 patients (11.7%). We didn't have iatrogenic complications, such as intestinal lesions, bladder or main vessels. No lethal case was registered.

Conclusion: The optimal operative approach is plastic reconstruction of the groin canal in accordance with the age, the degree of the posterior wall defect, the type of hernia and the duration of the disease. Surgical treatment of inguinal hernias with complex hernial defects requires good knowledge and experience in the field of herniology.

Keywords: inguinal hernia, surgical treatment, complex hernias

Peculiarities of diagnosis and surgical treatment of complex forms of anorectal abscesses

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Introduction: Complex forms of anorectal abscesses (CFARA) are a purulent inflammatory disease, characterized by an atypical clinical course and often delayed diagnosis. Distinctive for all variants of CFARA is the deep localization of the primary purulent focus.

Aim: To study the peculiarities of the diagnosis of CFARA in order to improve the results of their surgical treatment.

Patients and methods: Between 2015 and 2019, 254 patients with ARA were operated. Of these, 147 (57.9%) with data on complex forms were divided as follows: high intersphincteric – 17 patients (11.6%), ischiorectal – 89 patients (60.5%) and pelviorectal – 41 patients (27.9%). The topographic-anatomical localization of CFARA is closely related to their clinical symptoms. The signs of the disease vary and manifest in different clinical degrees, from a general somatic inflammatory reaction and manifestations of general malaise with fever to intoxication syndrome.

Results: Treatment for CFARA requires early radical surgery and thorough debridement of the purulent-necrotic focus. In all patients 1-2 incisions were performed, followed by revision, necrectomy, lavage and placement of 1-2 drainages. In the postoperative period, daily active control is required. Multi-stage surgical revision with redrainage was performed in 24 of the patients (16.3%). No lethal case was registered.

Conclusion: Prompt diagnosis and timely optimal surgical treatment are the basic factors to avoid unsatisfactory results. The main diagnostic method is the digital rectal examination and CT of the pelvis in unclear clinical cases.

Keywords: complex anorectal abscesses, diagnosis, treatment

Fat grafting in postburn facial reconstruction

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Introduction: Profound cicatrization resulting from deep burns of the face blocks animation, flattens natural curves and volumes and thus destroys facial individuality and expression.

Materials and methods: We report our experience with fat grafting for restoration of facial relief and animation following deep burns in 40 patients.

Results: Fat grafting as a single technique was applied in 27 cases and in combination with other techniques - in 13 cases. 40 patients had 101 lipofilling procedures, i.e. 6 patients had 1 procedure, 16 patients had two procedures, 13 patients had 3 procedures, 1 patient had 4 procedures and 4 patients had 5 procedures.

Outcomes: Fat grafting enhances and refines existing or restored relief rather than recreating it. It improves substantially quality of overlying skin as well as its mobility.

Keywords: lipofilling, facial reconstruction, deep burns

Neovascular glaucoma and diabetes: incidence, risk factors, management

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Objective: To study the aetiology and risk factors for neovascular glaucoma, the degree of visual disability associated with it and the methods of management.

Methods: A retrospective study of all cases of neovascular glaucoma for a period of 2 years in a university department of ophthalmology.

Results: A total number of 126 consecutive cases were evaluated. More than 70% of the cases were due to proliferative diabetic retinopathy. More than half of these patients had not received adequate pan-retinal photocoagulation. Other reasons for neovascular glaucoma were ischaemic central retinal vein occlusion, end-stage glaucoma with uncontrolled intraocular pressure and ocular ischemic syndrome. Most patients had visual acuity of the affected eye below 0.1 (20/200) at the time of presentation. Treatment included trabeculectomy with mitomycin C after intravitreal anti-VEGF and cyclocryotherapy for the eyes without useful vision.

Conclusion: Neovascular glaucoma is a secondary type of glaucoma, characterized by rapid progression, difficult medical and surgical treatment and poor long-term prognosis. Cause of neovascularization in the anterior segment is chronic ischemia due to diabetic retinopathy, occlusion of the central retinal vein and ocular ischemic syndrome.

Keywords: neovascular glaucoma, diabetic retinopathy

Vein of Galen malformations. A rare case from our practice

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The vein of Galen aneurysmal malformations (VGAM) are rare congenital vascular malformations that could present with high-output cardiac failure, enlarging of the head circumference and/or developmental delay. These malformations occur most commonly in neonates or older infants. We present a rare case of a 60-year-old male with complaints of headache, nausea, and deterioration of the mental and neurological status on the day after the symptom onset. At the time of presentation in the emergency department, he was GCS - 8 points and quadriplegic. A computed tomographic scan revealed a presence of obstructive hydrocephalus and round homogenous lesion in the region of vein of Galen. Emergency external ventricular drainage was performed, followed by computed tomography angiography that revealed vein of Galen aneurysmal malformation. Because of the poor neurological status of the patient, neither microsurgical nor endovascular treatment was possible to be conducted at the time of hospitalization. Most of the VGAM represent an abnormality of the development that results in shunting of arterial blood into the median prosencephalic vein (MProSV) of Markowski. Even though the vein of Markowski is a precursor of the vein of Galen, it is a separate anatomical structure and the term VGAM is a misconception. The rare nature of the VGAM, along with differences in their pathophysiology and evolution, makes their management a clinical challenge. The evolution of the treatment strategy had shifted from microsurgical to endovascular treatment for the obliteration of the malformation in good candidates for operative treatment and medical management for the others.

Keywords: Vein of Galen, malformation, aneurysm, hydrocephalus, management

Personal experience in the treatment of patients with retained foreign body

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Perforating traumas with an intraocular foreign body (IOFB) are one of the most severe ocular injuries, sometimes leading to loss of vision.

Purpose: To present our experience in the treatment of patients with IOFB. Patients and methods: In a retrospective study were included 92 patients with IOFB, of them 88 men and 4 women at an average age of 26 ± 17 y (range: from 4 to 71). In 84 eyes hybrid 20/23 G phacovitrectomy with implantation of an intraocular lens was performed and 8 eyes were left aphakic. IOFB was extracted through limbal (n=87) or pars plana incision (n=5). Best corrected visual acuity (BCVA), complete eye examination on admission, and during the follow-up period of 5 years have been performed.

Results: The mean preoperative BCVA was 0.02 (range: from \emptyset to 0.6). The size of the IOFB varied from 1 to 19 mm. Some of the most challenging cases were: a child with an intraocular air-gun pellet, a child with an intraocular particle of a darts arrow, a woman with a giant IOFB. Traumatic cataract (n=80), traumatic iridocyclitis (n=82), endophthalmitis (n=9), vitreous hemorrhage (n=76), and retinal detachment (n=17) were established. On the last checkup the mean BCVA was 0.3 (range: from 0.01 to 1.0). No patient developed phthisis of the eyeball.

Conclusion: With an individual approach of treatment and IOFB extraction good long-term functional and anatomical results could be achieved.

Keywords: intraocular foreign body (IOFB), hybrid 20/23 G PPV, long-term results

Ocular risk factors for progression of primary open-angle glaucoma in treated patients

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Purpose: To assess the weight of ocular risk factors for progression of treated patients with primary open-angle glaucoma (POAG).

Methods: We followed up 70 treated patients with OAG for period of 8 years. Fifty four of them showed progression in one or in both eyes. We analyzed 20 patients with Rate of Progression (RoP) > -1 dB/year, 20 patients with RoP < -1 dB/year and 18 patients with no progression of the disease. The progressive and non-progressive individuals are compared according to the following ocular risk factors: intraocular pressure (IOP) variables (initial IOP, peak IOP, mean IOP and IOP fluctuations), visual field changes before treatment (initial mean deviation – MD), pseudoexfoliations, central corneal thickness (CCT), myopia and previous IOP-lowering surgery.

Results: Progressors had more IOP fluctuations during the follow up period than non-progressors: 4.1 ± 1.7 vs 2.8 ± 1.7 (mean \pm SD), $p=0.04$. Peak IOP of fast progressors was higher than peak IOP of slower progressors (26 ± 6 mmHg vs 22 ± 7 mmHg, without significance, $p=0.09$). We observed correlations between peak IOP and RoP ($r=-0.282$; $p=0.032$) and between peak and IOP fluctuations ($r=-0.829$; $p<0.001$). We found that pseudoexfoliations were not significant predictor for POAG progression ($p=0.29$). Initial MD and thinner cornea have not been always associated with subsequent progression. Early IOP-lowering surgery was very important factor for stabilization of visual field changes.

Conclusions: Our results suggest that the long term IOP fluctuations are a significant risk factor for glaucoma progression. The IOP-lowering surgery is a factor for non-progression.

Keywords: ocular risk factors, progression, primary open-angle glaucoma

Mosaicplasty – minimally invasive approach for treatment of osteochondral defects in the knee

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The treatment of patients with chondral defects affecting the entire cartilage is very difficult. The osteochondral autograft transfer system (OATS) or mosaicplasty for treatment of osteochondral defects in the knee has been proposed with the aim to preserve the hyaline cartilage. The indications are: areas of inflammation in any part of the knee; chondral defects in the entire cartilage, including dissecting osteochondrite with in situ injury or injuries where the ligament is absent; size of the injured area ranging between 1 cm² and 4-5 cm² and depth in the subchondral bone not exceeding 10 mm; normal alignment of the knee joint without axial divergence; stable ligamentous apparatus. The surgery can either be open or performed arthroscopically. Routinely, the lateral or – where necessary – the medial periphery of facies patellaris femoris is used as a donor. The direction of the circular milling machine should be set so that the chondral surface is perpendicular to the horizontal axis of the cylinder. The blocks should be arranged from the periphery to the centre in a way that allows a certain degree of convexity of the central block. Prominence of the donor's block exceeding 1 mm is unacceptable. In the event of accurate indications, the mosaicplasty has its place in the algorithm for treatment of osteochondral defects of the knee.

Keywords: osteochondral defects, mosaicplasty, arthroscopy

ORAL PRESENTATIONS

Innovative methods of diagnosis and treatment

Retinopathy of prematurity as a cause of blindness in Plovdiv region

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Aim: To investigate blindness among children, treated for retinopathy of prematurity (ROP) in Plovdiv region.

Methods: Since year 2010, 125 prematurely born children were treated for ROP and followed-up in University eye clinic at St George University Hospital in Plovdiv. Fifteen of them (26 eyes) ended up in blindness. These patients underwent complete ophthalmological examination (visual acuity, light perception and projection test, biomicroscopy, binocular indirect ophthalmoscopy).

Results: At the time of the examination the age of children was between 3 and 10 years. Four patients (8 eyes) presented with already detached retina in our clinic. In the rest 11, the disease progressed despite the timely treatment. Mean gestational age was 27.6 weeks (23 – 32), mean birth weight – 1005 grams (590 – 1700). Nine eyes showed total blindness (lack of light perception), 17 eyes were legally blind (visual acuity 0.1, which allows relatively good orientation, but still classifies them as low vision patients).

Conclusion: Retinopathy of prematurity is still among leading causes for preventable, but irreversible blindness in children. Disease severity and lack of timely screening are basic reasons for unfavorable outcome.

Keywords: retinopathy of prematurity, blindness

Ischemic retinal vasculitis in a 34-year-old patient - what is the cause?

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Introduction: Ischemic retinal vasculitis is an inflammatory disease involving the retinal vessels. Visual acuity decreases due to macular ischemia, macular edema, neovascularization leading to vitreal hemorrhage, fibrovascular proliferation or tractional retinal detachment.

Purpose: To present a patient with ischemic retinal vasculitis.

Material and methods: A 34-year-old woman was presented. The following investigations were performed: FBC, biochemistry, coagulogram, rheumatological tests, serum calcium level, angiotensin-converting enzyme, CT of the lungs, MRI of the brain and spinal, serology for: cytomegalovirus, herpes simplex virus, varicella-zoster virus, toxoplasmosis, tuberculosis, syphilis, fluorescein angiography (FA) and optical coherence tomography.

Results and discussion: Best-corrected visual acuity was 20/20 for the right eye and 20/25 for the left eye. The intraocular pressure was normal for both eyes. The following pathological findings were detected in the left eye fundus: an old chorioretinal scar under the lower temporal vascular arch with ischemic exudate next to it, occlusion of the lower temporal retinal arterial and venous branches, neovascularization and a preretinal

hemorrhage. FA showed delayed filling of the affected vessels, neovascularization, and major ischemia in the lower temporal part of the retina. Serological tests for varicella-zoster virus and toxoplasmosis were above the reference ranges. We diagnosed past toxoplasmic chorioretinitis, which has led to ischemic retinal vasculitis with sectoral involvement of retinal vessels.

Conclusion: Patients with ischemic retinal vasculitis are a challenge to clarify the etiological diagnosis. Treatment on time prevents severe and irreversible loss of vision. Occlusive vasculitis is a rare complication of ocular toxoplasmosis, but should be considered in young patients.

Keywords: occlusive vasculitis, uveitis, ocular toxoplasmosis

Hertel exophthalmometry and computed tomography for the evaluation of exophthalmos in patients with thyroid-associated ophthalmopathy

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Objective: To compare the values of exophthalmos measured by computed tomography (CT) and Hertel exophthalmometry (HE) in patients with thyroid-associated ophthalmopathy (TAO).

Material and methods: One hundred and seventy eyes were examined in 85 patients with TAO. Each patient underwent a complete ophthalmic examination, Hertel exophthalmometry, and CT of the orbits through a 16-slice CT scanner (Bright Speed, General Electric), measuring the extraocular muscles, the total muscle thickness sum (MTS), and proptosis. The patients were divided into two groups – with activity and without TAO activity, the activity being assessed by means of the Clinical Activity Score (CAS) and the severity – according to the EUGOGO classification.

Results: TAO activity was detected in 45 patients (90 eyes, 53%) with MTS of 23.54 ± 5.73 mm, IOP of 19.78 ± 4.49 mm Hg, Hertel exophthalmos of 23.08 ± 4.19 mm and measured by CT – 23.32 ± 4.33 mm. Forty patients (80 eyes, 47%) were without TAO activity, with MTS of 19.28 ± 4.03 , IOP of 16.6 ± 4.51 mm Hg, Hertel exophthalmos of 20.03 ± 3.84 mm and measured by CT – 19.84 ± 4.47 mm. A correlation was detected between exophthalmos and: MTS, IOP, the activity and severity of TAO. High congruence was established between the two methods of measuring exophthalmos – CT and HE (Pearson correlation, $r=0.690$, $p=0.000$).

Conclusion: Our results showed a high degree of consistency between Hertel exophthalmometry and multidetector CT for the evaluation of exophthalmos in patients with TAO. Exophthalmos is an important clinical feature and its measurement and monitoring over time assess the clinical course and outcome of treatment.

Keywords: thyroid-associated ophthalmopathy, Hertel exophthalmometry, computed tomography

Evaluation of macular parameters in healthy children by SD-OCT

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Aim: To determine the normative values of macular thickness and macular volume in healthy Caucasian children using spectral domain optical coherence tomography (SD-OCT) and to analyze the correlation of these values with age, spherical equivalent and axial length.

Methods: This section study included 270 eyes from 270 healthy children aged 6 to 17 years (150 girls, 120 boys) without ocular and systemic diseases. Each child underwent a complete ophthalmological examina-

tion and measurement of axial length (AL) by OCT biometry. Macular thickness and macular volume were measured with SD-OCT (SOCT Copernicus REVO) using a 3D macula scanning protocol. The right eyes were selected for analysis. Results The mean age of healthy children in the study was 10.70 ± 2.82 years, the mean AL - 23.16 ± 0.94 mm and the mean spherical equivalent (SE) was $+ 0.81 \pm 0.58$ D. We found that the mean foveal thickness (MFT) was 232.10 ± 15.81 μm , the total macular thickness (TMT) - 286.70 ± 9.82 μm and the total macular volume (TMV) was 8.01 ± 0.28 mm^3 . We found that MFT and TMT were significantly thicker in boys. We found a positive correlation between MFT and age. We found a significant relationship between almost all macular parameters and SE, as well as with AL.

Conclusion: The study offers a normative database of macular thickness and macular volume in healthy Caucasian children aged 6-17 years using SD-OCT. These data can be very useful in the diagnosis and monitoring of macular diseases in childhood.

Keywords: axial length, macular thickness, macular volume, optical coherence tomography, spherical equivalent

ORAL PRESENTATIONS**Dental medicine**

Questionnaire study about the impact of the materials for temporary restoration of endodontically treated teeth on the final restoration of the endodontic access

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Multi visit endodontics requires temporary restoration and its impact on the final restoration is commonly discussed nowadays.

Aim: To investigate the opinion of dental practitioners in Bulgaria about the impact of the materials for temporary restoration on the final restoration of the endodontic access.

Materials and methods: Anonymous questionnaire study was conducted among 201 dental practitioners from Bulgaria. A 21-item questionnaire was specially developed for this study. Participants gave their opinion about preferable material and technique, qualities and possibilities for isolation of endodontic access, methods they use for visualization and removal of different materials for temporary restoration in cases of multi visit endodontics. Collected data were statistically analyzed using IBM SPSS (26/2019), Minitab (19/2019) and Fisher's exact test.

Results: 58% of the respondents think that ZnO-CaSO₃ based materials have negative effect and near 55% report that glass ionomer cements and light cure composites have no negative effect on the final restoration. 67% of the dentists say that they use only one additional method for removal of the materials and most commonly they use fine diamond burs (38%). 89.5% of the participants say that they use only one additional method for registration of remnants on the cavity wall, 46% use detailed view with naked eye.

Keywords: questionnaire study, temporary restoration, endodontic treatment

Rapid protrusion in upper jaw in cross bite in frontal segment

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Introduction: Cross bite in frontal area can be found in early mixed dentition, because it is an esthetic problem for the patients. Untreated cross bite in frontal area leads to underdevelopment in upper jaw.

Aim: We present diagnostic and treated process of two patients with cross bite. We will describe the fixed functional appliance used by us.

Material and methods: We used fixed functional appliance for non-cooperative patients, which contains plastic part – occlusal caps connected by trans-palatinal arch and protruding spring in frontal area. On base of indicators of Ceph analysis and virtual models we make diagnosis of our patients. The dentoalveolar form of cross bite and retrusion of upper frontal teeth is proved by data of analysis. The results are established by changed Ceph indicators.

Results: We achieved correction of the cross bite for 3 months in first case and 2 months in second case. The

value of \angle /SN are changed from 91.20 to 108.70 in first case and from 91.90 to 101.40 in second case. We observed minimal change in position of point A (\angle SNA) before and after treatment – from 82.30 to 83.0 in first case and from 77.20 to 79.30 in second case. In first case we found the difference in inclination of lower incisors from 100.10 to 95.40.

Conclusion: Anatomical and functional problems arising out of non-treated cross bite in frontal area are the lead factor for its early diagnosis and rapid treatment. The application of fixed appliances, through which the occlusion is disarticulated and the comfort during eating are the key for good results.

Keywords: Cross bite, fixed appliance, protrusion

Digital analysis of changes in tooth arch perimeter in non-extraction and extraction treatment

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Introduction: Severe crowding in frontal area is an esthetic problem for patients. It often leads to blockage in lower jaw movements and temporomandibular dysfunction.

Our **aim** is to compare the changes in tooth arch perimeter in patient treated with Pendulum appliance and case treated by extraction of four premolars.

Method: for measurement of tooth arch perimeter is by using software product. For application of this method we used digital models of patient before, during the treatment and at the end. We estimate tooth arch perimeter from distal surfaces of upper first molars on the course of central fissures and incisal edges of teeth.

Results: In case treated with Pendulum appliance we started with perimeter of 86.55 mm, and achieved prolongation of 92.91 mm after Pendulum appliance removal. The increase of 6 mm is mostly due to distalisation of molars and minimal protrusion of the frontal teeth. After leveling of upper tooth arch its perimeter changed to 88.29 mm. Therefore the tooth arch perimeter is increased with 2 mm which allows the achievement of good clinical result. In patient treated with extractions we started with perimeter 84.8 mm and finished with 79.66 mm. The extracted two molars are with total size of 14 mm, and tooth arch perimeter is decreased with only 5 mm. Therefore the crowded tooth in frontal area are aligned with 9 mm of that space.

Conclusion: Nowadays, digital technologies give us opportunity for analysis of our clinical results and also chances for forecasting and planning future treatments.

Keywords: intraoral scanning, tooth arch perimeter, severe crowding, Pendulum appliance

Tensile strength test of three types retraction cords for gingival retraction

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Gingival retraction is a basic stage in the clinic of fixed dentures. As a complementary and supporting element, retraction is mastered in other therapeutic procedures of dentistry. The use of materials with uncertain properties, as well as irrelevant technique in the displacement of the gingival pocket (retraction) can lead to

irreversible changes in the gingival tissues. Rupture of the retraction cord during insertion or removal results in tearing of tissue in the gingival sulcus and trauma to the connective tissue. The reason for this may be the insufficient tensile strength, it is crucial for the retraction cords and their satisfactory physico-chemical properties. The present study aims to evaluate the tensile strength of different types of retraction cords, by static test, using a microstretch apparatus LMT 100 (LAM Technologies, Italy). The study included a branded affordable commercial product - Ultrapak (Ultradent Products, South Jordan, Utah, USA) and two types of cords, which are prototypes and created for the study: retraction cord without core and retraction cord with core - monofilament. The data were analyzed and processed using SPSS version 21. As a preliminary result, when comparing the average durability of the three types of retraction threads, we note that the highest value of tensile strength is the retraction thread with monofilament $40.518 \pm 0.4663 \text{ N/mm}^2$, followed by cords without monofilament with $39.800 \pm 0.8785 \text{ N/mm}^2$ and lastly the commercial article Ultrapak # 00 - $22.110 \pm 0.6226 \text{ N/mm}^2$.

Keywords: gingival retraction, tensile strength, retraction cord, retraction materials

CAD/CAM technology used in prosthetic treatment without intraoral scanner in dental practice. A hybrid treatment approach using CAD/CAM technology. Case report

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Intraoral scanners have an important role in the transformation of dentistry towards a completely digital workflow. Does it mean that every dentist should acquire intraoral scanner in his/her dental practice? The aim of this case report is to present a hybrid approach towards the use of CAD/CAM technology without possessing an intraoral scanner, a combination of conventional impression and digital methods for design and production. A partially edentulous 76-year-old woman was referred to our practice with a chief complain of maxillary frontal teeth abrasion – around 2.5 mm in the incisal edge area. Loss of the mastication center, VDO reduction and a mandibular deviation towards the right were registered. The treatment plan included full arch rehabilitation of the upper jaw with a metal ceramic bridge with cantilevers. Diagnostic impressions were taken, and stone models were poured and mounted in an articulator (ASA dental). A diagnostic wax-up with the newly established VDO and position of the lower jaw was done. The vertical dimension was validated with provisional crowns (Dentalon, Kulzer, Germany). After tooth preparation full arch impressions and bite registration were taken and digitized with a laboratory scanner E2 (3Shape, Denmark). The FPD's framework was designed in EXOCAD and produced with SLM printer (EOS M100 Deantal, EOSgmbh). The metal framework was adjusted in the mouth, veneered with EX3 (Noritake, Japan) and cemented with Fuji One (GC, Japan). The hybrid treatment approach in complex prosthetic cases allows clinicians to take advantage of all the design and production benefits of the CAD/CAM technology, without investing in an intraoral scanner.

Keywords: CAD/CAM, intraoral scanner, lab scanner, abrasion

CAD/CAM software opportunities in creation of fixed restoration

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Introduction: Digital technologies are increasingly entering dental medicine. Their application is common in clinical and laboratory stages. When designing a bridge structure using modern techniques, it is necessary to work on a digital model and to design it virtually.

Aim: To demonstrate the opportunities of CAD/CAM 3Shape software in creation of bridge prosthesis.

Materials and methods: The patient was prepared with a slight shoulder preparation junction on the vital abutment teeth 35 and 37. Intraoral scan of the upper and lower jaw with a Panda 2 scanner (Fregty) was performed. The information was processed with 3Shape design software. Constructions with different anatomical features were created and the optimal one was chosen. The construction was completed with zirconium dioxide ceramics.

Results: It was achieved very good aesthetic effect and perfect adaptation to the preparation junction. Contact with the medially located natural tooth, as well as occlusion, also made no adjustments.

Conclusion: The application of digital technologies enables exceptional precision of work and accuracy of finished prosthesis.

Keywords: digital impression, digital model, digital software.

Device for mechanical cyclic loading

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Introduction: The load on the teeth is a repetitive cyclic process in the chewing act. It is specific by using different support-retaining elements. It is essential to establish the friction force during repeated loading in special equipment. According to the literature, the devices for the study of the load of different structures and materials must meet certain requirements.

Aim: Our development aims to design and offer a device for multiple mechanical-cyclic loading of various structures matrix-patrix retaining elements.

Materials and methods: The device has the following main parts: the mechanical part consists of upper, middle and lower plates connected by strictly parallel guide axes. Each of the plates carries different actuators; the retaining part fixes the support-retaining element and has a tank and a vessel with artificial saliva; The electro-programming part reads the values of the number of cycles, time to perform one cycle and adjusts the pressure force in newtons. This project was implemented with the participation of lecturers from the Technical University.

Results: The construction principle of the proposed device aims at multiple cyclic and mechanical loading in an environment of artificial saliva. Telescope crowns designed by CAD / CAM and made using a 3D-printer.

Conclusion: Preliminary tests for working with the device give us grounds to apply the approach for multiple cyclic loading for different prosthetic elements.

Keywords: prosthetic elements, mechanical loading, device

A 2-year study on clinical survival of indirect Y-TZP restorations

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Background: As (yttrium tetragonal zirconia polycrystals- Y-TZP) zirconia is progressively considered the contemporary material of choice for indirect all-ceramic restorations, the question of its survival performance becomes increasingly important among practitioners.

Aim: The aim of the present study is to evaluate the clinical survival rate of indirect zirconia restorations of extremely devastated vital molars for a two-year period.

Materials and methods: Thirty-two indirect (UTML KATANA™, Kuraray Noritake Dental Inc.) zirconia restorations were made in 19 patients. At 2-year recall 18 patients were present for check-up. Thermal and electrical tests were performed to monitor pulp condition. Cvar and Ryge criteria were directly clinically evaluated on 31 onlays and overlays. The gathered data was processed statistically.

Results: All of the examined restorations showed perseverance of pulp vitality during tests. Regarding Cvar and Ryge criteria all of the observed restorations showed the highest degree of clinical acceptance regarding color match, cavo-surface marginal discoloration, anatomic form, marginal adaptation, development of secondary caries, proximal contact, postoperative sensitivity, loss or fracture of restoration. We used the two-related-samples test to compare the distributions of the clinical features studied at baseline and after 2 years by applying the Wilcoxon signed-rank test. The level of significance was $P < 0.05$.

Conclusion: Concerning the performance of zirconia restorations our 2-year clinical study reveals that zirconia stand out other kind of ceramics with its high mechanical, biomimetic and survival properties.

Keywords: clinical survival, indirect restorations, zirconia

Cytokine secretion of peripheral blood mononuclear cells in pre- and post-treated patients with asymptomatic apical periodontitis

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Introduction: Asymptomatic apical periodontitis (AAP) is a chronic inflammatory process that involves the periradicular tissues. It is not clear whether the innate immune response influences the progression of the disease or the chronic inflammation "primes" the immune cells. The aim of the present study was to investigate this relationship and to explore a potential link between the systemic release of pro-inflammatory cytokines and the presence of AAP.

Materials and methods: Twenty patients with AAP and no systemic diseases were enrolled in the study. The in vitro release of TNF- α and IL-1 β by stimulated and non-stimulated peripheral blood mononuclear cells (PBMC) isolated from each patient was assessed by ELISA. The procedure was repeated 10 months following non-surgical endodontic treatment and the pre- and post-treatment levels of the cytokines were compared.

Results: The levels of IL-1 β secreted by non-stimulated PBMC increased after treatment, while the levels secreted by stimulated cells decreased ($p < 0.05$). The levels of TNF- α did not show a statistically significant difference following treatment.

Conclusion: Within the limitations of the present study no distinct relationship between the systemic release of pro-inflammatory cytokines and AAP was outlined. Further large scale research is needed to shed light on this multifactorial process.

Keywords: Asymptomatic apical periodontitis, PBMCs, inflammation

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ORAL PRESENTATIONS**Public Health/Healthcare****Art, religion and education as a form of socialization****Adriana Lyubenova**

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Objective: This study aims to clarify the experience of disabled patients/students and their family members, through a process of socialization and increasing their self-confidence through experiences based on art, religion and education.

Methods: Following a small group of people diagnosed with a disability - more than 70% and their progress in the period of 10 years. Educational standards are changing, with the emphasis on functional literacy and the ability to think independently, critically and creatively, rather than just to be based on the core notion of memorizing educational content. Accordingly to that, a variety of creative approaches are constantly sought in the pedagogical process. A new learning culture is emerging and this is to create competencies for self-education that lead to increased motivation, initiative and creative thinking and self-realization.

Results: More than 50% managed to obtain higher education (BA) degree and get a job, and in less than 10% of the group degradation can be observed.

Conclusions: By incorporating a religious, art and educational components in treatment programs - care system, can serve a broader purpose of increasing the collaboration with religious and other groups in the community and expand the resources available to the patient at their socialization process. These results suggest the beneficial aspects of religion, art and education.

Keywords: art, religion, socialization process, education

Building bridges between university environment and intercultural communication to achieve mutual understanding**Zhenya Gundasheva¹, Dimitar Mirchev², Gergana Petkova^{2,3}, Vanya Ivanova³**¹ Trakia University, Stara Zagora, Bulgaria² Medical University of Plovdiv, Plovdiv, Bulgaria³ Paisii Hilendarski University, Plovdiv, Bulgaria

This short communication reports the results from a research project conducted at three Bulgarian universities (Medical University of Plovdiv, Paisii Hilendarski University of Plovdiv, and Trakia University Stara Zagora) between 2017-2019.

The aim was to collect ethnographic data from foreign students, and to question the validity of a functioning university environment through observing and analyzing stereotypical expressions, cross-cultural communication incidents, and culture-related differences through all stages of adaptation. The methods comprise a survey based on Hofstede's dimensions of national cultures, a Likert scale questionnaire testing how academic environment is perceived, interviews recorded for an especially designed elective course in intercultural communication at Plovdiv University and the collection of idiomatic expressions in Bulgarian and English related to cultural stereotypes. The results and discussion section includes statistical analysis of the answers to the survey that link parameters of national cultures with dynamic behavioral changes that allow students to adapt to the university environment. Statistically significant differences have been noted when comparing individuals according to their demographics, cultural dimensions and reactions to local specifics.

A Guidebook for International Students (Medical University of Plovdiv and Trakia University Stara Zagora) has been compiled and distributed to newly admitted students at both universities. The work on the project has contributed to increasing the sensitivity, awareness and interest in intercultural communication by initiating a discussion on cultural tensions and incidents through direct interaction with student representatives and stakeholders.

Keywords: intercultural communication, university environment, cultural incidents, expressions

Internet dependence among medical students

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Introduction: The use of the Internet and social networks such as Facebook, Instagram, Twitter, LinkedIn, etc., change the opportunities of people to share information, learn, work, perceive others people and present themselves. This modern way of communication is easily available using computers, tablets or smart-phones at any time, but it can make users internet addicted.

Aim: The aim of this study is to analyse whether exist there Internet dependence among medical students.

Materials and methods: The questionnaire survey was conducted among 107 students at the Medical University of Plovdiv in 2019. Data were statistically analysed using SPSS v. 19.0.

Results: 100% of students use the Internet. 86.9% of students prefer to meet friends in his leisure time, 67.3% of the respondents prefer to surf on the Internet, 57.9% of them prefer to watch TV, 57.0% of students prefer to engage in sports. 18 (16.8%) students use the Internet for 4 or more hours per day, 23 (21.5%) students use the Internet from 3 to 4 hours, 52 (48.6%) use the Internet from 2 to 3 hours and 14 (13.1%) use the Internet for up to 1 hour per day. The majority of students (70.1%) use the Internet for up to 4 hours ($\chi^2 = 33.299$, $df = 3$, $p = 0.001$) per day.

Conclusion: The majority of medical students make an effort to comply a healthy lifestyle. We did not find dependence on the Internet among the study group - the students use the Internet at a reasonable period of time.

Keywords: Bulgaria, Internet dependence, leisure time, medical students

Influence of globalization in the contemporary world on the profession and training of medical laboratory assistants

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Background: Globalization is a process with influence on the competitiveness of the professional environment and increasing requirements towards the competence of the specialists. There are two opposite tendencies in Bulgaria: on the one side, the economic restrictions in the country have caused an outflow

of candidates for the professions from the healthcare department, and on the other side – the increasing emigration has led to an insufficiency of medical specialists in our country, including medical laboratory assistants.

Aim: to analyze the main global challenges imposing a clear system for continuing training of medical laboratory assistants.

Materials and methods: Theoretical and empirical sources from researchers, European and Bulgarian institutions have been studied and logically summarized. A comparative analysis of the practices in the continuing education and training in our country and in other European countries has been carried out.

Conclusions: Globalization invokes processes of educational convergence and functional professional specialization for work with new technologies in order to cover the high standards of healthcare. The significance of the continuing training has been incredibly increasing as a result of the rapid development of innovations, the consequence of which is knowledge outdated. The attitude that there is a 4-5 year period of half-life for knowledge outdated has become more and more popular and for that period professional competence has been reduced almost to the half. The free movement also imposes higher standards of training. The continuing opening of new laboratories increases the demand for highly qualified specialists.

Keywords: innovations, new technologies, knowledge outdated, professional competence, healthcare standards

The use of mobile health applications among the Bulgarian population

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Introduction: Mobile health applications provide new opportunities to patients which can help manage successfully their health condition.

Aim: The main aim of this research was to explore the distribution and attitudes toward the usage of mobile health applications among the Bulgarian population.

Material and methods: An online survey was conducted from July 2019 to February 2020. Among the 976 interviewed people 591 (60.6%) were female and 385 (39.4%) were male. The mean age is 43.25 ± 5.75 . A questionnaire for collecting information about the usage of mobile health applications was developed. Statistical analyses were performed using SPSS v.23.

Results: 83% of the respondents have smartphones. In all age groups more than 68% of the participants have used their mobile phones for access to information related to their own health. A statistically significant difference between the use of mobile applications and age groups was found. The young participants are more likely to use different mobile applications. More than 64% are willing to use a mobile application to monitor or control their health. Women are more likely to subscribe in mobile health applications. Older respondents and less educated people are the least likely to subscribe mobile applications and share health related personal data.

Conclusion: The development of mobile health applications for patients is necessary since they can offer new possibilities for treatment and monitoring of different diseases. Leveraging mHealth technologies such as mobile applications, which can help to monitor COVID-19 patients and suspected cases, is a good way to mitigate the effects of the pandemic.

Keywords: mobile health, mobile health applications, telemedicine

Public attitudes to the application of telemedicine in Bulgaria

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Introduction: Telemedicine has great potential to improve clinical management and healthcare delivery worldwide by improving access, quality, effectiveness and economic efficiency.

Aim: The main aim of this study is to examine public attitudes towards the use of distance medical services in Bulgaria.

Material and methods: Among the 329 interviewed people, 206 (62.6%) were female and 123 (37.6%) were male. The mean age of respondents is 44.95 ± 3.05 . An online survey was conducted from August 2019 to December 2019. We used our own toolkit – a questionnaire containing questions related to information about telemedicine services. Statistical processing of the data was performed using the software product SPSS v.17. Descriptive statistics, Student t-test and χ^2 test were used.

Results: More than 81% of the respondents have a positive attitude towards the application of telemedicine in Bulgaria. 42.4% are positive about prescribing treatment with the help of telemedicine services. The level of education affects the responses received ($p < 0.05$). Lower educated respondents are more likely to trust an unknown medical professional. They believe distance medical services should be less expensive than a standard examination. Respondents with a higher education degree are more concerned about the misuse of personal information.

Conclusion: The telemedicine consultation service for an encountered health problem was well received by the respondents. The implementation of telemedicine services would increase the satisfaction of patients. It is especially important for people with chronic diseases and those who live in small and remote settlements. In the conditions of COVID-19 telemedicine is a solution to limit the infection.

Keywords: telemedicine, remote access, health services, health care, healthcare.

Injury-caused temporary disability in workers

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Injuries, both general and work-related, can be a significant burden on workers' health, companies' performance and national healthcare systems. We analyzed indicators for temporary disability caused by injuries for the period 2015-2019 in 1480 employees from various economic activities - retail and services ($n=812$), manufacturing ($n=263$), crop production ($n=130$), education ($n=107$), healthcare ($n=86$), and construction ($n=82$). In contrast to the constantly decreasing average national occupational injury coefficient, the total injuries of the studied workers showed an increase in both the frequency of cases and the number of lost days due to temporary disability. The average duration of a case was over 20 days throughout the period and showed an increasing trend. The followed indicators were higher in men than in women. The highest frequency of cases and lost days due to injury in recent years was registered among construction workers. Construction is also an activity with a significant frequency of occupational injuries. 49% of injuries were found in workers aged 50 and over. The cases and lost days due to injuries to the ankle, foot, knee and lower leg had the largest relative share. Of all 310 injuries during the period, only 5 were officially registered as occupational accidents. The analysis suggests that a significant cause for the growing number of non-work-related injuries is the increase in the average age of workers. The observed trends show the need for injury prevention in workers over the age of 50.

Keywords: injuries, temporary disability, workers

Evaluation of computer vision syndrome among office IT workers in Varna, Bulgaria

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Introduction: In the 21st century digital device usage has increased its role substantially in all age groups, so that frequent daily use for both social and professional purposes is considered normal. Computer vision syndrome is the combination of eye and vision problems associated with the use of computers and digital devices. CVS affects the eyesight, visual comfort and occupational productivity of workers due to the different symptoms computer users and staff working with video displays experience: ocular discomfort, headache, asthenopia, dry eye, blurred vision.

Aim: To evaluate the symptoms of CVS among workers in a software company in Varna by subjective and objective tests.

Materials and methods: During periodical medical examination of workers in IT company, 40 participants - 31 men and 9 women were distributed with a questionnaire regarding most common symptoms of CVS. To the group was conducted Schirmer test to measure the tear film quantity. The average age of the participants is 28 ± 0.5 . All staff uses more than 4 hours daily computers. All participants have undergone medical examination by ophthalmologist and internist.

Results: 11 or 27,5% of reached score ≥ 6 in the survey – considered to suffer CVS. 10 or 25 % of the examined in the Schirmer test have reached results.

Keywords: CVS, evaluation, digital devices

Academic staff motivational attitudes and satisfaction with e-learning in medical education

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Introduction: Expanding the perspective of e-education has become a great challenge at universities amid the Covid-19 pandemic. During this process academic staff attitude is one of the most important predictors of its effective application.

Aim: To investigate the motivation and satisfaction of the academics with e-learning at Medical University of Plovdiv.

Materials and methods: An online Google Form questionnaire which consists of 36 questions was sent through institutional e-mail to the academics. The data was collected in June and August 2020. The pilot study consisted of 162 participants from all departments.

Results: Among the participants 48.8% had positive expectations towards e-learning. Both synchronous and asynchronous distant learning is perceived as an attractive method of interaction and communication with students according to 41% of the respondents. However, 47% responded that it is not a successful method for acquiring new knowledge and 89.5% - for practical skills in humanities education. The main limitations of e-learning are lack of sufficient experience and qualification, increase in working load, insufficient cohesion in the teacher-student relationship, shortage of technology provision and software problems. Different electronic applications and platforms were used – MS Office 365, Moodle, Edo.mup. More than half of the participants (63.6%) are highly satisfied with the electronic teaching.

Conclusion: This study outlines the main problems pertaining to web-based education among the academic staff. In addition, the shared experience and views for e-learning are a valuable feedback, which contributes to the improvement of teaching quality.

Keywords: E-learning, Medical University, Academic staff, Attitude, Limitations

COVID 19 impact on hospital resilience

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Introduction: COVID-19 pandemic has affected almost all elements of the healthcare system. The hospital care provision has proved to be extremely vulnerable. The COVID-19 ongoing pandemic is seriously questioning the hospital resilience to the biological disasters. A lot of articles and summaries have been published recently analyzing the negative impact on the both structural elements of the in-patients installations.

Aim: The objective of this study was to analyze the hospital resilience shortfalls revealed throughout COVID-19 pandemic healthcare system response.

Materials and methods: Review of publications related to the challenges Bulgarian hospitals were facing into first months of the COVID-19 pandemic was performed. Publications included were presenting insufficiencies or inadequacy of hospital resilience. The means of the descriptive and comparative methods were applied, in order to group the main shortfalls.

Results: Performed analyses present several elements of the hospital resilience that have to be elaborated. For the static resilience the majority of the authors are highlighting the absence of rooms dedicated for triage, isolation and transferring of the suspected for coronavirus infection patients, as well as the possibilities of transformation of hospital departments into infectious diseases wards. All the authors noted the sharp insufficiency of personal protective equipment into the early stages of the pandemic development. From the operative resilience the low level readiness and preparedness of the medics to protect themselves and patients in the hospital is noted.

Conclusion: The study present a modest list of initiatives to be implemented for increasing hospital resilience to biological disasters.

Keywords: COVID-19, hospital resilience, triage, biological disasters

Motivation, training and development of hospital staff

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The staff of each hospital structure must meet the knowledge and skills of the constantly evolving environment, technological progress and the growing demands of society. Competition in the field of medical services is strong and determined by health professionals who are driving force of the medical institution. In order to meet the requirements of the environment, legal regulation, healing structure policy, health professionals must develop their skills and build their knowledge, which leads to increased satisfaction with the profession. Undoubtedly, the leading role is played by the policy of healing structure, which should evaluate the desire and efforts of employees to train and improve their competence. Management should use their experience to conduct on-the-job training and improve the professional ability of other employees. Training also requires additional knowledge about medical and diagnostic procedures, building stereotypes about behavior in crisis and emergency situations, communication skills, working a safe work environment and etc. The choice of medical professionals is mostly difficult due to their scarcity. Due to the shortage, persons who do not always have

the necessary skills are also appointed. Management should define learning objectives in terms of knowledge, defining the desired, expected results to be achieved. The duration of training varies is determined according to the needs of the structures. Motivation and training are important for retaining highly qualified specialists, in the context a shortage of personnel and scarce resources in the healthcare system. By developing their staff, hospital structures ensure stability and guarantee the provision of high-quality medical care.

Keywords: training, hospital, staff, motivation, development

Health risks management of surgical teams in case of exposure to surgical smoke

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Introduction: Electrosurgery is a basic method in modern surgery and is used in almost every surgical procedure. It is applied both for cutting tissues and for controlling bleeding by coagulation of blood vessels. In modern electrosurgical procedures, high-frequency "cutting" and low-frequency "coagulations" are intertwined to achieve a clinically optimal combination of cutting and coagulation. The evaporation of the tissue produces a plume of smoke, hereinafter referred to as "surgical smoke" (SS).

Materials and methods: A review of the available literature on the content of surgical smoke and related health risks in the exposure of the operational team has been made.

Results: SS causes technical, physical, and professional health problems. One of the challenges is the closure of the field of vision, especially expressed in laparoscopic surgery. Proven SS contains live bacteria and viruses, exposing surgical staff to the risk of infection. The contained aerosol particles increase the risk of respiratory diseases and strokes. Some of the harmful effects are mediated by carcinogenic volatile molecules such as acrylonitrile (a precursor to cyanide) and carbon monoxide. The standard surgical mask does not protect the carrier from SS due to insufficient adhesion and inefficiency in filtering small particles. Although the risks of SS are recognized, smoke evacuation ventilation systems are not yet routinely used in most healthcare facilities.

Conclusions: There are few studies in the literature on the effects on staff exposure to SS in the operating room during various clinical procedures.

Keywords: surgical smoke, occupational health risks

POSTER SESSION I**Biomedicine****18F – FDG PET/CT and single-isotope 99mTc – tetrofosmin scintigraphy combined with SPECT in a patient with men type 1 syndrome****Albena Dimitrova Botushanova, Veselin Popov, Zhanet Grudeva-Popova**

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We present a case of 47 years old woman with multiple endocrine neoplasia (MEN) type 1 syndrome, primary hyperparathyroidism, insulinoma and pituitary adenoma. In July 2017 year, due to recurrent hypoglycemic episodes and high levels of insulin, she was referred to the Department of Nuclear medicine at St George University Hospital – Plovdiv for PET/CT. A whole-body PET/CT on a device PET/CT SIEMENS type Biograph mCT64 was performed 65 min after i.v. administration of 188 MBq 18 F-FDG. A 10 mm lesion with low metabolic activity, SUVmax – 2,00 located dorsally of the left thyroid lobe, suggestive for parathyroid adenoma, was noticed. The rest of the scanned body areas showed no areas with increased glucose uptake suggestive for malignancies that could be connected with the main disease. After two months, to specify the discovered lesion behind left thyroid lobe, we performed a single-isotope 99mTc – Tetrofosmin scintigraphy combined with SPECT using SPECT gamma camera "SYMBIA E DUAL". An area with increased uptake of the radiopharmaceutical, located behind and below the left thyroid lobe, that could be connected with hyperfunctioning parathyroid adenoma was visualized. This case allowed us to compare two nuclear medicine modalities using different devices and radiopharmaceuticals, 18F – FDG PET/CT and single-isotope 99mTc – Tetrofosmin scintigraphy combined with SPECT in one and the same patient. Several factors could explain the differences in obtained diagnostic information from the two methods.

Keywords: primary hyperparathyroidism, scintigraphy with 99mTc-tetrofosmin, PET/CT 18F – FDG, SPECT

Changes in the serum levels of estradiol and changes in expression of estrogen receptor alpha in the bone tissue of ovariectomized Wistar rats**Armine V. Grigoryan¹, Aneliya A. Dimitrova¹, Tatyana M. Betova², Alexander B. Blazhev³, Savelina L. Popovska²**¹ Department of Physiology and Pathophysiology, Medical University, Pleven, Bulgaria² Department of General and Clinical Pathology, Medical University, Pleven, Bulgaria³ Department of Anatomy, Histology, Cytology and Biology, Medical University, Pleven, Bulgaria

Background: 17 β -estradiol (E2) is an estrogen steroid hormone, which is produced mainly within the follicles of the ovaries and the adrenal glands. During menopause, serum estrogen levels drop dramatically. This disturbs the metabolic balance, changes the lipid profile, leading to visceral obesity and the development

of osteoporosis. Adipose tissue becomes an important extragonadal site of E2 biosynthesis thanks to the aromatase activity. In bone tissue, 17 β -estradiol exerts its influence by binding to its receptors: ER α and ER β , which are found in the osteoblasts, osteoclasts and osteocytes. We investigated the serum estradiol levels and changes in bone alpha estrogen receptor (ER α) expression in ovariectomized rats. For this purpose, we used 20 female Wistar rats at reproductive age – 2 months divided into 2 groups: group 1 (G1) – 10 animals were ovariectomized (OVX) and group 2 (G2) – 10 of which were sham-operated (SHAM).

Results: All animals from G1 showed weight gain compared to group G2. The results showed that the values of serum E2 in rats from G1 statistically increased compared to G2 ($p < 0.05$). Immunohistochemical analysis revealed no difference in ER α expression between both groups. Histomorphological analysis of femur from G1 showed the presence of pronounced osteoporosis.

Conclusion: OVX led to the development of obesity, which caused an increase in serum estradiol levels, through aromatase activity. We confirmed that OVX leads to the development of osteoporosis and does not alter the expression of ER α in G1 rats despite high E2 levels.

Key words: 17 β -estradiol, ER α , obesity, osteoporosis,

Survey of the opinion of students from the medical college on distance learning during the COVID-19 pandemic

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Introduction: In March 2020, a state of emergency was declared in Bulgaria in order to limit the spread of COVID-19, which required physical isolation and distance learning. The aim of the research was to survey the opinion of students from medical colleges in Bulgaria about distance learning and satisfaction with the quality of the e-learning environment.

Material and methods: An anonymous online questionnaire survey was conducted among students in the Assistant Pharmacist and Rehabilitator specialties from the colleges in Plovdiv – 110 (37.5%), Sofia – 44 (15%), Varna – 105 (36%), and Pleven – 34 (11.5%) in June 2020. 293 students took part – 225 (77.5%) assistant pharmacists and 65 (22.5%) rehabilitators from the first year students (42.3%), second year students (37.5%) and third year students (20.2%).

Results: Respondents stated that they used their own personal computer in 95.6%, mobile device in 98.3%. In 60.1% of the respondents had the opportunity to spend 10-15 hours per week for self-study and professional self-preparation. Students indicate that they have used means of information exchange through synchronous communication applications – Teams, Zoom, Skype and others – every day in 32.4%, 2-3/7 in 53.4%. The strong motivation of students, the challenge to be part of the learning community from different parts of the world, are positive factors that have contributed to the implementation of online learning.

Conclusion: Assessment of distance learning by students is a significant contribution to increasing the efficiency of the learning process during the COVID-19 pandemic and could increase satisfaction with a quality and streamlined learning process in a technological environment.

Keywords: distance learning, students, medical college

Serum levels of TNF- α , CXCL4 and TGF- β 1 in systemic sclerosis

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Introduction: Systemic sclerosis (SSc) is an autoimmune disease with unknown etiology. Processes like chronic inflammation and connective tissue fibrosis are among the main hallmarks of the disease. The aim of our study was to examine serum levels of key molecules participating in these processes and determine their biological significance.

Materials and methods: Sixty five female individuals with SSc and a control group of 14 healthy females were included in this investigation. Patients were further subdivided in such with diffuse cutaneous SSc (dcSSc) and with limited cutaneous SSc (lcSSc). Serum levels of TNF- α , TGF- β 1 and CXCL4 were examined by ELISA.

Results: Serum levels of TNF- α and CXCL4 were higher in SSc patients when compared to the control group ($p = 0.003$ and $p < 0.001$ respectively). Concentrations of TNF- α were significantly increased in patients with dcSSc in comparison with healthy subjects ($p = 0.001$). Statistically higher median values of serum CXCL4 were detected in dcSSc ($p < 0.001$) and lcSSc ($p = 0.005$) matched with levels of CXCL4 in the control group. No difference in serum TGF- β 1 among the examined groups was found. A positive correlation between concentrations of CXCL4 and TGF- β 1 ($r = 0.29$, $p = 0.025$) was determined.

Conclusion: We suggest that the increased levels of the pro-inflammatory cytokine TNF- α and the chemokine CXCL4 in patients reflect different aspects of the chronic inflammation accompanying SSc pathophysiology. The correlation between serum CXCL4 and TGF- β 1 may represent the relationship of the inflammatory response with the fibrotic process.

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Keywords: TNF- α , TGF- β 1, CXCL4 systemic sclerosis

Osimertinib – an opportunity for a personalized therapeutic approach

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Introduction: Genomic profiling is a way to define therapy in the era of personalized medicine.

Purpose: To prove the effect of treatment, determined after comprehensive genomic profiling.

Materials and methods: In the period from 2019 to 2020, in the Clinic of Medical Oncology at St George University Hospital, we treated five patients with histologically verified after fibrobronchoscopy lung adenocarcinoma in an inoperable stage. At the onset of the disease, four of them had pulmo-pulmonary metastases and two had cerebral metastases. Molecular genetic analysis was performed for EGFR, ALK and PD-L1. A deletion was found in exon 19 of the EGFR gene. Discussed at the General Clinical Oncology Committee for initiating targeted therapy with the tyrosine kinase inhibitor Osimertinib (Tagrisso).

Results and discussion: In all patients was reported significant clinical improvement in the first month after starting therapy. Control examinations have shown a significant reduction in tumor size. Stereotactic radiosurgery with a Cyber knife was also performed in both patients with CNS metastases. Control MRI reported remission of lesions in the absence of new ones. At present, patients tolerate the therapy well, without obvious side effects, while maintaining the quality of life.

Conclusion: NGS methods are standard in the diagnosis of NSCLC and the determination of therapy.

Keywords: genomic profiling, targeted therapy, osimertinib

Genomic profiling – optimized therapeutic options

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Introduction: Comprehensive genomic profiling provides extensive analysis of the tumor genome to detect clinically significant alterations. This approach allows to expand the therapeutic possibilities of patients.

Purpose: To demonstrate significantly improved survival after genomic profiling in a patient with synchronous neoplasia associated with poor prognosis.

Materials and methods: A clinical case of a 71-year-old patient treated at the Clinic of Medical Oncology at St George University Hospital is presented. On the occasion of consumptive and pain syndrome, a CT of the chest and abdomen was performed – data on tumor formations in the lungs and head of the pancreas. After fibrobronchoscopy and thick-needle aspiration biopsy, synchronous low-grade neurotic squamous cell carcinoma of the lung and moderately differentiated adenocarcinoma of the pancreas were demonstrated.

Results and discussion: Based on the performed genomic profiling (Foundation Medicine), the patient was considered to initiate a combination regimen with chemotherapy and immunotherapy. Against the background of both malignancies and satellite morbidity, a 12-month overall survival was achieved while maintaining quality of life.

Conclusion: Personalized therapy improves the effectiveness of treatment, reduces toxicity and significantly reduces financial costs.

Keywords: personalized medicine, genomic profiling

Applicability of C18 core-shell chromatographic columns for analysis of fatty acids in blood plasma

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Introduction: Free fatty acids (FFAs) are an essential participant in the body's energy and signaling system. There is 3-10% FFAs in the blood. A persistent change in their plasma levels is associated with the development of peripheral insulin resistance and impaired peripheral blood supply. In recent years, methods with

liquid chromatography with or without derivatization procedures and reversed-phase (RP) chromatographic have been proposed for the quantitative determination of FFAs. RP columns are the predominant type in the FFAs determination methods. Their diversity gives the researcher the opportunity to experiment and find the most appropriate column for the purpose of analysis.

Aim: The aim of the study was to develop a liquid chromatographic method with mass spectrometric detection for determination the concentration of FFAs in plasma with a C18 core-shell column.

Results: Experiments performed with a C18 core-shell chromatographic column showed constant retention of the tested fatty acids in the column.

Conclusion: The chromatographic column used is not suitable for achieving the set goal. It is necessary to perform additional experiments with a chromatographic column with lower hydrophobicity, in order to reduce the retention of the tested fatty acids.

Keywords: free fatty acids, liquid chromatography tandem mass spectrometry, C-18 core shell chromatographic column

Zonulin – a marker for increased intestinal permeability and its relationship with autoimmune diseases

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Introduction: Zonulin is a 47116 kDa protein that regulates the tight connections between cells in various tissues and organs in the human body. It is identical to prehaptoglobin 2, and its synthesis can be stimulated by various agents – substances ingested with food or bacteria involved in the microbiome. In the intestine, its increased concentration is associated with the opening of tight connections between enterocytes and increased intestinal permeability. Impaired protective function of the intestinal mucosa makes it possible for the cells of the immune system to come into contact with antigens that are foreign to the body, which can lead to inflammatory, allergic or autoimmune diseases.

Aim: The aim of the present review is to investigate the role of zonulin as a diagnostic / prognostic marker for increased intestinal permeability and its relationship with the development of autoimmune diseases.

Results: Increased intestinal permeability and changes in the microbiota, as a result of the influence of substances ingested with food, can be a significant factor in the development of autoimmune processes. Studies in recent years have found abnormalities in zonulin secretion in Hashimoto's autoimmune thyroiditis.

Conclusions: The mechanisms, underlying the impaired regulation of zonulin and its relationship to the development of autoimmune diseases, need to be further elucidated.

Keywords: zonulin, autoimmune diseases, Hashimoto

High-sensitivity CRP is elevated in women with gestational hypertension, while in normotensive pregnancy it correlates with BMI and BSA

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Background: Gestational hypertension the less investigated hypertensive pathology of pregnancy, compared to preeclampsia, but evidence exist of an unfavorable cardiovascular profile for women after such a pregnancy.

Aim: To determine serum hs-CRP levels in women with preeclampsia, gestational hypertension and in normotensive pregnancy in order to assess cardiovascular implications and to examine its correlations with some characteristics of the women.

Materials and methods: Thirty-six women with gestational hypertension, 37 with preeclampsia and 50 maternal and gestational age matched controls were included in a single-center prospective clinical-epidemiological study. Serum hs-CRP levels were determined using ELISA method.

Results: Significantly higher hs-CRP levels were present in the gestational hypertension group, compared to the controls ($p = 0.043$), but not in the preeclampsia group ($p = 0.445$). The levels between the two pathological groups did not differ significantly ($p = 0.247$). Odds ratio for hs-CRP levels higher than the provided cut-off was 3.31 (95% CI 1.32-8.29) for the presence of gestational hypertension. In the normotensive pregnant women hs-CRP levels had a positive correlation with BSA, pre-pregnancy and current BMI, but such correlations were absent in the hypertensive groups. There were no correlations with maternal or gestational age, current weight gain in any of the groups or with the highest detected blood pressure in the pathologies. Levels did not differ according to gravidity, smoking status and smoking during pregnancy.

Conclusion: Elevation of hs-CRP is more pronounced in women with gestational hypertension than in women with preeclampsia, which could indicate a different pathophysiological mechanism and a higher cardiovascular risk in those women.

Keywords: inflammation, biomarkers, cardiovascular risk, gestational hypertension, preeclampsia

Antimicrobial activity of extracts from *Scutellaria altissima* L.

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Introduction: *Scutellaria* extracts and its biologically active flavonoids, such as baicalin and baicalein, exhibit significant antimicrobial activity.

Aim: To investigate the antimicrobial activity of extracts obtained from aerial parts and roots of *Scutellaria altissima* from the regions of Mezek and Bachkovo, Bulgaria.

Material and methods: 70% ethanol and aqueous extracts of aerial parts and roots of *Scutellaria altissima* were used. Microbiological tests were done on clinical isolates of *Streptococcus mitis*, *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Minimal bactericidal and minimal bacteriostatic concentration of *Scutellaria altissima* extracts were determined by agar method.

Results: *S. altissima* extracts have effective antimicrobial activity against *Streptococcus mitis*, but had no effect on the other tested microorganisms. The minimal bactericidal concentration of ethanol extracts of *S. altissima* aerial parts and *S. altissima* roots is 2000 µg/ml and 8000 µg/ml at 24 hours, respectively. The bactericidal effect of aqueous extracts occurs at 48 hours at minimal bactericidal concentration of *S. altissima* aerial parts – 2000 µg/ml and of *S. altissima* roots – 6000 µg/ml.

Conclusion: The effective antimicrobial properties of extracts of Bulgarian *S. altissima* against *Streptococcus mitis*, suggests its potential as a source for the development of natural antimicrobial agents for the suppression of oral pathogens and prevention of some oral infections.

Keywords: *Scutellaria altissima* L., antimicrobial activity

Predictive model for severe osteoporosis in Bulgarian patients with transfusion-dependent beta thalassemia over 18 years of age

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Introduction: Fractures are the most severe manifestation of thalassemia bone disease and identify patients who are at risk for future fracture events.

Objective: To identify risk factors for osteoporotic fractures in transfusion-dependent beta-thalassemia patients (TDBTP). Patients and methods: 62 TDBTP (age 32±0.5 years) were evaluated. Information was collected about: 1) osteoporotic fractures; 2) thalassemia parameters; 3) bone mineral density Z-score, measured using dual-energy x-ray absorptiometry at spinal level (SL) and femoral neck (FN); 4) serum levels of bone turnover markers (beta-cross-links, osteocalcin, RANKL, osteoprotegerin, sclerostin), measured by ELISA. Data were processed using comparative analysis, binary logistic regression and ROC curve (Statistical Product of Social Science, v24) with determined $p = 0.05$.

Results: 19 out of 62 patients were identified with past fractures (29.70% total; men – 37.50%; women – 23.30%, $p = 0.270$). Patients with past fractures showed lower Z-score than those without fractures (-3.25 vs. -2.33, $p = 0.001$ for SL and 0.73 vs. 0.82, $p = 0.023$ for FN). Among the 11 potential predictors analyzed, the two-component regression model consisted of pretransfusion Hb and sclerostin showed 80.3% potential for diagnosing patients with past fractures. ROC analysis revealed sensitivity of 69% and specificity of 85.1% for pretransfusion Hb at level 826 ng/ml.

Conclusion: The regression model "pretransfusion hemoglobin and serum sclerostin" could be implemented in clinical practice to identify the TDBTP who need treatment optimization for their bone disease.

Keywords: fracture events, beta thalassemia, sclerostin

Annual dynamics of bone mineral density in adult transfusion-dependent beta thalassemia patients – assessment of the risk factors for bone loss

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Introduction: Bone mineral density (BMD) loss is a backbone in the management of thalassemia bone disease.

Objective: To establish a statistical model defining the transfusion-dependent beta thalassemia patients (TDBTP) at risk for significant bone loss for one-year. Patients and methods: BMD (Z-score and g/cm²) was measured in 62 TDBTP at baseline and one-year apart using dual-energy X-ray Absorptiometry at spinal level (SL) and femoral neck (FN). Thalassemia-related parameters were extracted from the patient's records. Serum levels of beta-crosslaps, osteocalcin, RANKL, osteoprotegerin and sclerostin were measured using ELISA. Data were analyzed via comparative analysis, binary logistic regression and ROC analysis (SPSS, v24) with level of $p = 0.05$.

Results: 74.20% of the patients showed a decrease in areal BMD and 61.30% in Z-score at SL one year later from the baseline. At FN, BMD decrease was 46.80% in areal BMD and 45.20% in Z-score. Applying binary logistic regression, among the 14 potential predictors for annual bone loss, the bi-component regression model, including constant ($B = 7.062$, $p = 0.030$), pretransfusion hemoglobin ($B = 0.77$, $p = 0.034$) and osteoprotegerin ($B = 0.243$, showed significance, $p = 0.030$); ($\chi^2 = 14.148$, $p=0.003$). This model properly selected 80.6% of the TDBTP at risk for future bone loss.

Conclusion: The bi-component regression model, consisted of pre-transfusion hemoglobin and serum osteoprotegerin levels shows a valuable potential for detecting the TDBTP at-risk for future bone loss and could be implemented in the management of thalassemia bone disease.

Keywords: bone mineral density (BMD), beta thalassemia, osteoprotegerin

Triage organization in the emergency department at St. George University Hospital

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Background: Clinical triage works as a dynamic system which increases the time for adequate reaction on the side of the medical staff and, at the same time, provides greater safety for the patient. Determining the triage category in patients evaluates the level of emergency and ensures differences in the medical priority and the time framework for applying diagnostic and treatment activity in outpatient and inpatient settings depending on the available human, instrumental and device resource.

Aim: The aim of the present article is to study the organization and triage of the emergency department at St George University Hospital.

Results: According to 70.5% of respondents the optimal space for the medical triage activities on the territory of the emergency department is provided. Despite the presence of markings, 51.2% of participants think there is still room for improvement in this respect. Almost half of the surveyed (47.4%) think there still is possibility for a delay in the transfer of a patient from the triage to the resuscitation room. Employees aged up to 30 years express the opinion that reliable control on the action of people accompanying the patient is partially or rather not provided $P = 0.011$ ($\chi^2 = 25.9$). Physicians experience difficulty in the transfer of patients to other departments $P = 0.022$ ($\chi^2 = 11.7$).

Conclusion: Effective application of triage as an instrument for risk management is essential and would contribute to better quality of the provided health care. Thus, the processes will be standardized and the overall work organization and legal certainty of medical specialists will improve.

Keywords: triage, emergency, risk management

COVID-19 influence on emergency department medics

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Introduction: COVID 19 pandemic has imposed a lot of changes into societies. The novel, unknown and powerful virus affected almost entire aspects of humans wellbeing, both physical and psychological. The most impacted is the medical community that has become the guardian of the population life. One of the most vulnerable from this community are the emergency medicine specialists.

The objective of this study was to analyze the COVID-19 influence on psychological stamina of the emergency medics.

Materials and methods: Survey regarding the psychological burden related to the COVID-19 pandemic was performed within the emergency department of St George University Hospital, Plovdiv in April 2020. The method applied was personal face-to-face interview. All of the 60 medics were asked to describe their psychological status and to note the factors that have a major influence on their psychological comfort.

Results: All the respondents have noted alteration in their psychological status. 75% ($n = 45$) were influenced by both in-hospital and out-of-hospital stressors. From out-of-hospital factors the most noted were related to the National Operational Headquarters briefings (80%, $n = 48$), contradictory statements from medical experts (70%, $n = 42$) and uncertainty of the governmental actions (67%, $n = 40$). From in-hospital stressors the majority of respondents listed the following – sufficiency of the preventive measures and possibility to infect the family (92%, $n = 55$), as well as the colleagues/friends avoidance due to infection transmission fear (75%, $n = 45$).

Conclusion: The results of the study clearly prove the significant negative psychological impact sustained throughout COVID-19 pandemic.

Keywords: COVID-19, psychological impact, stressors, emergency department

Use of glycated hemoglobin (A1C) as a biomarker for vascular risk in type 2 diabetes: its relationship with matrix metalloproteinases-2, -9 and the metabolism of collagen iv and elastin

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Background: HbA1c measurements may be useful not only in optimizing glycemic control but also as a tool for managing overall vascular risk in patients with diabetes. In the present study, we investigate the clinical significance of HbA1c as a biomarker for hyperglycemia-induced vascular damages in type 2 diabetes (T2D) based on the levels of matrix metalloproteinases-2, -9 (MMP-2, MMP-9), anti-collagen IV (ACIV), and anti-elastin (AE) antibodies (Abs) IgM, IgG, and IgA, and CIV-derived peptides (CIV-DP) reflecting collagen and elastin turnover in the vascular wall.

Objectives: The aim is to show the relationship of hyperglycemia with changes in the levels of vascular markers and the dynamics of this relationship at different degrees of glycemic control reported by HbA1c levels.

Materials and Methods: To monitor elastin and collagen IV metabolism, we measured serum levels of these immunological markers in 59 patients with T2D and 20 healthy control subjects with an ELISA.

Results: MMP-2, MMP-9, and the AEAbs IgA levels were significantly higher in diabetic patients than in control subjects, whereas those of the AEAbs IgM, ACIVAbs IgM, and CIV-DP were significantly lower.

Conclusions: A set of three tested markers (MMP-2, MMP-9, and AEAbs IgA) showed that vascular damages from preceding long-term hyperglycemia begin to dominate at HbA1c values $\geq 7.5\%$, which is the likely cut-point to predict increased vascular risk.

Keywords: type 2 diabetes, hemoglobin A1c, matrix metalloproteinases-2 and -9, vascular risk

Bioenergetic analysis of peripheral blood mononuclear cells in patients with autism spectrum disorder

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Introduction: The term Autism Spectrum Disorder (ASD) denotes a diverse group of psychiatric impairments that emerge in early childhood and are characterized by stereotypical behavior. Despite the intensive research efforts, the ASD etiology remains unclear, and the diagnosis is based on behavioral symptoms. In recent years, the link between ASD and mitochondrial dysfunction is discussed as a possible pathogenic mechanism, which may influence the development and severity of the disease.

Aim: This study aims at examining the cellular metabolic profiles in children with ASD and identifying variations in mitochondrial function associated with the disease.

Materials and methods: Twenty two children with ASD and healthy controls from 2 to 11 years are enrolled in the study. The ASD diagnosis was validated according to generally accepted clinical assessment scales

(ADOS, CARS). Mitochondrial activity in peripheral blood mononuclear cells (PBMC) isolated from ASD patients and from children with normal neuropsychological development was examined using a Seahorse XFp analyzer. The following bioenergetic characteristics were assessed: basal respiration, proton leak, ATP production, maximal respiration, spare respiratory capacity, coupling efficiency.

Results: We observed higher oxygen consumption, spare respiratory capacity, and decreased ATP production in patients with ASD compared to the control group. The results may potentially allow the stratification of patients into separate subgroups, depending on the parameters studied.

Conclusion: The obtained bioenergetic data allows the identification of the mitochondrial function and the metabolic profiles in ASD characterized with prominent changes in respiratory function. This, in turn, can facilitate diagnosis and develop new therapeutic approaches.

Keywords: ASD, mitochondrial function, PBMCs, Seahorse XFp

Application of 3D printing in medicine in the context of the COVID-19 pandemic

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Background: The COVID-19 pandemic has put global health systems under critical pressure. There was a serious shortage of hospital beds and medical equipment, on the one hand, and of reliable personal protective equipment (PPE) on the other, to protect health workers helping to treat critically ill patients during the pandemic.

Aim: The article presents some of the innovative applications of 3D printing for the design and manufacture of life-saving medical devices in the context of the COVID-19 pandemic.

Conclusion: 3D printer technology has competitive advantages in creating complex products and customized products. These advantages create significant opportunities for improving the safety, efficacy, and accessibility of medical devices to support patients and healthcare teams.

Keywords: 3D printing, medical devices, COVID-19

Participation of testicular isoform of the angiotensin converting enzyme in sperm surface changes

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Spermatozooids are rapidly mutable cellular structures which are very dependent on its interaction with the environment. These interactions lead to fundamental changes in the cells and sperm membrane. During the movement in the male and female reproductive tract the proteins located in the cell membrane take part in complex and diverse areas. On one hand these proteins stabilize the cell membrane but on the other hand they change the sperm surface. The change involves fine and complex modifications on spermatozooids membrane like the removal of suppressing factors and changes in the proteins and lipids organization on the sperm surface. Purpose. Immunohistochemical and immunofluorescent study of the testicular isoform of Angiotensin converting enzyme (tACE) during spermiogenesis and acrosomal membrane.

Materials and methods: Testicular biopsies were used for immunohistochemical and fixed spermatozoa for immunofluorescence testing of tACE in infertile men.

Results: The immunohistochemical study shows tACE expression during spermatogenesis and its participation in the differentiation stages of sperm in testis. The immunofluorescent study tracks tACE manifestation in untreated, capacitated and acrosome reacted sperm. In the process of capitalization and acrosome reaction we established a significant dynamic accompanied with change in tACE expression and manifestation on sperm membrane.

Conclusion: tACE manifestation during spermatogenesis, its visualization in the acrosome region proves its active role in the process of maturation, capacitation and acrosome reaction. Its manifestation could be used for selection of quality sperm in assisted reproductive technology.

Keywords: sterility, fertilization, acrosome, sperm, tACE

Antioxidant activity of extracts from *Sideritis scardica*, Lamiaceae

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Sideritis scardica is an endemic plant in Bulgaria and has been consumed for centuries as beverage (infusion or decoction) with multiple health promoting properties. It contains a wide variety of biologically active substances, such as polyphenols, flavonoids and organic acids. Its antioxidant activity has been well documented over the last decades and is considered a possible principle in the treatment and prevention of inflammatory and neurodegenerative diseases.

Aim: The aim of the current study was to compare antioxidant properties and extraction yields of various extracts from *Sideritis scardica*. Different decoctions and infusions have been prepared with varying temperatures, solvents and extraction times, and applying classical and green methods, such as microwave and ultrasonic irradiation at specific frequencies. After the solvents have been evaporated, the antioxidant potential of the resulting extracts was measured using DPPH, ABTS and FRAP methods. In addition, total phenolic content and total flavonoids have also been evaluated, using VIS spectrophotometry.

Results: The results showed that the highest extraction yields were obtained from water extracts as infusion and decoction (15 g/100 g), followed by 70% ethanol extracts from ultrasound-assisted extraction. The highest antioxidant potential was documented for the 70% ethanol solution, where the total phenolic content also had the highest values – 21 mg GAE/g dw. Therefore, the extracts of *Sideritis scardica* are a rich source of polyphenols with strong antioxidant potential.

Keywords: *Sideritis*, antioxidant, polyphenols

Optimisation of computed tomography protocol for lung investigations

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Computed tomography (CT) is well established method in the medical practice, thanks to its excellent resolution, allowing visualizations, where even at minor deviations from the health tissues electron densities may be distinguished. Obtaining reconstructions in CT is based on more than a million single scans, demands for this X-ray method high radiation doses. This is valid especially for the chest scans. Such are the investigations of lungs. Keeping the health of the patients, when dealing with ionization radiation, is based on ALARA (as low as reasonably achievable) principle. In the present report, the optimization of a standard CT lung protocol is shown, where the lowering of the dose was targeted. The experiments were performed on CT Bright Speed 16, GE (Avante, Health Solutions). An electron density phantom model 062M was employed. The voltage, current, noise level and the slice thickness (spiral scanning) were varied. For each combination of the parameters, the dependence of the Hounsfield units on the electron density was drawn and the doses were calculated (CTDIvol and DLH). The final decision was made based on the minimization of the artefacts and the dose, without affecting the resolution of the image. Based on the achieved results, including with patients, a new CT lung protocol is proposed, in which the voltage is 120 kV, the current up to 210 mAs, slice thickness – 5 mm, and noise level – 15.

Keywords: computer tomography (CT), optimization, CT lung protocol

How oncogenetics predicts & educates (HOPE)

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Every day, around the world, millions of people fight cancer, undergoing devastating therapies that have a huge impact on their quality of life. Over the next two decades, the number of new cases is expected to increase by about 70% (WHO, 2017). Oncogenetics can contribute to changing this future scenario if it is used in people for whom prevention is still possible and the onset of the disease can be avoided. Oncogenetics is in a stage of progressive growth. It focuses on detecting and monitoring the genetic predispositions of people at risk as a result of mutations or a family history of cancer. Targeted professional decisions and the implementation of science-based prevention strategies will significantly contribute to the improvement of clinical decisions and outcomes. On this basis, it will be possible to facilitate the proper inspection and early detection of previous symptoms, as well as the introduction of changes in harmful habits and behavior. This international project is focused on raising awareness of the importance of oncogenetics as a discipline, the study of genetic predisposition to cancer and care for people at risk. Implementation of the project activities are related to the creation of multidisciplinary groups of medical specialists to provide specialized consultations; training of specialists in the field of high-tech and specialized interventions in oncogenetics; creation of an open online course in the field of oncogenetics as well as specialized software and applications for mobile phones.

Keywords: oncogenetics, genetic tests, hereditary cancer

Subchronic effects of rimonabant on active avoidance learning in bulbectomized rats

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The abnormal activity of endocannabinoid system has been implicated in the mechanisms of some psychiatric and neurological disorders. The removal of the olfactory bulbs (OBX) is an experimental model of depression, which has also been proposed as a model of Alzheimer's disease. We examined the effect of the CB1 selective antagonist Rimonabant (SR 1411716) on the learning and memory processes of OBX rats tested in an active avoidance paradigm (shuttle box). Rimonabant (3 mg/kg) was administered by intragastric cannula (1 ml/100 g) to OBX rats once daily for 14 days period. OBX rats were divided into three groups, and Rimonabant was given before OBX; immediately OBX and on the background of depressive-like behavior. Rimonabant showed a memory enhancing effect in the sham-operated rats and partially ameliorated the memory disturbances induced by the bulbectomy, given before OBX or 14 days after OBX. Only upon administration immediately after OBX, it prevented the development of the memory deficits. The study provides evidence that impaired endocannabinoid signalling may be involved in the development of cognitive deficits accompanying the OBX syndrome.

Keywords: Olfactory bulbectomy, cannabinoid CB1 receptors, depression, memory, rat

Formulation for development of an active prosthesis for closing the ocular slit in patients with peripheral facial paralysis

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Aims: Project development for designing an active prosthesis, which resembles the blink of an eyelid, affected by severe peripheral facial paralysis. The goal is prevention of xerophthalmia and its consequences, as well as compensation for the patient's aesthetic problems.

Methods: 1. Presentation of the components of the prosthesis 2. Description of the way the prosthesis works.

Results: The components of the prosthesis (an electric coil, a piston, a switch, conductors) are connected in a suitable way with fine adhesive threads. These threads are attached to the upper and lower eyelids of the good and bad eye. The connecting conductors and the power supply (battery) are installed in a selected accessory (headband, tiara, glasses). Way of working: when the good eye blinks, an electrical circuit is closed, which activates the mini-coil on the affected side. It attracts the piston, which pulls the adhesive threads laterally and the affected eye closes. When the good eye is open, an interruption of the electrical circuit happens, the piston returns to its original position, the adhesive threads are released and the affected eye is open.

Conclusion: 1. The suggested prosthesis provides activity of the affected eyelid in sync with the blinking of the good eye. 2. The placement and use of such a prosthesis is easy and does not require surgery. 3. The prosthesis can be used in the process of rehabilitation of peripheral facial paralysis.

Keywords: lagophthalmos, facial palsy, xerophthalmia

Sectra 3D human body visualization table use in brain abscess diagnostics in a child. Case report

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Brain abscess in children is a rare and particularly severe complication of acute otitis media/chronic suppurative otitis media. We present a child with a brain abscess developed as a pre-surgical complication of CSOM with cholesteatoma. Visualization of the abscess on a 3-D Sectra Visualization table was performed. An 8-year-old child, who often suffered with runny ear, not treated for the condition. The child was admitted in severe condition, with history, clinical and laboratory data suggestive of severe chronic inflammation of the right middle ear. The examination did not reveal signs of meningeal irritation, increased intracranial pressure, excitation, sensory disorders and focal symptoms. Surgical treatment of the right ear had performed: radical mastoidectomy with removal of a cholesteatoma. A three-day normal post-operative period was followed by worsening of the condition. A brain abscess in the right temporal lobe had been visualized on the CT scan. A craniotomy was performed by opening the brain abscess, aspiration of the pus and lavage of the cavity. After surgical and conservative treatment, the child was discharged clinically healthy from hospital on the fourteenth day. Processing the image check-ups on a 3-D Sectra visualization table helps to determine the size and localization of the abscess, as well as the choice of surgical access.

Keywords: Brain abscess, Chronic supp. otitis media, child

Nutritional models in stress in managerial personnel

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Psycho-emotional stress (PES) is defined as a condition in which the subject perceives external stimuli as depleting or overwhelming his adaptive capabilities. One of the most often quoted professions with high levels of PES is that of managerial personnel. The research aims to reveal the influence nutrition has on PES and the capabilities of adequate nutritional models, which could benefit PES control. This review is based on available scientific literature. The online databases "Google Scholar", "Pubmed" and "Scopus" were employed, using the keywords "stress", "eating", "managerial personnel" and "managers". The search yielded n = 39 pertinent articles. The quantitative assessment of stress includes some subjectivism and can often lead to multiple outcomes due to the specificity of the reaction of the subject. Different fields of work, age, geographical location, and even gender influence adaptive processes. The relationship between stress and eating is often interpreted as the former being a factor for the appearance of pathologies in the latter (stress eating, emotional eating, hyperphagia), in the evaluation of which the "Salzburg stress eating scale" is an adequate resource. The therapeutic role of nutrition is less often researched – the focus is on the paradoxical effect of carbohydrate consumption and the significance of certain micronutrients. PES leads to behavioral changes, which affect nutritional behavior and choice. Currently, available data is insufficient to evaluate the capabilities of adequate nutritional intake in PES control in managerial personnel. Future research should focus on the potential of specific nutritional strategies in the management of PES.

Keywords: managers, nutrition, psycho-emotional stress, managerial personnel, stress

Role of TNF- α in the development of chronic venous insufficiency

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Introduction: Chronic venous insufficiency (CVI) is a serious, modern, social and health problem requiring early diagnosis and up-to-date methods of therapy. Tumor necrosis factor alpha (TNF- α) is a key cytokine in the development of endothelial damage to the venous wall. We aimed to examine serum TNF- α levels and expression in patients with CVI.

Materials and methods: The study group included 40 operated patients (22 men and 18 women) and 40 blood samples from a control group. Plasma TNF- α levels were investigated by ELISA. Patient biopsy material was examined immunohistochemically and TNF- α expression was compared to serum levels.

Results: Significantly higher TNF- α levels were found in the CVI group compared to the control group (30.26 pg/ml vs. 28.4 pg/ml, $p = 0.032$). We compared the expression of TNF- α with serum cytokine levels. The results revealed that higher serum levels were also associated with expression in endothelial cells, but without statistical significance ($p > 0.05$).

Conclusion: The small group of the study does not allow general conclusions, however the data obtained confirm the importance of cytokine TNF- α in the endothelial damage and its key role in the progression of CVI.

Keywords: TNF- α , Chronic venous insufficiency, endothelium damage

Impact of IL-23-positive cells in gastric cancer progression

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Introduction: Gastric cancer (GC) is one of the most common malignant tumors worldwide. Dendritic cells (DCs) and IL-23 cytokine secretion plays a pivotal role in anticancer immunity. The aim of this study is to investigate infiltration with IL-23-positive DCs and its relation with clinicopathological parameters and survival in patients with gastric cancer.

Materials and methods: Using immunohistochemistry we investigated 33 patients with GC for infiltration with IL-23-positive dendritic cells. The clinicopathological parameters and survival were analyzed retrospectively.

Results: We found tumor infiltration with IL-23-positive DCs in all of 33 cases of GC. The number of IL-23-positive DCs in tumor stroma and tumor border was inversely correlated with T-stage ($\chi^2 = 2.75$; $p = 0.038$ and $\chi^2 = 4.19$; $p = 0.05$, NS; Log-rank test).

Conclusion: In conclusion our results suggest that the infiltration with IL-23-positive DCs could be useful as a marker of progression and had prognostic value for gastric cancer patients.

Keywords: IL-23, dendritic cell, gastric cancer

POSTER SESSION I**Biopharmacy****Priority medicines in Europe: concept, development and future****Violeta Getova¹, Radiana Staynova², Hristina Lebanova³**¹ Bulgarian Drug Agency, Bulgaria² Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University of Plovdiv, Bulgaria³ Department of Pharmaceutical Sciences and Social Pharmacy, Faculty of Pharmacy, Medical University, Pleven, Bulgaria

In 2016, European medicines agency launched a new program entitled Priority Medicines (PRIME). It is aimed at improving access to medicines in areas where there are unmet therapeutical needs. Main tools of the program are scientific support and consultation of the applicant as well as an accelerated assessment procedures of marketing authorization applications for the products which met the PRIME criteria. The current study aims at pointing out the main characteristics and advantages of the Priority Medicines program by analyzing both the development until the present moment and some future directions. The conducted analysis shows the interest towards the PRIME program is rather satisfactory with almost ten applications for assessment of compliance monthly. The main areas of interest are oncology, hematology and neurology. It is important to point out that there are also applications for orphan drugs and pediatric medicines. These tendencies correspond to the trend in clinical trials and are not surprising, having in mind the lack of satisfactory treatment in numerous conditions of these areas. In 2019 three products in compliance with the PRIME program were granted marketing authorizations in Europe. Although the period of action of PRIME program is still too short to assess whether it meets its predefined objectives, the results from the conducted study show that it does have an added value in key therapeutic areas, especially in early stages of drug development.

Keywords: access to medicines, therapeutic needs, marketing authorization

Design and evaluation of sustained release matrix tablets with dry birch leaves extract**Dimitar Penkov¹, Plamen Katsarov¹, Stela Z. Dimitrova², Margarita Kassarova¹**¹ Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University of Plovdiv, Bulgaria² Department of Chemical Sciences, Faculty of Pharmacy, Medical University of Plovdiv, Bulgaria

The **aim** of the present work was to carry out a technological development and biopharmaceutical characterization of sustained-release matrix tablets containing dry extract of white birch leaves (*Betula pendula*, Roth). The development of the model tablet formulations was done using 33 full factorial design. The tablets were prepared by the method of tableting after wet granulation with a mass of 0.700 g. Different concentrations and ratios of ethylcellulose and hydroxypropyl methylcellulose (40/60, 25/75 and 10/90 respectively) were used, with varying viscosities of the HPMC used (500 kDa, 750 kDa and 1150 kDa), and different pressing forces applied (1t, 1.5t and 2t). The influence of the individual factors, as well as the combination of them, on the dependent variable t₈₀, showing the release time of 80% of the extract included in the tablet, was evaluated by a complete 33 factorial analysis of variance (ANOVA). The statistical significance of both the individual factors and the partial significance of their combination is established. The EC concentration significantly affects the release process, with the EC/HPMC:25/75 ratio being best suited to prolong the process as well as

eliminate the initial intensive release. Increasing the molecular weight of the HPMC used leads to a delay in the release process. Although with a more insignificant effect, the increase of the applied compression force leads to a slowing down of the release process. The most promising was the model obtained at a ratio of EC/HPMC: 25/75, molecular weight of HPMC 1150 kDa and compression force 2t, showing $t_{80} = 7.97$ h.

Keywords: matrix tablets, sustained release, dry birch leaves extract

Chemical composition of Ginkgo biloba L. kernels

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Ginkgo biloba leaf extracts are one of the top-selling phytopharmaceuticals due to their proven positive effect on Alzheimer's disease and other forms of dementia. The seeds of the tree have even longer history in Chinese folk medicine, but their chemical composition is far less studied. The analysis of seeds, collected from the Plovdiv region showed that they are relatively poor in protein (average content in raw nuts 5%) and lipids (1%). Among the fatty acids, unsaturated acids predominate (81%), 38.5% of which refer to ω -unsaturated acids. The content of microelements depends on the population of the tree source; the values found for Fe are 18 – 64 ppm, for Cu 6.5 – 11.4 ppm and for Zn 8.8 – 24 ppm. The physicochemical characteristics of starch, which is more than 50% of the dry matter, showed a high content of amylose fraction in it, a higher degree of swelling and orderliness of the polysaccharide chains compared to wheat and corn starch. Additional in vitro studies and comparisons with the two commercial products showed that the starch obtained from Ginkgo biloba contains a lower percentage of digestible starch and a higher percentage of resistant starch, and subsequently, a low glycemic index could be expected. These properties of Ginkgo biloba starch, combined with the lack of gluten in it, make it suitable as an excipient in the preparation of dosage forms for patients with specific diseases (diabetes, celiac disease).

Keywords: Ginkgo biloba L., trace elements, fatty acids, starch, glycemic index

Biopharmaceutical characterization of ketoprofen emulgels and bigels for dermal use

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Aim of the study: The aim of the present work is to investigate the in vitro release of ketoprofen from emulgels and bigels for dermal application.

Materials and methods: An in vitro study of the release of ketoprofen from the prepared formulations was performed in Dissolution Apparatus 1. The amount of active substance was determined spectrophotometrically at $\lambda = 260$ nm. To assess the kinetics of ketoprofen release, data from in vitro dissolution tests were fitted to the zero-order, first-order and Higuchi equations.

Results: In vitro dissolution profiles of ketoprofen from emulgels showed an amount of drug release ranging between $88.48 \pm 0.82\%$ and $99.11 \pm 0.69\%$ over a period of 150 minutes. In vitro release data showed first-order kinetics for the models studied, with the exception of two models for which Higuchi kinetics were established. Dissolution profiles of ketoprofen from bigels for 5 hours showed drug release between $82.4 \pm 6.39\%$

and $94.7 \pm 2.3\%$. In vitro release data showed first-order kinetics and Higuchi kinetics.

Conclusion: As a result of the in vitro release, it has been found that the emulgel and bigel formulations show a large amount of released ketoprofen and selected models can be considered as an effective dosage form for dermal administration.

Keywords: ketoprofen, emulgel, bigel

New analytical method for quantitative determination of biologically active compounds in Ginkgo biloba L. kernel extract

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In a previous study we showed that aqueous-methanol extract of Ginkgo biloba kernels stimulates learning and memory functions in rats, and its effect is comparable to that of the nootropic medicine piracetam. Analysis of the chemical composition of the extract showed that it contained significant amounts of sesquiterpenes (bilobalide and ginkgolides) but the content of free flavonoids was low. For better characterization of the extract, a method has been developed to determine the total amount of flavonoids (free and glycosylated). The flavonoid rutin was used as a model compound for investigating the most appropriate conditions for the hydrolysis of glycosylated flavonoids. The change in the concentrations of rutin and the product of its hydrolysis quercetin under set of experimental conditions was monitored by liquid chromatography – tandem mass spectrometry (LC-MS/MS). The results obtained were used to determine the most suitable temperature, duration and concentration of HCl for complete hydrolysis of glycosylated flavonoids. The use of a standard additive rutin during hydrolysis of the total extract showed a significant matrix effect under LC-MS/MS conditions which was minimized by pre-analytical purification of hydrolyzed extract by solid phase extraction. The developed method of analysis is an important step towards standardization of Ginkgo biloba kernel extract with a view to future pharmacological applications.

Keywords: Ginkgo biloba L., LC-MS/MS, rutin, quercetin, solid phase extraction

Results of treatment of prostate cancer in Bulgaria

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Aim: To compare the incidence of prostate cancer (PC), diagnosis, therapeutic approaches, application of European and national clinical guidelines and the results of treatment between Bulgaria, Europe and the United States.

Materials and methods: The study is based on official data from the World Health Organization, the National Cancer Registry, the National Health Insurance Fund, the recommendations of the European Society of Medical Oncology and the Pharmacotherapeutic Guide to Medical Oncology. The possible reasons for the discrepancy of the Bulgarian survival data with the data from other countries are discussed.

Results: There is a discrepancy between the data on morbidity in Bulgaria, presented by the WHO and the National Cancer Registry. Despite the lower incidence in Bulgaria compared to data for Europe and the United States, mortality is higher and 5-year survival is lower. Therapeutic inertia in drug treatment is also often ob-

served. The specifics of the national legislation, related to the course of the procedure for inclusion of new international non-patent names in the Positive Drug List, influence the speed of entry of innovative medicinal products into clinical practice.

Conclusion: There is a discrepancy between national and international data on the incidence of prostate cancer in Bulgaria. There is a delay in access to new medicines due to the inclusion in the Positive Drug List, a poorly established “path” of the patient, which leads to unsatisfactory results compared to European and world practice.

Keywords: prostate cancer, regulation, clinical guidelines

Patient empowerment and patient participation – analysis of modern concepts

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Introduction: There are nearly 3 million people with chronic diseases in Bulgaria. Despite better diagnostics, the existence of new therapies, and easier access to them, healthcare costs are increasing. Good health outcomes require constant participation by patients to achieve therapeutic goals.

Aim: The study aims to present the concept of a patient-centered approach to chronic disease management.

Materials and methods: A review of published literature was performed. Studies published in the period 2004-2020 are analyzed to identify the essence of the basic concepts for the application of patient empowerment and patient participation concept.

Results: The basic principles, the implementation, and the expected results are determined for each of the approaches. The similarities and differences between patient empowerment and patient participation are discussed. The connection between the two concepts has also been examined.

Conclusion: Patient empowerment is a broad concept that includes the development of patient-centered treatment approaches with their active participation and involvement in the process. The implementation of these approaches in chronic disease management leads to better treatment results and reduced costs for the healthcare systems.

Keywords: patient empowerment

POSTER SESSION I**Contemporary surgical techniques****Role of extracorporeal shock wave lithotripsy in the modern era of endourology****Petar Antonov¹, Atanas Ivanov¹, Nikolay Kolev²**¹ Department of Urology and General Medicine, Faculty of Medicine, Medical University of Plovdiv, Bulgaria² Student at Faculty of Medicine, Medical University of Plovdiv, Bulgaria

Introduction and purpose: Extracorporeal shock wave lithotripsy (ESWL) is a minimally invasive method of treating urolithiasis. The development of endourology leads to a reduction in the number of patients treated by this method. The aim is to present the results of safety and efficacy treated with this method and conclusions.

Materials and methods: A retrospective study of 112 patients treated at the Clinic of Urology of St George University Hospital in 2019 with kidney stones below 1.5 cm. From a study of excluded cases with a presented patients. All treated patients had radiopositive stones and a BMI of up to 30.

Results: The mean success rate for complete fragmentation was 42.8% (48 patients) after the first ESWL procedure, 52% (58 patients) after the second, and 77% (86 patients) after the third procedure, respectively. The average hospital stay was 1.2 days. The observed complications were: pain after the procedure – 14 cases, macroscopic hematuria – 1 case, kidney trauma – absent, fever – 3 cases. Emergency endoscopic treatment was required in 6 patients due to upper urinary tract obstruction.

Conclusion: In the modern era of endourological treatment, extracorporeal lithotripsy in suitable patients for its implementation is a safe and effective method that should be offered to patients when making an informed decision on their treatment.

Keywords: extracorporeal shock wave lithotripsy, urolithiasis, kidney stone disease

Lower pole stones – endoscopic treatment by retrograde intrarenal surgery

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Introduction: Lower pole calculus concretions present a therapeutic challenge in the treatment of urolithiasis. The possibilities of extracorporeal lithotripsy, retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy are possible therapeutic options including various advantages and disadvantages.

Materials and methods: A retrospective study of 21 patients with stones in the lower pole of the kidney with a size of less than 2 cm treated in the Clinic of Urology at the University Hospital "St. George" in Plovdiv in the period 06.2020 to 09.09.2020 was used flexible ureterorenoscope for single use with a flexion angle of 275°. Lithotripsy was performed with a Holmium-YAG laser.

Results: The average size of the stones is 11 mm, all located in the lower pole of the kidney. The average time of lithotripsy – 50 min. Use of ureteral access sheath, facilitating the penetration of the ureterorenoscope – in all patients. Lithotripsy directly in the lower cup was performed in 16 (76.2%) cases, and transposition of the calculus through a basket in 5 (23.8%). Complete fragmentation was obtained in 18 patients (85.7%) and the presence of fragments below 5 mm in 3 patients (14.3%). Postoperative complications are typically, according to the Clavien-Dindo scale all are 1st degree – pain and hematuria [7 (33.3%) patients].

Conclusion: The single-use ureterorenoscopes provides a good option with RIRS for lower calculus stones with a high degree of success and minor intra and postoperative complications on the Clavien-Dindo scale.

Keywords: retrograde intrarenal surgery, ureterorenoscopy, urolithiasis

POSTER SESSION I**Innovative methods of diagnosis and treatment****Programed necrosis and inflammatory bowel disease****Elena Panayotova¹, Antonia Atanassova²**¹ Department of Propedeutics of Internal Disease, Faculty of Medicine, Medical University of Varna, Bulgaria² Department of Anatomy and Cell Biology, Faculty of Medicine, Medical University – Varna, Bulgaria

Intestinal epithelial integrity is a key component in maintaining intestinal tissue homeostasis and intestinal barrier stability, which is only achieved if there is a strict balance between cell survival and cell death. The traditional concept that apoptosis and necrosis are major forms of cell death has been challenged by the recent discovery of a new type of programmed cell death called necroptosis. Necroptosis is a regulated form of cell death that is observed with extracellular apoptotic stimulation in cells in which apoptosis is inhibited. It is a process dependent on the activity of receptor interacting serine / threonine-protein kinase 3 (RIP3) and the mixed line of kinase domain-like protein (MLKL).

Objective: The aim of the present study is to review the literature data for the link between the programed necrosis and the pathogenesis of Inflammatory Bowel Disease (IBD).

Materials and methods: For the period from 2013 to 2020 in the available databases (Scopus, ScienceDirect, Web of Science, Access Medicine, PubMed) the following keywords are used in English, programed necrosis, necroptosis, receptor-interacting protein kinase-3 (RIPK3) and IBD.

Results: Necroptosis is similar to necrosis in terms of morphological features but can be regulated. Loss of membrane integrity and release of intracellular content induce an inflammatory response. Recent in vivo studies based on mouse models have shown that necroptosis of intestinal epithelial cells induces intestinal inflammation with IBD-like characteristics in humans.

Conclusion: Therefore, controlling key molecules involved in the necroptosis pathway may provide new opportunities for the treatment of IBD.

Keywords: programed necrosis, necroptosis, receptor-interacting protein kinase-3, inflammatory bowel disease

Prevention in children's healthcare through an educationally consistent program following the natural stages of development (KindyROO), suitable for children aged 6 weeks to 7 years

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Aim: Focusing on the basics of neuronal health and foundation of the neuroplasticity theory. The brain and the nervous system change due to a reaction from certain stimulus. The brain can be formed and integrated by sensory, motor, cognitive or emotional experience.

Method: KindyROO is a science based sensory-motor proprioceptive program which represents a system of activities and games that stimulate the intellectual, emotional, social and physical development of babies and kids.

Result: The kids attending the program develop better: balance, coordination, motor skills, concentration, skills to work in a team, visual and speaking skills, which promote smooth transition to the phase of academic learning and (reading), strong arms, fingers and back (important for the phase of writing), abilities to perform tasks sequentially and in rhythm.

Conclusion: KindyROO is a innovative method for preventing developmental delays and neuromotor immaturities, even diseases like functional neurological disorders (which are best described as a group of physical, sensory and cognitive symptoms that do not seem to have an organic etiology, autism spectrum disorders, ADHD, Asperger's syndrome, Tourette's syndrome, dyslexia, process disorders and developmental delay, tics.

Keywords: prevention, functional neurology

Analysis of the types of diseases in the period 2017 – 2019 from working environment risk factors of patients participating in projects for hospital based diagnosis and treatment

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Aim: The aim of the present study was to analyze the data on patients included in different nosological groups who have passed the program of the Fund "Working Conditions" in three consecutive years. The data used is from the final report analyzes performed in the Department of Occupational Diseases at UMHAT "St. George" EAD – Plovdiv diagnostic and treatment procedures for the different nosological groups to the Executive Director of St George University Hospital, EAD, Plovdiv for the period 2017 – 2019.

Results: The results obtained from patients who underwent treatment and diagnosis in different groups of nosological units show variability in the type of labor expert assessment and the observed frequency. The inpatient programs and the activities performed under the contract concluded with the Working Conditions Fund help to increase the medical efficiency of the performed activities in bedridden patients with suspected or recognized occupational etiology of the diseases. They also provide an opportunity for dynamic monitoring – clinical and paraclinical in patients exposed to occupational exposure to harmful substances from the work environment.

Keywords: occupational diseases, analysis, Working Conditions Fund

Angioedema in the practice of allergists

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Angioneurotic edema is a common condition in the allergist's clinical practice. It is distinguished by variety of etiological and pathogenetic mechanisms and often forms an issue in the right therapeutic approach in emergency term. The aim of this presentation is to summarize available evidence published in the specialized medical literature during recently years and also to present modern diagnostic algorithms for the disease. All the information in forms of guidelines and consensuses issued by leading scientific teams all over the world (World Allergy Organization, European Academy of Allergy and Clinical Immunology, British Society for Allergy and Clinical Immunology, The American Academy of Allergy, Asthma & Immunology, Australasian Society of Clinical Immunology and Allergy) in the past decade was used and analyzed. Modern aspects of the epidemiology, etiology, pathogenesis, clinical presence and different forms have been taking into consideration as well as criteria for diagnosis and differential diagnosis of the disease. The experience gained in the clinical practice of allergy specialists working in the clinical structure at St George University Hospital in Plovdiv has also been shared. Special attention is paid to hereditary angioedema as a rare disease and a specific type of angioneurotic edema. Presented material would contribute to building a correct diagnostic algorithm and an adequate approach in the treatment of angioedema in a particular patient.

Keywords: angioedema, clinical practice, allergy

POSTER SESSION I

Dental medicine

Correlation between thickness and translucency of CAD/CAM zirconia veneers

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Introduction: Low-temperature degradation affects the long-term success of zirconia restorations. The transformation from tetragonal to monoclinic phase of the material may lead to translucency change.

Aim: The purpose of the study is to prove a correlation between thickness and translucency of zirconia after the ageing of material.

Materials and methods: Via CAD/CAM technology, 27 veneers are milled from multilayered ultra-translucent zirconia (UTML KATANA Kurraray, Noritake Japan). The samples are divided into 3 groups (n = 9) and 3 sub-groups (n=3) according to the color – A1, A2, A3, and thickness of the veneer – 0,5 mm, 0,8 mm, 1,00 mm. The optical properties of each sample are from spectrophotometer (Spectroshade Micro System, USA) according to CIE-Lab. Translucency is counted via the equation $[(L^*B - L^*W)^2 + (a^*B - a^*w)^2 + (b^*B - b^*w)^2]^{1/2}$. In order to reproduce the conditions and changes occurring to the zirconia after 1 year inside the oral cavity, all of the veneers are subjected to artificial aging via hydrothermal aging. The analysis of the data is done via IBM SPSS Statistics v. 22 and the level of significance is $p < 0,05$.

Results: ANOVA analysis found statistically significant differences between translucency of the veneers colored A1, A2, A3 according to the thickness of the samples: before ageing: A1 (t = 450.930, p = 0.000); A2 (t = 160.248, p = 0.000); A3 (t = 246.870, p = 0.000) and after ageing A1 (t = 252.303, p = 0.000); A2 (t = 676.000, p = 0.000); A3 (t = 1199.678, p = 0.000).

Conclusion: The correlation between thickness and translucency of the zirconia CAD/CAM veneers is proven – increasing the thickness, the translucency decrease. The translucency of the veneer decreases after hydrothermal aging.

Keywords: zirconia, veneers, CAD/CAM, translucency

Comparative evaluation of the effect of class II intermaxillary traction and EF braces trainer in the treatment of class II 1 malocclusion

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Introduction: Class II intermaxillary elastics are routinely used in the treatment of distal bite in combination with braces which, however, according to studies have a predominantly dentoalveolar effect. On the other hand, the myofunctional trainer EF Braces has an orthopedic action by medializing the lower jaw.

Aim: To compare the skeletal effects of class II intermaxillary elastics and EF Braces in distal bite treatment of growing patients on a lateral cephalogram.

Materials and methods: The study included 31 patients aged 14.87 ± 3.48 undergoing treatment with fixed appliances. They were divided into two groups – the first one was given intermaxillary elastics and the second one – EF Braces appliance. All materials were provided by HO 01/2019 project. Lateral cephalograms were made in the beginning and end of the treatment to assess the skeletal effect using the SNA, SNB and ANB parameters.

Results: The group treated with elastics showed a statistically significant decrease of SNA angle ($79.56^\circ \pm 3.94$ before and $78.43^\circ \pm 3.89$ after). The group treated with trainers showed a statistically significant increase of SNB angle from $77.26^\circ \pm 2.78$ to $79.87^\circ \pm 2.62$ after the treatment. This difference of 2.61° represents an average increase in the angle with 3.37% of high statistical significance.

Conclusion: The treatment resulted in significant decrease of ANB angle in both groups – the patients treated with elastics this was due to decrease in SNA angle, while in these treated with trainers – due to increase of SNB.

Keywords: distal bite, intermaxillary elastics, EF Braces

A comparative study of clinical efficacy of tacrolimus 0.1% and clobetasol propionate 0.05% in the management of desquamative gingivitis, manifestation of oral lichen planus

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Background: Topical corticosteroids are considered as the first-line treatment of choice in the management of desquamative gingivitis (DG), manifestation of oral lichen planus (OLP). To date studies on the efficacy of tacrolimus in the treatment of OLP are several and quite controversial.

Aim: To compare the clinical effectiveness of topical application of tacrolimus 0,1% and clobetasol propionate 0.05% in the management of desquamative gingivitis, manifestation of OLP.

Materials and methods: The study comprises 20 patients with gingival manifestation of OLP. All of the participants had clinically and histopathologically confirmed OLP. The patients were randomly divided into two groups: Group A – treated with tacrolimus 0.1% and Group B – clobetasol propionate 0.05%. All the two groups were instructed to apply the topical ointments twice daily, 20 minute each time for the first two weeks and once daily – third week with individual custom trays.

Results: Patients treated with tacrolimus 0,1% showed 74% reduce the feeling of pain and discomfort using visual analogue scale (VAS), VAS 6.70 ± 3.02 to 1.70 ± 1.76 ($p < 0.001$). Whereas subjects treated with clobetasol propionate 0.05% showed 57% reduction, VAS 7.80 ± 1.22 to 3.30 ± 1.94 ($p < 0.001$). Similarly both group showed reduction in efficiency index, especially moderate improvement was seen in tacrolimus 0.1% group (53%) and clobetasol propionate group 0.05% (47%).

Conclusion: Although the obtained results show a similar degree of effectiveness in both types of therapy, at present topically applied tacrolimus may be a valuable addition to the already existing therapeutic modalities for treating subjects with DG.

Keywords: desquamative gingivitis, tacrolimus, clobetasol propionate

Occlusal splint and retainer manufactured through modern 3D technologies

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Introduction: In today's stressful world, the number of patients with bruxism is increasing. After the orthodontic treatment of such a patient, a complex approach for preserving the outcome is required. Thermo-vacuum molding technology for the production of bruxism splints and retainer is widely accepted today. A modern manufacturing method is 3D printing, which discovers new laboratory and clinical capabilities. This precision technology is still poorly researched and popularized.

Purpose: To present the protocols for the design and fabrication of two types of three-dimensional printed appliances - an occlusal splint and an orthodontic retainer.

Materials and Methods: On a 33 year old orthodontically treated bruxist patient two constructions – an occlusal splint and a retainer were designed. The steps include: alginate impressions from both jaws; gypsum models' scanning with inEos X5 laboratory scanner (Dentsply Sirona); computer processing and digital design using Sirona inLab (Dentsply Sirona); 3D printing with Form 2 SLA printer (Formlabs) and post-polymerisation processing. The material used was Dental LT Clear (Formlabs Inc., USA) – a photopolymer biocompatible resin.

Results: The operating protocols for both splints are similar. They offer shorter laboratory steps and, at the same time, more precise final products. 3D printed appliances address some of the essential issues of enamel protection and preserving orthodontic result in complex patients.

Conclusion: Through digital technology, it is possible to design, modify and manufacture various structures with high precision, accuracy, predictability and rapid reproducibility.

Acknowledgments: This study was funded by the project No 13/2020, Medical University – Plovdiv, Bulgaria.

Keywords: digital impression, 3D printing, occlusal splint, retainer

Buffered and non-buffered Articaine during mandibular nerve block

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Articaine is the most widely used local anesthetic in dentistry. Buffering local anesthetic solution with 8.4% sodium bicarbonate reduced injection pain, the speed of onset of the anesthetic should increase, as well as shortens the duration of soft tissues anesthesia. To achieve our goal we assign a following task: comparing the effect of conventionally buffered 4% Articaine with non-buffered 4% Articaine.

Materials and methods: 21 mandibular nerve blocks with buffered 4% Articaine and 39 mandibular nerve blocks with non-buffered 4% Articaine were done.

Results: No difference in injection pain exist between buffered and non-buffered anesthetic ($p > 0.05$). Evaluation of mean latency time – period in seconds from the time of administration of the local anaesthetic until

the onset of the sensation of labial numbness is significantly shorter with the buffered Articaine (58.58 ± 55.5 sec) compared to non-buffered anesthetic (162.57 ± 135.44 sec.), ($F = 5.553$, $p < 0.05$). Evaluation of the duration of anaesthesia – the time at which the sensation of anaesthesia (numbness) disappeared in the lower lip is significantly shorter with the buffered Articaine (76.67 ± 29.17 min) compared to non-buffered (120.59 ± 62.66 min), ($F = 8.441$, $p < 0.05$).

Conclusions: There aren't statistically significant differences in injection pain by usage of buffered and non-buffered 4% Articaine. The buffered anesthetic increased the onset of the anesthetic action more than non-buffered and reduce the time of soft-tissue anaesthesia.

Acknowledgments: The present project is funded by a grant from National Science Fund, No KP-06-M23/2, 2018.12.18.

Keywords: Articaine, buffering, mandibular anesthesia

Buffered and non-buffered lidocaine during mandibular nerve block

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Lidocaine is widely used local anesthetic in dentistry. Buffering local anesthetic solution with 8.4% sodium bicarbonate reduced injection pain, the speed of onset of the anesthetic should increase, as well as shortens the duration of soft tissues anesthesia. To achieve our goal we assign a following task: comparing the effect of conventionally buffered 2% Lidocaine with non-buffered 2% lidocaine.

Material and methods: 38 mandibular nerve blocks with buffered 2% lidocaine and 22 mandibular nerve blocks with non-buffered 2% lidocaine were done.

Results: No difference in injection pain exist between buffered and non-buffered anesthetic ($p > 0.05$), also in the duration of anaesthesia ($p > 0.05$). Mean latency time – period in seconds from the time of administration of the local anaesthetic until the onset of the sensation of labial numbness is significantly shorter with the buffered Lidocaine (104.16 ± 98.3 sec) compared to non-buffered anesthetic (218.19 ± 244.46 sec), ($F = 5.553$, $p < 0.05$).

Conclusions: There aren't statistically significant differences in injection pain and duration of anaesthesia by the usage of buffered and non-buffered 2% lidocaine. The buffered anesthetic increased the onset of the anesthetic action more than non-buffered.

Acknowledgments: The present project is funded by a grant from National Science Fund, No KP-06-M23/2, 2018.12.18.

Key words: buffering, lidocaine, mandibular anesthesia

POSTER SESSION I

Public Health-Healthcare

Influence of the type of bite of children with neuropsychiatric disorders on their nutritional status

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Introduction: Nutritional status (NS) has a significant impact on the overall health of children. The etiology of malnutrition, common in children with neuropsychiatric disorders (ND), is multifactorial. Occlusion disorders and non-physiological bites are an important risk factor for masticatory efficiency.

Objective: To assess the impact of the type of bite of children with ND on nutritional status.

Material and methodology: The study conducted in Varna in the period April – December 2017 included 54 children with ND. After informed consent, the nutritional and oral status of the children was assessed through clinical examination, anthropometric and biochemical examinations, extra- and intraoral examination of the masticatory apparatus.

Results: The results of the study of the type of bite of children with ND found that the predominance of children with non-physiological bites, in which chewing is suboptimal – 59.30%, with bites class II and III by Angl are 51.7% of children raised in residential care homes and 68% of children raised in a family environment. The relationship between chewing skills and nutritional status was statistically significant, as assessed by anthropometric weight-for-age indices ($\rho = 0.225$, $p = 0.029$) and subscapular skin fold thickness ($\rho = 0.405$, $p = 0.003$).

Discussion: Patients' chewing efficiency affects nutritional status. The type of bite creates preconditions for disorders in the chewing cycles. Oral problems contribute to eating difficulties and can lead to malnutrition in children with ND.

Conclusion: Our study found a predominance of non-physiological types of bites and their relationship to malnutrition in children with ND.

Keywords: nutritional status, oral status, bite

Sleep disorders in heavy-duty vehicle drivers

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Introduction: The work schedule of heavy-duty vehicle drivers is accompanied by a disturbed work-rest time-unregulated work time, night work, a prolonged psychoemotional load, unfavorable work conditions.

Polysomnography is a highly specialized test, which is the gold standard in the diagnosis of sleep disorders. Sleep apnea is a quantitative sleep disorder. It is divided into obstructive, central and mixed sleep apnea and it presents with multiple breathing pauses with a length of 10 or more seconds. Sleep apnea, depending on AHI (apnea-hypopnea index) is divided into mild ($5 \leq \text{AHI} < 15$), moderate ($15 \leq \text{AHI} < 30$) and severe ($\text{AHI} > 30$).

Aim: To investigate the sleep disorders in heavy-duty vehicle drivers with polysomnography.

Methods and materials: We have conducted polysomnography and tested by the Epworth sleepiness scale 11 heavy-duty vehicle drivers from April 2018 to October 2019 Second neurological clinic in "St. Marina" hospital Varna. Their age is between 38 to 60 (mean age 49), all men.

Results: All patients had complaints of fatigue, sleepiness regardless of hours of sleep, falling asleep during work, snoring with cessation of breathing during sleep. All of the examined had blood hypertension and obesity (mean BMI 39.3). 10 (90%) of the patients had severe sleep apnea (mean AHI 69,5/h) and 1 (10%) was with a moderate one (AHI 23.5/h). On the Epworth sleepiness scale all of the examined showed results of a moderate sleepiness (mean 15 points) and all of them reported of occasions when they fell asleep during driving.

Conclusion: Obstructive sleep apnea is the most common sleep disorder in heavy-duty vehicle drivers and can be the cause for road accidents.

Keywords: sleep apnea, polysomnography, drivers

Data mining techniques applied to electronic health records – literature review

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The development of information technologies and the digitalization of healthcare and medicine lead to the rapid growth of data every day. Electronic Health Records Systems are developed to store different kinds of patient information and could be very useful in improving the quality of medical care. Maintaining and analyzing Big Health data is challenging because of the complexity and diversity of medical data. Specified data mining techniques provide opportunities in handling a large amount of medical data and discovering hidden knowledge in electronic health records and other multiple data sources. The main **purpose** of this article is to present the application of data mining techniques to EHR and the importance that this methodology has in the diagnostic and treatment process as well as in the analysis of risk factors for disease prevention and control. It can be defined as a process of discovering meaningful new correlations, patterns, and trends by digging into large amounts of data, using statistical methods, machine learning, and artificial intelligence techniques. The implementation and application of data mining techniques are extremely effective for decision support in many aspects of the healthcare. This article highlights some future trends of data mining and its impact on healthcare and medicine as well as some limitations of these techniques applied to healthcare and medical data.

Keywords: data mining, electronic health record, big data

Occupational stress and asymptomatic ischemic cerebrovascular disorder

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Introduction: Multiple studies have proven the negative effects of chronic stress leading to high blood pressure, diabetes mellitus, high serum lipid levels, which on their own are risk factors for cerebrovascular disease (CVD). One of the first subclinical stages of CVD is asymptomatic ischemic cerebrovascular disorder (AICD), and it is associated with high risk of stroke. Patients with AICD have nonspecific complaints which are typically manifested under stress

Methods: Our study is based on twenty adult patients with MRI test results showing signs of chronic microvascular leukoencephalopathy. We did research on their risk factors for CVD, their career choices and current job specifications. For measuring our patients level of occupational stress we used The workplace stress scale.

Results: Patients' mean age was 54.9 years, with SD 7.48. 75% of whom are at least with one high risk factor for CVD and 15% have no risk factors. Most of them (60%) report that they are under stress more than 50% of their working hours. 35% did report being under stress for less than 50% on their working hours and 5% do not feel under stress. When rated with the stress scale the highest number of patients have average level of occupational stress (40%), followed by those with low level of stress (30%) and accordingly (10%) without stress, (10%) with high levels of stress, and (10%) with extremely high levels of stress.

Conclusions: study did not prove that high levels of occupational stress as a risk factor for asymptomatic ischemic cerebrovascular disease.

Keywords: asymptomatic ischemic cerebrovascular disease, cerebrovascular disease, occupational stress, Stroke, risk factors

Survey about some aspects of health education of kindergartners' parents (second report)

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Introduction: Forming correct attitude to the health is a key element of healthy lifestyle.

Objective: The aim of this study was to investigate health education of kindergartners' parents.

Materials and methods: We interviewed the parents of 731 kindergartners aged 3 to 6 years in the city of Plovdiv. Participants completed a questionnaire.

Results: Most families included one (39.3%) or two (54.5%) children, and only 6.2%, three or more children. The majority (75.72%) of children had been breastfed during the first year of life and received all compulsory immunizations (99.45%). 85.50% of the parents considered the immunizations effective means of infectious disease prevention. 76.06% of the parents reported adequate health knowledge. 19.29% of the parents declared that they considered their health knowledge insufficient, and about 2% of them lacked health information. Statistically significant association between parents education level and their health knowledge and culture was found ($\chi^2 = 35.26$, $P < 0.001$).

Conclusion: We advocate for continuous health promotion in order to expand health culture and to improve health education of kindergartners' parents.

Keywords: health education, health habits, childhood, parents, family education

Interdisciplinary, multiculturalism, and work with the patient in a non-standard situation in the context of conducting didactic classes in the field of medical sciences and healthcare sciences in centers for medical simulation – project' results

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This project is part of the Key Action 2: Cooperation for innovation and the exchange of good practices KA 203: Strategic partnerships for higher education. The project has been prepared perfectly by the main organization – Polish team of Opole Medical School in collaboration with Medical University of Plovdiv, as partners and Czech Republic team. Duration 34 months. Period of duration, from 1.10.2019 to 31.07.2022. Planned activities: O1: Unification of therapeutic methodology procedure and development optimal interdisciplinary team communication methods. O2: Implementation and dissemination innovative solutions in the form of handbook. O3: Subject "Proceedings of the therapeutic team towards patients in difficult non-standard situations and towards culturally different patients" and syllabuses for the subject.

Results: The results, so far are in two main directions: 1. Intellectual activities; 2. Project management activities. The Bulgarian team has been handed over the needed documents in English.

Conclusion: We are happy and excited to work together with our international partners and we hope, that under the epidemiological conditions of COVID-19, we all will succeeded to fulfil our future activities. By preparing the materials for the textbook, we are happy to develop and work in the field of our intellectual and science interests. We have received a lot of positive feedbacks about the project from the governance of Medical University of Plovdiv.

Keywords: Partnerships, higher education, patient in a non-standard situation, medical and health sciences, Centers of Medical Simulation.

Contemporary strategies and technologies for coping with disordered eating attitudes and behaviors in adolescents

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Disordered eating attitudes and behaviors are significant bio-psycho-social diseases associated with disordered eating habits and body dissatisfaction. The widespread of the problem, as well as physiological, psychological, and social consequences of eating disorders, need to search for new methods and applications of modern technology for prevention, control, healthy lifestyle promotion, etc.

The article presents some of the most common contemporary strategies and technologies for coping with disordered eating attitudes and behaviors in adolescents.

Considering the importance of the problem, researchers are looking for effective approaches to solving it. Scientific studies have proven the positive impact of professional online consultations and specialized programs that provide a person-centered approach. The huge potential of mobile applications for building healthy eating habits in adolescence is well recognized. The results of studies prove that SMS control is more successful compared to traditional methods/supervision in the treatment of obese adolescents. Technology-Assisted Dietary Assessment (TADA) is a software application that identifies the type and the amount of food a person eats by image processing and the information could be used for the analysis of the entire population food consumption. Specially developed subliminal audio albums with affirmations can contribute quickly, easily, and effectively to cope with the problem through long-lasting changes in the adolescents thinking, emotions, and habits.

The application of a comprehensive approach and the elaboration of contemporary strategies are required to cope with the complexity of the disordered eating attitude and behaviors as well as with the risk factors for their occurrence.

Keywords: disordered eating attitudes and behaviors, contemporary technology, coping strategies, adolescents

Feeding of children aged 1 to 3 years old in conditions caused by corona virus infection pandemic (COVID-19)

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The epidemic of corona virus has changed many families' life from all over the world. Schools, kinder gardens, children's kitchens and social dining rooms have been closed. Those parents who have been using the services of children's kitchens had to prepare food for their children themselves. The aim of the current study is to determine to what level closing of kitchens affected the diet of children aged 1-3 years old. For the purposes of this study we have developed our own questionnaire with questions of choice and open answers. 169 customers of the children's kitchen service of "Zvezdichka", city of Plovdiv, including its affiliates "Patilantsi", "Vyara", "Treti mart" participated in the study. One third of the parents (36.68%) have been concerned about the closure of the children's kitchens. 80.47% of the participants in the x always appreciated the convenience of the kitchens. The closure of those kitchens has changed the model of feeding among 30.17% for the children using the service. However 22.48% of the parents could not provide the variety offered by the kitchens. Conclusions: Only one parent shared that, his child is consuming breast milk between the separate feedings. It is concerning that relatively high percentage of the participants' in the survey children in the age of 1-3 years are consuming the food that has been prepared for all the members of the family, such as barbecue, pizza, sandwiches and other food typical in Bulgarian families.

Keywords: children, feeding, kitchen

Occupational risk factors in the epidemiology of stroke

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Introduction: Strokes are a disease that has been documented even 3 thousand years in the past, and are still one of the leading reason for death or a prolonged or permanent disability in patients in many countries. There have been many studies about the main risk factors for stroke, but there is still insufficient data about the connection between occupational risk factors and strokes.

Aim: To study the role of occupational risk factors in the epidemiology of stroke. In the presented data we have analysed all of the patients of a work able age, diagnosed with a stroke, treated in Second Neurological clinic in "St. Marina" Varna for a period of 3 months.

Results: All of the patients (40 total – 60% men, 40% women), with a mean age of 54, were divided into two groups depending on the kind of job they have (mainly physical or mainly intellectual work) and the length of their work experience (10 or less years on the job or more than 10 years). The results showed that 80% of the patients with stroke had a job that was mainly physical. The patients with more than 10 years of work experience were 85.7%. The comorbidity of the patients was as follows-high blood pressure (100%), high cholesterol (92.5%), diabetes (17.5%), heart rhythm disorders(10%) and a interventricular septum defect (5%).

Conclusion: Occupational risk factors have a role to play in the epidemiology and pathogenesis of strokes.

Keywords: occupational risk factors, stroke

Radiation terrorism as public threat – are Bulgarian physicians prepared?

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Terrorist acts have occurred more frequently in recent years in various parts of the world. A nuclear and radiation accident is defined by the International Atomic Energy Agency (IAEA) as an event that has led to significant consequences to people and the environment. The biological effects of radioactive contamination are caused by external and internal radiation and are associated with immediate health hazards, as well as social and psychological effects. The question we ask ourselves in the present study is to what extent Bulgarian doctors are prepared theoretically and practically to deal with the consequences of such terrorist act. The study presents the evaluation of doctors of different specialties about their readiness to treat victims of radiation exposure, as well as the availability of medication for such treatment. The focus of the study is to emphasize the need to introduce an algorithm for action in case of a radiation incident that imposes serious public threat.

Keywords: terrorist act, radiation terrorism, readiness, algorithm for treatment and action

Study of physical activity and attitude to sports during free time among adolescents from different ethnic groups in the municipality of Plovdiv

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Introduction: Modern human science proves, that one of the most powerful means for preventing growing organism's diseases is the increment of physical, mental capacity, and active motor activity. The decrease in it is a spreading phenomenon, and adolescents are the most sensitive to insufficient motor activity.

Objective: To study and analyze the physical activity of adolescents (11-14 years old) from different ethnic groups in the Municipality of Plovdiv, as an indicator of good health.

Material and methods: In the research have been studied 185 children from three different ethnic groups. Have been developed, specifically for this purpose, an author's questionnaire for students, which contains open, closed, and mixed questions. The data has been analyzed by the SPSS software package.

Results: Of all respondents, 101 (56.6%) were boys and 84 (45.4%) were girls. There have been 96 Bulgarian children ($51.89\% \pm 3.67$), 30 Turkish children ($16.22\% \pm 2.71$), and 59 Gypsy children ($31.89\% \pm 3.43$), and there were no other ethnic groups in the survey. About 61 (32.97%) of Bulgarian children, 29 (15.67%) of Gypsy and 16 (8.65%) of the Turkish children, play sports out of school.

Conclusion: The results so far show a bigger interest in sports and more intense FA during the free time of Bulgarian children in comparison to students from other ethnic groups.

Keywords: sports, adolescents, ethnicity

Impact of the COVID-19 pandemic on blood donation in Varna district

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Maintaining the right amount of blood and blood components during a pandemic is essential, as blood transfusions are life-saving in many conditions. The past experience on health systems have shown that pandemics have a negative impact on the blood supply.

Aim: The aim is to investigate the impact of the COVID-19 pandemic on blood donation and demand for blood and blood components in the Regional blood center Varna and based on the results to develop an effective strategy for managing blood supply and blood demand and blood components during a pandemic.

Material and methods: For the period March – July 2020, a retrospective analysis of the data on the attendance of donors in the blood center was made and based on this an assessment was made of the impact of COVID-19 on blood donation and demand for blood and blood components. Data were processed using SPSS, using comparative and correlation analyzes.

Results: Following the announcement of the first cases of COVID-19 and the declaration of the state of emergency and the ensuing state of emergency, donor blood center attendance showed a decline of 15.4% over the same period last year, with results most pronounced in March, April and May (down 22.7%).

Conclusion: The COVID-19 pandemic has a negative impact on blood donation, which significantly complicates the provision of the necessary amounts of blood and blood components. This necessitates the creation of an effective strategy to deal with the effects of pandemics on blood donation and the supply of blood and blood components.

Keywords: blood donation, pandemic, shortage, management, strategy

Influence of the emergency situation with the COVID-19 pandemic on the activity of an institution for integrated health and social care "Home Care Center" at the Regional Council of the Bulgarian Red Cross – Varna

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The state of emergency caused by the COVID 19 pandemic has changed the functioning of public life around the planet. Some industries and tourism have been completely blocked, and education has been switched entirely to electronic platforms so that young people can complete the school year. Social activities are particularly risky, especially those helping the elderly, where mortality from coronavirus infection is extremely high. This paper presents the digital parameters of the changes in the activities of the Home Care Center at the Regional Council of the Bulgarian Red Cross – Varna in the conditions of the COVID-19 pandemic. A comparative analysis of comparable time periods in the previous three years from 2017 to 2019 is presented.

Keywords: epidemic situation, emergency situation, COVID 19 pandemic, modeling of bioterrorism, public health in bioterrorism

Research and development of questionnaires to study the attitudes of e-health users

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Background: The digital transformation in healthcare and the development of a unified digital health system require research of the attitudes and motivations of people as users of healthcare as well as health professionals as participants in e-Health. The usability and acceptance of health digital technologies are important for their efficiency and are essential aspects of eHealth.

Aim: The aim of the present study is the development of surveys examining the e-Health expectations and attitudes of health professionals and the public and their motivation for the use of digital health technologies.

Materials and methods: An extensive review of international studies has been made for the research. With reference to the actual situation in Bulgaria, it was necessary to adapt and reformulate most of the methods. After a systematic analysis a combination of methods was chosen, including Likert scale questions, Matrix questions, Multiple choice questions and additional fields for feedback. The questions are focused on the attitudes for use and benefit of the electronic health record and health mobile applications, and awareness, expectations and opinions toward e-Health implementation in Bulgaria.

Results: A pre-test of the questionnaires was conducted among the participants in a workshop of the NSP "Electronic Healthcare (e-Health)". Following the feedback comments received, the relevant changes were made.

Conclusions: The developed questionnaires are suitable for researching the attitudes and expectations of e-Health users. However, a special module for investigating the accepting of health digital technologies as a key component of e-Health is going to be developed.

Keywords: digital health, attitudes, expectations, users

The role of risk assessment in specific healthcare environment

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Introduction: Safety is one of the main criteria for the quality of medical care and is a priority in national and European health policy. Having a wide range of health activities, working in a specific environment, using a range of medical devices and medicines, and patient care requires an appropriate system for continuous risk assessment and risk control in healthcare organizations.

Purpose: The aim of this presentation is to review the role of risk assessment for quality assurance and safety of patients and personnel in healthcare organizations.

Materials and methods: A review and analysis of scientific publications, normative documents and work manuals has been performed using descriptive and comparative methods.

Discussion: The main principles and steps in the risk management process, and the factors influencing the probability and consequences of an adverse event were presented. The most frequently used methods and techniques for quantitative and qualitative risk assessment in healthcare were considered. The types of risks associated with specific medical activities were analyzed in order to create a system for assessment and control of hazards to reduce and prevent errors and injuries affecting both patients and professionals working in a specific environment.

Conclusion: The implementation of effective and proactive risk management in healthcare organizations contributes to their development and the provision of quality of care and patient safety, as well as a safety occupational environment for staff.

Keywords: risk assessment, safety, quality, healthcare

Eating behavior of people living in Stara Zagora region

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Introduction: Nutrition has an important role for man. It is not an ordinary physiological process. It depends on many factors such as gender, age, professional commitment, physical activity etc.

Purpose: To study the eating behavior related to the number, timing of meals, consumption of breakfast, hot food at lunch and dinner, depending on some basic socio-demographic characteristics of people living in Stara Zagora region.

Material and methods: An anonymous random survey of 550 people of different ages from Stara Zagora region, was conducted. The data was processed by mathematical and statistical methods (SPSS for Windows).

Results: The analysis of variants proves that men eat more times than women. On average, people with primary education eat the less per day. There is no statistically significant effect on both the place of residence and employment on the number of meals per day ($p = 0.77$). The ANOVA analysis showed a statistically significant effect of occupational employment on time ($p = 0.042$) and breakfast ($p = 0.0002$). Gender also affects breakfast time ($p = 0.000276$) and breakfast consumption ($p = 0.000327$). Hot food for dinner is consumed more than for lunch, 71.75% and 51.16%, which shows more attention to dinner. There is a trend among women's different feeding time and men having dinner later.

Conclusion: The study shows various aspects of eating behavior of people living in Stara Zagora region, arising from some socio-demographic factors. Future large-scale research is needed to gain an accurate picture of people's eating habits, health and lifestyle.

Keywords: nutrition, number of meals, eating behavior

Research on the microclimate in children

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Introduction: The microclimate is a combination of physical parameters of the internal environment in a room, affecting the heat exchange in the body. The main microclimatic indicators are temperature, humidity, air velocity.

Purpose: To study the indicators of the microclimate in children's institutions in Stara Zagora region.

Material and methods: The survey was conducted in all 11 municipalities in Stara Zagora region, covering 108 kindergartens and 18 nurseries. The analysis of the received data is in compliance with the requirements of Ordinance №26/18.11.2008. for the structure and activity of the nurseries and children's kitchens and the health requirements to them and Ordinance №3/05.02.2007 on the health requirements to the kindergartens.

Results: The analysis of the obtained data shows that on the territory of Stara Zagora district the humidity on the premises is not reported in 114 (90.48%) kindergartens, the air temperature-in 3 (2.38%). The speed of air movement, which is related to its exchange, is not measured in any of the studied objects. Regular ventilation is required to ensure a constant supply of fresh air in the rooms yet in 15.08% of kindergartens those requirements are not met.

Conclusion: The microclimatic parameters with fluctuations within the comfort conditions, regulated in the normative documents, cause stress on the thermoregulation of the child's organism, which has a negative impact on its health and self-esteem. Strict control and observance of the health requirements over the microclimate in the kindergartens are necessary, in order to prevent the diseases related to this environmental factor.

Keywords: microclimate, nurseries, kindergarten

Kinesitherapeutic treatment of osteochondrosis – presentation of a clinical case

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Introduction: Osteochondrosis, also called dysarthrosis, is a degenerative process that develops in the discus intervertebralis of the columna vertebralis. In most cases, the disease occurs due to a combination of several etiological factors. We present a 59-year-old patient diagnosed with osteochondrosis. Computed tomography objectifies L4-L5 disc protrusion. Initial osteoporosis has been identified.

Aim: To determine the effect of applied kinesitherapy in a patient with osteochondrosis. Functional examination: Increased thoracic kyphosis with the presence of upper cross syndrome was identified. A reduced tone of m. quadriceps femoris was established, as well as muscle innervation by n. fibularis communis of the left lower limb. Painless crepitations in the shoulder girdle, hips and spine was also observed. Hyperesthesia of the left leg was found on the L4 dermatome.

Results: The applied treatment from the position reduced the pain symptoms. Scapula mobilization improved the range of motion and scapular-humeral rhythm and reduced the risk of impingement syndrome. The strength of m. quadriceps femoris and fibular muscles were significantly increased, as a result of the

applied eccentric training. Gait parameters improved through cross training for m. gluteus maximus m. latissimus dorsi. This workout helped to improve lumbar stability and gait stability.

Conclusion: As a result of the performed kinesitherapy the functional condition of the patient has improved, the muscle imbalance has been ameliorated, together with the proprioception of the spine. Gait parameters developed positively, but pain symptoms in the left hip continued to persist.

Keywords: kinesitherapy, osteochondrosis, disc protrusion

Information exchange into hospital disaster resilience

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Introduction: The disparity between available and required means and capabilities for disaster medical support in case of imminent or ongoing disaster, imposes noticeable changes into routine prehospital and hospital care standard operating procedures. They are directly related to the nature and type of occurred changes in the medical situation. In order to ensure the hospital care system resilience to disasters, it is mandatory everyone of the medical staff to be capable for prompt medical information exchange.

The **objective** of this study is to analyze the hospital medical professionals in Plovdiv region readiness to participate in the information exchange as a prerequisite for hospitals disaster resilience.

Materials and methods: An anonymous survey was performed among 295 hospital professionals within Plovdiv Region between July and September 2019. Medical information exchange capabilities were explored. Alternative, non-parametric and correlation analysis were applied. A value of $p < 0.05$ is considered statistically significant.

Results: More than half of the respondents (56.6%, $n = 167$) have declared that they are not familiar with the system for notification of disasters in the hospital they are working in. Significantly higher is the percentage of respondents (83.4%, $n = 246$), who do not know how to communicate with the hospital disaster managerial team, as well as with the elements of the Unified Rescue System.

Conclusion: The results of the study highlight an unsatisfactory level of medical professionals readiness and capabilities to efficiently, fully participate in the exchange of information, which is a prerequisite for assuring the hospital disaster resilience.

Key words: hospital disaster resilience, medical information, information exchange, medical specialists

Study of movement qualities in preschool children – prerequisite for general physical stimulation

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Background: Exercise is a natural need and a major preventive measure to strengthen children's health. Insufficient physical activity adversely affects the normal development of the child's organism and healthy lifestyle.

Aim: The purpose is to establish the degree of development of the motor qualities of preschool children,

determining the general physical capacity to stimulate the potential of the child's body.

Material and methods: The study was conducted in Plovdiv kindergarten in 2019 of 26 children aged 5-6 years, of whom boys (46.2%) and girls (53.8%). The quantitative parameters of the physical qualities were studied through tests for diagnostics of the motor activity from the Program „The activity of the child in the kindergarten“ (Vitanova, 1994).

Results: Respondents achieved the same results in the study of the qualities „speed“ and „explosive force“ of the legs – „satisfactory“ assessment (42% – boys and 64% – girls). In the case of the „explosive force“ of the arms, shoulder girdle and back, in girls the assessment is „poor“, in boys „satisfactory“. The correlation between the values of speed and strength of the legs in boys is ($r = 0.58$); between speed and endurance in boys is ($r = 0.43$), in the girls is ($r = -0.19$). There is a tendency for uneven and non-complex development and disharmony of motor skills.

Conclusions: During the preschool age, children need an intense motor regime. It is necessary to develop motor skills and movement qualities to provide the needed level of physical capacity as a prerequisite for general physical stimulation of children's growth, strengthening the body, psyche and health.

Keywords: motor qualities, preschool age, stimulation

Influence of the sources of information on the parental attitudes for vaccination of children

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Introduction: High self-esteem for knowledge of vaccines is considered a promoter in the formation of a positive attitude to vaccination, and the sources of information – a determining factor in this process.

Objective: To study the parents' main sources of information about vaccines and their influence on the immunization process of the children.

Materials and methods: 1195 parents of children under 7 years old, were surveyed between 2015-2017, in the cities of Varna, Shumen, Sliven and Ruse.

Results: More than half of the surveyed parents declare insufficient knowledge about vaccines (53%), and 1 out of 5 has no knowledge at all. The relative share of respondents for whom GPs are the primary source of information, regardless of their education, age, ethnicity, and place of residence is 82.2%. Parents who trust their GP are less afraid and hesitant to vaccinate their child ($r = 0.09$; $p = 0.002$), so their children's immunization coverage is 92.4%. One-third of the respondents (37.5%) use the Internet as a main and/or additional source of knowledge about vaccines. Most often they are highly educated, 30-39 years old, ethnic Bulgarians. The children of these parents are more likely to have missed vaccines, or have not been vaccinated at all ($r = 0.13$; $p = 0.001$).

Conclusion: Low self-esteem for knowledge of vaccines affects the formation of a negative attitude towards vaccination. Measures are needed to increase parents' knowledge of the benefits of vaccines for individual and public health and to increase the amount of reliable information in their preferred media.

Keywords: vaccine, source of information, parents, vaccine hesitancy

Burnout syndrome among Bulgarian employees

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Burnout syndrome is a worldwide phenomenon. Due to globalization and the accelerated growth of technology, ever more employees are affected by it.

Aim: The aim of this study was to investigate the level of burnout among Bulgarian workers.

Material and methods: In this cross-sectional study, employees from all economic fields (n = 305) were enrolled. The data collection instrument was the web-based Bulgarian Version of the Boyko's Burnout Inventory, which contains 84 statements grouped in 12 symptoms and 3 phases and field of activity. Most were women (n = 229; 75.1%) with mean age of 38.9±10.8 years, received higher education (n = 230; 75.4%), married/in a stable union (n = 200; 65.5%), with children (n = 132; 43.3%). The mean duration of employment was 15.3±10.7 years. The majority (n = 196; 64.3%) were healthcare workers and teachers. Data collected were analysed using descriptive statistics, chi-square tests, The Mann-Whitney U and the Wilcoxon tests (SPSS; version 17.0).

Results: The results indicated a high level of emotional exhaustion at 83% (n = 263), a high level of resistance at 98.7% (n = 301) and a high level of strain at 92.1% (n = 281). The overall high level of burnout was found among 42.6% (n = 130) employees. The relative share of people with a high level of burnout was highest in the Trade and Tourism sector (n=9; 75%), lowest was in Production sector (n = 12; 26.7%)(p = 0.020). With respect to the demographic description of the sample, emotional exhaustion was significantly higher in women (n = 197; 86%) than in men (n = 56; 73.7%) (p = 0.013).

Conclusion: The prevalence of employees experienced burnout was high.

Keywords: burnout, employees

POSTER SESSION II**Projects with national/international funding****Chronic piromelatine treatment alleviates affective responses and abnormal hypothalamic-pituitary-adrenal axis activity in prenatally stressed male and female rats****Natasha Ivanova¹, Zlatina Nenchovska¹, Mihaela Shishmanova-Doseva², Katerina Georgieva³, Jana Tchekekarova¹**¹ Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia, Bulgaria² Department of Pharmacology and Drug Toxicology, Faculty of Pharmacy, Medical University of Plovdiv, Bulgaria³ Department of Physiology, Faculty of Medicine, Medical University of Plovdiv, Bulgaria

Adverse events during pregnancy can negatively affect offspring mental development, which leads to different abnormal responses in adult life. In order to assess the efficacy of piromelatine, a mixed melatonin 1/2 receptor agonist, serotonin 1A/1D receptor agonist, and serotonin 2B receptor antagonist, we applied a model of prenatal stress in male and female offspring rats. Adult prenatally stressed rats from both sexes showed comparable emotional disturbance associated with high levels of anxiety and depressive responses. Both males and females with a history of prenatal stress demonstrated impaired feedback inhibition of the hypothalamic-pituitary-adrenal axis and increased glucocorticoid receptors in the hippocampus compared to their intact controls. Oppose to females, prenatally stressed male rats showed increased expression of mineralocorticoid receptors in the hippocampus. Piromelatine (20 mg/kg, i.p., for 21 days from postnatal day 60) drug attenuated the high anxiety level indicated in the open field and the light-dark tests, and depressive behavior in the forced swimming test in a sex-dependent manner. This drug reversed to control level the increased plasma corticosterone 120 minutes after stress in both sexes. Simultaneously, it corrected to control level the alterations of the corticosteroid receptors induced by prenatal stress only in male offspring. These data provide evidence that piromelatine treatment can exert beneficial effects on impaired emotional responses and dysregulated hypothalamic-pituitary-adrenal axis in both sexes, but it is able to correct the changes of the hippocampal corticosteroid receptors, caused by the stress during pregnancy, only in male offspring.

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Keywords: prenatal stress, piromelatine, sex differences, behavior, hypothalamic-pituitary-adrenal axis corticosteroid receptors.

Endurance training exerts time-dependent modulation on depressive responses and circadian rhythms of corticosterone and BDNF in the rats with pinealectomy

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Pinealectomy can cause a disturbance in emotional status and circadian rhythms of the endocrine and metabolic functions in the body. Endurance training is considered a part of the complex therapy of dysfunctions driven by changes in circadian dynamics of many physiological indicators. In the present study, we aimed to study the effect of endurance training on depressive behavior induced by pinealectomy in rat. We tested the hypothesis that endurance training can have a beneficial impact on depressive behavior induced by pinealectomy in rat via correction of desynchronized circadian rhythms of corticosterone secretion in plasma and brain-derived neurotrophic factor (BDNF) in the hippocampus. The continuous exercise program attenuated depressive responses characterized by the disrupted diurnal rhythm of home-cage motor activity, anhedonia in the sucrose preference test, decreased grooming in the splash test, and despair-like behavior in the forced swimming test of rats with pinealectomy to values resembling those of sham-treated controls. Parallel to the observed positive effect on the emotional status, exercise training diminished total plasma corticosterone levels and corrected its flattened pattern. While the melatonin deficiency did not affect the fluctuations of the BDNF levels, the exercise program induced a considerable and time-dependent increase in its level. These findings suggest that the antidepressant-like effect of endurance training might be mediated via correction of the disturbed circadian rhythm of corticosterone release and enhancement of hippocampal BDNF levels in rats with pinealectomy. Therefore, this alternative mode might have a potential therapeutic application in a subpopulation of people characterized by a melatonin deficiency.

Acknowledgements: This work was supported by the National Science Fund of Bulgaria (research grant No DN 03/10).

Keywords: pinealectomy, endurance training, depression, circadian rhythms, corticosterone, BDNF

Effect of endurance training on diurnal rhythms of superoxide dismutase activity, glutathione and lipid peroxidation in plasma of pinealectomized rats

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Melatonin deficit is characterized by disturbed circadian rhythms of many physiological and biochemical parameters including markers of oxidative stress. Moderate endurance training exerts protection against oxida-

tive stress. In the present study, we aimed to explore the impact of endurance treadmill training on disturbed rhythmic fluctuations of some markers of oxidative stress in pinealectomized rats. Animals were divided into four groups: sham-operated sedentary rats (sham-sed), a sham group with exercise (sham-ex), pinealectomized sedentary rats (pined) and pin rats with exercise (pin-ex). Animals were sacrificed by decapitation at 4-h intervals for biochemical analysis of plasma melatonin and markers of oxidative stress. The activity of superoxide dismutase (SOD) and the levels of glutathione (GSH) and lipid peroxidation demonstrated diurnal variations in the sham-sed group. The peak values of SOD were detected during the dark period that coincided with the peak plasma levels of melatonin in the sham-sed rats. The malondialdehyde (MDA) levels also showed a tendency to a progressive raise during the dark period. Pinealectomy was characterized by a remarkable melatonin deficit in plasma of sedentary rats, compromised fluctuations with decreased SOD activity and increased lipid peroxidation. While endurance training was unable to restore the melatonin deficit, it partly prevented the oxidative stress at selected time points in the pinealectomised rats. Our findings indicate the important role of endurance training against oxidative stress both in physiological conditions and melatonin deficit.

Acknowledgements: This work was supported by the National Science Fund of Bulgaria (research grant # № DN 03/10).

Keywords: Melatonin deficit, Endurance training, Diurnal rhythms, SOD, GSH, MDA.

Agomelatine treatment corrects impaired sleep-wake cycle and sleep architecture and increases MT1 receptor as well as BDNF expression in the hippocampus during the subjective light phase of rats exposed to chronic constant light

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The antidepressant agomelatine has a chronotropic activity. In the present study, we report that rats exposed to chronic light exhibit disturbed home-cage locomotor activity and sleep/wake cycle with decrease in NREM sleep and delta power and increased expression of REM sleep and theta power. Both, the number of episodes and duration of the wake episodes were decreased during the subjective dark period in CCL-treated group. No change in the circadian rhythm of MT1 and MT2 receptor expression in the hippocampus and FC was detected in CCL regime. However, a decrease of BDNF levels in the hippocampus decreased during the subjective light phase was shown. Agomelatine exerted beneficial effect on disturbed diurnal rhythm of motor activity, sleep/wake cycle, and sleep architecture, which effect might be mediated by the MT1 receptor and BDNF in the hippocampus which expression was increased at 10:00 in CCL rats. These findings suggest that the antidepressant agomelatine has chronotropic effect and can correct motor activity and sleep/wake cycle in a CCL model.

Acknowledgements: This work was supported by the National Science Fund of Bulgaria (research grant No DN 03/10 and research grant No DN 12/6).

Keywords: chronic constant light, agomelatine, motor activity, sleep/wake cycle, MT receptors, BDNF

Technology in rehabilitation (TechReh)

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The main objective of the TechReh project was to define a learning environment to access new competences related to the rehabilitation activities and jobs. These new competences referred in particular to the use of advanced ICT solutions and new technologies in rehabilitation in order to optimize the healthcare organizations network and to make rehabilitation services accessible for all that need them.

Partners in the project were technical and medical institutions in Uzbekistan and EU partners – Medical university of Plovdiv, Vilnius university, University of Sannio, Sorbonne Université, European Society of Physical and Rehabilitation Medicine, PLUX – Wireless Biosignals.

The specific objectives of TechReh were:

- 1) identification of technological needs for rehabilitation in Uzbekistan, and based on the knowledge of EU partners in the field to define how EU experiences, policies, best practices could improve the current situation;
- 2) Modernisation of the existing Master programmes in Medical Rehabilitation by elaborating a module on new technologies in rehabilitation.
- 3) Development of a two-year Master programme for Computer Systems for Medicine for Tashkent University of Information Technologies – curriculum, educational materials, internship for teaching the teachers/trainers.
- 4) Deploying of short courses for medical and technical professionals on new technologies in rehabilitation.
- 5) Setup of offices for Cooperation and Dissemination of Technology in Rehabilitation (OCDTRs) in order to consolidate the technology adoption and development in rehabilitation fields;
- 6) Setup of an ICT platform for e-learning.

Acknowledgements: Project Number: 561621-EPP-1-2015-1-IT-EPPKA2-CBHE-JP

KA2 – Cooperation for innovation and the exchange of good Practices Capacity Building in Higher Education

INTRA-UNIVERSITY PROJECT SESSION**Intra-university projects 2016 - 2018****Markers of inflammation related to the nature and instability of plaques in carotid atherosclerosis**

CONTRACT: Project № NO-04/2016

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RESEARCH AREA: Biomedical

AIM: To investigate the importance of serum biomarkers (Hs-CRP, ICAM-1, VCAM-1, fibrinogen) associated with vascular dysfunction and atherosclerosis processes and to determine their relation with carotid atherosclerosis and ischemic stroke.**MATERIALS AND METHODS:** The study enrolled 153 patients divided into two main groups - patients with acute ischemic stroke and patients with vascular risk factors, but with no history of stroke. Blood samples for hs-CRP, sICAM-1, sVCAM-1 and fibrinogen were taken from all patients.**RESULTS:** The presence of carotid atherosclerosis is associated with significantly higher levels of hs-CRP and fibrinogen. Our results show no variation in the levels of hs-CRP, VCAM-1, ICAM-1, and fibrinogen associated with atherosclerotic plaque type. Based on hs-CRP, stroke patients can be diagnosed with good precision at an optimal hs-CRP value of > 4.29 mg/l. The levels of hs-CRP and VCAM-1 show a positive linear relation with neurological deficits in stroke patients. Patients with VCAM-1 levels >740 ng/ml have a 3.45-fold greater risk of ischemic lesions. The mean fibrinogen level is significantly higher in patients with ischemic stroke. Increased levels of hs-CRP, fibrinogen and VCAM-1 and the presence of atrial fibrillation are predictors of a real risk of ischemic stroke.**CONCLUSION:** Increased serum levels of Hs-CRP and fibrinogen are associated with the presence of carotid atherosclerosis. Hs-CRP, fibrinogen, and VCAM-1 are reliable serum markers characterizing inflammatory processes in acute stages of ischemic stroke.**PRACTICAL APPLICATIONS:** Use of serum markers that characterized carotid atherosclerosis and determined the risk of ischemic stroke.**SCIENTIFIC PUBLICATIONS:**

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2. Peycheva M, Zahariev Z, Deneva T. Serum markers for endothelial dysfunction in a carotid atherosclerosis pilot study. *Proceedings of the National Scientific Conference "15 Years of Pharmacy at the Medical University-Plovdiv, 2018;* 188–90.
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A contemporary look at familial hypercholesterolemia - one of the most common genetic diseases and at the same time the most undiagnosed and untreated in the world at the moment - a pilot study in Plovdiv and the region

CONTRACT: Project N° NO -14/2016

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RESEARCH AREA: therapeutics

AIM: To conduct a pilot study of familial hypercholesterolemia (FH) in southern Bulgaria with the aim of primary and secondary prevention of affected families.

MATERIALS AND METHODS: 100 physicians from southern Bulgaria were randomly selected. Total number -185 000 patients.

RESULTS: Out of all patients, 550 meet the Dutch criteria for clinical diagnosis of FH. Of these, 100 have confirmed genetic analysis. Detected frequency - 1:113 per 100 000. The average age of detection of FH is very late - 57 ± 14 years. All patients with more than 5 points by Dutch criteria were genetically screened. The strong correlation between clinical and genetic diagnosis indicates that Dutch criteria are applicable to our population. Two new world-class LDL receptor mutations have been detected. Genetic analysis and family screening revealed 30 affected families. Genetic analysis was performed on five children (9, 11, and 12 years old) and among the few in the world started taking a monoclonal antibody treatment. High-informative biomarkers of FH-lipoprotein(a), hsCRP and Vit D3 were investigated. An analysis of the data on antilipidemic therapy - 62% of these patients were treated. A very important result for practice are the factors which affect statin intolerance - age, weight, glomerular filtration rate, hypovit D3, high dose of statin depends. The project is the first to work in collaboration with the Pediatric clinic and Genetic diseases in Plovdiv .

CONCLUSION: The established high incidence of FH in southern Bulgaria justifies the active detection and treatment of infants with new therapeutic options, equalizing risk with patients without FH.

PRACTICAL APPLICATION: The data are entered into the general data in Bulgaria for the establishment of a disease registry.

SCIENTIFIC PUBLICATIONS:

PUBLICATIONS IN REFERENCE LETTERS:

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2. Vladimirova-Kitova L, Kitov S. Biomarkers of endothelial function. *Science Endocrinology* 2016; 3:89–97.
3. Borisov B, Georgiev B, Vladimirova-Kitova L. Screening, diagnosis and therapeutic approaches to patients with familial hypercholesterolemia. *Science Cardiology* 2017; 1(101):39–48.
4. Vladimirova-Kitova L, Asenova R, Dobрева B, et al. Screening of patients with clinical diagnosis of family hypercholesterolemia in Plovdiv and the region - initial data. *GP news* 2018; 6(216):22–13.

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1. Vladimirova-Kitova L, Kitov S, Gencheva, D et al. New recommendations for the use of non-statin therapy for the treatment of dyslipidemias. Facts, contradictions, debates in the diagnosis and treatment of heart and vascular diseases. 2016, ISBN 978-612-7063-21 9, 345–358.
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PARTICIPATIONS IN THE COLLECTION

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2. Vladimirova-Kitova L, Kitov S. From Unsuccessful to Successful Vascular Aging (Part 2). Family Hypercholesterolemia - Scientific Works of the Union of Scientists, Plovdiv, Series D, Medicine, Pharmacy and Dental Medicine 2019, Vol XXIII, 2019, ISSN 1311-9427 (Print), ISSN 2534-9392, 4–11.

Validation of innovative for Bulgaria ICP-MS method for multielement analysis and reference values for copper, zinc, selenium and magnesium in serum

CONTRACT: Project № NO-1/2017

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RESEARCH AREA: Biomedical

AIM: To validate ICP-MS method for multielement analysis, to determine reference limits for copper, zinc, selenium, and magnesium in serum in subjects from a Bulgarian population and to verify the applicability of the method by patients with endocrine diseases.

MATERIALS AND METHODS: 120 clinically healthy subjects aged 18-70 years, 30 patients with hyperthyroidism and 30 patients with hypothyroidism were studied. The development of the method and the multielement analysis were performed using ICP-MS analyzer (ICapQ, Thermo Fisher Scientific, Germany). Comparative analysis of the studied elements was performed by flame and electrothermal atomic absorption spectrophotometry.

RESULTS: A method for acid mineralization of serum samples (0.3 mL sample + 1.5 mL HNO₃ and 1.5 mL water, MW treatment for 25 min at 190°C) was developed. The method of calibration was optimized by matrix-matched preparation of the calibration solutions in 15% v/v HNO₃, with 130 mg/L sodium content. The method is validated and compared with AAS methods for monoelemental analysis. After determination of the reference limits for copper, zinc, selenium and magnesium, the method was tested in patients with thyroid pathology.

CONCLUSION: The highly sensitive, highly specific ICP-MS multielement method for the determination of copper, zinc, selenium and magnesium in serum has been successfully validated and proposed for scientific and clinical purposes.

PRACTICAL APPLICATIONS: The method can be used for investigation of the pathogenetic mechanisms of various pathological conditions associated with deficiency of the studied elements, and suitable for personalization of the therapeutic approach to the patient in need of supplementation.

SCIENTIFIC PUBLICATIONS:

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2. Davcheva D, Kirova G, Tsvetkova T, et al. Contamination control in quantitative analysis of trace elements in human serum. *Proceedings of the National Scientific Conference "15 Years of Pharmacy at the Medical University - Plovdiv", SPA Hotel "Orpheus", Devin, 01 - 03 June, 2018, 165–8, ISBN 978-619-237-013-8 (CD); ISBN 978-619-237-014-5 (online).*

Study of bone mineral density and markers of bone metabolism in adult patients with thalassemia major and intermedia in Bulgaria

CONTRACT: Project N° NO-02/2017

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RESEARCH AREA: Biomedical

Aim: To characterize bone mineral density (BMD) and markers of bone metabolism in adult Bulgarian patients with transfusion-dependent beta thalassemia (TDBT) and to evaluate their relationships with the disease-specific parameters.

Material and methods: 64 TDBT patients (30 M: 30 F) and 30 healthy controls (15 M: 15 F) were tested for BMD parameters via dual-energy X-ray absorptiometry. ELISA was used for measurement of sRANKL, B-Ctx, OPG, OCN, and sclerostin in serum. SPSS (v. 26) was used for data analysis, with an accepted level of statistical significance $p < 0.05$.

Results: The prevalence of OOS in males with TDBT was as follows: osteoporosis 53.1%, osteopenia 40.6%, and normal BMD 6.2%. The distribution of OOS in TDBT female was: osteoporosis 56.7%, osteopenia 36.7%, and normal BMD 6.6%. The patients with TDBT showed significantly lower BMD compared to controls. Significant linear correlations of BMD parameters were found with pre-transfusion hemoglobin, peripheral erythroblast count, liver and cardiac iron overload. Splenectomized patients had significantly lower BMD than nonsplenectomized and significantly higher levels of sclerostin. Serum sclerostin levels were found to be higher in patients with past fragility fracture event. TDBT patients showed significantly higher serum levels of sRANKL, B-Ctx, and OPG compared to the HC, and significantly lower levels of OCN.

Conclusions: The severity of the chronic anemic state, ineffective hematopoiesis, the severity of iron overload and splenectomy significantly contribute to the development of OOS in adult TDBT patients. Sclerostin is a prognostic marker for severe osteoporosis.

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In vitro study for fracture resistance of 3-unit all-ceramic bridge CAD/CAM restorations

CONTRACT: Project № NO-03 / 2017

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RESEARCH AREA: Medico-Biological

AIM: The aim of the Project is an in vitro comparison of the strength needed for fracturing of 3-unit CAD / CAM bridge restorations, fabricated in full contour of ceramics based on ZrO₂, with different distal retainers – a full crown and an endocrown, in the distal area of the dentition.

MATERIALS AND METHODS: With a CAD/CAM software a 3D model was created and 3D printed 20 times. The bridge restoration was designed digitally, milled, sintered and cemented on a model also 20 times. The loading test till fracturing was made in Zwick apparatus in Austria.

RESULTS: The results were evaluated statistically. The mean and standard deviation values were 1099.66±386.98 for all tested specimens. The t-test revealed no statistically significant difference in the maximum force required to fracture the test specimens, depending on the preparation design of the distal abutment tooth [t = 1.8088 (17.39), p=0.087; P>0.05]. The area of fracture was systematized in order to assess if any trends occurred during the tests. Nineteen of the FPDs fractured in the distal connector zone and one in the mesial connector area.

CONCLUSION: Within the limitations of this study it can be concluded that both tested preparation designs show similar results regarding the load required to fracture. The weakest area of an all-ceramic 3-unit FPD is its distal connector.

PRACTICAL APPLICATIONS: This results give an option for design of bridge restorations with reduced distal connector area, but with optimal strength.

SCIENTIFIC PUBLICATIONS:

FULL TEXT ARTICLES OF THE PROJECT IN BULGARIA AND ABROAD:

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2. Vlahova A, Hadzhigaev V, Tomova Z, et al. CAD/CAM screw retained implant supported all-ceramic crown. A clinical case. *Scientific works of the Union of Scientists in Bulgaria – Plovdiv. G Series. Medicine, pharmacy and dental medicine. Iss. XXII. ISSN 1311-9427 (Print), ISSN 2534-9392 (On-line), 2018, p. 213–5.*

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PRESENTATIONS OF THE PROJECT IN BULGARIA AND ABROAD:

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Investigation of relationship between some antioxidant enzymes activity and insulin resistance in chronic liver disease patients

CONTRACT: Project N° HO-04/2017

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RESEARCH AREA: Biomedical

AIM: To investigate the influence of oxidative stress on chronic liver disease on the basis of relationship analysis between malondialdehyde, superoxide dismutase and glutathione peroxidase and metabolic and biochemical disturbances in patients with compensated and decompensated disease.

MATERIALS AND METHODS: The present investigation included 26 patients with chronic hepatitis, 29 patients with liver cirrhosis, and 29 healthy controls. Serum concentrations of malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase-1 (GPx-1), fasting glucose, insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were measured.

RESULTS: Compared to the controls, the hepatitis patients had significantly higher MDA mean level and lower SOD. GPx-1 levels in the hepatitis patients were similar to that in the controls. The cirrhosis patients had significantly higher MDA and GPx-1 and lower SOD as compared to the controls. Of the two patient groups, the

cirrhosis group had a higher MDA level than the hepatitis group. There were no correlations between MDA, SOD, GPx and metabolic parameters in hepatitis group. In the cirrhosis group SOD correlated negatively with triglycerides. In the control group MDA correlated negatively with SOD and GPx-1, SOD correlated positively with HDL-cholesterol and negatively with glucose.

CONCLUSION: Analyzing the relationship between oxidant and antioxidant parameters with insulin resistance in patients with chronic liver disease it is important to clarify the role of oxidative stress in liver pathology.

PRACTICAL APPLICATIONS: To determine an individual therapeutic approach in patients with chronic liver disease.

SCIENTIFIC PUBLICATIONS:

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Investigation of the oral health of children with obesity

CONTRACT: Project № NO-05/2017

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RESEARCH AREA: Dental Medicine

AIM: To assess the oral health of overweight and obese children

MATERIALS AND METHODS: A cross-sectional study was conducted among 1826 schoolchildren aged 6-11 years from Plovdiv.

RESULTS: The participants were divided into four categories by their BMI, where 66% was normal weight, 5% - underweight, 18% - overweight, and 11% was obese. The boys were more affected by obesity than girls with statistically significant difference ($\chi^2=8.245$; $p<0.05$). In the primary dentition it was found a reverse statistically significant relationship between BMI and dft ($\gamma^2(3)=10.12$, $p<0.05$), while in the permanent dentition the association between BMI and DMFT was positive ($\gamma^2(3)=10.12$, $p<0.05$). The distribution of dental erosion increased with the age, but not in relation with BMI ($\chi^2=6.396$, $p>0.05$). There were no significant differences in the quality of oral hygiene among children with different BMI, and gingivitis was associated with higher BMI only in the girls group ($\chi^2=3.73$, $p<0.05$). Children with increased BMI have accelerated permanent tooth eruption, and those with overweight presented with 1.1 more erupted teeth on average than their normal-weight counterparts.

CONCLUSION: Childhood obesity affects the oral health and is associated with increased risk for caries in the permanent dentition, gingivitis and accelerated tooth eruption.

PRACTICAL APPLICATIONS: Specific preventive programs may be applied, aiming to prevent the main risk factors for oral health associated with obesity.

SCIENTIFIC PUBLICATIONS:

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Aspiration biopsy-diagnostic standard for M. Hirschsprung in childhood

CONTRACT: Project № NO-06/2017

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RESEARCH AREA: Biomedical

AIM: Introduction to the practice of aspiration colon biopsy as a screening method in children with chronic constipation.

MATERIAL AND METHODS: One patient with ileus and lack of passage was examined. The baby was operated on as a newborn on the occasion of ileus and peritonitis. An ileostomy was removed. Hirschsprung's disease was suspected due to a revision of the abdomen and colon. The baby was premature, born prematurely, with a severe distress syndrome. Successfully treated, ileus and peritonitis were overcome. At 3 months of age, a rectal aspiration biopsy was performed and the histological result revealed a lack of nerve ganglia and Hirschsprung's disease. Subsequently, a correction of the ileostomy of ostensible evagination was required and four open colon biopsies were taken. The results are available, but in insufficient atypical nerve ganglia, with no nerve endings.

RESULTS: Patient with ileus and peritonitis in the neonate who underwent colon aspiration biopsy and Hirschsprung's disease was found. The result was confirmed with an open biopsy of the colon.

CONCLUSION: An aspiration biopsy is a quick, easy-to-perform, and sparing method for detecting the presence of nerve ganglia in the colon wall, which is a way of diagnosing Hirschsprung's disease.

PRACTICAL APPLICATIONS: Aspiration biopsy is a screening method in children with chronic constipation to diagnose Hirschsprung's disease.

Fetal Morphology. Fetal Brain Development. Physiology and pathology of the nervous system

CONTRACT: Project № NO-07/2017

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RESEARCH AREA: Biomedical

AIM: Using functional magnetic resonance tomography (fMRI) on pregnant women to evaluate fetal development by examining fetal brain structures, skull and internal organs.

RESULTS: 18 Pregnant women (14 of Bulgarian, 4 of Romany origin) were examined using fMRI after the 22nd gestational week, with suspected fetal birth defects found on ultrasonography. For 10 of the women (55.6%) this was their first pregnancy. The neuroimaging showed 6 neural-tube defects in the fetuses: anencephaly (n=1), encephalocele (n=1), spina bifida (n=2), craniorachischisis (n=2). Other defects found: hydrocephalus (n=3), Dandy walker malformation (n=3), agenesis of the corpus callosum (n=2), vacterl association (n=1), holoprosencephaly (n=1), syrenomelia (n=1), placenta previa (n=1). 90% of the sonographic diagnoses were confirmed using fMRI. In 14 of the pregnant women, abortions were performed on medical basis. In four (28.6%), fetal autopsy did not confirm the neuroimaging results, however it reinforced the diagnosis. The baby with the placenta previa was successfully delivered via C-section. The pregnancies with hydrocephalus were carried till term.

CONCLUSION: Despite the small size of the study group, the results support the use of fMRI in suspected fetal central nervous system pathology detected using prenatal ultrasonography. Confirming additional malformations helps parents make a definitive decision on the pregnancy's outcome, the results form an important stage in the multidisciplinary diagnosis of congenital abnormalities such as neural tube defects, chromosomal, cardiac abnormalities and rare syndromes.

PRACTICAL APPLICATION: The results obtained are of applied and theoretical importance as it may be helpful in prenatal diagnosis, embryology, and embryonic organogenesis.

SCIENTIFIC PUBLICATIONS

FULL TEXT PUBLICATIONS ONLY:

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2. Tenev A, Milkov D, Stoilov B, et al. Fetal functional magnetic resonance tomography and its role in the precise diagnosis of congenital anomalies. Collection of Scientific Communications from Competition Session 2018. Science and Youth 2018: 120.

Development and effect assessment of a method based on serious games for early diagnosis and therapy in adults with cognitive impairments

CONTRACT: Project № NO-08/2017

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RESEARCH AREA: Public health

AIM: To investigate the effect of a web-based cognitive training program in adults older than 60 years of age.

RESULTS: After a baseline cognitive assessment, 31 participants are randomly assigned to one of two groups: experimental conducting computerized cognitive training (CCT group, N=16) and control (N=15), in which participants did not use the web-based platform for cognitive stimulation. The effect was assessed by comparing outcome measures in pre- and post-tests of the neuropsychological battery CERAD and the computerized cognitive assessment battery of the web-based platform CogniFit™, before and after the 8-week training program. The initial outcome measures showed that the training group, compared to control group, significantly improved in working memory as well as in following cognitive domains: auditory perception, contextual memory, focused attention, inhibition, naming, processing speed, recognition, response time, visual perception, visual scanning (Cohen's *d* effect size ranged from 0.82 to 2.08). Based on the analysis of individual assessments, a clinically significant change to improvement in overall cognitive result and in inhibition were observed in 12.5% and 38% of people respectively. These results are supported by the observed outcomes in CERAD verbal fluency subtest, where a statistically significant improvement was found in the CCT group compared to the control group.

CONCLUSION: Computerized cognitive training has shown encouraging initial results as a method for improving cognitive functioning and preventing cognitive decline in the elderly.

PRACTICAL APPLICATIONS: A conceptual model for computerized cognitive training has been developed that integrates theoretical concepts from cognitive and computer sciences and describes an interdisciplinary approach for conducting and analyzing its effectiveness.

SCIENTIFIC PUBLICATIONS:

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2. doi: <http://dx.doi.org/10.12955/cbup.v5.1066>
3. Yaneva A, Dimcheva T, Kilova K, et al. Web-based platforms for cognitive training in adults, Management & Education/Upravlenie i Obrazovanie. 2019; 15(5): 19-24.

T315I mutation - in patients with chronic myeloid leukemia, Ph(+). Opportunity for personalized targeted therapy

CONTRACT: Project № NO-10/2017

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RESEARCH AREA: Biomedical

AIM: Establishment of the T315I mutation at the earliest possible stage in failure of treatment with tyrosine kinase inhibitors in patients with chronic myeloid leukemia Ph + as a criterion for personalized prognosis of relapse-free survival.

MATERIAL AND METHODS: Detection of T315I in the ABL gene from genomic DNA by performing allelic discrimination by highly sensitive and specific RT PCR.

RESULTS: 80 patients were allele-specific real-time PCR assayed for the detection of the T315I mutation by administering the qBiomarker Somatic Mutation PCR Assay. The analysis showed the presence of the mutation in two patients. Despite the low frequency of detection of this mutation (shown by other authors (3-5%)), it is critically important for clinical practice. The T315I mutation is associated with absolute resistance to the routinely used TKIs (tyrosine kinase inhibitors) - imatinib, dasanitib, nilotinib and bosutinib and is sensitive to

ponatinib. The implementation of the project enabled the monitoring of patients with chronic myeloid leukemia during therapy and led to the early detection of a T315I mutation (in two patients) leading to tyrosine resistance kinase inhibitors (1st and 2nd generation).

CONCLUSION: Screening for the T315I mutation is recommended for all CML patients.

PRACTICAL APPLICATIONS: Mutational analysis (the clinical minimum is screening for the T315I mutation) is mandatory, in each case of CML failing with TKI treatment, as well as at any point in treatment in the absence of response or loss of therapeutic response, judged by standards for monitoring therapeutic response in patients with CML, PH +.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Linev AJ, Ivanov HJ, Zhelyazkov IG, et al. Mutations associated with imatinib mesylate resistance - review. *Folia Med (Plovdiv)* 2019; 60(4): 617–23, ISSN: 1314-2143.
2. Linev AJ, Ivanov HJ, Zhelyazkov IG, et al. Case report of two mutations in BCR-ABL kinase domain in a patient with chronic myeloid leukemia resistant to first and second generation tyrosine kinase inhibitors. National Scientific Conference "15 years of pharmacy in Medical University, Plovdiv 01-03.07.2018. ISBN 978-619-237-014-5
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Development of a web-based platform for recording and evaluating the level of hospital patient safety culture and conducting a representative national study

CONTRACT: Project № NO-11/2017

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RESEARCH AREA: Public health

AIM: To develop a web-based platform in order to record and assess the level of patient safety culture in hospital healthcare settings and to conduct a representative nationwide survey.

MATERIALS AND METHODS: A national web-based survey was performed among hospital healthcare professionals. The questionnaire for assessment of Hospital Survey on Patient Safety Culture (HSOPSC) was developed by the Agency for Healthcare Research and Quality, USA and includes 42 questions, organized in 12 domains. To the Bulgarian version of B-HSOPSC a question was added, allowing hospital staff to report, on a voluntary basis and adhering to confidentiality rules, cases of medical errors and adverse events.

RESULTS: A conceptual frame and updated term definitions are proposed, reflecting the healthcare system and cultural specifics in Bulgaria. Linguistic validation and cultural adaptation of the B-HSOPSC was performed. It demonstrated acceptable level of psychometric properties, which gave us the grounds to develop a web based platform (<https://rsps.bg>), applicable for the Bulgarian hospital staff. Among, the 545 hospital health professionals, positive assessments of patient safety culture were prevalent, regardless of a number of

exceptions in dimensions „Staffing“ and „Non-punitive response to error“ of the survey.

CONCLUSIONS: For the first time in Bulgaria, with the aid of a web based platform to report adverse events and errors in medical practice, the level of hospital patient safety was measured.

PRACTICAL APPLICATIONS: The web-based platform, is accessible and feasible to all hospital staff. It could be used as a basis for implementation of new policies, aimed at development of positive patient safety culture and national quality standards in this area.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

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2. Dimova R, Stoyanova R, Doykov I. Mixed-methods study of reported clinical cases of undesirable events, medical errors, and near misses in health care. J Eval Clin Pract 2018;1–6. (IF=1.483).
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Study on chemical composition, antioxidant and antimicrobial activities of extracts of *Scutellaria altissima*

CONTRACT: Project № NO-01/2018

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RESEARCH AREA: Biomedical

AIM: To study the flavonoid content, antioxidant and antimicrobial activities of extracts of *Scutellaria altissima*.

RESULTS: An HPLC method has been developed and validated to determine and applied to compare the quantitative flavonoid composition of extracts of *Scutellaria altissima* from different geographical areas, as well as those from other species of *Scutellaria*, distributed in Bulgaria. Spectrophotometric determination of the amounts of total polyphenols and flavonoids was performed, as well as liquid chromatographic determination of organic acids and carbohydrates in the plant biomass of the studied *Scutellaria* species. The antioxidant activity of these extracts was determined by three methods - ORAC, HORAC and electrochemical.

The antimicrobial effect of aqueous extracts of root and aerial part of *Scutellaria altissima* against *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mitis* and *Candida albicans* was studied. This has only been shown against *Streptococcus mitis*.

CONCLUSION: The studied plants of the genus *Scutellaria*, growing in Bulgaria, contain the characteristic baikalin and scutellarin in different proportions depending on its species and habitat. The content of primary metabolites in *Scutellaria altissima*, *Scutellaria albida* and *Scutellaria galericulata* was analyzed for the first time

PRACTICAL APPLICATIONS: The developed HPLC method for analysis of flavonoids can be used to establish the authenticity of *Scutellaria* species, to control the quality of the raw material or a finished product. The results can serve as a basis for future biomedical research on the properties of extracts of *Scutellaria altissima* for a reasoned creation of a phytopreparation with antimicrobial action.

SCIENTIFIC PUBLICATIONS (FULL TEXT PAPERS ONLY):

FULL TEXT PAPERS ONLY

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2. Georgieva Y, Katsarova M, Gercheva K, et al. HPLC analysis of flavonoids from *Scutellaria altissima*. Bulgarian Chemical Communications 2019; (51, Special Issue D):119-123

Antibacterial activity of physically and chemically modified aluminum samples

CONTRACT: Project № NO 03/2018

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RESEARCH AREA: Biomedical

AIM: To study the antimicrobial activity of new metal biomaterials, developed on the basis of modified aluminum and their application in medical practice.

MATERIAL AND METHODS: Forty-four samples of anode films formed on the surface of aluminum alloy were investigated. A new method for porous coatings in sulfuric acid was developed. Silver particles are chemically embedded in the pores. The study was performed in two steps: formation of porous oxide structures by anodizing the technical alloy and chemical deposition of silver using the modified method of Tollens. A new methodology for analysis of silver was created by liquid-liquid extraction in the systems BTC, TTC and SCH. Tests for antimicrobial activity were performed using *E. coli*, *S. aureus* and *C. albicans* reference strains.

RESULTS: Eleven experiments with different concentrations of microorganisms were performed. Samples of aluminum alloy were placed in test-tubes with varying concentrations of the tested microorganism. Minimum concentration of microorganisms suppressed by the examined alloys were surveyed. The optical density was measured by ELISA-reader. No antimicrobial activity was reported for any of the samples in the study.

CONCLUSION: The lack of effect may be due to: high concentrations of the microorganisms in the test suspensions; samples were not sufficiently saturated with silver; electrochemical relationship of silver to the

substrate was very strong and ions were not released in sufficient quantity in the solution.

PRACTICAL APPLICATIONS: The topic of the project is new, which determines a more complex organization of experimental activities, creation of innovative methodologies and staff training.

SCIENTIFIC PUBLICATIONS:

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2. Slavova I, Kiradzhyska D, Mancheva R. Antibacterial activity of metals with medical application. Radiation & Application 2018; 3(2):71-87, ISSN 2466-4294(online), doi: 10.21175/RadJ.2018.03.013

Histological and three-dimensional assessment of bone changes after socket preservation procedure, following an implant placement

CONTRACT: Project № NO-04/2018

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RESEARCH AREA: Oral surgery

AIM: Comparative analysis of the changes in the alveolar bone after socket preservation and assessment of the implant stability.

MATERIAL AND METHOD: Ninety patients were enrolled in the clinical study. Each patient was randomly assigned to one of the two test groups or to the control group. They underwent a socket preservation procedure with allograft with PRF membrane or PRF as a sole grafting material – test groups. The vertical and horizontal bone resorption were assessed on virtual models of the bone at the operation field, which were obtained with Trios intraoral scan. CBCT scanner was assigned prior to implant placement in order to assess the bone density. Four months after the socket preservation procedure, during the surgical re-entry a bone biopsy was harvested with a trephine drill. Immediately after implant insertion, the primary stability was measured. The secondary stability was measured 4 months after implant placement.

RESULTS: Socket preservation with cortico-cancellous, freeze-dried and serum-albumin impregnated allograft or PRF as a sole-grafting material showed better results in terms of bone resorption, bone density, newly formed bone after 4 months, as well as primary and secondary stability of the dental implants.

CONCLUSION: The results revealed that socket preservation either with bone substitute or biomaterial (PRF) gives more reliable results in subsequent implant treatment.

PRACTICAL APPLICATIONS: Socket preservation is an accessible surgical manipulation that has a beneficial effect on the processes of resorption and remodeling of the alveolar bone.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

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Study of the immunogenicity of TNF- α blockers for the formation of drug-induced neutralizing antibodies in patients with rheumatic diseases

CONTRACT: Project No NO-5/2018

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RESEARCH AREA: Therapeutic

AIM: To study the drug-induced neutralizing antibodies in patients with RA, AS and PsA treated with TNF- α blockers, the factors influencing their synthesis and their predictive value regarding the effect of this therapy.

MATERIALS AND METHODS: The present study included 213 patients divided into three groups - patients suffering from RA - 121, patients suffering from AS - 50 and patients with PsA - 42, who were compared with 31 healthy controls, with average age, sex and body mass index corresponding to the patients with rheumatic diseases.

RESULTS: Drug-induced neutralizing antibodies in patients with RA, PsA, AS treated with adalimumab appear in 11.5% of patients 6 months after the start of treatment, at 12 months are 17.6%, at the end of the second year - 24.8%. Patients treated with etanercept had no proven neutralizing antibodies 6 months after the start of treatment, at the end of the first year they were 7.7%, at the end of the second year - 9.6%.

Patients who had proven neutralizing antibodies to adalimumab and etanercept had a significantly worse clinical response than patients without antibodies at 24 months of follow-up ($p < 0.001$).

Patients with proven neutralizing antibodies to adalimumab were significantly more likely to have no serum drug bioavailability of adalimumab.

CONCLUSION: Patients who have proven drug-neutralizing antibodies to TNF- α blockers are significantly more likely to have a poor clinical response than patients without antibodies. The drug-neutralizing antibodies against TNF- α blockers correlates with high levels of proinflammatory cytokines and acute phase proteins, high indices of disease activity and deteriorated quality of life and serve as a prognostic biomarker for the outcome of rheumatic diseases.

PRACTICAL APPLICATIONS: An algorithm has been developed for the study of drug-induced neutralizing antibodies in the treatment of patients with RA, AS and PsA with TNF- α -blockers, which is necessary for monitoring biological therapy in rheumatological patients.

SCIENTIFIC PUBLICATIONS:

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9. Kraev K, Geneva-Popova M. 2020. Drug-induced neutralizing antibodies against TNF- α blocker drugs. Monograph, Neofeedback ISBN 978-619-7329-51-3, p. 310.
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Neuropharmacological study on the effects of lacosamide, topiramate and aerobic training in an experimental model of temporal lobe epilepsy

CONTRACT: Project № NO-6/2018

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RESEARCH AREA: Biomedical

AIM: The aim of the present study was to investigate the effect of long-term treatment with lacosamide (LCM) and topiramate (TPM), as well as aerobic training during epileptogenesis on cognitive dysfunctions, markers of oxidative stress and levels of pro-inflammatory cytokines-TNF- α , IL-1 β .

RESULTS: LCM and TPM prevented the Pilocarpine-induced increase in lipid peroxidation, restored the CAT activity to control levels, and only LCM increased SOD activity 24 hours after status epilepticus (SE). Both drugs did not affect the levels of reduced glutathione. LCM and TPM reduced also the elevated levels of IL-1 β . During the chronic phase of epilepsy, LCM significantly reduced the number of motor seizures. Both drugs improved passive and spatial learning and memory. LCM restored motor activity, while TPM further aggravated rat hyperactivity. Both drugs had beneficial effects on depressive and anxiety symptoms. LCM increased SOD activity and decreased MDA levels and CAT activity compared to epileptic animals, while the effect of TPM was mainly on CAT and SOD activity. Both drugs had a beneficial effect on inflammatory processes and

reduced neuronal loss in the hippocampus.

Applied aerobic training improved recognition and spatial memory, reduced depressive symptoms and anxiety during the chronic phase of epilepsy. It has beneficial effects on oxidative stress and also reduced the levels of both pro-inflammatory cytokines.

CONCLUSION: Data from our study show that both anticonvulsants as well as aerobic training favorably affect the epileptogenesis and concomitant cognitive and behavioral disorders due to correction of oxidative status, reduction of pro-inflammatory cytokines, and hippocampal neuronal loss.

SCIENTIFIC PUBLICATIONS:

1. Shishmanova-Doseva M, Tchekalarova J, Nenchovska Z, et al. The effect of chronic treatment with two antiepileptic drugs, lacosamide and topiramate, on cognitive functions and impaired emotional responses in a pilocarpine-induced post-status epilepticus rat model. *Folia Medica* (in press).

CBCT analysis of chronic apical lesions and assessment of the healing process following endodontic treatment

CONTRACT: Project № NO-07/2018

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RESEARCH AREA: Biomedical

AIM: Investigation of the radiographic characteristics of osteolytic periapical lesions by means of cone beam computed tomography (CBCT) and evaluation of the healing process dynamics following non-surgical endodontic treatment.

MATERIALS AND METHODS: Thirty-one patients with a single chronic periapical lesion of endodontic origin were enrolled in the study. Limited field of view (FOV) CBCT was performed on all affected teeth with accordance to the ALARA principle. A new scoring system designed for the pre- and posttreatment evaluation of endodontically diseased teeth was developed and tested. An individual treatment plan was outlined on the basis of the collected data and non-surgical endodontic treatment was performed on all affected teeth. The follow-up examination was performed in 10 months following the same diagnostic protocol. The healing process of each lesion was assessed.

RESULTS: The pre-surgical treatment planning allowed for the utilization of proper preparation techniques which enabled the complete cleaning of the root canal system. Complete healing was evident in 57% of the cases, while 40% showed decrease in lesion volume. Only one case was assessed as failure as no change in lesion volume was detected.

CONCLUSION: CBCT is a reliable tool in preoperative endodontic treatment planning. It is also a sensitive method for the assessment of periapical healing.

PRACTICAL APPLICATIONS: The implementation of limited FOV CBCT in the endodontic clinical practice and the application of the new scoring system for pre- and postoperative assessment, in accordance with strict patient selection criteria.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Karteva T, Manchorova N, Karteva E, et al. Quality of endodontic treatment and prevalence of apical radiolucencies in a Bulgarian subpopulation: a CBCT analysis. *Folia Medica* (in press).

Sensitization to occupational allergens among dental staff

CONTRACT: Project № NO-08/2018

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RESEARCH AREA: Dental medicine

AIM: To assess the prevalence of work-related skin and respiratory symptoms and associated factors among dental staff.

RESULTS: A total of 5,993 dental staff members participated in the cross-sectional questionnaire survey. The prevalence of self-reported skin symptoms ranged from 29.3% to 33.3% in the different dental staff subgroups, the highest being in dental nurses. Significantly associated factors included a history of atopic dermatitis (OR 2.72, 95% CI: 2.24–3.31), allergic rhinoconjunctivitis and/or asthma (OR 1.85, 95% CI: 1.56–2.19), work experience >30 years (OR 2.21, 95% CI: 1.78–2.74), personal history of contact allergy (OR 1.79, 95% CI: 1.48–2.17), female gender (OR 1.87, 95% CI: 1.59–2.19), hand washing >8 times a day (OR 1.32, 95% CI: 1.03–1.69), daily contact ≥4 hours with protective gloves (OR 2.09, 95% CI: 1.64–2.67), and use >10 pairs of gloves per day (OR 1.51, 95% CI: 1.11–2.04). The prevalence of self-reported work-related respiratory symptoms ranged from 12.4% to 26.2%, the highest being in dental technicians. Logistic regression showed the associated factors to be history of asthma (OR 2.50, 95% CI: 1.71–3.64), work experience >20 years (OR 2.17, 95% CI: 1.74–2.70), and female gender (OR 2.14, 95% CI: 1.81–2.56). The lack of ventilation system was a significant factor for respiratory symptoms in dental technicians (OR 4.26, 95% CI: 2.39–7.58).

CONCLUSION: The results indicate the need for developing effective programs for prevention of occupational diseases in dental staff.

PRACTICAL APPLICATIONS: National statistical data can further contribute to the development of effective programs for prevention of occupational diseases in dental staff.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Stoeva I, Dencheva M, Georgiev N, et al. Skin reactions among Bulgarian dental students: A self-reported questionnaire survey. *Contact Dermatitis* 2019; 81(4):274-279 IF 5.504
2. Stoeva I. Work-related skin symptoms among Bulgarian dentists. *Contact Dermatitis* 2020; 82(6):380-386 IF 5.504
3. Stoeva I, Dencheva M, Mircheva K, et al. Respiratory symptoms of exposure to substances in the workplace among Bulgarian dental students: a self-report questionnaire survey. *Folia Med (Plovdiv)* 2020; 62(1):141-6.

The Effect of Chlorhexidine Digluconate 0.2% (Mouthwash) on Postextraction Bacteremia

Contract: Project № HO-09/2018

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RESEARCH AREA: Medico-biological

AIM: To study the effect of preoperative rinsing of oral cavity with a mouthwash containing chlorhexidine digluconate 0.2% (Parodontax, GlaxoSmithKline) on bacteremia after tooth extraction.

RESULTS: Two groups of patients were formed - 60 persons who needed extraction of a single tooth, and 60 persons who needed atypical extraction. Each group was divided into two subgroups: 50% of the subjects rinsed their oral cavities preoperatively with a mouthwash containing chlorhexidine digluconate 0.2%; the remaining 50% did not undergo preoperative preparation. Venous blood samples were taken from each subject three times - preoperatively, at second 30, and at minute 15 after the end of the extraction, and they were placed in a growth medium and transported to the microbiological laboratory. The study found that preoperative rinsing of oral cavity with parodontax did not result in reduction of postoperative bacteremia after conventional tooth extraction both at second 30 ($p=0.548$) and at minute 15 after the end of the procedure ($p>0.05$). No reduction of postoperative bacteremia was found after atypical tooth extraction - at second 30 ($p=0.647$), and at minute 15 ($p=0.322$).

CONCLUSION: Preoperative rinsing of oral cavity with parodontax did not result in a statistically significant reduction in bacteremia, tested 30 seconds and 15 minutes after the end of both conventional and atypical extraction.

SCIENTIFIC PUBLICATIONS:

1. Gavazova G, Hristozova E, Kisselov S, et al. Bacteremia Following Closed and Open Dental Extraction. *Folia Med (Plovdiv)* 2019; 61(4):600-4.
2. Gavazova G, Hristozova E, Kisselov S, et al. Effect of preoperative rinsing with 0.2% chlorhexidine digluconate on the bacteremia following open dental extraction. *ARC Journal of Dental Science* 2019; 4(4):14-7.
3. Gavazova G, Hristozova E, Kisselov S, et al. Preoperative use of 0.2% chlorhexidine digluconate mouthwash does not affect the bacteremia following closed dental extraction. *ARC Journal of Surgery*. 2019; 5(4):13-6.
4. Gavazova G, Pechalova P. The Effect of Mouthwash Containing Chlorhexidine Digluconate 0.2% on Halitosis in Smokers and Non-Smokers. *ES J Dent Sci* 2020; 1(2):1010.

Study of the relationship between serum concentration of melatonin and dyglycaemia in metabolic syndrome

CONTRACT: Project № NO-10/2018

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RESEARCH AREA: Biomedical

OBJECTIVE: To study the role of melatonin in the pathogenesis of carbohydrate disorders in metabolic syndrome (MetS) by determining the relationship between serum hormone concentrations at 3:00 and 8:00 and certain hormonal and metabolic parameters in patients with proven MetS.

MATERIAL AND METHODS: The study included 60 women with MetS (30 with dysglycemia and 30 without dysglycemia) and 25 clinically healthy women (controls). Serum concentrations of melatonin, IGF1, ghrelin, leptin and growth hormone, glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, insulin and cortisol.

RESULTS: The melatonin of women with MetS at 8:00 was statistically significantly higher than that of controls (130.01 ± 57.77 pg/ml vs. 50.69 ± 30.78 pg/ml, $P<0.01$). The two groups did not differ in melatonin at 3:00 ($P>0.05$). We found a higher mean leptin in women with dysglycemia compared to those without dysglycemia (21.32 ± 5.70 ng/ml vs. 8.69 ± 3.37 ng/ml, $P=0.046$) and a tendency to higher melatonin at 3:00 in women

without dysglycemia compared to those with dysglycemia, but the difference did not reach statistical significance (176.63 ± 22.28 pg/ml vs. 119.60 ± 11.82 pg/ml, $P=0.063$).

CONCLUSION: The comparative analysis of serum melatonin at 3:00 and 8:00 between women with and without dysglycemia and controls and the study of the correlations between melatonin and metabolic parameters of MetS are expected to outline the role of melatonin in the development of the syndrome as in general and carbohydrate disorders in particular.

APPLICATION IN PRACTICE: In addition to scientific and theoretical contribution to the study of the various effective melatonin, the results of the study will have practical significance related to the possible inclusion of melatonin in the diagnostic and therapeutic approach in patients with MetS with different phenotypic manifestations.

SCIENTIFIC PUBLICATIONS:

1. Peneva V, Terzieva D, Mitkov M, et al. Melatonin correlate with insulin resistance in women with metabolic syndrome. 24th International Congress of Clinical Chemistry and Lab Medicine. 06-10.01.2021, SEOUL, Korea

Immobilization of teeth with pathological mobility with composite splints made by CAD/CAM technology

CONTRACT: Project № NO-11/2018

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RESEARCH AREA: Dental medicine

AIM: The aim of the research was to assess the degree of polishing of splints from composite materials, manufactured by the CAD/CAM technology.

RESULTS: Samples were cut in the form of a disk with diameter of 10 mm and thickness of 5 mm from 4 types of materials (fibrous composite (Trilor), hybrid ceramics (Vita Enamic), zirconia-based ceramics and BioHpp). Three groups of samples from each of the materials were prepared (1 - non-treated/control, 2 - polished, 3 - glazed) and subjected to 3D profilometry with an atomic force microscope.

The observations were conducted with "Easyscan 2" (Nanosurf, Switzerland). The device was equipped with TAP 190-AI G working nozzle (Budgetsensors, Bulgaria).

The images were taken under the following conditions:

- Working area per image: a square area with linear size of $49.5 \mu\text{m}$
- Resolution: the area was divided into 256 points per line on 256 lines. The recording speed was 5 to 10 s/line.

CONCLUSION: The tested materials for the CAD/CAM technology showed very good polishing and glazing results.

PRACTICAL APPLICATIONS: The results for the tested materials in laboratory conditions can be taken into account by the clinicians in the manufacturing of splints.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Zhekov Y, Firkova E, Vlahova A, et al. CAD/CAM Fiber-Reinforced Composite Adhesive Splint. International Journal of Science and Research (IJSR) ISSN: 2319-7064.
2. Zhekov Y, Alexandrov S, Kissov H, et al. Possibilities of CAD/CAM technology in the treatment of periodontally damaged teeth. Scientific papers of the Union of Scientists in Bulgaria - Plovdiv. Series D. Medicine, pharmacy and dentistry XXIV. ISSN 1311-9427 (Print), ISSN 2534-9392 (On-line). 2020.

Immunohistochemical phenotype of colorectal carcinoma in patients with KRAS mutation and Mismatch repair status

CONTRACT: Project № NO-12/2018

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RESEARCH AREA: Biomedical

AIM: Investigation of specific morphological and immunohistochemical characteristics of colorectal carcinoma with KRAS mutation status and microsatellite instability.

RESULTS: Immunohistochemical analysis for CK7, CK20, CDx2, PMS2, MSH6 and was performed on 71 patients with colorectal carcinoma. Most of the cases, included in the investigation (90%) showed CDx2/CK20 positive and CK7 negative immunohistochemical profile. Highest sensitivity and specificity was established for CDx2 with 93% of the cases demonstrating positive nuclear expression in the tumor cells. As for the microsatellite status, 30 % of the examined colorectal cancers, showed loss in expression for one or both of the mismatch repair proteins - PMS2 and MSH6, which was associated with loss of the expression for CK20 and CDx2 as well. Downhill correlation was estimated also between CK20 expression and the presence of mutation in the gene for KRAS.

CONCLUSION: Statistically significant correlation was established between the expression of CK20 and CDX2 and MSI- and KRAS mutant colorectal cancers.

PRACTICAL APPLICATIONS: Application of immunohistochemical screening panel for selection of patients with colorectal carcinoma for further genetic testing.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Mollova A, Tashkova D, Staykov D. Morphological and immunohistochemical characteristics of colorectal carcinoma in patients with microsatellite instability. Science and Youth 2018, 190-4.

Retrospection of the color stability of temporary constructions

CONTRACT: Project No NO-14/2018

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RESEARCH AREA: Dental Medicine

AIM: To trace the change in the color of the temporary constructions made of different types of materials.

RESULTS: The survey showed that the most preferred method for making temporary constructions is the direct one, and the most used material is Protemp. The matrix with its own design was carried out by precise casting of brass by means of vacuum. To perform a laboratory test, we made 150 test specimens of three different materials for temporary constructions (Protemp II, Protemp IV and LuxatempStar). They were subjected

to the action of five different coloring solutions: Coca-Cola, coffee, tea, orange juice and red wine. Measurements of color changes were performed using two spectrophotometric devices - Vita EasyShade and Spectro Shade. Coffee and red wine have the strongest coloring effect of the liquids we studied, followed to a lesser extent by tea, natural orange juice and Coca-Cola.

CONCLUSION: Protemp IV showed more color stability than Protemp II and LuxatempStar for a 7-day stay in dyes. The longer the residence time in the staining solution, the more it reduces the color stability.

PRACTICAL APPLICATIONS: The use of Protemp IV is proposed for longer stays of the temporary constructions in the oral cavity.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Doshev A, Bozhkova T, Slavchev D, et al. Elaboration of temporary constructions for non-removable prosthetics - survey. Scientific works of the Union of Scientists in Bulgaria-Plovdiv. Series D. Medicine, pharmacy and dentistry. 2018; 22: 243-246.
2. Doshev D, Slavchev V. Creating a matrix with our own design for making test bodies. Scientific works of the Union of Scientists in Bulgaria-Plovdiv. G. Medicine, Pharmacy and Dentistry series. 2019; 23:452-6.
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4. Doshev A, Slavchev D, Doshev V, et al. Accuracy of temporary crowns in the marginal area - an overview. Scientific works of USB-Plovdiv. Series G. Medicine, pharmacy and dental medicine. 2020; XXIV: 308-311.

INTRA-UNIVERSITY PROJECT SESSION**Doctoral projects 2015 - 2017****Investigation on the effects and mechanism of action on the dopaminergic mediation of two anti-Parkinsonian drugs – pramipexole and tolcapone**

CONTRACT: Project № SDP-11/2015

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RESEARCH AREA: Biomedical

AIM: to investigate anti-inflammatory and immunomodulatory activity of pramipexole (PMX) and tolcapone (TCP), and their effect on memory.**MATERIALS AND METHODS:** The experiments were performed on male Wistar rats. Memory was assessed by using tasks for working memory (active and passive avoidance) and spatial memory (Y- and T - maze), and object recognition test (ORT). PMX was administered at doses of 0,5; 1 and 3 mg/kg bw; TCP-5; 15 and 30 mg/kg bw.**RESULTS:** In naïve rats pramipexole and tolcapone improved memory in hippocampal-dependent tasks and in T-maze which depends on prefrontal cortex. In haloperidol-induced dopamine blockade, PMX improved memory in active and passive avoidance, but TCP enhanced memory only in passive tasks. PMX antagonized the effect of reserpine-induced amnesia in active avoidance whereas TCP increased latency in step-down passive test. After repeated lipopolysaccharide (LPS) administration both drugs improved memory in Y-maze and ORT and increased only IL-10 level. Following single LPS injection the investigated drugs increased serum IL-10, TGF-beta1 levels and decreased TNF-alpha. The neuroprotective effect of pramipexole and tolcapone, evaluated by their ability to increase BDNF levels, was observed only after single administration of LPS. Serum levels of aforementioned markers were measured by enzyme-linked immunosorbent assay (ELISA).**CONCLUSION:** PMX and TCP enhance memory by stimulating dopaminergic mediation in the hippocampus and prefrontal cortex.**PRACTICAL APPLICATIONS:** PMX and TCP improved cognitive decline in experimental settings, which could be considered in clinical practice. IL-10 might be used as a target molecule in experimental studies of neuro-protective agents.**SCIENTIFIC PUBLICATIONS:**

FULL TEXT PAPERS ONLY

1. Mihaylova A, Doncheva N, Zlatanova H, et al. Effects of pramipexole on learning and memory processes in naïve and rats with haloperidol-induced dopaminergic blockade. *Science & Technologies* 2018; 8(1):34-41.
2. Mihaylova A, Kostadinov I, Delev D, et al. Study the effects of pramipexole on learning and memory processes in rats using two passive avoidance tests. Collection of articles from the National Scientific Conference "15 Years of Pharmacy in Medical University – Plovdiv" 2018; 160-164. ISBN 978-619-237-014-5.
3. Mihaylova A, Zlatanova H, Doncheva N, et al. Effects of pramipexole on learning and memory in rats. *Scientific reports "Science and Youth"* 2018;15-21. ISSN 1314-9229.

- Mihaylova AS, Zlatanova H, Doncheva N, et al. Investigating the effects of tolcapone a catechol-o-methyltransferase inhibitor on learning and memory in passive avoidance task. *Journal of Advances in Medicine and Medical Research*, 2018; 28(5):1-11.
- Mihaylova AS, Kostadinov ID, Doncheva ND, et al. Effects of pramipexole on learning and memory processes in naïve and haloperidol-challenged rats in active avoidance test. *Folia Med (Plovdiv)*, 2019; 61(2):95-102. doi:10.2478/foimed-2018-0063.
- Mihaylova AS, Zlatanova H, Doncheva N, et al. Catechol-o-methyltransferase inhibitor tolcapone improves learning and memory in naïve but not in haloperidol challenged rats. *Iran J of Basic Med Sc* 2019; 22(6):695-702. doi: 10.22038/ijbms.2019.33025.7890 IF₂₀₁₈=1.854
- Mihaylova AS, Kostadinov I, Doncheva N, et al. Effects of pramipexole on learning and memory processes in reserpine-induced parkinsonism. *Scientific Works of the Union of Scientists in Bulgaria – Plovdiv, Series G. Medicine, Pharmacy and Dental Medicine*, Vol. XXII 2019, 290-294. ISSN 1311-9427 (print)

Determination of oncometabolites in urine

CONTRACT: Project № SDP-02/2017

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RESEARCH AREA: Biomedical

AIM: To develop an HPLC- MS/MS analytical method for the determination of oncometabolites in urine samples of patients with prostate cancer (PCa) and evaluate their role as diagnostic and predictive biomarkers.

MATERIALS AND METHODS: Urine samples from 154 patients were analyzed with a chromatographic system UHPLC Thermodionex Ultimate 3000, with a mass detector Thermo TSQ QuantumAccessMax.

RESULTS: We developed and validated an analytical method for eight metabolites in urine-sarcosine, leucine, isoleucine, GABA, ethanolamine, kynurenine α -alanine and β -alanine. Patients were divided in three groups: patients diagnosed with PCa, without surgical or other treatment (n=69), with benign prostate hyperplasia (BPH) (n=41) and a control group of healthy men (C) (n=44). Kynurenine concentration was elevated in the PCa and BPH groups compared to the controls, but there was no significant difference between the PCa and BPH groups.

β -alanine and isoleucine concentrations were lower in the PCa group compared to controls. In the PCa group additional analysis was performed according to Gleason score and prostate serum antigen (PSA) levels. Significantly higher concentrations of β -alanine, GABA, sarcosine, were observed when Gleason score was >6 , while GABA concentrations were elevated in patients with PSA values >10 .

CONCLUSION: The results of our study provide further information on the role of amino acids and amines in the pathogenesis of PCa and give an opportunity to differentiate between patients with pathologies of the prostate gland and healthy individuals.

PRACTICAL APPLICATIONS: The compounds found in significantly different concentrations, could be studied as potential biomarkers in prostate cancer.

SCIENTIFIC PUBLICATIONS:

- Delkov D, Ioanidu L, Uzunova J, et al. Oncometabolites in urine-a new possibility for early detection and prognosis of clinical progression of prostate gland cancer 2018;1:32-35.

Modern and alternative methods for achieving local analgesia in pediatric patients

CONTRACT: Project № SPD-03/2017

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RESEARCH AREA: Dental medicine

AIM: To study the efficacy of new non-pharmacological means for reduction of pain and anxiety associated with local analgesia in pediatric patients.

MATERIAL AND METHODS: The efficacy of vibrotactile DentalVibe and virtual reality (VR) device for reducing pain during local anesthesia (LA) was studied in n=81 patients. The possibility of photobiomodulation with an Er: YAG laser for achieving of preemptive laser analgesia (n=41) was investigated after studying the enamel surface morphology on scanning electron microscopy (SEM).

RESULTS: The mean pain score for patients receiving traditional LA (3.35 ± 2.03 points) was statistically significantly higher ($t=13.41$, $p=0.001$) in comparison to patients undergoing DentalVibe-LA (1.24 ± 1.1 points). Patients anesthetized with a VR-device received a lower average pain rating statistically significantly more frequently than patients anesthetized traditionally ($H=5.442$; $d=1$; $p=0.020$). No statistically significant difference between mean pain, anxiety, and pain-related behavior for DentalVibe- and VR-assisted injection was demonstrated. Mean pain scores in the cavity test, depending on prior laser or placebo analgesia, showed no statistically significant difference.

CONCLUSION: Investigated modern nonpharmacological agents help reduce pain and anxiety and have a positive effect on local analgesia acceptance in children. In conservative caries treatment with an Er: YAG laser, the operator can provide comfort to the patient, even without performing preemptive analgesia.

PRACTICE APPLICATION: DentalVibe and virtual reality devices are applicable, affordable and effective aids for the everyday dental practice when local anesthesia is required. Our results can be applied in laser caries treatment, saving operating time.

SCIENTIFIC PUBLICATIONS:

1. Veneva E, Belcheva A. Local anesthesia in pediatric patients – a review of current and alternative methods, devices and techniques. *Folia Medica* 2018;60(3): doi: 10.2478/foimed-2018-0015
2. Veneva E, Belcheva A, Tarpomanov J, et al. Effect of a virtual reality device on pain and anxiety during local anesthesia in childhood - a randomized clinical trial. *Collection of scientific communications, Science and Youth* 2018; ISSN 1314-9229 (233-238).
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4. Veneva E, Raycheva R, Belcheva A. Dental fear and anxiety associated with local anesthesia in pediatric patients in two consecutive visits. *Scientific works of the Union of Scientists in Bulgaria - Plovdiv. Series D. Medicine, pharmacy and dentistry* ISSN 1311-9427 (Print), ISSN 2534-9392 (On-line), 2019:23 (429-32).
5. Veneva E, Raycheva R, Belcheva A. Efficacy of erbium-doped yttrium aluminium garnet for achieving pre-emptive dental laser analgesia in children: A study protocol for a randomized clinical trial. *Medicine (Baltimore)* 2018; 97(51):e13601.
6. Veneva E, Cholakova R, Raycheva R, et al. Efficacy of vibrotactile device DentalVibe in reducing injection pain and anxiety during local anaesthesia in paediatric dental patients: a study protocol for a randomised controlled clinical trial. *BMJ Open* 2019; 9(7):e029460. doi: 10.1136/bmjopen-2019-029460.
7. Veneva E, Raycheva R, Belcheva A. Surgical or conservative treatment - which is a stronger stress factor for children. *Scientific works of the Union of Scientists in Bulgaria - Plovdiv*.

Antimicrobial activity examination of probiotic strains of lactobacillus and bifidobacteria against periodontal microorganisms

CONTRACT: Project № SDP - 04/2017

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RESEARCH AREA: Dental medicine

AIM: To select lactic acid microorganisms - LAMs (lactobacilli and bifidobacteria) with antimicrobial activity against periodontal pathogenic microorganisms (*Porphyromonas gingivalis*) and their subsequent clinical investigation.

MATERIALS AND METHODS: The antimicrobial activity of 25 strains LAM against *P. gingivalis* DSM 20709 was determined by the agar diffusion method. The inhibition of the growth of pathogenic microorganisms was indicated by measuring (in mm) the areas around the wells in which no growth of *P. gingivalis* DSM 20709 was observed. The clinical trial (pilot) included 8 patients with moderate periodontitis, that, after periodontal, microbiological examination and initial therapy, were divided into four groups - 3 taking probiotic for 1 month - *L. bulgaricus* LBB.B1054, *S. thermophilus* 187/4, BioGaia, and one control group. After 1 month, a control microbiological study was performed and the clinical follow-up of the patients lasted for 6 months.

RESULTS: Of all probiotic strains tested, *L. bulgaricus* LBB.B1054 and *S. thermophilus* 187/4 showed the optimum bacteriostatic effect against *P. gingivalis* and were applied in clinical trial. Patients taking probiotics demonstrate better and more stable results in terms of clinical and microbiological parameters.

CONCLUSION: The results obtained from the laboratory studies determine that *L. bulgaricus* LBB.B1054 and *S. thermophilus* 187/4 are suitable for the clinical application. Clinical and microbiological results are promising, but more investigations are needed.

PRACTICAL APPLICATIONS: A lyophilized lactic acid product with *L. bulgaricus* LBB.B1054 and *S. thermophilus* 187/4 has been developed for oral administration.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

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3. Yaneva B, Dermendzhieva Y, Dobrev I, et al. Investigation of the application of probiotics on clinical parameters in the treatment of periodontitis. Scientific works of the Union of Scientists in Bulgaria - Plovdiv, series G. Medicine, Pharmacy and Dental medicine, Vol. XXIII. 2020 – in print.

Clinical – laboratory evaluation of coagulation and fibrinolysis in cancer patients

CONTRACT: Project № SDP-05/2017

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RESEARCH AREA: Biomedical

AIM: To investigate the changes in the laboratory parameters for coagulation and fibrinolysis – factor von Willebrand (vWF), fibrinogen, thrombin-antithrombin complex (TAT), Tissue factor (TF), prothrombin fragment (F1+2), Antithrombin III (AT III), D-Dimer and t-PA in cancer patients treated with chemotherapy and radiotherapy.

MATERIALS AND METHODS: The current investigation included 75 patients, divided into 3 groups: breast cancer (n = 25), lung cancer (n = 25), lymphoma (n = 25) and a control group of 30 healthy volunteers.

RESULTS: We measured the levels of vWF, F1+2, fibrinogen, TAT, AT III, TF, D-Dimer and t-PA baseline – before treatment (visit 1); visit 2 - after the 4th course of treatment and after termination of treatment (visit 3). The levels of vWF, F1+2, fibrinogen, TAT, AT III, TF, D-Dimer and t-PA in cancer patients were significantly higher than these in the controls, while the activity of ATIII was significantly lower (P<0.001). During the follow-up vWF, F1+2, TAT, TF decreased, and baseline levels were significantly higher vs. visit 2 and visit 3 (P<0.001). We did not find statistically significant difference in the activity of AT III.

CONCLUSION: The higher levels of TF, TAT, F1+2, vWF and t-PA and lower activity of AT III in cancer patients support our hypothesis of association between malignant disease and coagulation disorders. Chemotherapy influences significantly the dynamic of the measured parameters.

PRACTICAL APPLICATIONS: Determination of the diagnostic-therapeutic approach and active follow up in cancer patients, considering antithrombotic therapy for improving outcome and quality of life.

SCIENTIFIC PUBLICATIONS:

1. Stoencheva S, Deneva T, Grudeva-Popova Z, et al. Determination of plasma tissue factor antigen and tissue factor-bearing microparticles activity in healthy Bulgarian subjects. BJSTR 2019; 19(3):14281-6, ISSN: 2574 -1241.

Changes in sperm parameters, condition of sperm cell chromatin, DNA damage and HBA test in men with infertility after treatment with nutritional supplement

CONTRACT: Project № SPD-06/2017

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RESEARCH AREA: Biomedical

AIM: Influence of nutritional supplement PAPA on sperm parameters, condition of nuclear sperm cell chromatin, DNA damage and attachment capacity of spermatozoa in men with infertility

MATERIALS AND METHODS: 118 men were assessed, control group (n=20) without treatment, and experimental group (n=98) with PAPA treatment for 3 months. 9 sperm parameters were monitored as well as tests: Cytochromical-Aniline blue (AB) and toluidine blue (TB), fluorescent – chromomycin A3 (CMA3), acridine orange (AO) and hyaluronan-binding assay (HBA).

RESULTS: Compared to the control group the nutritional supplement PAPA has a positive effect in all parameters in addition to the conducted tests. The percentage change after treatment is best expressed in morphology by Kruger (21.01), progressive motility (17.26) and viability (13.92). A relationship was discovered between the effect of treatment and the conditions of work environment. Jobs that lead to increased scrotal temperature have negative effect on treatment. In non-smokers the effect is better than in smokers. A direct relationship was assessed between the effect of the treatment and the amount of cigarettes smoked per day. No general trends can be drawn regarding the impact of the dietary supplement and the diagnosis. For all age groups, the percentage change after treatment is well pronounced for motility, morphology and vitality. The tests showed the following percentage change after treatment: AB-18.15, TB-9.59, CMA3-15.08, AO-14.51, and the lowest in the HBA test-7.07.

CONCLUSION: The administration of the PAPA nutritional supplement enhances men's fertility.

PRACTICAL APPLICATIONS: Three month course with nutritional supplement PAPA for treating male infertility.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Tomov S, Stoyanova R, Dechev I, et al. Changes in sperm parameters in sub/infertile men after treatment with PAPA dietary supplement. Scientific works of the Union of Scientists in Bulgaria Plovdiv, series G. Medicine, Pharmacy and Dental medicine, Vol. XXII. ISSN 1311- 9427 (Print) ISSN 2534-9392 (On-line). 2018; 57-61.
2. Tomov S, Stoyanova R, Atanasova P, et al. Changes in the level of DNA fragmentation in sperm cells, established by acridine orange test in men with sub/infertility, treated with nutritional supplement PAPA. Folia medica ISSN 1314-2143 (online) ISSN 0204-8043 (print), 2018, in press.
3. Tomov S, Stoyanova R, Georgieva E, et al. Alterations of sperm chromatin integrity in sub/infertile men treated with nutritional supplement PAPA®. Scientific works of the Union of Scientists in Bulgaria-Plovdiv, series G. Medicine, Pharmacy and Dental medicine, Vol. XXII. ISSN 1311-9427 (Print), ISSN 2534-9392 (On-line). 2019; 259-265.

Radiation effects on bioelectrical and mechanical processes in smooth muscle cells and tissues of the gastrointestinal tract of rats following total body irradiation with electron beam (linear accelerator Siemens Primus HE 3561)

CONTRACT: Project № SDP 12-2017

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RESEARCH AREA: Biomedical

AIM: To determine the nature, the force and the corresponding mechanisms causing changes in rat stomach tissues following total body irradiation with electron beam.

MATERIALS AND METHODS: 130 male rats (Wistar 250 g)

Electron beam total-body irradiation – 1,3,5 Gy

Isometrical registration of mechanical activity

Single sucrose gap for registration of bioelectrical activity

Ellman's method for cholinesterase activity

RESULTS: Electron radiation effects on cholinergic and serotonergic cellular signaling pathways of stomach SM cells have been studied through its effects on the contractile activity (CA) after exposure to exogenous acetylcholine and 5-HT, and immunohistochemically.

1 and 3 Gy did not affect the spontaneous phasic activity neither the contractile effects in the presence of acetylcholine and 5-HT. SM homogenates revealed non-significant change in acetylcholinesterase activity.

SM tonic contractions, under the influence of 5-HT (10^{-6} - 10^{-4} mol/l), as well as the amplitude of the spontaneous phasic contractions (10^{-8} - 10^{-6} mol/l) increased on the fifth day, after 5Gy irradiation. Consecutive multiple effects with equimolar concentration of 5-HT (10^{-6} mol/l) resulted in significant increase of the force of 5-HT-induced contractions but at a concentration of 10^{-4} mol/l, they decreased significantly.

Similar dependencies have not been observed in SM of non-irradiated rats.

Increased expression of 5-HT_{2A,2B} receptors of SM cells was demonstrated immunohistochemically in irradiated rats.

CONCLUSION: CA changes are function of the absorbed dose and the period between tissues irradiation and dissection. The increased reactivity of irradiated tissues to serotonin is a result of augmented expression of 5-HT_{2A,2B} receptors and their sensitization.

PRACTICAL APPLICATIONS: There are no recommendations for clinical practice.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Xenodochidis C, Ardasheva R, Popov V, et al. Changes in the contractile activity and reactivity to 5-HT of smooth muscles of rats following total body irradiation with accelerated electrons. *Folia Med (Plovdiv)* 2019; 61(3): 411–8. doi: 10.3897/folmed.61.e39394

Joint assessment in children and young adults with haemophilia

CONTRACT: Project № SDP-13/2017

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RESEARCH AREA: Biomedical

AIM: To assess the joint status of children and young adults with Hemophilia.

MATERIALS AND METHODS: The authors investigated 95 hemophilic joints in patients, treated at Department of Pediatrics, St George University Hospital, Plovdiv between February 2016 and February 2019. Joint ultrasound (US) by HEAD-US protocol was performed for ankles, knees and elbows. The physical examination followed the HJHS 2.1 score. Magnetic resonance imaging (MRI) according to the Compatible scale was done for 41 (43.2%) of the joints.

RESULTS: US detects articular damage in 18 (30%) of the joints, assessed by the HJHS 2.1 as pristine. The MRI shows 5 (12.2%) pristine joints. The ankles are most severely damaged, followed by knees. Articular alterations on MRI are found in 12 (75%) and on US - in 14 (24.1%) of the asymptomatic joints. There is strong correlation between the total and separate domains' HEAD-US and MRI joints' score. The level of agreement between US and MRI is strongest for the cartilage damage (kappa: 0.66; P < 0.001). The sensitivity of joint US, compared to MRI is 100% for the ankles and 80% for the knees and elbows.

CONCLUSION: The functional compensation could delay the detection of the early joint damage by the physical examination. The US, compared to MRI, demonstrates excellent sensitivity for the evaluation of a cartilage damage and for the ankles.

PRACTICAL APPLICATIONS: The introduction of regular US follow-up of the hemophilic joints is strongly recommended for the clinical practice and could contribute for better informed treatment strategy.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Spasova M, Spasov N. The individualized treatment approach to the patient with Hemophilia – or what stays behind „annual bleeding rate = 0-1“? *Pediatrics* 2017; LVII (Suppl): 30-36.
2. Spasov N, Spasova M, Dimitrova D, et al. Assessment of the joint status in patients with hemophilia, correlation MRI/ultrasound. *Practical Pediatrics* 2018; XX (11): 20-21.
3. Spasov N, Dimitrova D, Traikova-Djambazova N, . Magnetic resonance imaging of the hemophilic joints: correlations with the bleeding phenotype and physical examination. *Folia medica* 2019 – in print.

In vitro evaluation of marginal adaptation of CAD/CAM veneers

CONTRACT: Project № SDP-15/2017

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RESEARCH AREA: Dental medicine

OBJECTIVE: To investigate the accuracy of indirect CAD/CAM veneers according to the factor marginal adaptation through measurement of the internal and external marginal gap.

MATERIALS AND METHODS: For the aim of the study 16 natural extracted maxillary incisors were used. CAD/CAM veneers were produced and cemented. A cut in bucco-sagittal direction was then preformed. The specimens were examined via a scanning electron microscope in the mode of backscattered electrons and secondary electrons at magnification $\times 300$. Marginal adaptation was measured at 8 points: cervical, incisal, three points on the internal sagittal section and three points on the external proximal wall.

RESULTS: The mean values of the measurements for the marginal gap were as follow: external marginal adaptation $79.88 \mu\text{m} \pm 3.71 \mu\text{m}$; internal marginal adaptation $79.14 \mu\text{m} \pm 15.70 \mu\text{m}$; cervical area $82.39 \mu\text{m} \pm 28.55 \mu\text{m}$; incisal area $86.85 \mu\text{m} \pm 21.72 \mu\text{m}$.

CONCLUSION: The results of the electron microscope scans of CAD/CAM zirconium veneers show excellent parameters of marginal adaptation.

PRACTICAL APPLICATION: It has been proven that the CAD/CAM method of manufacturing indirect veneers is sufficiently accurate to ensure the long-term success of restorations.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Pecheva A, Tsanova S. Marginal adaptation of indirect veneers manufactured via two different technologies. *Scientific Research of the Union of Scientists in Bulgaria – Plovdiv, series B. Natural Sciences and Humanities, Vol XIX, ISSN: 1311- 9192: 151-154,2019*
2. Pecheva A, Tsanova S, Raycheva R. *In vitro* evaluation of marginal adaptation of CAD/CAM zirconium veneers. *Dentalna Medicina* 2019; 100:11-16.
3. Pecheva A, Georgiev K, Tsanova S, et al. A comparative *in vitro* study evaluating the marginal adaptation of zirconium computer-aided design/computer-aided manufacture and press-ceramic veneers. *Folia Medica*. 2020 (under review)

INTRA-UNIVERSITY PROJECT SESSION**Post-doctoral projects 2018****Phytochemical composition and pharmacological potential of Ginkgo biloba seed extract**

CONTRACT: Project No DPDP-01/2018

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RESEARCH AREA: Biomedical

AIM: To investigate the composition of Ginkgo biloba seed extract and study its potential for pharmacological application.**MATERIAL AND METHODS:** Extraction with 70% methanol was used to isolate low molecular mass secondary metabolites from the seeds. Flavonoids, terpenes, and ginkgotoxin were quantified by chromatographic methods. Antioxidant and antimicrobial properties of the extract, as well as its effect on rats' short-term and long-term memory were studied.**RESULTS:** LC-MS analysis of flavonoids showed similar levels of quercetin – 20.7 µg/g, kaempferol – 55.9 µg/g and isorhamnetin – 25.8 µg/g. The quantities of triterpenes in the extract were ginkgolide A – 242 µg/g, ginkgolide B + J – 388 µg/g, ginkgolide C – 143 µg/g and bilobalide 122 µg/g; ginkgotoxin was 335 µg/g.

The extract obtained demonstrated good antioxidant properties, determined by two methods, moderate antimicrobial activity mainly against Gram (+) microorganisms and improvement of spatial recognition memory in rats in two tested concentrations – 50 mg/kg and 100 mg/kg, its effect being commensurable with that of piracetam used as a positive control.

CONCLUSION: Phytochemical composition of Ginkgo biloba seed extract is similar but not identical to that of leaf extract which is widely used in phytomedicine. The amount of triterpenes characteristic of this tree species, to which the main therapeutic properties of leaf extract is attributed, is significantly higher in seed extract.**PRACTICAL APPLICATIONS:** The results obtained so far suggest that Ginkgo biloba seed extract is rich in biologically active compounds, which, after purification and additional biological tests, can be used to develop a new phytochemical product.**SCIENTIFIC PUBLICATIONS:**

1. Tomova T, Petkov V, Slavova I, et al. Naturally present metal ions in plants could interfere with common antioxidant assays. *MethodsX* 2020; 7:100995. doi.org/10.1016/j.mex.2020.100995.
2. Tomova T, Doncheva N, Mihaylova A, et al. Experimental study on the phytochemical composition and memory enhancing effect of Ginkgo biloba seed extract. *Folia Medica* (accepted for publication).

Study of the prevalence and some pathogenetic mechanisms of *Clostridium difficile*-associated diarrhea in hospitalized patients at St. George University Hospital, Plovdiv

CONTRACT: Project No DPDP-02/2018

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⁵ Research Institute, Medical University of Plovdiv, Bulgaria

RESEARCH AREA: Biomedical

AIM: Study on the prevalence of *Clostridium difficile*-associated diarrhea (CDAD) in patients with diarrhea hospitalized in the Clinic of Infectious Diseases, University Hospital "St. George", in the period 03.09.2018-03.03.2020 and the concentrations of cytokines in serum and fecal samples of patients, and look for correlation.

RESULTS: Fecal study of 27 patients with diarrhea for *Clostridium difficile* (multiplex PCR and ELISA). The level of cytokines TNF, IL-1, IL-6, IL-8, IL-10 in serum and feces was studied in 27 patients with infectious diarrhea using a human ELISA Kit (Sigma Aldrich). Patients were divided into 2 groups: a control group, which included patients with unspecified intestinal infection, and a target group - patients with CDAC. The research was performed in the Department of Microbiology and Immunology, MU-Plovdiv. Mild and moderate forms predominate. The leading risk factors for developing CDAD are old age, previous antibacterial therapy, comorbidity, and hospitalization. In patients in the acute period of CDAD, serum, and fecal concentrations of TNF- α , IL-6 and IL-10 did not differ significantly from those in controls. In patients, with acute period of CDAD, fecal concentrations of IL-1b and IL-8 are significantly elevated and are several times higher than serum analogs.

CONCLUSION: In CDAD, concentrations of IL-1b in feces and IL-6 in serum increase with increasing disease severity.

PRACTICAL APPLICATIONS: The introduction of highly specific and rapid diagnostic methods is key to timely diagnosis and initiation of adequate targeted therapy in CDAC. Serum and fecal concentrations of cytokines provide additional information on the severity of the disease.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Vasilev P, Murdjeva M, Hristozova E, et al. Colitis, challenge of *Clostridium difficile* in a fatal output patient. 2019; 1:20-3.
2. Vasilev P, Hristozova E, Murdjeva M, et al. Recurrent *Clostridium difficile*-associated enterocolitis in patients with multiple risk factors (clinical case report). 2020; 1: 58-61.
3. Vasilev P, Ivanovska M, Lengerova G, et al. Coinfection of the intestinal tract with *Aeromonas hydrophila*, *Clostridium difficile* and *Rotavirus*. (A clinical case). Collection of abstracts from the competition session "Science and Youth 2020". The article will be prepared and offered for publication in Folia Medica.

Effects of thyroid dysfunction on molecular markers of bone turnover and Wnt inhibitors sclerostin and dickkopf-1

CONTRACT: Project № DPDP-03/2018

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RESEARCH AREA: Biomedical

AIM: To investigate the markers of bone metabolism and Wnt inhibitors sclerostin and Dickkopf-1 in thyroid dysfunction and the relationship between their serum concentration and the indicators of functional and immunological activity of the gland.

MATERIALS AND METHODS We investigated 149 females with newly diagnosed autoimmune thyroid disease and 75 healthy controls.

RESULTS: There was no difference in parathyroid hormone in hyperthyroid patients compared to controls and higher levels in the hypothyroid group and no statistically significant difference in 25 (OH) D in both groups compared to controls. ALP, B-ALP (Ostase) and OC were elevated in the presence of a significant difference in total alkaline phosphatase. OPG was higher in hypo- and hyperthyroidism (OPG 52.96 ± 5.76 pg/ml and 90.07 ± 16.54 pg/ml vs. 40.61 ± 6.12 pg/ml, $p < 0.05$) and correlated with thyroid hormones CT3 ($r=0.42$, $p=0.001$), CT4 ($r=0.43$, $p=0.001$). Sclerostin had higher mean serum values among hypo- (488.71 ± 123.02 pg/ml) and hyperthyroid (302.23 ± 66.93 pg/ml) patients compared to controls (235.24 ± 49.29 pg/ml) without statistically significant difference, ($p > 0.05$). Dkk-1 was higher in the hypo- (787.95 ± 101.27 pg/ml) and hyperthyroid group (701.20 ± 88.28 pg/ml) than controls (245.01 ± 74.12 pg/ml), ($p < 0.001$).

CONCLUSION: Modulation of Wnt by thyroid hormones may contribute to the bone changes in thyroid dysfunction and the altered expression of Wnt inhibitors may appear as a potential therapeutic target.

PRACTICAL APPLICATIONS: For defining the therapeutic approach in patients with thyroid dysfunction and potential in the prevention and treatment of osteoporosis induced by hyperthyroidism with antibodies to sclerostin and Dickkopf-1.

SCIENTIFIC PUBLICATIONS:

1. Miteva MZ, Nonchev BI, Orbetzova MM, et al. Vitamin D and Autoimmune Thyroid Diseases. Review. Submitted to Folia Medica, has been assigned a number FOLIAMED-D-19-00081
2. Miteva MZ, Nonchev BI, Orbetzova MM, et al. Effects of thyroid dysfunction on molecular markers of bone turnover and Wnt inhibitors Sclerostin and Dickkopf-1-. Endocrinologia vol. XXIV №3/2019;126-136

Effect of Atovaquone on cell metabolism in childhood acute lymphoblastic leukaemia (cALL)

CONTRACT: Project № DPDP-04/18

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RESEARCH AREA: Biomedical

INTRODUCTION: One of the well-known characteristics of the cancer cell is the deregulation of its metabolism. ALL is no exception to the rule: lymphoblastic cells from children with ALL have been documented to exhibit altered metabolism, while therapeutic modulation of energy pathways in leukaemic cells lead to reduced proliferation and higher levels of apoptosis *in vitro*. Atovaquone (hydroxy-1,4-naphthoquinone, C₂₂H₁₉ClO₃) is a mitochondrial inhibitor, widely used for the treatment of some infectious diseases caused by protozoa and bacteria, with minimal toxicity and side effects.

AIM: The aim of this pilot study is to investigate the potential metabolic and anti-tumour effects of the mitochondrial inhibitor Atovaquone in cell lines and primary patient samples from bone marrow aspirates.

MATERIALS AND METHODS: B-lymphoblastic cell lines and lymphoblastic cells from newly diagnosed patients. A novel protocol for metabolic analysis of live ALL cells with Seahorse XFp analyzer and Mito Stress kit (Agilent) was optimised. Muse cell analyzer (Luminex) was used for flow cytometric cell analysis.

RESULTS: The results from our *in vitro* experiments with this clinically approved inhibitor of the electron transport chain (ETC) on cell lines demonstrate decreased proliferation, arrest in G1 phase of the cell cycle, and concomitant inhibition of basal mitochondrial respiration and of ATP levels.

CONCLUSION: The hypothesis that inhibition of the ETC can exhibit anti-leukemic effect and presents a potential therapeutic target in cALL is confirmed.

PRACTICAL APPLICATIONS: Laboratory protocols have been developed and the scientific results may lead to further pre-clinical studies.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Sbirkov Y, Burnusuzov H, Sarafian V. Metabolic reprogramming in childhood acute lymphoblastic leukemia. Paediatric blood & cancer 2020, IF=2.49, Ranking: 2018:43/73 (Hematology)151/230 (Oncology)29/125 (Pediatrics) <https://doi.org/10.1002/pbc.28255>
2. Sbirkov J, Gercheva K, Burnusuzov H. Development of a prednisolone-resistant cell line from childhood acute lymphoblastic leukemia. Proceedings of Conference "Science and Youth" (2020) of Asclepius Youth Scientific Society. 2020: 209-213. <https://asclepius.bg/images/nm2020/sbornik-NM2020.pdf>
3. Sbirkov Y, Ivanova T, Burnusuzov H, et al. The antimalarial inhibitor Atovaquone effectively targets mitochondrial function in childhood acute lymphoblastic leukemia cells. Frontiers in Oncology (pre-submission).

Comparative study of microbiological methods for rapid diagnosis of pathogens from blood cultures

CONTRACT: Project № DPDP-05/2018

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RESEARCH AREA: Biomedical

AIM: To establish the possibilities of rapid methods in the diagnosis of septic conditions

MATERIAL AND METHODS: Fluorescent *in situ* hybridization (FISH), multiplex PCR (mPCR) and MALDI-TOF.

RESULTS: Although blood cultures are the "gold standard" in the diagnosis of bacteremia/sepsis, the conventional diagnosis is slow (5-7 days) and requires new methods to shorten the diagnostic time and provide higher sensitivity.

FISH accelerates the identification of the most common 10 types of bacteria and fungi causing bacteremia. The sensitivity to all tested microorganisms is 84.5% because not all microorganisms are included in the spectrum of the test. The pathogens proven with FISH showed 100% coincidence with conventional blood culture methods.

mPCR is an accurate test for simultaneous detection of several pathogens and resistance genes directly from positive blood cultures. It reduces the identification time to 70 minutes. Our study recorded a general assay sensitivity of 90.1% for identification, and 100% for detection of resistance genes.

The results were confirmed with the standard identification methods and antibiotic susceptibility tests.

MALDI-TOF reduced the diagnostic process from 24-72 hours to few minutes. The high sensitivity of 94.4% and the ability to detect more than 2000 microorganisms require its implementation as a routine method in laboratory practice.

CONCLUSION: The studied methods have a high diagnostic value. They show significant advantages over the conventional methods and contribute to an adequate assessment of the status and treatment in patients with bacteremia.

PRACTICAL APPLICATIONS: Implementation of FISH, mPCR and MALDI-TOF for the rapid microbiological diagnosis in patients with bacteremia.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Kalchev YI, Lengerova GB, Asif U, et al. Fatal chemotherapy-induced combined infection in a Hodgkin lymphoma patient: case report. *Folia Med (Plovdiv)* 2019; 61(4):620-3.

Clinical and biological approaches to clarify the role and regulation of YKL-40 in systemic sclerosis

CONTRACT: Project № DPDP-06/2018

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RESEARCH AREA: Biomedical

AIM: To assess a comprehensive clinical and molecular-biological approaches to systemic sclerosis (SSc) based on YKL-40.

RESULTS: All the patients and healthy controls underwent clinically and high-frequency ultrasound assessment of articular and periarticular structures. Joint involvement was scored according to the new US10SSc score. Based on the specific clinical characteristics patients were divided in two subgroups: a) with diffuse cutaneous SSc; b) with limited cutaneous SSc. Serum concentrations of the following inflammatory markers were evaluated: YKL-40, TNF- α , IL-6, IL-17 and their relationship with clinical features was investigated. Serum levels of YKL-40 and IL-6 was significantly higher in SSc patients compared to the healthy controls. In the patient subgroups, YKL-40 and IL-6 levels were significantly elevated in dcSSc compared to lcSSc patients. Clinical data about the SSc patients showed significantly higher mRSS, synovitis and tenosynovitis in the dcSSc patients. A statistically significant correlation of high magnitude was observed between YKL-40 and the US10SSc and between IL-6 and the US10SSc score. We observed higher levels of TNF- α in patients in comparison with controls and between dcSSc and lcSSc patients.

CONCLUSION: We demonstrate correlation of serum levels of YKL-40 and IL-6 with articular and periarticular involvement in SSc patients. Serum biomarkers in combination with ultrasonographic results US may have a potential role in defining disease activity and stratification, predicting organ involvement, and in the prognosis of SSc.

PRACTICAL APPLICATIONS: To support clinical diagnosis and prognosis of SSc by clarifying the biological role of multifunctional proteins like YKL-40 and IL-6.

SCIENTIFIC PUBLICATIONS:

1. Karalilova R, Kazakova M, Sapundzhieva T, et al. Serum YKL-40 and IL-6 levels correlate with ultrasound findings of articular and periarticular involvement in patients with systemic sclerosis. *Rheumatol Int* 2019, doi: 10.1007/s00296-019-04402-9, IF₂₀₁₈ = 2.20

Possibilities for early diagnosis and microinvasive treatment of initial non-cavitated approximal caries lesions

CONTRACT: Project № DPDP-08/2018

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⁵ Students, Faculty of Dental Medicine, Medical University of Plovdiv, Bulgaria

RESEARCH AREA: Dental medicine

AIM: To compare the diagnostic accuracy of several methods for early proximal caries detection and the penetration ability of an infiltrant and an adhesive into non-cavitated caries lesions.

MATERIALS AND METHODS: Fifty-eight proximal surfaces of extracted premolars and molars were examined by visual inspection, bitewing radiography, DIAGNOdent with proximal contact and DIAGNOdent directly in the lesion. Results were compared to histological gold standard. Statistical analysis with ROC curve, sensitivity, specificity and diagnostic accuracy was performed for initial, developed and advanced demineralization. Paired lesion halves were randomly allocated for treatment with either an infiltrant or an adhesive, labeled with 0.1% TRITC. Specimens were observed by confocal laser microscopy in dual fluorescence mode. Lesion depths, penetration depths and percentage of penetration were measured.

RESULTS: Sensitivity of visual inspection 16-33%, specificity 93-100%, sensitivity of bitewing radiography 54-67%, specificity 93-94%, sensitivity of DIAGNOdent with proximal contact 88-91%, specificity 79-89%, sensitivity of DIAGNOdent directly 89-92.5%, specificity 81-93%. The highest diagnostic accuracy, increasing with the increase of demineralization, showed DIAGNOdent directly, followed by DIAGNOdent with proximal contact, bitewing radiography and visual inspection with the lowest accuracy. The infiltrant demonstrated higher penetration ability (penetration depth 318 µm, percentage of penetration 49.78%) than the adhesive (penetration depth 57.69 µm, percentage of penetration 8.85%).

CONCLUSION: The use of contemporary diagnostic devices increases the possibility for early detection. Resin infiltration is a promising approach to arrest lesion progression.

PRACTICAL APPLICATIONS: The combination of several diagnostic methods makes early caries detection possible. Infiltration fills the gap between prevention and operative treatment.

SCIENTIFIC PUBLICATIONS:

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A pilot study on the role of the epitranscriptome and the N6-adenosine-methylation complex in the tumorigenesis of colorectal cancer

CONTRACT: Project № DPDP-10/2018

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RESEARCH AREA: Biomedical

AIM: To clarify the role of the mRNA N⁶-adenosine methylation apparatus in the tumorigenesis of colorectal cancer (CRC)

MATERIAL AND METHODS: The expression of 8 m6A-related genes (*METTL3*, *METTL14*, *RBM15*, *WTAP*, *VIRMA*, *ZNF217*, *FTO*, *ALKBH5*) was measured by qPCR in tissue samples from high-grade gliomas and colorectal cancer, as well as in cell culture samples. To quantify m6A-RNA in total RNA isolated from the samples, we used a colorimetric ELISA test.

RESULTS: There is increasing evidence that methylation of N6-adenosine (m6A) in mRNA plays an important role in the control of various physiological and pathological processes. Our results indicate dysregulated expression of methylases and demethylases in tumor tissue isolated from patients with high-grade gliomas. In particular, the transcription levels of the m6A RNA methylation inhibitor ZNF217 are significantly upregulated. Changes in the transcription levels of the studied genes and the amount of m6A in tumor versus normal tissue were not observed in CRC. Thus, our results do not suggest a significant role for m6A methylation in the carcinogenesis of CRC, but further analyses are needed to support this conclusion. In epithelial cells of colon carcinoma cell lines, the expression of the studied genes is dysregulated relative to control cells. In the future, these results should be confirmed by other more appropriate control cells and protein expression studies.

CONCLUSION: N6-adenosine methylation of mRNA has differential activity in the oncogenesis of various cancers.

PRACTICAL APPLICATIONS: Optimization of the manufacturer's transfection protocol for small interfering RNAs in the HCT-116 colon carcinoma cell line.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

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Investigation of some characteristics of the biological activity of a new isoquinoline compound with the papaverine-like chemical structure

CONTRACT: Project № DPDP-11/2018

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RESEARCH AREA: Biomedical

AIM: The investigation of the potential biological activity of a newly synthesized isoquinoline derivative molecule with a papaverine-like chemical structure.

RESULTS: The IQP molecule (2-chloro-N-(1-(3,4-dimethoxyphenyl)propan-2-yl)-2-phenylacetamide) was synthesized by the Grignard method. Isometrically and by the single sucrose-gap method, IQP effects of contractile activity and bioelectrogenesis on isolated smooth muscle preparations (SMPs) from the stomach corpus of male Wistar rats were established. Male white rats were tested for active and passive training; and for horizontal and vertical motor activity under IQP. An acute toxicity studying was performed on white mice (Albino).

IQP relaxes SMPs in a range $1 \times 10^{-5} \div 2.5 \times 10^{-4}$ mol/l. Relaxation was statistically reduced in the presence of 1×10^{-7} mol/l nifedipine (blocker of L-type Ca^{2+} channels) or 5×10^{-6} mol/l KT-5720 (inhibitor of protein kinase A (PKA)). At an IQP value of EC_{50} (5×10^{-5} mol/l), the bioelectrical parameters of the slow wave are affected.

IQP impacted *in vivo* improves the active and passive training of rats, increases horizontal and vertical motor activity. The LD_{50} of IQP was 3500 mg/kg determined on white mice. IQP showed lower acute toxicity to rodents than the well-known isoquinoline papaverinehydrochloride

CONCLUSION: An association between the probably IQP-induced blocking function at Ca^{2+} influx through the potential-dependent membrane Ca^{2+} channels can be suggested, leading to a decrease in $[\text{Ca}^{2+}]_i$ and activation of the cAMP signaling pathway because PKA-phosphorylation of L-type Ca^{2+} channels in SM provokes an inactivation reaction.

PRACTICAL APPLICATIONS: The established degree of biological activity characterizes IQP as a substance with functional characteristics of an antispasmodic with myotropic action and could lead to the development of a new papaverine-based pharmacological drug.

SCIENTIFIC PUBLICATIONS:

1. Gledacheva VN, Stefanova ID, Slavchev VI, et al. Impact of a newly synthesized molecule (2-chloro-N-(1-(3,4-dimethoxyphenyl) propan-2-yl)-2-phenylacetamide) on the bioelectrogenesis and the contractile activity of isolated smooth muscles. *Folia Med (Plovdiv)* 2020 doi: 10.3897/folmed.62.e47844. in print ID 47844.
2. Gledacheva V. Determination of Half Maximal Effective Concentration by Application of Papaverine and IQP on Rat's Stomach Smooth Muscles. *Scientific Reports "Science and Youth"* 2020, p. 27-30.

Comparative study of the accuracy of spatial objects created by different methods

CONTRACT: Project No DPDP – 12/2018

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RESEARCH AREA: Dental medicine

AIM: Comparative study of the accuracy of objects created by different methods - classical (casting a plaster model) and modern (3D printing and CAD/CAM technology).

MATERIAL AND METHODS: Teeth 11, 16, 37 of the phantom model were used as a base for creation of the objects. The classical experimental units were created by the classical method for casting of metal structures. For the production of the experimental units by the modern technologies, the phantom model was scanned with an intraoral scanner and a digital file is created. ProC[®] DMP 200 Dental system sintered CoCr alloy test samples. Experimental units from Dental Model Resin and Dental LT Clean Resin were created using Formlabs2. CAD/CAM technology was used to mill PMMA disc patterns. The created experimental units and the standard were measured with a digital caliper at 4 points.

RESULTS: Statistical processing was performed with SPSS v19 In comparison of the standard and the digital file, no significant difference was observed in three of the dimensions - MD at the cervical part and equator, and VL at the cervical part. In comparison of the all created objects by the three technologies, no significant statistical difference in the measured sizes was found. The differences were minimal and the obtained objects corresponded to a large extent to the dimensions of the standard.

CONCLUSION: The objects made of different materials and different techniques differ minimally in size from the digital model.

PRACTICAL APPLICATIONS: For production of: metal prosthetic constructions; models; splints; dentures; implant guides.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Shopova D, Bozhkova T, Slavchev D. Cobalt-chromium experimental bodies by 3D printer technology. Scientific Works of the Union of Scientists in Bulgaria – Plovdiv, series B. Natural Sciences and Humanities. 2019;XIX: 215-218.
2. Shopova D, Bozhkova T, Slavchev D, et al. Comparative research of scanning accuracy with 3 Shape intraoral scanner. Knowledge International Journal. 2019: 35(4):1087-91.
3. Shopova D, Bozhkova T, Slavchev D. Clinical case of non-removable prosthetic construction by 3D and classical technology. Scientific Works of the Union of Scientists in Bulgaria – Plovdiv, series B. Natural Sciences and Humanities. 2019;XIX: 211-214.
4. Bozhkova T, Shopova D, Slavchev D. Application of 3D printers in dental practice. Scientific works of the Union of Scientists in Bulgaria - Plovdiv. Series D. Medicine, pharmacy and dental medicine. 2020: XXIV; 364-367.
5. Bozhkova T, Shopova D, Slavchev D. Application of 3D printers in medicine. Scientific works of the Union of Scientists in Bulgaria-Plovdiv. Series D. Medicine, pharmacy and dentistry. 2020: XXIV; 368-71.
6. Bozhkova T, Shopova D, Slavchev D. 3D printing of experimental bodies through FORMLAB 2. Scientific works of the Union of Scientists in Bulgaria-Plovdiv Series D. Medicine, pharmacy and dental medicine. 2020: XXIV; 372-5.
7. Bozhkova T, Shopova D. Comparative investigation of objects made by classical technology and additive manufacturing. Knowledge international journal 2020; 40(4):655-9.

Immunologic characteristics of chronic periapical periodontitis – clinical, diagnostic and prognostic aspects

CONTRACT: Project № DPDP-13/2018

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RESEARCH AREA: Dental medicine

AIM: The aim of this study was to investigate the diagnostic potential of aMMP-8 and YKL-40 levels in gingival crevicular fluid (GCF) in teeth with asymptomatic apical periodontitis (AAP) and a clinically healthy marginal periodontium. The goal was to propose a non-invasive approach for AAP diagnosis and design a prognostic model for the disease's dynamics.

MATERIALS AND METHODS: Thirty-one patients with a single chronic periapical lesion of endodontic origin and clinically healthy marginal periodontium were enrolled in the study. GCF was collected from all teeth with AAP (n=31) and their healthy contralaterals (n=31). The samples were sent to a laboratory and the levels of aMMP-8 and YKL-40 were established via ELISA. Limited field of view cone-beam computed tomography was performed on all lesions and their volume was calculated. The results were compared with the GCF biomarker levels.

RESULTS: aMMP-8 levels were significantly higher in the samples collected from teeth with AAP (p<0,00), while the YKL-40 levels were significantly lower (p<0,05). A moderate positive correlation between lesion volume and aMMP-8 levels were established.

CONCLUSION: GCF composition is modified by chronic inflammatory processes in the periapical area. aMMP-8 is a potential diagnostic biomarker for the assessment of AAP. The GCF levels of YKL-40 can be used to monitor the disease's dynamics.

PRACTICAL APPLICATIONS: The utilization of GCF biomarkers for the assessment of AAP provides an alternative, non-invasive, easy and fast diagnostic tool.

SCIENTIFIC PUBLICATIONS:

FULL TEXT PAPERS ONLY

1. Karteva T, Manchorova-Veleva N. Biomarker for Asymptomatic Apical Periodontitis in Gingival Crevicular Fluid: aMMP-8. Eur J Dent 2020;14:239–244.

Comparative analysis of different types of CAD/CAM fabricated single crowns over implants

CONTRACT: Project № DPDP-14/2018

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RESEARCH AREA: dental medicine

AIM: Prospective comparative analysis of different types of single-unit implant restorations.

MATERIALS AND METHODS: Ninety-six single-unit restorations over implants were fabricated – 64 using the CAD/CAM technology and 32 in a conventional manner. Longevity, success, modified USPHS criteria, modified bleeding, plaque, and calculus index as well as marginal bone loss around the implants were investigated.

RESULTS: The results of the current study show 100% success and longevity rate for all the fabricated constructions. The modified USPHS criteria showed mostly "A" scores for color and morphology of the crowns. There is a tendency for stable modified plaque and calculus indexes. The values for the modified bleeding on probing index show improvement over the 12-month study period, whereas the periodontal pocket depth increased with 0.5 mm on average for the same period [F=60.53, p<0.001]. There is a significant increase in the marginal bone-loss around all the restored implants [F=666.90, p<0.001]. The comparative analyses between the different study groups – according to the way of manufacturing, fixing the restoration to the implant, type of alveolar preservation material and implant inclination, did not show any statistically significant differences.

CONCLUSION: The method for manufacturing, inclination of the implant and type of alveolar preservation method as well as the type and method of fixing the restoration does not seem to affect any of the studied parameters for the studied period.

PRACTICAL APPLICATIONS: Based on the results of the current study a recommendation towards the routine use of both methods for manufacturing (conventional and digital) and fixing (cement or screw-retained) of single crowns over implants can be given.

Epithelial to mesenchymal transition in carcinomas of the endometrium, carcinomas of the uterine body and endometriosis

CONTRACT: Project № DPDP-15/2018

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RESEARCH AREA: Biomedical

AIM: To investigate the significance of the epithelial-mesenchymal transition (EMT) in the evolution of endometrial adenocarcinomas, carcinosarcomas of the uterine body and endometriosis with the following immunohistochemical markers: E-cadherin, Beta-catenin, Vimentin, p53, Estrogen and Ki67.

MATERIALS AND METHODS: Our study includes a retrospective analysis of 261 cases of tumors of the uterus and cases with endometriosis in the biopsy archive of Departments of Clinical Pathology at St George University Hospital and Pulmed University Hospital for a 3-year period (2016-2018). The histological and immunohistochemical tests were done at the morphological center of MU-Plovdiv. The methods used include classical histological staining with hematoxylin-eosin, immunohistochemical testing and statistical methods.

RESULTS: We studied 261 cases, which were distributed in groups - 32 cases of endometrial carcinoma (EC) type1, 10 cases with EC type2, 208 cases with endometriosis with different localization and 11 cases of uterine carcinosarcomas. There were selected 75 cases for testing with the above-mentioned markers of EMT and the proliferative marker Ki67. The results were presented in a suitable form for statistical analysis. All the results were integrated in the dissertation of Dr. Serteva.

CONCLUSION: EMT is a key mechanism for the invasion and more aggressive course of the malignant tumors of the uterine body and aids for the quicker progression of EC in patients who suffer from both endometriosis and EC.

PRACTICAL APPLICATIONS: The immunohistochemical markers we used are accessible to every pathologist and can help identify the cases with endometriosis, EC and uterine carcinosarcomas with positive EMT-status, which have more aggressive course.

SCIENTIFIC PUBLICATIONS:

1. Serteva D, Poryazova E. Endometrial carcinomas and endometriosis - morphological characteristics and the role of the epithelial to mesenchymal transition. Medical Review No 3/2019.
2. Serteva D, Poryazova E. Carcinosarcomas of the uterine body - hypotheses of development and differentiation. Bulgarian Medical Journal No 1/2019
3. Serteva D, Poryazova E, Velikova TV. Endometriosis Locations and Coexistence with other Uterine Conditions in a Bulgarian Sample of Patients. American International Journal of Multidisciplinary Scientific Research, 14 May 2019, 5(2):5. Available from: <https://www.cribfb.com/journal/index.php/aijmsr/article/view/255>.
4. Serteva D, Poryazova E, Velikova TV. Morphological aspects and comparative study of endometrioid and non-endometrioid carcinomas of the endometrium in a sample of Bulgarian patients. Znanstvena misel No 30/2019, ISSN 3124-1123 VOL.1, 17-21pg

Index

A					
Abrashev, H	89	Bivolarska, A	39, 46, 47	Dimcheva, T	128
Ahmad, NT	127	Blandino, G	10, 41	Dimitrov, I	39
Ailles, L	10	Blazhev, AB	74, 83	Dimitrov, M	138
Aladjova, M	157	Bodurov, I	35	Dimitrova, AA	74
Aleksandrov, S	62, 139	Bodurov, I	132	Dimitrova, M	40
Alexandrova, E	89	Boeva, T	130	Dimitrova, N	97
Alexandrova, V	140	Bolozneva, EV	12	Dimitrova, T	71, 73, 88
Ambrus, R	19	Bosheva, M	148	Dimitrova, D	108, 157
Ananiev, J	89	Botushanova, AD	74	Dimitrova, S	30
Andonov, B	61	Boyadjiev, N	117	Dimitrova, S	61
Andonov, V	125	Boyanov, K	39	Dimitrova, SZ	79, 90,
Andreev, V	147	Boyuklieva, R	135		131
Angelova, P	43	Bozhkova, R	112	Dimitrova-Kirilova, V	104, 105,
Antonov, P	33, 94, 95	Bozhkova, T	64, 140,		108
Antonova, D	46		158	Dimitrova-Popova, D	42,148
Ardasheva, R	147	Bozkurt, S	19	Dimov, I	39
Argatska, A	33	Bozov, PI	79,131	Dimov, R	130
Argirova, M	91, 92,	Buchinska-Simeonova, N	108	Dimov, T	95
	150	Burnusuzov, H	37, 45,	Dimova, R	71,130
	128		152	Divarova, V	77, 132
Arolska, S	121	Buttigieg, G	10	Dobrev, G	86
Asenova, R	51, 52	Byandova, A	51	Dobrev, H	26
Atanasov, B	117, 118			Dobrev, I	145
Atanasova, M	41	C		Dobrev, B	121
Atanasova, N	146	Chakarov, D	53, 54	Docheva, D	11
Atanasova, P	105	Chenchev, I	133, 159	Doikov, I	130
Atanasova, V	117, 135	Chenchev, L	133, 159	Doncheva, D	87
Atanasova-Dimitrova, D	32, 55	Chervenkov, L	120	Doncheva, N	142
Atanassov, A	32, 55, 58	Chochkova-Bukova, L	121	Doshev, A	140, 158
Atanassov, M	96	Cholakova, R	144	Dourado, M	20
Atanassova, A	81, 82	Choneva, M	39	Draganova, K	132
Atliev, K	53	Chonin, A	137	Draganova-Filipova, M	40
Apostolov, G	40	Coneva, V	89	Duhlenki, BI	88
Apostolova, M		Cuisinier, F	26		
				E	
B				Eloy, JA	11
Babacheva, V	123	D		Enev, I	88
Bacelova, M	37	Dachev, D	127	Esad, M	47
Bachurska, S	133, 140	Daskalova, E	36	Exner, G	86
Bakova, D	84, 106	Davarski, A	43		
Bambin, YT	112	Davcheva, D	122, 152	F	
Batalov, AZ	44, 76,	Dechev, I	143, 146	Farkas, H	12
	154	Delchev, S	36, 39	Feodorova, Y	140, 156
	76,154	Delev, D	85, 142	Filipov, I	155
Batalov, ZA	112	Delkov, D	143	Fokkens, W	8
Becheva, MV	144	Dencheva, M	137	Fontemaggi, G	10
Belcheva-Krivorova, A	35, 51, 52	Denev, P	36, 46		
Belev, N	32,146	Deneva, T	80, 81,	G	
Beleva, E	127		120, 121,	Gabbianelli, R	21
Belovejdov, V	111	de Vries, N	123, 146	Ganci, F	10
Benkova, K	74	Dermendzhiev, S	25	Ganev, M	121
Betova, TM	10	Dermendzhieva, Y	97, 98	Gardjeva, PA	38, 79,
Bicciato, S	19	Dichev, A	145		131
Bilge, B		Dichev, VD	41	Gatseva, P	105
		Dilova, T	76, 154	Gavazov, K	132
			51		

Gavazova-Hristozova, G	137	Hodzhev, V	40	Kavlakova, L	100
Gencheva, D	79	Hristova, D	88	Kazakova, MH	65, 76, 154
Geneva-Popova, M	38, 44, 134	Hristova, E	153	Keat, SJ	14
Georgescu, A	21	Hristova, P	111	Kehayov, I	43, 56
Georgiev, K	99	Hristozova, E	137, 151	Kepcheleva, A	126
Georgiev, N	137	Hugdahl, K	22	Keskinova, D	65
Georgiev, P	123	I		Khalique, A	155
Georgiev, Y	46	Ilieva, E	119	Kichukova, K	68
Georgiev, Zh	139	Ioanidu, L	135, 143	Kilova, K	69, 70, 104, 127
Georgieva, K	39, 116, 117, 118, 135	Iordanov, G	133	Kiradzhiska, D	132
Georgieva, K	131	Isheva, A	144	Kirev, I	127
Georgieva, LH	72	Ivanov, A	33, 94, 95	Kireva, D	107
Georgieva, M	40	Ivanov, B	127	Kirina, V	153
Georgieva, M	72, 113	Ivanov, H	32, 34, 129	Kiselov, S	101, 102, 137
Georgieva, M	126	Ivanov, I	54, 83	Kitov, B	43
Georgieva, Y	63	Ivanov, K	92, 93	Kitov, S	36, 121
Georgieva, YP	79, 131	Ivanova, H	129	Kitova, T	127
Gercheva, K	131, 152	Ivanova, J	109	Kmetov, V	122
Gerginska, F	39	Ivanova, K	79	Koeva, Y	84
Gerov, V	30	Ivanova, K	89	Kolev, N	94
Gesheva, Y	64	Ivanova, L	45	Koleva-Georgieva, D	59
Getov, I	49	Ivanova, N	116, 117, 118, 135	Kolesnyk, Y	22
Getova, V	48, 90	Ivanova, Ts	152	Komarowska, H	17
Gevezova, M	83, 154	Ivanova, V	133, 159	Komitova, R	43
Gidikova, P	70	Ivanova, V	67	Konareva-Kostianeva, M	32, 57, 59
Gizdakova, V	77	Ivanovska, M	142, 151	Kondova, Y	55, 58
Gledacheva, V	157	J		Konstantinova, D	103
Gogova, T	41	Jopek, K	17	Kopchak, A	22
Goranova-Marinova, V	30, 32, 34, 80, 81, 123, 129	K		Korovska, S	107
Graklanov, V	32	Kaisheva, V	156	Kortenska, L	118
Grigoryan, AV	74	Kalaydzhieva, M	99	Kostadinov, I	142
Grudeva-Popova, Zh	30, 32, 34, 74, 76, 80, 81, 146, 147	Kalinova, K	55	Kostadinov, R	27, 72, 82, 113
Gulubova, M	89	Kalnev, M	56	Kostianeva-Zhelinska, S	57
Gundasheva, Zh	67	Kan, B	19	Kostov, G	156
Gurgurova, G	61, 62	Kanarev, M	36	Kostov, K	83
Gvozdeva, Y	48, 49	Kanazirski, N	133	Kovachev, N	51, 52
Gyimah, P	136, 159	Karabova-Hambarova, I	110	Kozev, P	41
H		Karaboydeva, V	112	Kraev, K	44, 134
Hadzhi, M	89	Karalilova, RV	76, 154	Kraeva, M	134
Hadzhiev, D	53, 54	Karamitev, S	57	Krastev, AD	147, 157
Hadzhieva, B	75	Karamiteva, M	40	Krasteva, M	58
Hadzhieva, E	53, 54	Karpishchenko, SA	12	Krasteva, S	99
Hadzhieva, S	114	Karteva, E	65, 136, 159	Krastinova, D	55
Hadzhigaev, V	124	Karteva, T	65, 136, 159	Kratchanova, M	46
Hadzigeorgieva-Kanazirska, P	133	Kasnakova, P	75, 113	Krumova, S	58, 59
Hanna, R	17	Kassarova, M	48, 49, 90, 91	Kukleva-Todorova, M	126
Harizanova, N	106	Katsarov, P	48, 90	Kuneva, M	97
Harizanova, S	106, 115	Katsarova, MN	79, 131	Kussovski, V	46
		Kavlakov, G	105	Kyuldzheva, Y	40
				L	
				Lalova, V	106, 109
				Lazarov, S	51
				Lebanova, H	48, 49, 90, 92, 93

Lengerova, G	132, 153	Moshekov, E	51, 53, 54,	Petkova, N	85
Levallois, B	26		127	Petkova, S	136, 159
Levterova, B	78	Mourdjeva, M	155	Petrov, J	30
Linev, A	32, 34,129	Mumdjiev, I	45	Petrov, MM	132, 153
Lupanov, S	127	Murdjeva, M	39, 45,	Petrova, A	148
Lyubenova, A	67		132, 151,	Petrova, G	106, 109
			153	Petrova, R	155
M		Musurlieva, N	158	Persson, M	15
Maes, M	14	N		Peychev, L	135
Makakova-Tilova, D	62	Naimov, S	156	Peycheva, M	120
Maksymov, D	22	Nakov, V	43	Pigliónico, S	26
Mancheva, R	132	Naseva, E	49	Pilicheva, B	47, 48, 49
Manchorova-Veleva, N	27, 65,	Naydenov, V	128	Platikanova, M	111, 112
	136, 159	Nenchovska, Z	116, 117	Popov, I	41
Manolova, D	40, 86	Nenov, M	127	Popov, V	74, 76, 77,
Marinov, P	118	Nenova, I	77		146, 147
Marinov, V	58, 59	Nestorova, V	104, 105,	Popov, S	128
Marinova, I	110		108	Popova, M	47
Massaldjieva, R	128	Nihtianova, T	126, 144	Popova, S	38, 44,
Matev, B	88	Nikolov, GN	88		134
Mateva, N	69, 70, 86,	Nikolov, F	79	Popova, V	38, 44,134
	104, 110,	Nikolov, P	71	Popovska, SL	74
	125, 128	Nikolov, P	121	Poryazova, E	160
Mateva, TB	88	Nikolova, D	108	Prissadova, N	147
Mehterov, N	41, 140,	Nikolova, J	37	Poumay, Y	16
	154	Nikolova, S	157	Pulito, C	10, 41
Merdzhanova, E	109	Nikolova, S	103	R	
Meurman, JH	15	Nonchev, B	33, 152	Radeva, SY	72
Michaylova, M	145	O		Radinov, A	108
Micheva, I	30	Ognyanov, M	46	Raycheva, G	76, 77
Mihajlova, V	78	Onov, M	144	Raycheva, R	99, 137,
Mihaylov, R	79	Orbetzova, MM	28, 77, 78,		144
Mihaylova, A	142		122, 152	Raynova, S	35
Mihaylova, A	75, 113	Ovchynnykov, O	22	Rhee, CS	23
Mikhaylovskiy, M	8	Oz-Arslan, D	19	Romieu, O	26
Milcheva, N	132	P		Rosenova, D	104, 105
Milecka, P	17	Pacheva, I	83	Rucinski, M	17
Mileva, D	132	Panayotov, I	26	Rusev, M	63
Milkov, D	127	Panayotova, E	96	S	
Milkov, MP	88	Pancheva, R	103, 114	Sacconi, A	10
Milkova, T	110	Panova, M	138	Sakakushev, B	51, 52
Miloshev, G	40	Pashai, B	136, 159	Sandeva, G	70
Minchev, D	83	Pavlov, GK	112	Sándor, GK	18
Minchev, D	67	Pavlova, GS	112	Saracheva, K	157
Mishchenko, O	22	Pechalova-Petrova, P	137	Sarafian, VS	9, 35, 37,
Mincheva, M	135	Pecheva, A	99, 149		40, 41, 65,
Mirchev, D	67	Pehlivanov, B	28		76, 83,
Mirchev, SI	87, 88	Pencheva, B	79		136, 152,
Mircheva, K	137	Pencheva, M	84	Sarpanov, A	154, 159
Miteva, M	33, 122,	Peneva, V	138, 146	Sapunarova, K	53
	152	Peneva, P	48, 91		80, 81,
Miteva, Ts	121	Penkov, D	48, 90	Sapunarova, P	123
Mitkov, M	125	Penkova, M	157	Sbirkov, Y	126, 144
Mitkova-Hristova, V	58, 59	Petkova, G	67		35, 37, 83,
Mitov, G	124				152
Mladenov, R	131				
Mladenova, Ts	47				
Molander, D	35				
Mollova, A	140				

Semerdjieva, M	81, 84, 106	T	Taneva, I	101	V	Valkov, AV	88
Serteva, D	140, 160	Taneva, T	68	Vasilev, P	151		
Shishmanova-Doseva, M	116, 117, 118, 135	Tarnovska, M	71, 130	Vasileva, B	40		
Shopova, D	64, 84, 101, 140, 158	Tarpomanov, Y	144	Vasileva, M	79		
Signori, E	24	Tashev, R	87	Velikova, M	87		
Simeonova, S	47	Tashkova, D	140	Velizarova, M	25		
Simitchiev, K	156	Tchekalarova, J	116, 117, 118, 135	Velkova, K	120, 127		
Sirakov, A	56	Teodosieva, V	40	Veneva, E	126, 144		
Sirakov, S	56	Terziev, D	125	Venkov, K	31		
Sirakov, N	120, 127	Terzieva, D	122, 125, 138	Verma, P	155		
Sivkov, S	29	Theoharides, T	7	Viraneva, A	132		
Sivkova, N	35, 56, 58, 59	Todorov, A	40	Viteva-Velkova, E	128		
Slavchev, D	140, 158	Todorov, G	124, 139	Vladimirov, B	41		
Slavchev, V	157	Todorov, R	64, 159	Vladimirova-Kitova, L	36, 121		
Slavova, D	119	Todorova, T	65, 136, 159	Vladova, A	127		
Slavova, I	91	Todorova, V	155	Vlahova-Petrova, AP	124, 139		
Sopadzhieva, M	147	Todorova-Plachiyska, K	99	Vlaikova, M	146, 147		
Spasov, A	41	Tomov, S	146	Vlaykova, T	39		
Spasov, E	30	Tomov, D	77, 78, 92, 101, 102, 143, 150	W			
Spasov, N	45, 123, 148	Tomova, T	91, 92, 150	Won, TB	18		
Spasova, M	45, 148	Tonev, T	147	X			
Stabholz, A	24	Toneva, A	103	Xenodochidis, Ch	147		
Staneva, D	40	Tornyova, B	68	Y			
Stankova, A	113	Toseva, E	68	Yanchev, N	85		
Stavrev, D	109, 110	Tosheva, A	9	Yaneva, A	69, 104, 106, 128		
Stavrev, V	35	Traikova-Djambazova, N	40, 41, 42, 86, 148	Yaneva, B	145		
Staykov, D	140	Troev, D	78	Yankov, Y	30		
Staynova, R	48, 90, 93	Tsalta-Mladenov, M	105	Yankova, A	104, 105, 108		
Stelcer, E	17	Tsankova, K	111	Yamakova-Vladova, G	79		
Stefanova, I	157	Tsanova, S	99, 149	Yildiz, M	88		
Stefanova, P	51, 127	Tsanova-Stamatova, M	65	Yordanova, G	61, 62		
Stoencheva, S	123, 146	Tsvetanov, Ts	101, 102	Yordanova, M	101		
Stoev, S	49, 92, 93	Tsvetkova, S	80, 81, 123	Yordanova, M	31		
Stoeva, I	137	U		Yordanova, R	83		
Stoeva, M	120	Uchikova, E	79, 127	Yordanova, S	101		
Stoilov, B	127	Ulus, IH	19	Yovcheva, T	132		
Stoilova-Todorova, M	99	Urshev, Z	145	Yungareva, Ts	145		
Stojanova, A	155	Urumova, M	64	Z			
Stoyanov, P	47, 131	Usheva, N	114	Zagorchev, P	40		
Stoyanova, A	45	Uzunov, T	101	Zahariev, N	47, 48		
Stoyanova, N	58, 59	Uzunova, I	126	Zahariev, Z	120		
Stoyanova, R	71, 115, 130	Uzunova, S	70	Zhelyazkov, I	32, 34, 129		
Stoyanova, Ts	117, 135	Uzunova, Y	77, 135, 143	Zhekov, Y	139		
Stoyanova, V	32, 34, 129			Zlatanova, H	142		
Stoycheva, M	151			Zlatev, S	63, 64, 124, 133, 159		
Strano, S	10						
Suzdalov, V	8						
Svinarov, D	29						

Frieze of the healing family (Front Cover)

One of the most beautiful reliefs of the healing cults in the Greco-Roman pantheon is the unique “Frieze of the healing family” exhibited in the Archeology Museum in Plovdiv.

It was excavated in the foundations of an old ruined Turkish mosque in 1921. The correct identification of all figures was performed by Professor Zapryanov in 1964 - Department of Social Medicine. The frieze, according to him, used to adorn a Roman valetudinaria - a military hospital - off the walls of the east entrance of the ancient city which was called Trimontium by the Romans in the late III century. It weighs about 3000 kg and is 2.80 m long and 1.08 m high. The figures on it are framed in a wide rim; it bears the personified images of the Moon (on the left) and the Sun (on the right).*

Presented on the frieze are (from left to right): Jaso and Panacea - Asclepius' daughters, Telesphor - the fortunate genius of the healing process, Asclepius - the god of healing art, Hygeia - his daughter, Epione - Asclepius' wife, Machaon and Podaleirios - his sons worshipped as military physicians.

All figures, except Panacea, are entirely in full face which is very rare in a general composition picture. The frieze's sculptor depicted in great detail the figures' anatomic features, clothes and peculiar attributes. All deities in the composition are on a par with the only association seen between Panacea and Asclepius (Panacea touches a bundle of herbs next to Telesphor's cowl with her left hand, while pouring the cure all (panacea) in Asclepius' bowl).

* Folia Medica 1964; 6(3): 152 - 156