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**Prof. Daniel E. Wainstein, University of Buenos Aires, Argentina**

# **Proceedings of the World Medical Conference**

**Bypass**

**Proceedings of the 2<sup>nd</sup> International Conference on Pathology (Pathology '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Surgery (Surgery '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Cardiology (Cardiology '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Neurology (Neurology '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Gastroenterology (Gastroenterology '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Obstetrics and Gynaecology (Obstetrics and Gynaecology '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Ophthalmology (Ophthalmology '11)**

**Proceedings of the 2<sup>nd</sup> International Conference on Endocrinology (Endocrinology '11)**



**Prague, Czech Republic, September 26-28, 2011**

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## Plenary Lecture 1

### Advances in Laser Surgery



#### Professor Helio Plapler

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**Abstract:** Laser has been used in surgery for the last 50 years, but technological advances and laser/tissue interaction knowledge date from the end of the 90's. Not only the surgical or high power laser but also the low intensity laser and even the light emitting diode (LED) became extremely useful tools for surgeons and other professionals as well. However, the use of this kind of technology brought other problems to be solved. To use laser devices requires training and a learning time. Many surgeons started to use laser devices with no other knowledge than the retailer's handbook and results were mostly inconsistent, bringing the concept of laser surgery to something near to a fraud. Since 1996 we have been studying new surgical techniques and researching on laser/tissue interaction, especially on healing and cell proliferation process, looking for pro-inflammatory and anti-inflammatory regulation factors for both high and low power laser. Laser plays an important role on tissue release of interleukins and vascular endothelial growing factor (VEGF) among others. Our lecture will focus on surgical procedures – mainly in gastrointestinal surgery – and on research findings so to raise new questions to challenge surgeons and researchers.

#### **Brief Biography of the Speaker:**

Helio Plapler graduated from Paulista School of Medicine - Federal University of Sao Paulo, Brazil in 1976. He specialized in General Surgery by the Brazilian College of Surgeons in 1981 and practices as a General Surgeon since 1982 in the Federal Government Healthcare system. He has a Master degree in Health Science (1985) and a Ph.D. in Surgical Technique (1990). He worked as a postdoctoral fellow in the University of Toronto (1991-1993). In 1989 he became Assistant Professor and Associate Professor in 2002, teaching surgical technique at the Federal University of Sao Paulo. Since 1996 he has been working with laser and leads a research group in laser surgery, focused mainly in new techniques and laser/tissue interaction. He is author of 41 papers, one book and 10 book chapters. He was the President of the Brazilian Society for Laser Medicine and Surgery (2006-2008) and is a fellow of the American Society for Laser Medicine and Surgery since 2007.



## Plenary Lecture 2

### Surgical Repair of the Mitral Valve: Can Engineering Do More?



#### **Dr. Daniel M. Espino**

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**Abstract:** Surgical intervention of mitral regurgitation is necessary when severe; at the extreme it leads to death. Early surgical intervention has clear benefits even for asymptomatic patients with severe mitral regurgitation, with clear advantages of valve repair over replacement. However, surgical repair methods for failure of subvalvular mitral apparatus have not been extensively analysed unlike replacement prostheses/devices. Prosthesis development involves a great deal of engineering analysis; both experimental and computational. Such rigor is not currently applied to repair procedures despite both having the same application. Several repair procedures can be used to repair subvalvular failure, including edge to edge repair (i.e. the Alfieri stitch), chordal replacement and chordal transposition (a Carpentier technique). However, little objective evidence is available to aid a surgeon when performing a repair as to which repair procedure to use or how best to perform the repair.

Our Laboratory (in collaboration with other institutes) has been applying engineering methods with the aim of providing objective evidence to aid repair of the subvalvular apparatus. We have compared repair techniques following chordal injury and found edge to edge and chordal replacement to be preferable to chordal transposition for anterior leaflet correction of regurgitation. We intend to develop this to include flow visualisation. In parallel, we are developing a computational simulation to predict force concentration, and unsteady blood flow, that reduce repair efficiency. This requires measurement of certain parameters. Therefore, we have tested subvalvular components to determine their stiffness and likelihood of failure. We have found that despite variations in size and properties chordae share similar stiffness. This is also relevant to chordal replacement and development of better replacement materials. Our collaborators, for example, have started developing constructs that may be suitable for chordal replacement.

With the advent of greater computational resource, subject specific and multi-scale models, this may in future be a useful resource for surgeons. Regenerative medicine may also provide improved repair materials. In the mean time, though, we are continuing research to provide clear and objective guidance not currently available for surgical repair of mitral regurgitation. This is of ever increasing relevance with an advancing population age.

#### **Brief Biography of the Speaker:**

Daniel is currently a Research Fellow at the University of Birmingham, funded by an Intra-European Personal Fellowship. Over the last 10 years he has developed his research experience in Bio-medical Engineering through modelling and mechanical testing of heart valves, with emphasis on mitral valve surgical repair. He obtained his PhD in Bio-Engineering at the University of Aberdeen. Following his PhD, he was awarded a Junior Fellowship by the British Heart Foundation which he held at the University of Birmingham. He has since developed his expertise outside the UK, as a Research Fellow at both the University of Auckland (New Zealand) and the Istituto Ortopedico Rizzoli in Bologna (Italy).

He has been invited to present his research in Switzerland and the UK. He has served on the Conference committee for the World Congress on Engineering and 2nd Workshop on 3D Physiological Human and the international editorial board for the Journal of Clinical Rehabilitative Tissue Engineering Research.

ACKNOWLEDGEMENT: "This researcher is supported by a Marie Curie Intra European Fellowship within the 7th European Community Framework Programme" (Programme number: FP7/2007-2013; under grant agreement n°252278).

## Plenary Lecture 3

### Application of Growth Factors to Anterior Cruciate Ligament Surgery



**Professor Harukazu Tohyama**  
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**Abstract:** Anterior cruciate ligament (ACL) injury is a relatively common knee injury during sports activities. A torn ACL usually occurs through a twisting force being applied to the knee whilst the foot is firmly planted on the ground or upon landing. The standard surgical treatment for ACL rupture is ACL reconstruction by an autogenous tendon graft. After ACL reconstruction, fibroblasts of the tendon graft are necrotized immediately after transplantation and then extrinsic fibroblasts infiltrate in the graft, even if an autogenous tendon graft is used. During this process, the grafted tendon weakens in the early phase after ACL reconstruction surgery. In addition, previous studies suggested that the cell infiltration into the graft occurs very slowly after ligament reconstruction. The slow graft maturation may result in graft failure during the postoperative rehabilitation period. It has been known that growth factors enhance proliferation, migration, and matrix synthesis of cells in vitro. Our laboratory conducted a series of experimental studies for the application of growth factors to ligament reconstruction. The present lecture will review our recent findings of experimental studies that intended to enhance healing of grafted tendon after ACL reconstruction using growth factors.

#### **Brief Biography of the Speaker:**

Dr. Harukazu Tohyama is Clinical Professor of the Rehabilitation Division, Hokkaido University Hospital and Associate Professor of the Department of Orthopaedic Surgery, Reconstruction Surgery, and Rehabilitation Medicine, Hokkaido University School of Medicine, Sapporo, Japan. Dr. Tohyama specializes in Orthopaedic Sports Medicine. He earned his medical degree in 1985 at Hokkaido University School of Medicine and completed his orthopaedic residency training at Hokkaido University Hospital. From 1991 to 1993, Dr. Tohyama was a Research Fellow at the Department of Orthopaedics & Rehabilitation, University of Vermont, Burlington, VT, to study orthopaedic sports medicine under Robert J. Johnson, M.D. and Per A. Renstrom, M.D., Ph.D. He also studied physics and mechanics of articular cartilage as a Research Fellow under Van C. Mow Ph.D. at Orthopaedic Research Laboratory, Columbia University, New York, NY from 1993 to 1994. He received his Ph.D. degree in Medical Science from Hokkaido University School of Medicine in 1996. In 2004, Dr. Tohyama was selected as an AOA(American Orthopaedic Association)/JOA(Japanese Orthopaedic Association) Traveling Fellow and in 2008 as an Anterior Cruciate Ligament (ACL) Study Group Travelling Scientist. During these fellowships, he visited over 20 sports medicine centers in United States and Europe. Dr. Tohyama's research focuses on the stimulation of healing of grafted tendons inside joints, particularly the anterior cruciate ligament (ACL) of the knee. Treatment of this injury remains one of the most challenging problems facing orthopedic science today. Dr. Tohyama is the author or co-author of more than 70 peer-reviewed articles, four review articles and three book chapters on the management of sports injuries.

## Plenary Lecture 4

### Management of High Output of Enterocutaneous Fistulas with a Vacuum Compaction Device



#### **Professor Daniel E. Wainstein**

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**Abstract:** Enterocutaneous fistulas (ECF), are an abnormal communication between the gastrointestinal tract and the body surface, occurring as a complication in 0.8%-1.5% of abdominal operations among other etiologies. Its management is a challenging problem because of high morbidity and mortality and represents a significant health care as well as economic burden. In 1960, Edmunds et al. reported a mortality rate of 43% in 157 patients with this condition. In 1964, Chapman et al. defined guidelines for conservative treatment, improving outcome over the following decades. Nevertheless the mortality rate remains high, ranging between 5% and 30%. Despite attempts at parenteral replacement, electrolytic abnormalities and malnutrition occur in patients with high-output fistulas, and sepsis increase catabolism. Such factors could raise the mortality rate up to 60%. In 1992, Fernandez et al., from Buenos Aires, developed a technique to occlude intestinal communications with the surface using a vacuum compaction device with high negative pressure values, named SIVACO (Spanish acronym: Vacuum-compaction system)

Thus, by enteric fluid loss reduction and its redirection into the normal intestinal pathway, EFC management is significantly simplified. Also parenteral nutrition reduction or suppression, as well as spontaneous closure of the fistula, may occur. Otherwise, definitive surgical fistula repair can be carried out choosing the best opportunity in clinical and nutritional recovered patients. The aim of this lecture is to present the results of our experience concerning the management of high-output of EFC using a vacuum-compaction system.

#### **Brief Biography of the Speaker:**

Daniel E Wainstein graduated from School of Medicine at the University of Buenos Aires, Argentina. He made the Surgical Residence at Churruca Police Hospital in Buenos Aires and obtained his speciality in General Surgery by the Argentinian Association of Surgery in 1990. He has been practicing as a General Surgeon since 1988 at the Hospital "E. Tornu" from the Government of Buenos Aires City. He became Assistant Professor in 1989 and Authorised Professor in 2010, teaching Surgery at the University of Buenos Aires. Since 1991 he has practised laparoscopic surgery, topic on which he has lectured and published copiously. In 1997 he started to research into enterocutaneous fistulas and topical negative pressure therapy. Since then, he has presented his experience in national and international congresses, and he has published his works at the Revista Argentina de Cirugia, World Journal of Surgery, International Journal of Surgery and invited book chapters. He also presented a Doctoral Thesis about this subject and because of that he was appointed Doctor of University of Buenos Aires in 2009. Finally, he became Member of the Argentinian Academy of Surgery last year.

## Plenary Lecture 5

### Suggestion to Add Cushing's Syndrome to the List of the Diseases with High Cardiovascular Risk in Relevant Guidelines



#### **Associate Professor Goran Pante Koracevic**

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**Abstract:** The aim of the paper is to give rationale and to propose listing Cushing's syndrome among high CV risk conditions. Respectable amount of published data points to several-fold enhanced mortality in Cushing's syndrome. Reasons are high prevalence of numerous cardiovascular risk factors in Cushing's syndrome, such as arterial hypertension, diabetes mellitus, dyslipidemia, obesity. Consequently, virtually all patients with Cushing's syndrome have also the metabolic syndrome, which is recognized as loaded with high cardiovascular risk. Specifically, despite the young mean age, 80% of CS patients presented a 'high' or a 'very high' CV risk, a > 20% risk of a major CV event within the next 10 years. Hypertension -induced target organ damage, including left ventricular hypertrophy and retinopathy, are frequently found in Cushing's syndrome, adding to the global cardiovascular risk. Moreover, diabetes mellitus is listed as high risk condition, but Cushing's syndrome (with majority of patients having either diabetes mellitus or impaired glucose tolerance) is not. In recent guidelines Cushing's syndrome is mentioned as a risk factor for aortic dissection, and it should be also cited as a disease with high cardiovascular risk (like diabetes mellitus and chronic renal failure) in the pertinent guidelines.

#### **Brief Biography of the Speaker:**

Koracevic Pante Goran was born in 1961; he graduated in 1985 as the Best student of the University. He finished the specialization in Internal Medicine (1995), and became Master of Science in Endocrinology (1991, supported by The Serbian Academy of Sciences and Art). Doctoral thesis „Hypertensive Emergencies and Urgencies in Cardiology“ (Total: 6264 patients) was finished in 2003. He works at Department for Cardiovascular Diseases, Clinical center Nis since 1988, mostly the in Coronary Care Unit. He is the leader of the Multidisciplinary Team for Venous Thromboembolism in Clinical Centre Nis. He became Assistant in Internal medicine - Cardiology, Medical Faculty of Nis in 1992, Assist. Professor in 2005 and Assoc. Professor in 2011. He won The Young Investigator Award of The International Society of Electrocardiology in 1991. He participated in writing of the 6 books in Internal medicine. He has over 500 presented / published papers, being the first author in half of them. He has over 30 entries in PubMed, including classifications of Troponin, D dimer, suggestions for the improvement of protocol for pulmonary embolism and the Universal definition of myocardial infarction, etc. He wrote 15 Reviews for International journals. He is the member of the Working Group 27 on Acute Cardiac Care of the European Society of Cardiology, as well as a member of the International Society for Holter and noninvasive Electrocardiology (ISHNE).

## Plenary Lecture 6

### A Method to Calculate the Parameters of Non-Linear Espvr in the Ventricles



#### **Professor Rachad M. Shoucri**

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**Abstract:** A challenging area of research in cardiology over the past years has been the study of the properties of end-systolic pressure-volume relation (ESPVR) in the left or right ventricle in a way to determine results that can be used for clinical applications. ESPVR refers to the relation in the ventricles between pressure  $P_m$  and volume  $V_m$  near end-systole when the myocardium reaches its maximum state of activation. Of particular interest in the linear approximation has been the study of the variation in the slope  $E_{max}$  and/or the volume axis intercept  $V_{oL}$  (L for linear) of the ESPVR. The non-linear model is based on a mathematical relation previously derived by the author in which the active pressure  $P_{iso}$  developed by the myocardium during the contraction phase (also called isovolumic pressure) is included in the formalism describing the pressure-volume relation (PVR) in the ventricles. Slope, intercept  $V_o$  and  $P_{iso}$  can be calculated at intermediate positions during the contraction phase, and the same parameters (slope,  $V_{om}$ ,  $P_{isom}$ ) can be calculated along the ESPVR when the maximum state of activation of the myocardium is reached. The calculation of  $V_o$  (or  $V_{om}$ ) can be done in a completely non-invasive way by measuring the volume of the ventricle and the volume of the myocardium by ultrasound or MRI. The study shows that the non-linear model of ESPVR contains a rich collection of information that can be exploited for clinical applications. The work is an example that illustrates the impact that mathematical physiology can have on the progress of physiology, it is similar to the impact that mathematical physics had on the progress of physics.

#### **Brief Biography of the Speaker:**

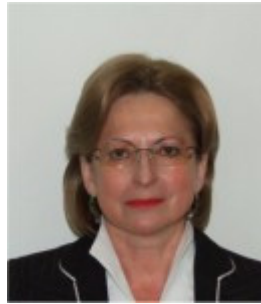
The author is professor in the Department of Mathematics and Computer Science of the Royal Military College of Canada. He has a BSc in Electrical Engineering (Alexandria University, Egypt), an MSc and a PhD in Physics from Laval University (Quebec, Canada).

After obtaining his PhD, he worked for five years as analyst at the Institut de Cardiologie de Quebec where he developed his interest in mathematical physiology and medical physics.



## Plenary Lecture 7

### Non-Thrombotic Neurological and Cardiac Manifestations in Antiphospholipid Syndrome



#### Professor Ljudmila Stojanovich

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**Abstract:** Antiphospholipid syndrome (APS) or Hughes syndrome is traditionally described as a syndrome consisting of recurrent fetal loss, vascular thrombosis, and positive aPL levels. Nowadays, APS is increasingly recognized as a multisystem disease, the clinical expression of which may include cardiac, neurological, hematological, cutaneous, and other manifestations. Different types and levels of aPL appear to be important for the frequency of non-thrombotic APS manifestations. Central nervous system involvement is one of the most prominent manifestations of APS; including thrombotic (CVI, Cerebral venous sinus thrombosis) and various non-thrombotic CNS manifestations, such as dementia, epilepsy, migraine, cognitive dysfunctions, and chorea. Additionally, a lot of studies have suggested associations with carotid artery intima-media thickness (IMT), a possible manifestation of early atherosclerosis, and abnormal left ventricular (LV) diastolic filling. Objectives: The aim of this study was to investigate the association between nonthrombotic neurological and cardiac manifestations in patients with antiphospholipid syndrome (APS), as well as their connection with type and level of antiphospholipid antibodies. Methods: Our prospective study comprises 333 patients: 218 with primary and 115 with secondary APS. Antiphospholipid antibody (aPL) analysis included detection of aCL (IgG/IgM), ?2GPI(IgG/IgM) and LA, and served to evaluate associations with distinct neurological manifestations. Results: Presence of aCL IgG was more common ( $p=0.001$ ) in SAPS, while LA was more common in PAPS patients ( $p=0.002$ ). High ?2GPI IgM levels ( $>100\text{PLU/ml}$ ) were more common in epilepsy ( $p=0.00001$ ) in PAPS, and in transient ischemic attack ( $p=0.029$ ) in SAPS. High ?2GPI IgG levels ( $>100\text{PLU/ml}$ ) were more common in epilepsy ( $p=0.035$ ) in SAPS. Chorea, migraine and epilepsy occurred more often in SAPS, and headache and depression in PAPS. We revealed statistical significance considering the presence of aCL IgG and acute ischemic encephalopathy in SAPS, aCL IgM and epilepsy in SAPS, aCL IgM and migraine in PAPS, ?2GPI IgG and chorea in SAPS, and ?2GPI IgM and TIA and epilepsy in PAPS. LA was linked to depression, transient global amnesia and migraine in PAPS. Patients with unstable angina pectoris were more likely to develop TIA in both PAPS and SAPS, epilepsy and transient global amnesia in PAPS, and acute ischemic encephalopathy in SAPS. Patients with valve vegetations were more prone to epilepsy and depression. Conclusion: Certain aPL types and levels are associated with distinct neurological non-thrombotic manifestation, suggesting their predictive role. There is a strong link between some non-thrombotic neurological and cardiac manifestations in APS patients, suggesting complexity and evolutionary nature of APS.

#### Brief Biography of the Speaker:

Ljudmila Stojanovich graduated from Medical School in the Russian Federation in 1979. From 1979 to 1984 she worked as a general practitioner, and received her Board certifications in Cardiology and in Rheumatology in 1984 and 1986, respectively. From 1984 to 1990 Dr. Stojanovich was a Research Fellow at the Institute of Rheumatology of the Russian Academy of Medical Sciences in Moscow, where she defended her M.S. thesis "Clinical significance of antiphospholipid antibodies in patients with Systemic Lupus Erythematosus" in 1986. In 1990 Dr. Stojanovich relocated to Belgrade, Serbia, where she received her Ph.D. in Medicine, with the thesis "Neuropsychiatric manifestations in patients with Systemic Lupus Erythematosus" in 1999. She is affiliated with the Bezhanijaska Kosa University Medical Center of Belgrade University, where she is currently a Research Professor. Dr. Stojanovich's research focuses on Systemic Lupus Erythematosus, Antiphospholipid Syndrome, and on Neuropsychiatric Lupus. She is an author of three monographs and of about 250 articles on various aspects of Rheumatic disorders, published in international and domestic journals and in conference proceedings.

## Plenary Lecture 8

### Inborn Errors of Metabolism and the Heart



#### Professor Anibh M. Das

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**Abstract:** Energy demand of the heart is high and may vary enormously according to physical activity. The main fuels of the heart are fatty acids and to a lesser extent glucose. The heart relies on aerobic energy metabolism therefore the mitochondrial respiratory chain performing oxidative phosphorylation is essential. The mitochondrial ATPsynthase (complex V of respiratory chain) has been shown to be actively regulated in response to cellular energy demand. Increased contractility and/or heart rate rapidly lead to up-regulation of the mitochondrial ATPsynthase which is mediated by calcium. Also enzymes of the citric acid cycle are up-regulated in response to elevated calcium levels.

Inborn errors of energy metabolism can compromise heart function. Defects in fatty acid oxidation (including carnitine deficiency) and of respiratory chain are well known. Furthermore, defects in glycogen catabolism lead to reduced energy generation from carbohydrates, like in glycogen storage diseases type III a (Cori/Forbes) and type II (Pompe). The latter being based on a lysosomal enzyme deficiency, this leads us to the second class of inborn errors of metabolism affecting the heart, the so-called lysosomal storage diseases. By mechanical deposition of storage material, heart function and anatomy are compromised. Examples for this group of diseases are M. Anderson-Fabry, M. Gaucher, MPS I, II and VI, Danon disease. Some of them lead to secondary dysfunction of respiratory chain enzymes, e.g. M. Anderson-Fabry.

Other systemic inborn errors of metabolism affecting the heart include organic acidurias, some of them cause secondary mitochondrial dysfunction. Congenital defects of glycosylation may affect the heart.

Apart from pathophysiological aspects, diagnostic procedures and therapeutic options shall be discussed.

#### Brief Biography of the Speaker:

Anibh Das graduated from Georg-August University Gottingen (Germany) in 1986. In 1988 he finished his MD PhD-thesis at the Department of Systemic Physiology in Gottingen on the topic "Effect of oleic- and palmitic acid on myocardium and heart mitochondria under low-flow anoxia" (summa cum laude). From 1987-1988 he worked in the Department of Lung Physiology at Max-Planck Institute for Experimental Medicine in Gottingen as a Max-Planck scholar. He spent two years at the Department of Biochemistry, University of Oxford, UK as a postdoctoral fellow working on the active regulation of ATPsynthase in rat cardiomyocytes. Anibh Das specialized in Paediatrics at Hannover Medical School (Germany) from 1990-1996 and worked from 1996-2000 as a specialist registrar for inborn errors of metabolism at the Department of Paediatrics, university hospital in Hamburg, Germany. Since 2000 he is head of paediatric metabolic medicine at the Department of Paediatrics, Hannover Medical School (Germany). In 2002, Anibh Das finished a PhD-thesis ("Habilitation") on "Active regulation of mitochondrial ATPsynthase in health and disease" at Hannover Medical School and in 2006 he became professor (Paediatrics). From 2004-2006 he worked part-time at the "Sreening laboratory Hannover" which performs extended newborn screening. His main clinical interest is in inborn errors of metabolism, his research interest in energy metabolism. He published more than 90 papers in peer-reviewed journals and a dozen of review articles. Anibh Das is paediatric member of the ethics commission at Hannover Medical School.

## Plenary Lecture 9

### **The Place of Digoxin/digitalis Cardiac Agent/ Today in the Treatment of Elderly Population: The Challenges of Undefined Dose Effect Relationship and State of the Art**



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**Abstract:** In ancient times plant extracts containing we know today as cardiac glycosides (digitalis) were used either for curing or poisoning purposes. Native people of old Egypt and ancient Romans had also used digitalis as medicine against several disorders including state of oedema. Only later was known by Sir William Withering, who described digitalis in particular as medicine for oedema of cardiac origin. Withering also emphasized the significant toxicity behind the cardiac glycosides extracted from Foxgloves. Centuries later the Digitalis Investigation Group (DIG) in 1997 concluded that digoxin as cardiac glycoside has no influence on mortality, but reduces rate of hospitalization. However, later commentators declared yet beneficial effect of digoxin through not clear mechanism of action on the well being of the patients. Whatsoever, digoxin continues to be an important drug in long-term heart failure patient management. Digoxin serum levels monitoring is aimed to optimise therapy, whereas the concentration required for optimal efficacy without risking toxicity remains not clearly defined even post DIG conclusion. The very challenging matter is that concentration/dose effect relation ship of digoxin, especially in elderly population, to whom digoxin is frequently prescribed. Farther more, elderly people are prone to toxicity due to natural changes conditioned by aging. Besides knowing underlying pathophysiology in the elderly patient population and the drug itself better, therapeutic drug monitoring with very qualified interpretation my help to better control the toxicity risk at the same time avoiding sub therapeutic levels. The present paper brings into attention, how significantly high number of patients on long term digoxin therapy is exposed to levels beyond recommended and evidently within potentially toxic levels. The challenge of poly pharmacy and possible drug–drug interactions based on clinical experience and benefit of therapeutic drug monitoring (TDM) is also discussed.

#### **Brief Biography of the Speaker:**

The author is MD, and PhD graduate of the Charles University, in Prague. Trained as Paediatrician and later as Clinical Pharmacologist, holds Board Certificate from the Institute for Postgraduate Education in Medicine. His present position is consultant in clinical pharmacology at the faculty hospital. The main interest and consultancy area of the author is in particular therapeutic drug monitoring in needy patients including, paediatric and geriatric populations given their pharmacokinetic/pharmacodynamic differences and vulnerability. The author participated in digoxin bioequivalence studies and clinical trials including as principal investigator and co-investigator. He is also dedicated to aid dosage adjustment for transplantation patients, oncology patients and others in intensive care including those with renal failure. The author participates in pregraduate and post graduate education both as a faculty member and as invited speaker in the field of clinical pharmacology. The author is dedicated for safe and better use of medicines for human wellbeing.

## Plenary Lecture 10

### Collagen I Scaffold and Valve Interstitial Cells a Promising Approach for Heart Valves Tissue Engineering



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Co-workers: Elena Filova<sup>1</sup>, Jaroslav Masin<sup>2</sup>, Yuan-Tsan Tseng<sup>3</sup>, David Schornik<sup>2</sup>, Eva Honsova<sup>2</sup>, Alena Lodererova<sup>2</sup>, Lucie Bacakova<sup>1</sup>, Jan Pirk<sup>2</sup>

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**Abstract:** At the present time, used heart valve replacements have several limitations. Mechanical heart valves are constructed of pyrolytic carbon and require anticoagulation therapy. Biological heart valve prosthesis evokes fibrotic tissue production, leading to valve dysfunction with an incidence of 2-4% of patients/year and re-surgery of biological valve prosthesis 15 years after its implantation into the body is indicated in 65% of patients. That is why it is the challenge of heart valve tissue engineering to create a new type of biological heart valve for clinical use.

Extracellular matrix (ECM) of the normal aortic heart valves contain about 50% collagen and approximately 75% of this is collagen I. Collagen I is responsible for the mechanical properties of the aortic heart valve and is located predominately in the lamina fibrosa. The purpose of our study was to evaluate the adhesion, growth and differentiation of pig valve interstitial cells (VIC) cultured under static and dynamic conditions on a laboratory produced porous collagen I scaffold, prepared from 1% bovine collagen (Devro plc) using a freeze-drying method and chemically cross-linked by 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide. Scaffolds were seeded on both sides with VICs and cultured under static and dynamic culture conditions for up to 4 weeks. Control samples were cultured only under static conditions. After 4 weeks, VICs covered the scaffold surface confluenty, penetrated into deeper layers and were strongly positive for vimentin and smooth muscle alpha-actin, which proved the presence of both activated myofibroblast-like and quiescent phenotypes. VICs also produced new extracellular matrix. VIC penetration was influenced by dynamic loading.

We confirmed that laboratory produced 1% collagen I scaffold that mimics the natural architecture of ECM in vivo may be a promising approach in the tissue engineering of heart valves. Collagen scaffolds do not appear to have cytotoxic effects on the seeded cells and support VIC proliferation, differentiation and ECM production.

Acknowledgements: Supported by the Grant Agency of the Ministry of Health of the CR (project No. NT 11270), and the Centre for Cardiovascular Research (project No. 1M6798582302).

#### **Brief Biography of the Speaker:**

The author is cardiologist in the Institute for Clinical and Experimental Medicine in Prague, Czech Republic. 2007 – present time - PhD studies at the Charles University, Prague. Major subject : Heart Valve Tissue Engineering - supervisor - Lucie Bacakova, MD, PhD, Dept. of Growth and Differentiation of Cell Populations, Institute of Physiology, Academy of Sciences of the Czech Republic, Prague.

## Plenary Lecture 11

### Is it Worthwhile to Systematically Assess Sleep Habits in Cardiac Patients?



**Professor Carlos Rivas-Echeverria**

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**Abstract:** Although cardiovascular diseases are the leading death cause worldwide and the leading costs generating disease, and that risk factors for these diseases have been exhaustively investigated, sleep disorders of breathing are almost unknown among general population and among many doctors. Generally sleep habits are simple non-assessed or ignored when evaluating a cardiac patient. A public health problem has a high prevalence, high morbidity and mortality, usually generates great costs, and should be preventable or treatable. Cardiovascular diseases are certainly a major public health problem, so: identifying the most appropriate interventions, considering the effect on resources for proposed interventions and assessing their cost-effectiveness, supporting decision making in health care and planning health services are some of the strategies that public health policymakers must do. Improvements in management of cardiovascular diseases have decreased the mortality, but costs are still very high; while preventive strategies generally receive less funding and attention. Recently an editorial in The Lancet stated that: "The fact that type 2 diabetes, a largely preventable disorder, has reached epidemic proportion is a public health humiliation". Therefore what could we say about sleep disorders and their relationship with cardiovascular diseases? Coronary heart disease, hypertension, arrhythmias (being atrial fibrillation the most frequent), sudden death, stroke, heart failure, pulmonary hypertension, renal failure, obesity and diabetes account most of the visits to an emergency room or a cardiovascular clinic. What if the vast majority of these patients have sleep apnea? Do we ask these patients if they snore or they suffer sleepiness? Robust evidence has been published about the high prevalence of sleep apnea in cardiovascular patients, but is there a causal relationship between these conditions? Sleep disorders of breathing are problems that are easily and cheaply treatable while significantly improving the quality of life. Why aren't they considered systematically as cardiovascular risk factors, if they are potentially treatable? The purpose of this paper is to present some of the data that suggest that sleep apnea is a primary independent risk factors for most cardiovascular diseases, as well as traffic and occupational accidents and other medical problems. We will try to reveal if there is a link and, if so, we would like to propose some diagnostic strategies and present to the medical community the idea that systematically assessing sleep disorders in all cardiovascular patients is a worthwhile public health policy and strategy. So the core of this plenary session is to know if sleep apnea is a cardiovascular risk factor. And if we should systematically assess sleep habits in cardiac patients?

**Brief Biography of the Speaker:**

Dr. Carlos Rivas-Echeverria, MD, PhD, FACP. Specialist in Internal Medicine and in Critical Care. Has a Master Degree on Sleep Medicine and a Diplomate on Franchising Systems Management. Is the Head of the SLEEP CARE Sleep Clinics. Is Full Professor at the University of Los Andes, Head of the Department of Pharmacology. He is cofounder and active Member of the Intelligent Systems Laboratory. Over 60 publications in high level conferences and journals: the main topics of his papers are: Hypertensive disorders of pregnancy, sleep disorders, traffic accidents and artificial intelligence.



## Plenary Lecture 12

### Personalized Neurological Diagnostics from Biomedical Physicist's Point of View and Application of New Non-Linear Dynamics Methods in Biosignal Analysis



**Professor Włodzimierz Klonowski**

Lab. Biosignal Analysis Fundamentals

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**Abstract:** In Physics there exist well defined normal values. It is important to understand that normal values are not independent from one another. Normal boiling temperature of pure water is 100°C but only under normal atmospheric pressure 760 mm Hg. In Medicine normal values practically do not exist. The only such value seems to be 'normal body temperature' - 36.6°C. It is an erroneous belief that in Medicine normal value equals population average value - 'normative databases' no matter how large do not give a possibility of 'reliable comparison' to decide if the given case is 'normal' or 'abnormal'. Even the concept of a disease is relative and should take into account e.g. genetic differences between local populations. For example, sickle cell anemia is genetically inherited and in USA and Europe it is considered to be a serious blood disorder; but in Africa it gives evolutionary advantage - those with sickle cell anemia are resistant to malaria. Human organism (and human brain in particular) is a highly complex nonlinear system, and that is why standardized approach based on protocols may lead to serious errors of judgement. There are differences in defining 'normal' ranges even between quite reliable sources. For example, according to NLM 'Normally, the ICP [Intracranial Pressure] ranges from 1 to 15 mm Hg' (<http://www.nlm.nih.gov/medlineplus/ency/article/003411.htm>) but other sources give ranges like 8 to 18 mm Hg; anyway, what for one person is a quite high ICP for another may be quite low, and if this person was treated according to a protocol that said 'decrease the patient's high ICP' he/she might die. Markers supplied by Biomedical Physicists, e.g. quantitative descriptors of EEG-signal adapted from Nonlinear Dynamics, may help in better assessment of various spontaneous or evoked, normal and pathological functional states of the brain in neuropsychiatric patients, and so may be helpful in deciding diagnosis, treatment and prognosis. But in Medicine two plus two not always equals four [A.Wiland-Zera, MD – private opinion] and that is why there is no alternative to Personalized Medicine provided by a well trained Medical Doctor. It is unbelievable but in the XXI century some scientists still maintain they have demonstrated, using methods like linear forecasting or surrogate data tests of EEG time series, that human brain is a linear system. A geodesist who would maintain that the Earth is for sure flat since he/she had measured many triangles on the Earth surface and found that the sum of angles in each of those triangles were not statistically different from 180°, would he/she still be invited to international conferences and listened to? I will demonstrate use of fractal and symbolic methods for analysis of sleep-EEG and EEG under anesthesia, for revealing influence of electromagnetic fields generated by cellular phones on EEG, as well as for analysis of HRV, posturographic signals, and in biofeedback. Classical neurofeedback is based on spectral characteristics of EEG-signal obtained by FFT; as we have suggested, neurofeedback may be based on non-spectral characteristics, like fractal dimension of EEG-signal. For a special purpose - treatment of stuttering persons - we have constructed a peripheral biofeedback based on capnographic signal i.e. on the concentration of carbon dioxide in the exhaled air.

#### **Brief Biography of the Speaker:**

Włodzimierz Klonowski is the Head of Lab. of Biosignal Analysis Fundamentals at the Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw. Previously he has served as President and Computer Consultant with Canadian Consulting and Tutoring Services, Halifax, NS, Canada (1988 – 1998); Professor and Division Chairman, World Open University, Raleigh, NC, USA, and Halifax, NS, Canada (1986 – 1994); Visiting Professor, Brandeis University, Waltham, Ma, USA (1984 – 1986); Max Planck Fellow, MPI Biophysikalische Chemie, Goettingen, Germany (1982 – 1984); Professor, National University of Zaire, Kinshasa, Congo-Zaire (1980 – 1982). He has Ph.D. from Institute of Physics, Polish Academy of Sciences, Warsaw (1973) and D.Sc. (Dr hab.) from Humboldt University, Berlin, Germany (1990). He has been the leader of several scientific projects, the Coordinator of European Interdisciplinary Schools on Nonlinear Dynamics for System and Signal Analysis EUROATTRACTOR (FP5. 2000-2002) and Leader of the Group of Biosignal Analysis Fundamentals (GBAF) in SENSATION (IP FP6. 2004-2008), Member of Management Committees of COST Actions B27, BM0601,

BM0605. He is the author of numerous scientific papers on interdisciplinary problems concerning Nonlinear Dynamics and Networks Structure-Property Relationships. He has served as Associate Editor of IPCT - Interpersonal Computing and Technology, Electronic Journal for the 21st Century and Editorial Board Member of Computational Biology and Chemistry (Elsevier). He is the Founding Editor and an Editor-in-Chief of open access journal Nonlinear Biomedical Physics (BioMed Central, London, now belongs to Springer). His biograms are included in several European and American Who's Who's, in Wikipedia, and he has a molecular informational structure named after him (Klonowski-Klonowska Conformation, term proposed by S.Ji in 'Molecular Theories of Cell Life and Death', Rutgers U. Press, 1991). W.Klonowski is also interested in philosophical problems, in particular in theory of consciousness, and emotions vs logical thinking, the so called Chaosensology.

## Plenary Lecture 13

### Hepatitis C Infection in Man: A Disappearing Plague as a Result of the Interactions between Virologists, Pharmacologists, Geneticists and Clinicians



**Professor David H. Van Thiel**  
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**Abstract:** The hepatitis C genome has been elucidated and shown to transcribe both structural and non-structural proteins essential for HCV replication. The mechanisms of HCV entry into hepatocytes have only begun to be elucidated, with several different receptors being involved, separately and together (CD81, the VLDL receptor, among others). The transport of the uncoated HCV-RNA once in hepatocytes to and from the endoplasmic reticulum and its replication in the 'replication complex' have been shown to be dependent upon triglyceride levels within the hepatocyte. As a result, agents that modulate triglycerides (statins, fish oils, niacin, fibrates and others) have been shown to down-regulate but not eliminate HCV replication. The current therapy of HCV infection consists of interferon alpha, ribavirin and inhibitors of the serine protease and RNA polymerase (non-structural proteins) encoded by the HCV-RNA. Over the last 2 decades, the efficacy of HCV therapy has increased from 2-6% with interferon alone to 80-90% with triple therapy (IFN, RIBA, protease inhibitor) and reportedly near 100% with quadruple therapy (with the addition of a RNA polymerase inhibitor). Important host and viral parameters to consider in HCV infection and treatment include BMI, lipid levels, type 2 diabetes, race, IL-28B genotype (host factors); and, viral genotype, viral load, viral resistance to IFN and its intracellular actions (viral factors), all of which contribute to define viral virulence. As a result of these advances, the current epidemic of HCV infection may be coming to an end. Unfortunately, the down-stream consequences of HCV infection: chronic hepatitis, cirrhosis, and hepatic cancer will continue to present major health issues for the next 20-30 years.

#### **Brief Biography of the Speaker:**

David H Van Thiel graduated from the University of California Los Angeles School of Medicine in 1967. He completed residency in Internal Medicine at Cornell University Hospitals from 1967-1969, and Boston University from 1971-1972, interrupted by a two-year exposure in Endocrinology at the National Institutes of Health (USA), followed by a fellowship in Gastroenterology & Hepatology at Boston University. He spent 20 years at the University of Pittsburgh where he was the Director of Gastroenterology & Hepatology, as well as the Medical Director of the liver transplantation program. He subsequently was the Director of Hepatology and Medical Director of liver transplantation at Baptist Medical Center, Oklahoma City (1993-1996), University of Kentucky (1996-1997), Loyola University, Chicago (1997-2004), Aurora Healthcare, Milwaukee, Wisconsin (2004-2007), and is currently the Medical Director of liver transplantation at Rush University Medical Center, Chicago since 2008. He is the past president of the American Association of the Study of Liver Diseases (AASLD), Research Society of Alcoholism (RSA) and Midwest Section of the American Federation for Clinical Research. His current research focuses upon the metabolic and genetic factors that enable hepatitis C virus to either be eliminated or survive in the human host. His research has shown that triglycerides are important in HCV-RNA intracellular transport and transcription in the endoplasmic reticulum, and how the manipulation of serum lipids with statins and other agents modulate HCV replication. Finally, he has served on the editorial boards of many journals and has contributed over 1100 peer-reviewed papers to the body of knowledge in Hepatology and liver transplantation.

## Plenary Lecture 14

### Antitumor Drug (Methotrexate) Induced Small Intestinal Toxicity



#### **Professor Toshiharu Horie**

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**Abstract:** Antitumor drugs like methotrexate (MTX) often cause damage to the small intestine, which is one of the most serious side effects in the MTX treatment. Administration of MTX to rats results in severe enterocolitis and death. However, the mechanism of the toxicity has not been completely clarified, which may be the reason why symptomatic therapy is carried out. Epithelial barrier function is determined in large part by a multiprotein complex located at the most apical part of the lateral membrane, which is referred to as a tight junction (TJ). We examined the alteration of zonula occludens-1 (ZO-1), which is a scaffolding protein that plays a pivotal role in the formation of TJs, to identify a molecular mechanism for epithelial barrier dysfunction. Paracellular permeability increased in MTX-treated rats. The reactive oxygen species (ROS) production was observed preceding the increase of paracellular permeability. Treatment with N-acetylcysteine (NAC) prevented the MTX-induced ROS production and the increase of paracellular permeability. In addition, mucosal inflammation was linked to enhanced intestinal permeability. Quantitative analysis of ZO-1 expression showed the absence of significant differences in MTX-treated rats, whereas tyrosine dephosphorylation of ZO-1 was observed. Moreover, we also detected an obvious reduction of ZO-1 immunostaining along the apical membrane of intestinal villi. ZO-1 alterations may contribute to disturbance of the TJ barrier in MTX-treated rats, which leads to enhanced intestinal permeability.

#### **Brief Biography of the Speaker:**

Toshiharu Horie graduated from The University of Tokyo, Faculty of Pharmaceutical Sciences in 1972. After he graduated from its Graduate School of Pharmaceutical Sciences, he got a position of an assistant professor in Tokyo University of Pharmacy and Life Sciences, and then, became an associate professor in 1992. He moved to Chiba University, Faculty of Pharmaceutical Sciences as a professor in 1994 and became a professor of Chiba University, Graduate School of Pharmaceutical Sciences in 2001. His research area is biopharmaceutics and drug toxicity.

## Plenary Lecture 15

### Pharmacokinetics of Routinely Administered Compounds During Pregnancy Reflect Pregnancy Related Physiological Changes



#### Associate Professor Karel Allegaert

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**Abstract:** The general pharmacokinetic principles of disposition and elimination of exogenous compounds apply, irrespective of population specific characteristics. However, pregnancy and delivery warrant a focussed approach because important alterations in physiology (e.g. renal, hepatic, metabolism, body composition) affect drug disposition in a clinical relevant way. During pregnancy, there are changes in distribution volume due to changes in body composition, in metabolic activity affecting drug metabolism and in renal elimination (GFR, tubular) capacity. The link between pregnancy related changes in medical physiology and changes in drug disposition will be illustrated based on aspects of cefazolin and paracetamol disposition during pregnancy and after delivery. Beyond these anecdotal observations, patterns related to medical physiology are unveiled.

#### Brief Biography of the Speaker:

Karel Allegaert graduated from the University Leuven, Belgium in 2000 as paediatrician-neonatologist. After an additional training at Sophia Children's Hospital in Rotterdam, he was appointed as clinical consultant neonatology at the University Hospitals Leuven. After his PhD thesis on neonatal analgesia (2002-2005), he further developed his clinical research in the field of neonatal pain treatment and developmental pharmacology in neonates and was appointed as associated professor at the same university (2005-ongoing). His current clinical research is supported by a grant of the national research council (Fund for Scientific Research, Flanders (Belgium) by a Fundamental Clinical Investigatorship (1800209 N, 2008-2012). This clinical research resulted in about 140 papers published in international peer reviewed journals, conferences proceedings and book chapters. He recently (2009) received the Galenus price for research in clinical pharmacology and the Govaerts price for clinical toxicology of the Royal Academy of Medicine of Belgium.

## Plenary Lecture 16

### Laboratory Production of Mammalian Embryos



**Associate Professor Saber Mohamed Abd Allah**

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**Abstract:** This is the review of original data concerning the effect of some factors on oocyte development in vitro of mammals (mouse, cows, buffalo, and sheep). In vitro production of embryos is a multi – step process: oocytes maturation, fertilization and embryo culture. In vitro embryo development is strongly influenced by events occurring during oocyte maturation, fertilization and the subsequent development of the fertilized oocytes. With the advancement of IVP procedures, variability in developmental rate and viability of in vitro produced embryos among mammals. So, improving the efficiency and identifying the sources of variations between IVF systems are more important when routinely producing blastocysts from individuals of high genetic merits. Also, the development of specific culture regimes capable of supporting in vitro maturation (IVM), in vitro fertilization (IVF) and in vitro culture (IVC) to the blastocyst stage is highly desirable in breeding systems. This paper discusses the technical aspects of the procedures involved in the production of embryos in vitro.

**Brief Biography of the Speaker:**

- Dr. Abd-Allah graduated from Faculty of Veterinary Medicine, Cairo University (Beni-Suef Branch) in 1993 (Very Good grade), and also obtained Master degree (1998) in the field of Reproductive Cytogenetics and Ph. D. (2003) in the field of Reproductive Biology from Faculty of Veterinary Medicine, Cairo University (Beni-Suef Branch), Egypt.
- He worked as Associate professor in Theriogenology, Faculty of Veterinary Medicine, Beni-Suef University, Egypt.
- His teaching activities included lectures in university and reseach centers, as well as the supervision of more than 500 undergraduate and PhD student works.
- The scientific research of Dr. Abd-Allah is focused on various areas of reproductive biology including In vitro fertilization, in vitro embryo production, Embryo Transfer, cryopreservation of ovaries, oocytes, embryos and semen, reproductive genetic and molecular biology in addition reproductive disorders in cattle, buffaloes, camel, horses, sheep and goat.
- Actually, he has more 25 publications mainly in international journals and several books in LAMBERT and VDM Publishing house, Germany in areas of reproductive biology and genetics including recent monograph "Laboratory production of buffalo embryos" (LAMERT-VDM, 2011).



## Plenary Lecture 17

### Course and Outcome of Pregnancy after the Heart Surgery



**Associate Professor Snezana Plesinac**

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**Abstract:** Advance in cardiac surgery significantly improved life expectancy and quality of life of patients with congenital or acquired heart disease. **METHODOLOGY:** Our study included 146 pregnant women who had antenatal care and gave birth at the Institute of gynecology and obstetrics in 10 years interval. (1994-2004). Patients were divided in 4 groups according to the type of heart surgery. Group I included 4 patients with surgically corrected Coarctation of Aorta. Group II included 27 patients with correction of the ostial stenosis. Group III had 68 patients with correction of congenital heart diseases and group IV 47 patients with artificial heart valves. **RESULTS:** There was 4% of heart failure after delivery. The incidence of hemorrhagic complications during pregnancy was 2.7% and 4.1% after delivery. The incidence of postpartum thromboembolic complications was 6%. Four newborns died, one of hydrocephalus and three of hypoxic ischemic encephalopathy. Two patients died. **CONCLUSION:** Patients with artificial heart valves need an enhanced level of medical care during pregnancy and labor.

**Brief Biography of the Speaker:**

Born in Belgrade 1962. Finished Medical Faculty Belgrade 1986. Master and PhD degree in 1996 with theme of COURSE AND OUTCOME OF PREGNANCY AFTER THE HEART SURGERY. Employment: Clinics for obstetrics and gynecology from 1989, Medical faculty University Belgrade from 1998. as teaching assistant and associate professor from 2008. Actual position Chief of the ward for fetal anomalies. Invited speaker for many times in an area of maternal fetal medicine in Serbia.

## Plenary Lecture 18

### **The Eye is Moving! Sclera Deformation by the Ocular Movements and its Role on the Development of the Clinical Signs of Various Macula Disorders. A New Hypothesis**



**Dr. Ioannis P. Theocharis**

Retina Consultant

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**Abstract:** The eye is constantly moving and simultaneously the sclera wall at the posterior pole of the eye is continuously deformed. All tissues of the posterior pole are under mechanical strain and load. This fact has never been studied in association with the clinical expression of various macula diseases. The purpose of this lecture is to focus on the consequences that sclera deformation may have on the anatomy and structural integrity of the posterior pole. The posterior pole is a stratified system that includes tissues of different mechanical properties. The inner surface of the sclera wall as seen in optical coherence tomography (OCT) images is not even and smooth, but it shows faults and folds that are under a constant deformation as proved on CT and MRI images. The anatomy of the macula with its characteristic contour does not follow the changes of the contour of the sclera wall. This inconsistency implies a dampening mechanism that eliminates the deformation of the retina in the macula region. The choroid and the choroidal trabecular meshwork of the posterior pole may serve as a dampening pillow. The compromise of this mechanism and the basic principles of applied mechanics are presented to interpret the major clinical signs of posterior pole diseases such as drusen and pigment epithelial detachments in age related macula degeneration, the evolution of vitreoretinal changes and to complement the pathogenesis of macula hole, central serous choroidopathy and cystoid macula degeneration.

#### **Brief Biography of the Speaker:**

Dr. I. P. Theocharis is a retina consultant specialized in surgical and medical retina diseases. He currently practices in private sector in Athens, Greece and in Belgrade, Serbia and runs the Primevision Institute of Ophthalmology. He had served as a senior retina consultant at Academic Hospital in Uppsala, Sweden for six years and his training was concluded in Greece, in USA and in Sweden. Dr Theocharis is involved in clinical research and has proposed the topical anaesthesia in sutureless vitrectomy, the OCT-based photodynamic therapy without the need of angiography, the role of fibrinogen in the retinal detachment process, the role of traction in central serous choroidopathy, the deformation of the posterior pole as a significant factor in macula disorders. He speaks the English and Swedish language and he has been a reviewer in scientific journals.

## Plenary Lecture 19

### Morphological Impairment of the Macula and Optic Nerve in Parkinson's Disease Patients without Vision Loss



**Dr. Marilita M. Moschos**  
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**Abstract:** It is well documented that Parkinson's disease (PD) is characterized by a widespread deficiency of the neurotransmitter dopamine in the central nervous system. This results in an involvement of the multisynaptic visual pathways. Visual functions controlled at least partially by dopamine, such as absolute sensitivity, spatial contrast sensitivity, temporal sensitivity and color vision are impaired in Parkinson's disease. This impairment is usually thought to be a result of attenuation of visual retinal signal at an early stage in the visual process.

Optical Coherence Tomography (OCT) is a non-invasive objective method which can provide diagnostic information and quantitative data on biologic tissues at high resolution of  $\sim 10$  microns.

We studied the morphological changes of the macula and the optic nerve in patients with Parkinson's disease in order to provide a clearer view of the disease process on the retina. We found that the mean RNFL thickness was significantly lower in PD patients than in control volunteers. OCT can objectively detect early subclinical PD-associated visual functional impairment.

#### **Brief Biography of the Speaker:**

Marilita M. Moschos graduated the Pharmacy School of the University of Patras and the Medical School of the University of Athens. She is actually working as a senior lecturer of Department of Ophthalmology of Athens University where she has the clinical and scientific co-responsibility of the Laboratory of Electrophysiology of Vision and the department of Glaucoma. She authored or co-authored over 45 scientific papers in pubmed reviewed journals and presented over 60 at international conferences, in some of them as invited speaker. She also wrote the chapter on 'Multifocal-Electroretinogram in retinal vascular diseases' in the annual edition of SFO (Societe Francaise d'Ophthalmologie). Finally she is a member of many international ophthalmological societies and reviewer in several ophthalmological journals, like, Clinical and Experimental Ophthalmology, Expert Review of Ophthalmology, Journal of Neuroscience Methods, Graefe's Archive for Clinical and Experimental Ophthalmology, BMC Ophthalmology, Clinical Ophthalmology, Indian Journal of Ophthalmology and others.

## Plenary Lecture 20

### New Regulators of Ovarian Functions



**Associate Professor Alexander V. Sirotkin**

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**Abstract:** This is the review of original data concerning the role of some metabolic hormones (GH, leptin, ghrelin, obestatin), growth factors (IGF-I, IGFs, EGF, thrombopoietin), intracellular mediators of their action (cyclic nucleotides, protein kinases, transcription factors and related cDNA, siRNA and miRNA gene constructs) on basic ovarian functions (cell proliferation, apoptosis, secretion, oogenesis, ovulation, production and viability of pups) in different species (humans, pig, rabbit and chicken). Practical applications of some these molecules for characterisation, prediction and control of reproductive processes in these species was examined too. Whole animals, ovarian follicles and their fragments, ovarian granulosa cells or oocyte-cumulus complexes were treated with hormones, antisera against these hormones, blockers of protein kinases (PKA, MAPK, CDK), cDNA constructs for transcription factors (CREB, STAT-1, p53, NFkB), siRNAs constructs down-regulated a number of protein kinases, as well as by constructs down- and up-regulated the ovary-specific miRNAs. Expression of these substances, as well as the markers of proliferation, apoptosis, hormone secretion, stages of meiosis and fertility were evaluated by using RIA/EIA, SDS PAGE-Western blotting, immunocytochemistry, RT-PCR and morphometry. It was shown that these hormonal and intracellular regulators are able to control apoptosis, proliferation and secretory activity in porcine, rabbit, human and chicken ovarian cells and maturation of porcine oocytes and cumulus oophorus in vivo and in vitro, as well as to suppress or promote the response of ovarian cells to other hormones (gonadotrophins, IGF-I, ghrelin). Immuno-blockade of these hormones prevented their effects. Effects of hormones on rabbit, human and chicken ovarian cells and on porcine and bovine oocytes were associated with changes in PKA, MAPK and CDK and transcription factors CREB, STAT-1, NFkB and p53 in such cells, whilst blockers of these kinases prevented or promoted hormones action. Transfection of porcine and rabbit granulosa cells with gene constructs for these transcription factors affected ovarian cell functions and prevented or reversed hormones action. Down-regulation of approx. 1/3 known protein kinases by specific siRNA constructs resulted not only decrease in accumulation of these kinases within human ovarian granulosa cells, but also changes in expression of kinase-dependent transcription factors, markers of cell proliferation, apoptosis and release of steroid hormones, oxytocin, prostaglandins and IGF-I. Transfection of human granulosa cells with constructs up and down regulating expression of some miRNAs are able to increase or decrease ovarian cell proliferation, occurrence of apoptosis, as well as the hormones release. In-vivo experiments demonstrated that leptin, IGF-I, steroid hormones and some regulators of PKA, MAPK and CDK could be used to predict reproductive efficiency, for direct in-vitro control of maturation of oocytes and for in-vivo stimulation of reproduction in pigs and rabbits. These observations suggest, that metabolic hormones, growth factors and intracellular regulators and mediators of their action (protein kinases, transcription factors, siRNAs, miRNAs) can be used for characterization of state of ovarian cells, for identification signaling pathways (hormones-growth factors-protein kinases-transcription factors-genes regulating proliferation, apoptosis and secretory activity) controlling reproductive processes, as well as for prediction and control of basic ovarian cell functions (proliferation, apoptosis, secretory activity, maturation of oocyte-cumulus complex and fertility).

#### **Brief Biography of the Speaker:**

Alexander Sirotkin is known specialist in biology of reproduction and leader in studies of some ovarian signaling substances (small RNAs, transcription factors, protein kinases, metabolic hormones a.o.). He has got his RNDr. degree in the University of Leningrad (USSR), PhD degree in the Institute of Evolutionary Physiology and Biochemistry (Leningrad, USSR) and DrSc degree in the Research Institute of Animal Production (Nitra, Slovakia). He worked as Research Scientist, Senior Research Scientist, Head of the Laboratory and Project Leader in the Research Institute of Animal Breeding and Genetics (Leningrad-Pushkin, USSR), International Laboratory for Biotechnology (Nitra, Czechoslovakia), Research Institute of Animal Production/Animal Production Research Centre (Nitra, Slovakia) and Constantine the Philosopher University (Nitra, Slovakia). He had fellowships in Institute of Physiology and Genetics (Libechov, Czechoslovakia), Institute of Experimental Endocrinology (Bratislava, Slovakia),

Research Centre of Animal Production (Dummerstorf, Germany), Institute for Animal Science and Animal Behaviour (Celle, Germany), Institute of Animal Science (Mariensee, Germany), University of Colonia (Colonia, Germany), Babraham Institute (Babraham, UK), University of Bristol (Bristol, UK), University of Nottingham (Sutton Bonington, UK) and other international research centers. His teaching activities included lectures in more than 10 universities and research centers, as well as the supervision of more than 50 undergraduate and PhD student works. Actually he have more than 400 publications, mainly in international biomedical journals and several books including recent monograph "Regulators of Ovarian Functions" (NY, USA, 2011). For the results obtained during his basic and applied studies and related publications in area of biology and endocrinology of reproduction he was nominated to a number of national and international awards.