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ABSTRACTS

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HYPOXIA-INDUCIBLE ERYTHROPOIETIN SIGNALING IN CERVICAL CARCINOMA

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Aim: Tissue hypoxia is a characteristic property of cervical cancers that makes tumors resistant to chemo- and radiation therapy. Erythropoietin (Epo) is a hypoxia-inducible stimulator of erythropoiesis. Acting via its receptor (EpoR), Epo upregulates bcl-2 and inhibits

apoptosis of erythroid cells and rescues neurons from hypoxic damage. In addition to human papillomavirus infection, increased bcl-2 expression and decreased apoptosis are thought to play a role in the progression of cervical neoplasia. In this study we examined whether Epo signaling is active and may play a role in the pathogenesis and progression of cervical carcinoma.

Methods: Using RT-PCR and Western blotting we examined the expression and biological activity of Epo and EpoR in HeLa and SiHa cervical carcinoma cells under normoxic and hypoxic conditions. Using immunohistochemistry, we examined the expression of Epo, EpoR, p16, hypoxia inducible factor (HIF)-1a and bcl-2 in benign and dysplastic cervical squamous epithelia and invasive squamous cell carcinomas (ISCC).

Results: We found that HeLa and SiHa cervical carcinoma cells and human cervical carcinomas express EpoR, and that hypoxia enhances EpoR expression. Exogenous Epo stimulated tyrosine phosphorylation and inhibited the cytotoxic effect of cisplatin in HeLa cervical carcinoma cells. Using immunohistochemistry, EpoR expression in benign epithelia was confined to the basal cell layers, while in dysplasias it increasingly appeared in more superficial cell layers and showed a significant correlation with severity of dysplasia. Diffuse EpoR expression was found in all ISCC. Expression of Epo and HIF-1a was increased in dysplasias compared to benign epithelia. Focal Epo and HIF-1a expression was seen near necrotic areas in ISCC, and showed correlation in their spatial distribution. Significant correlation was found between expression of EpoR, and p16 and bcl-2 in benign and dysplastic squamous epithelia.

Conclusions: Our results suggest that increased expression of Epo and EpoR may play a significant role in cervical carcinogenesis and tumor progression. Hypoxia-inducible Epo signaling may play a significant role in the aggressive behavior and treatment resistance of hypoxic cervical cancers.

OUTCOMES OF DIASTOLIC HEART FAILURE IN A RACIALLY BALANCED COHORT

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Objectives: The view that diastolic heart failure (DHF) has a better prognosis than systolic heart failure (SHF) has been challenged recently. Also, most studies of outcomes in DHF have included only small numbers of African

Americans (AA), a group that may have a higher prevalence of DHF due to more frequent hypertension (HTN) and left ventricular hypertrophy. Therefore, the objective of our study was to compare the characteristics as well as outcomes of patients (pts) with DHF versus SHF in a racially balanced patient population, in an equal access health care system. **Methods:** In a retrospective cohort study at a tertiary-care VA hospital we evaluated 351 pts admitted for congestive heart failure (CHF) between 1/98 and 6/00, and outcomes were examined for 18 to 36 months of follow-up. **Results:** Data was analyzed for 166 AA and 185 non-Hispanic white (NHW) pts who met Framingham criteria for CHF. DHF as defined by an LVEF > 40%, was present in 29% (n = 102). The mean age was similar in the SHF and DHF groups (68 years). AA accounted for 44% and 48.6% of the DHF and SHF groups (p=0.5), respectively. Pts with DHF had a significantly higher frequency of HTN, diabetes and higher systolic blood pressures, and a lower frequency of CAD as compared with SHF pts. 83% of SHF patients and 63% of DHF patients were on ACE inhibitors at discharge. In pts with DHF, 36% had a repeat LVEF assessment within 2 years, of which 27% showed a decrease in LVEF to < 40%. On log-rank analysis, mortality was similar in both groups (Kaplan Meier estimate of 36 month survival 55%) as was time to first CHF readmission. The independent predictors of mortality after adjusting for age and ACE inhibitor use were: AA race (RR 0.47, 95% CI: 0.3-0.7), HTN (RR 0.62, 95% CI: 0.4-0.9), PVD (RR 1.97, 95% CI: 1.3-2.9), creatinine>2mg/dl (RR 1.8, 95% CI: 1.1-2.9). In pts with DHF, there was no significant difference in time to death or to first CHF readmission in AA compared with NHW. **Conclusions:** In this unique population, pts with SHF and DHF had a similar mortality and morbidity. Contrary to expectations, AA did not have a higher prevalence of DHF. In an equal access health care setting morbidity and mortality was similar in AA and NHW with DHF.

SUSPECTED OPIATE-RELATED ENCOUNTERS IN MAINE: DO EMS DATA SUPPORT MEDIA REPORTS OF ALARMING TRENDS?

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Background: Reports from news organizations and governmental agencies have described significant

increases in the number of opiate-related overdose cases (ODs) over the past several years.

Objective: Describe the utilization of emergency medical services (EMS) for ODs in a rural state over the past five years.

Methods: Statewide EMS records were reviewed for the calendar years 1997 through 2001. Data reviewed included prehospital diagnosis, medications given to all patients (pts) by prehospital providers, pupil size and respiratory rate. All records were reviewed in a defined sequence. Data from 1997 to 2001 was compared.

Results: During the study period, 957,836 total pt encounters occurred. 2,028 (0.2%) pts were administered Narcan by the EMS provider. 15,924 (1.7%) were diagnosed with poisoning or overdose. Of the pts diagnosed with poisoning or overdose, 1,022 (6.4%) had pupil size 1-2 mm, 296 (1.9%) had a respiratory rate of less than 10, and 1,185 (7.4%) were administered Narcan. Of the 173,871 pt encounters in 1997, 282 (0.2%) were administered Narcan and 2,634 (1.5%) were diagnosed with poisoning or overdose of whom 107 (4.1%) had miotic pupils, 39 (1.5%) had a respiratory rate of less than 10 and 151 (5.7%) were administered Narcan. Of the 208,822 pt encounters in 2001, 496 (0.2%) were administered Narcan and 3,617 (1.7%) were diagnosed with poisoning or overdose of whom 291 (8%) had miotic pupils, 89 (2.5%) had a respiratory rate of less than 10 and 316 (8.7%) were administered Narcan. Total pt encounters increased 20% from 1997 to 2001. Pts diagnosed with poisoning or overdose increased 37%, in whom the incidence of miotic pupils increased 172%, respiratory rate less than 10 increased 128% and Narcan administration increased 109%.

Conclusion: Cases highly suspicious for ODs increased at a much greater rate from 1997 to 2001 than the increase in both total EMS encounters and pts diagnosed with poisoning or overdose.

TRENDS IN PEDIATRIC EMS UTILIZATION FOR HIGH-RISK BEHAVIORS

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Objective: To compare the EMS utilization rates for high-risk behaviors in pediatric patients with overall pediatric encounters.

Methods: Since 1992, the Maine EMS office has collected copies of all state standardized run sheets. Data fields

describing demographics, type of call, patient condition and EMS interventions are transcribed into a central database. We reviewed five years of data 1996-2000. Groups were divided into pre-teen (ages 6-10), early teen (ages 11-15) and late teen (ages 16-20). Characteristics of scene calls for these groups were then analyzed, including size of municipality, day of week, month of year, gender, chief complaint, and whether or not alcohol was suspected.

Results: From 1996-2000, 907,150 total records were generated. Total EMS traffic increased by 4.9%, correlating with a 4% annual population growth for the same period. 48,319 of the 78,904 EMS pediatric encounters were logged as primary scene calls within the age groups described above. There was a slight female predominance for both teen and late teen groups. Weekend calls represented 33-45% of primary scene calls. EMS utilization increased at a slightly faster rate in suburban areas (defined as population 100-300/sq. mile). EMS utilization was higher in the summer months (defined as mean daily temp. > 60 F). A majority of scene calls were for accident or injury encounters, especially in the older group. EMS encounters for the late teen group related to high-risk behavior saw dramatic increases during the study period when compared to the overall pediatric EMS call increases.

Conclusions: Pediatric EMS encounters represent a small but growing minority of the total EMS volume. EMS utilization for high-risk behaviors, especially in late-teenage patients, demonstrated tremendous growth over the study period. A heightened awareness of and preparation for pediatric EMS encounters related to behavioral and traumatic emergencies will be important if current trends continue.

EFFECT OF P-GLYCOPROTEIN EXPRESSION ON CELL-BIOLOGICAL CHARACTERISTICS OF TUMOR CELLS

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P-glycoprotein (Pgp), the product of MDR1 gene, is expressed constitutively in humans at blood brain barrier, intestine, kidney and liver. In addition to these, tumors treated with anticancer drugs in vitro or in humans overexpress Pgp as part of cellular defense mechanism. It is not known whether the expression of Pgp per se would change general characteristics of cells. To answer this question, we transfected a mouse cell line derived from a double (mdr1a/1b) knockout mouse and the human HeLa cells with human MDR1 cDNA repressed by tetracycline

and induced in the absence of tetracycline. We have then compared cell biological characteristics, such as plasma membrane potential and plasma membrane physical status between the transfected and drug selection induced resistant, Pgp expressing, human KB epidermal carcinoma and human liver 7404 cells. We have found that expression of Pgp per se does not effect these characteristics of the cells while multiple cell biological changes occur in cells after drug selection. These findings relate to tumor cells grown in humans, and indicate a general cell biological change in Pgp expressing drug-resistant cells as compared to their parental cells located at the place of origin of the tumor.

THE WEAKEST LINK OF PREVENTIVE CARDIOLOGY IN A TRANSYLVANIAN COMMUNITY

Erika Ban, Balazs Zsenits

Introduction: Cardiovascular and cerebrovascular illnesses are the leading cause of premature mortality and morbidity in the developed world. Hypertension is a major modifiable risk factor of atherosclerotic disease. The effects and limitations of antihypertensive therapy are topics of intensive research due to their major public health interest.

Objectives: Evaluate the prevalence and control rate of hypertension in a small rural Transylvanian community. Identify the most important barriers of hypertension control and compare these factors to those from a nearby urban referral center and to American "standards". Obtain baseline data for longitudinal follow up and estimate current atherosclerosis prevalence.

Study design: Cross sectional survey (personal interview and examination)

Methods: We measured blood pressure, body mass index and ankle brachial index of the entire population of Vármezo, a small Transylvanian village. We evaluated the patients' awareness of preexisting hypertension, current antihypertensive therapy and achievement of blood pressure control. We evaluated a cohort of inpatients at a Transylvanian cardiology referral center and reviewed the American hypertension literature for comparison.

Results: The prevalence of hypertension was 71% (80/112). Of those patients, 72% (57/80) were aware of their diagnosis and 54% (47/80) were under treatment. Only 4% (3/80) of cases were "controlled" as defined by BP < 140/90 mmHg. In the American literature hypertension prevalence is 35%; 70% of hypertensive patients are aware of their diagnosis, 59% are under treatment and 34% have their blood pressure controlled.

All patients in the inpatient clinic were hypertensive, aware of it and treated for it; control rates improved from 49% to 100% during the inpatient stay.

Discussion: Hypertension is an extremely prevalent illness in the evaluated rural population: primary prevention (diet, exercise, other lifestyle and weight control) should be a major target of intervention of the Romanian healthcare system. Other cardiovascular risk factors were measured and will be discussed as well. Hypertension awareness and treatment rates are comparable to the American data: access to health care and medications are apparently not major barriers. Control rates are very poor: patient and physician education for more efficient blood pressure management should also be a focal point of system-wide intervention. The choice of prescribed medications, compliance and possible benefit of inpatient blood pressure management will be discussed.

DYNAMICS OF PI 3-K SIGNALING IN HT-2 T CELLS: PROLIFERATION AND PI 3-K SIGNALING ARE SEPARABLE EVENTS

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Clonal expansion of T cells after antigen stimulation is driven by cytokines, particularly IL-2. IL-2 receptor (IL-2R) signaling promotes progression through the G1 phase cell cycle, inducing proliferation. Proliferative signaling by the IL-2R is thought to occur through at least three distinct pathways, one mediated by STAT5 and one by the p85-MAPK pathway and one by the PI 3-K pathway. The relative importance of these pathways remains unclear. The IL-2-dependent T cell line HT-2 has served as a useful model for understanding T cell signaling. However, many human and murine T cell lines show constitutive activation of PI 3-K signaling, and consequently the role of PI 3-K in many signaling pathways has been underestimated. Therefore, we tested PI 3-K activity and found that HT-2 cells do not show basal high level of PtdIns(3,4)P₂ or PtdIns(3,4,5)P₃. Moreover, they are not defective in the major routes for lipid degradation, as they express PTEN and SHIP. Thus, HT-2 cells appear to be relatively normal with respect to PI 3-K signaling. To assess the role of PI 3-K in IL-2 dependent proliferation, HT-2 cells were transfected with erythropoietin (EPO)-IL-2 receptor chimeric receptors in which IL-2Rbeta chain contains mutations in its cytoplasmic tyrosine (Y) residues. Mutations that do (Y338F) or do not (Y392F, Y510F) activate

phosphorylation of the PI 3-K subunit p85 are able to proliferate and survive apoptosis triggered by cytokine withdrawal. Proliferation occurs in a wortmannin-independent manner, indicating that p85 activation is dispensable for IL-2-dependent proliferation. In conclusion, PI 3-K signaling in HT-2 cells appears to be normal compared to other T cell lines and is not essential for proliferation and cell survival of HT-2 cells.

COMMON OCCURRENCE OF NEONATAL JAUNDICE AND URINARY TRACT INFECTION IN NEONATES

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Common occurrence of urinary tract infection and hyperbilirubinaemia in the newborn period is a well-known fact among neonatologists, but statistically it has not been proven yet. The association between the occurrence of pathological neonatal jaundice and urinary tract infection (UTI) was examined in neonates treated at the Neonatal Unit of the Department of Paediatrics.

In a retrospective study, data were obtained from 442 neonates with hyperbilirubinaemia and/or urinary tract infection. Hyperbilirubinaemia was diagnosed in 315 cases, urinary tract infection was diagnosed in 91 cases, both in 36 cases. According to the detailed analysis, 10.2% of newborns treated with hyperbilirubinaemia had UTI, whereas 28.4% of 91 UTI neonates were treated for hyperbilirubinaemia as well. The significant ($p < 0.001$) difference between these percentages supports the theory that neonatal UTI may play an important role in the pathogenesis of neonatal jaundice. It may also contribute to our knowledge on the specific etiopathogenesis of neonatal UTI.

MAJOR SPINE SURGERY, CAN IT BE HAZARDOUS?

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Rapid advances in the fields of spinal instrumentation, tissue banking and bone graft substitutes have led to the proliferation of major spine surgeries. While clearly indicated in a limited group of patients, it is the author's opinion that the majority of these heroic and complex

procedures are driven by the greed of certain surgeons for financial gain in a system driven by generous worker's compensation for industrial injuries. Neither patients nor employers have an understanding of correct indications and are unaware of potential devastating complications such as recurrent refractory giant fluid collections and/or major infections. As an orthopedic tumor and sepsis surgeon, the author of this study had the opportunity to salvage these surgical disasters and to develop a novel surgical technique that allows the repair and eradication of these serious wound complications after major spine surgery in a single stage. The method consists of an extensive excision of non-viable bone and soft tissue, removal of all necrotic graft material, repair of any CSF leak, re-exploration of nerve roots and complete removal of epidural infected fibrous membranes. This is followed by soft tissue reconstruction over drains by quilting the skin and underlying soft tissues to the transverse processes and pedicles of the lumbar spine, the ala of the sacrum and posterior iliac crests with Mitek Anchor sutures to eliminate all dead space. In most cases the spinal instrumentation is left in place, it is only removed in cases where it is loose or bathed in pus. Adjunctive therapy consists of long-term intravenous antibiotics, hyperbaric oxygen, nutritional support and strict bed rest on a low-pressure mattress for a minimum of five days. Nineteen repairs in a group of 18 patients (11 males, 7 females, ages 28-78 years, average age 45.4 years) were performed in this fashion and followed prospectively. The complications that were treated consisted of 7 refractory giant fluid collections and 12 major post-operative infections. All cases were referred to the author by spine surgeons from other centers. The major procedures leading to these devastating problems were: 360 degrees fusion-instrumentation (9), posterior fusion-instrumentation (8), laminectomy (1), and removal of spinal instrumentation (1). Successful primary healing occurred after 18 of 19 procedures. One patient had delayed healing but no additional surgery was needed. At a mean prospective follow-up of 5.3 years (3.1-6.3 years) there was no recurrence of fluid collection or infection. While these results show the effectiveness of a single-stage salvage surgery for these devastating complications and removes major morbidity that would be caused by prolonged open wound care and secondary muscle flap coverage as practiced in the past, it would be far better if such problems after spine surgery could be prevented by meticulous surgical technique. Furthermore, it would be to the benefit of all if unnecessary major spine surgeries could be avoided altogether by rigorous and honest peer review.

HORMONAL THERAPY OF BREAST CANCER

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Approximately 200,000 women are diagnosed with breast cancer in the United States annually. In spite of programs promoting breast self examination and annual mammography, the majority of patients present with invasive carcinoma at diagnosis and these women are at risk of recurrence and death.

The role of the estrogen receptor in the development and growth of breast cancer is now well understood. Methods of hormonal manipulation in the past have included medical or surgical oophorectomy in premenopausal women and tamoxifen in both pre- and postmenopausal women with advanced breast cancer. The benefits of hormonal manipulation were initially noted in some women with advanced metastatic breast cancer. Subsequent clinical trials completed in the 1980's and 1990 have demonstrated the benefits of adjuvant therapy with tamoxifen in reducing the risk of recurrence and death following primary surgical therapy. Finally, in a randomized, placebo controlled trial tamoxifen prevented the development of breast cancer in approximately 40% of women who were at an increased risk of developing breast cancer.

The recent approval of the peripheral aromatase inhibitors anastrozole, letrozole, exemestane and the selective estrogen receptor downregulator, fulvestrant, have expanded the role of hormonal therapy in both early and advanced breast cancer.

This presentation will review the mechanisms of hormonal control in breast cancer and provide an updated summary of current hormonal management strategies for women with this disease.

NEW IMPERATIVES IN THE DETECTION AND TREATMENT OF PERIPHERAL VASCULAR DISEASE

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Peripheral Vascular Disease (PVDz) is only one manifestation of atherosclerosis; although not regularly addressed by the clinician as coronary or cerebral circulation, it is nonetheless associated with considerable morbidity and mortality. There should be close examination of these associations, and an aggressive

approach toward detection and management should be made.

Much research has been done on the cellular level to demonstrate the free-radical injury to the mitochondrial DNA, as well as progressive skeletal muscle denervation and subsequent weakness. Clinical research has also focused on restoration of flow, either surgically or by newer non-invasive means. Therapies for those in the early/intermediate range (i.e. not truly at limb risk, or functional/job related impairment) are mostly exercise, and limited pharmacotherapy, until recently.

There is sufficient recent data to suggest that, cilostazol (cAMP, PDE-III inhibitor) may be an effective adjunct treatment that can promote increased circulation for most stable claudicators; and improve wound healing in those with ulcerative atherosclerotic disease. This combined with lifestyle/habit modification, can maintain claudicators in the stable range, avoiding future morbidity/mortality.

THE ROLE OF FRONTAL-SUBCORTICAL CIRCUITS IN THE THERAPEUTIC EFFECT OF ATYPICAL ANTIPSYCHOTICS

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Frontal-subcortical circuits form the principal organizational networks, which are central to brain-behavioral relationships. At least five parallel frontal-subcortical circuits are defined, which link regions of the frontal cortex to the striatum, globus pallidus, and thalamus. The frontal circuits originate in the supplementary motor area, frontal eye fields, dorsolateral prefrontal cortex, lateral orbitofrontal region, and anterior cingulate cortex. The circuits mediate motor and oculomotor functions as well as executive functions, social actions, and motivation. Impairment of the frontal-subcortical circuits may lead to deficits in executive functions, disinhibition, and apathy. The neurobiological correlates of psychiatric disorders including depression, mania, obsessive-compulsive disorder, and schizophrenia imply involvement of these circuits. Transmitters, modulators, receptors subtypes, and second messengers within the loops provide a chemoarchitecture that can guide pharmacotherapy and explain the effectiveness of atypical antipsychotics in multiple psychiatric disorders.

BIOMECHANICAL FOOT PROBLEMS, WITH SYMPTOMS REFERING ON OTHER PARTS OF THE MUSCULOSCELETAL STRUCTURE

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Severe pain in the knee-hip-posterior lumbosacral joints could be referred from misalignment of the ligaments and bones of the ankle and foot. General symptoms, such as fatigue, muscle cramps, posture changes are also common and difficult to detect.

Treatment: custom-made orthosis or footwear modification. Orthopedic, neurological and vascular problems could be controlled with relatively simple measures.

The different biomechanical abnormalities are discussed and demonstrated on a live model.

Available modifications and orthotic technic are of utmost importance to restore the proper angle of the joints of the ankle and foot, to relieve the abnormal strain on the ligaments of the more proximal structures, and eliminate the debilitating pain.

THE HISTORY OF MODERN CARDIOLOGY

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In the early part of the 20th century cardiovascular disease became the most frequent cause of death in the United States. In 1903 Einthoven a physician in a small Dutch city of Leyden discovered the electrocardiograph. Myocardial ischemia and infarction and various arrhythmias could be recognized. Physicians reading electrocardiograms became cardiologists, and a new specialty of cardiology was born. However, the first half of the century was busy with two world wars, and not much was done for medicine. After 1950, the industrialized nations turned their attention toward internal problems including health care. By that time, cardiovascular diseases reached epidemic proportions. In the USA, the National Institute of Health was founded and immediately began to stimulate clinical and basic research. The Framingham study under the direction of William Kannel concentrated on the causes of coronary artery disease and stroke. In a 6-year follow-up they identified hypertension, high levels of cholesterol and smoking as the main risk factors. Until 1961, patients with acute myocardial infarction were treated with strict bed rest for weeks, scattered around the hospital. After Paul Zoll discovered external cardiac resuscitation of patients

in ventricular fibrillation, patients with acute myocardial infarction were concentrated in coronary care units where instant help was available. The mortality was reduced from about 30% to 15%. In 1958, Mason Sones demonstrated the feasibility to enter the ostium of the coronary arteries with a catheter. The availability of coronary angiography paved the way for coronary bypass surgery, for angioplasty by Andreas Gruentzig in 1977, for thrombolysis of the occlusive clot in acute myocardial infarction in the late 1970s and for stenting in the 1980s. Echocardiography, radionuclide imaging, magnetic resonance, computed tomography immensely increased our diagnostic accuracy. Cardiac catheterization in the catheterization laboratory, or at the bedside with flow-directed balloon-tipped catheters allowed quantitation of hemodynamic changes. New medications including antiplatelet agents, statins, beta-blockers, ACE-inhibitors contributed to reduction of acute cardiac mortality to 5-7%. The future: In the next 20 years we can expect application of genetics for prevention and tailored treatment, and movement toward less invasive interventions.

MASTERING INTRAOPERATIVE MONITORING OF RETROGRADE CEREBRAL PERFUSION BY DIGITAL POWER M-MODE TRANSCRANIAL DOPPLER (PMD/TCD)

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Background: Profound hypothermic circulatory arrest (PHCA) with additional retrograde cerebral perfusion (RCP) has been used for cerebral protection during ascending aorta repairs. Transcranial Doppler (TCD) has been used to monitor cerebral blood flow during RCP with varying success. Using digital Power M-Mode TCD (PMD) we attempted to improve monitoring of cerebral blood flow dynamics during RCP.

Methods: PMD/TCD was performed with hands-free, fixed probe during PHCA for patients undergoing ascending aortic repair. Data of intraoperative parameters and patients outcomes were collected prospectively.

Results: Between 8/2001 and 3/2002, we performed 40 ascending and arch repairs monitored by PMD/TCD during RCP. Reversal of cerebral blood flow during RCP was detected all but one who had no acoustic temporal

window (97.5%). RCP lasted for a mean of 33.6 minutes, during which the average of mean cerebral blood flow velocity was 15.5 cm/sec. 3 patients (7.6%) had stroke and 14 patients (35%) had temporary neurological deficits subsequent to surgery. 30-day mortality was 10%.

Conclusions: PMD/TCD detect retrograde cerebral blood flow during RCP in nearly all cases. Improved cerebral blood flow monitoring by PMD/TCD has the potential to decrease operative morbidity and mortality.

COLON IMAGING BY MULTISLICE CT - REVIEW OF CT COLONOGRAPHY

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CT Colonography, commonly referred to as Virtual Colonoscopy is a new method in gastrointestinal radiology that was developed primarily for the identification of colonic polyps and cancer. It combines spiral CT technology and advanced three-dimensional graphics software to generate endoluminal images of the colon. CT Colonography can provide a rapid, noninvasive complete colon examination without the need for sedation. The preliminary sensitivities compare well with conventional colonoscopy for polyps 5 mm or larger. With the introduction of multi-slice CT technology, CT Colonography is increasingly becoming an attractive alternative for colorectal mass screening. In this lecture, the current status of screening methods used to detect colorectal carcinoma and the significance of early detection will be summarized. Patient preparation, imaging protocols, postprocessing methods, the risk of radiation, as well as the costs and future directions will be discussed. Finally, I will present our one-year experience obtained with the first multi-slice spiral CT in Hungary.

PROGNOSIS OF CHILDHOOD BRONCHIAL ASTHMA IN HUNGARY. A LONG-TERM FOLLOW-UP

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The objective of this study was to determine the prognosis of childhood bronchial asthma in Hungary. 145 adults (96 men and 49 women) with a clinical history of childhood bronchial asthma were examined at the age of or over 28 years (37.6±5.9 years). The patients filled out

questionnaires about asthmatic and concomitant allergic symptoms in their childhood, as well as at the age of 18 and at present. All patients had prick tests with 12 inhalant allergens. 42.8% of the patients became symptom-free, but 57.2% still had intermittent or persisting asthmatic symptoms at adulthood. Incidence of intermittent day and night symptoms (59% and 67%) was higher than that of persisting ones (41% and 33%). The concomitant allergic diseases (rhinitis, conjunctivitis, skin and gastrointestinal diseases, drug and food allergy) in childhood had little prognostic value. The rate of women with allergic diseases increased and it was significantly higher among patients with skin diseases. At the age of 18, the occurrence of allergic rhinitis was more frequent than in childhood. The incidence of other allergic disorders did not change significantly. Among patients with asthmatic symptoms, moulds and cat hair allergies were more frequent than in the symptom-free group. The long-term prognosis of childhood bronchial asthma is relatively good, however only part of the patients became symptom-free. The complaints of most of the patients were mild, but 1/7 of all the adults suffered from moderate or serious bronchial asthma. The indoor allergens may contribute to the persistence of asthmatic symptoms.

HOW THE PLACENTA COMPROMISES INNATE AND ADAPTIVE MATERNAL IMMUNITY? HOW MALIGNANT TUMORS IMITATE THE PLACENTA? HOW MATERNAL NATURAL KILLER (NK) CELLS RESTRAIN THE TROPHOBLAST? HOW NK CELLS OF THE TUMOR-BEARING HOST CONTROL THE TUMOR?

I. THE DEFINITION, CHARACTERIZATION, FUNCTION AND THERAPEUTIC USE OF NK CELLS.

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In the human blood NK cells appear as large granular lymphocytes. NK cells evolved to protect the host against viral infections: NK cells kill virally infected cells before the full maturation of the viral progeny. (Other modalities of antiviral immunity include the production of interferons by plasmacytoid dendritic (and other) cells; virus-neutralizing antibodies by plasma cells; and cellular cytotoxicity carried out by immune T cells). NK cells also recognize MHC-incompatible cells or cells not expressing MHC antigens. Since tumor cells frequently conceal their MHC antigens, NK cells seek out and kill tumor cells. NK

cells kill their target cells by releasing granzymes and perforins lysing the cytoplasm, or by expressing Fas ligand (L) that induces apoptosis by nuclear DNA fragmentation of the attacked cell. The most important NK cell receptors are the killer immunoglobulin-like receptors (KIRs) and the CD94-NKG2A receptors which recognize HLA-A,B, C molecules. Some NK cell receptors are referred to as "inhibitory receptors": normal cells expressing self MHC class I neutralize the signal transduction from these NK cell receptors and thus escape lysis. NK cells may undergo malignant transformation and appear as NK cell leukemia-lymphoma, One of us (JS) presented the first case of "cytotoxic lymphoma" in 1970 (Acta Microbiologica Immunologica Hungarica 44: 295 '97; ASCO 17: 38a #148 '98). EBV or HTLV-I genomic sequences were found in malignantly transformed NK cells. Malignant NK cells indiscriminately express the cytotoxic FasL and kill hepatocytes and hematopoietic stem cells of their host (Acta Microbiologica Hungarica 40: 165 '93).

Malignant tumors responding best to NK cell therapy are kidney carcinoma and melanoma. We prepare autologous lymphokine-activated killer (LAK) cells extracted from blood for adoptive immunotherapy of these tumors following a NCI protocol; when live tumor material is available we prepare tumor infiltrating lymphocytes (TIL) for the same purpose. TIL are a heterogenous population of CD4 helper and CD8 immune T cells admixed with various subtypes of NK cells responding with clonal expansion to IL-2 and to other cytokines (Acta Microbiologica Hungarica 38: 321 '91; 41: 205 '94; Leukemia 8/S1: 121 '94).

HYPERCOAGULABLE DISORDERS. ROLE OF FACTOR V LEIDEN MUTATION IN HYPERCOAGULABLE STATE

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Venous thrombosis is a significant cause of mortality in the U.S., with annual incidence of 1/1000. It accounts for a half a million hospitalizations and causes over 50,000 deaths annually. Hereditary disorders predisposing to thrombosis include the factor V Leiden genetic mutation, the Factor II (prothrombin) gene G to A 20210 mutation, protein C deficiency, protein S deficiency, AT III deficiency and dysfibrinogenemia.

Of the hypercoagulable disorders, the Factor V Leiden mutation is by far the most common, accounting for up to 40% of all cases, and up to 75% of cases of recurrent

thrombosis. It has an approximately 5% prevalence in the general population and is at least 10 times more common than any other known thrombophilic genetic defect.

Presence of Factor V mutation increases the risk for venous thrombosis 7-fold in heterozygotes and 80-fold in homozygotes. This risk is increased even further in situations such as pregnancy, oral contraceptive use, estrogen therapy, malignancy, diabetes mellitus, immobilization or surgery. 10% of heterozygotes and almost all homozygotes experience venous thrombosis in their lifetime.

Clinical criteria for thrombophilia include venous thrombosis or thromboembolism, which occurs before the age of 45 or is recurrent, a family history of venous thrombosis or thromboembolism or a history of thrombosis in an unusual anatomic location, or recurrent superficial thrombophlebitis.

Discovery of the factor V mutation in 1994 has revolutionized the diagnostic work-up of patients with hypercoagulability. The ability to detect this mutation in asymptomatic relatives offers the opportunity to prevent venous thrombosis through special management of those at risk. Factor V Leiden mutation can be diagnosed using simple PCR genetic assay. Unlike conventional coagulation assays, it can be performed in anticoagulated patients.

THE BENEFITS OF REGULAR PHYSICAL EXERCISE IN SENIOR AGE

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In the small villages in Hungary, one can often encounter cardiovascular- and locomotor diseases and obesity in patients over 60 years of age. Landmark studies of the last years as well as the experience in our family and sport medicine practice underline the importance of regular physical exercise (swimming, cycling, walking, etc.). Therefore, regular physical exercise should be considered a useful adjunct therapy to medical treatment with pharmaceutical agents.

LIGHT POLLUTIONS AND THE PINEAL GLAND

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The existence of the pineal gland has been recognized since ancient times. It was described by Herophilus in approximately 300 B.C. Galen is responsible for the name. Descartes was convinced that the pineal gland is the seat of the soul. There was little knowledge, however, about the pineal gland until the end of the 19th century when two case reports presented conflicting data that there is a relationship between the pineal and maturation of the reproductive system.

The modern pineal era started in 1958 when Lerner and coworkers isolated a pineal hormone and named it melatonin. After 1958 the literature exploded and while medicine paid little attention to the pineal gland, significant works were done in the field of basic science presenting the pineal as an important endocrine gland.

There is increasing evidence that the pineal gland has a role in the control of neoplastic processes. According to Cohen and coworkers, the pineal gland has a role in the etiology of breast cancer.

One of the most important aspects of the function of the pineal gland is that it is responsible for the appreciation of light and darkness. Melatonin is produced only in darkness.

In 1990 our group put forward a hypothesis that one of the most important etiologic factors in the increasing occurrence of cancer is the change of light exposure that has taken place in the last 100 years. This increased light exposure decreases the amount of time that is available for melatonin production, reducing the non-specific Oncostatic effect of the pineal gland. Our group surveying workers who every day worked 6 or 7 hours in darkness in the Canadian Kodak Factory found that they have a reduced risk of breast cancer and of malignant melanoma. Recent publications indicate that blind women have a reduced risk of breast cancer while night shift nurses in hospitals have an increased risk. Our preliminary results and these recent findings seem to prove our hypothesis that "light pollution" has an important role in the development of these malignant tumors.

Considering all these facts raises the question whether melatonin replacement could be beneficial for the light-exposed night shift workers. A controlled clinical study would be helpful to answer this question.

LAPAROSCOPIC RESTAURATIVE PROCTOCOLECTOMY FOR ULCERATIVE COLITIS

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INTRODUCTION: With increasing experience, laparoscopic techniques have been applied even to extended colorectal operations as restaurative proctocolectomy in ulcerative colitis and familial adenomatous polyposis.

METHODS: After initial medial transection of the three main vascular pedicles, the colon is dissected free laterally, from the sigmoid orally towards the ileum. The rectum is mobilized down to the pelvic floor and transected at the level of the dentate line. Over a Pfannenstiel incision, the bowel is extracted. After transection of the ileum, a J-pouch is created. The anastomosis is completed laparoscopically in double-stapling technique.

RESULTS: Within 26 months, 12 patients have been operated on. The median age was 25.5 years (22 – 45), the median time of operation was 425 min (330 – 510). There was no conversion to an open procedure. The median length of the Pfannenstiel incision was 7.6 cm (4 – 12). In all cases, a protective diverting ileostomy was created. The median length of hospital stay was 12 days (8 – 65). There was no postoperative mortality. Major complications occurred in 2 patients. In one case, a pouch-vaginal fistula developed on postoperative day 17 demanding secondary laparoscopic loop ileostomy. In another case, an intraabdominal abscess originating from a small leak of the pouch-anal anastomosis had to be treated by reoperation and suction drainage.

CONCLUSIONS: In restaurative proctocolectomy, laparoscopic techniques prove to be safely feasible. They have the potential to become an appealing alternative to open surgery.

HOT TUB LUNG

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A number of pulmonary diseases are associated with Mycobacterium avium complex (MAC). The best known include mimics of classic cavitary tuberculosis, opportunistic infections in immunocompromised individuals, and patchy nodular disease associated with bronchiectasis.

Hot tub lung is a recently described manifestation of MAC: diffuse lung disease in otherwise healthy individuals – not associated with bronchiectasis. The most common clinical symptoms include dyspnea, cough, hypoxia, and fever. All patients have a history of hot tub use prior to their illness. Histologically, exuberant non-necrotizing granulomatous inflammation is seen. MAC organisms have been isolated from both patient specimens and hot tub water. Discontinuation of hot tub use usually leads to prompt improvement in symptoms, pulmonary function, and radiographic abnormalities.

In light of this new manifestation of MAC, clinicians should advise their patients of the potential risk associated with hot tub use.

PROGNOSTIC INDICATORS IN PITUITARY TUMORS

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The majority of pituitary tumors are expansively growing, histologically benign adenomas. Others, however, are invasive and spread to adjacent tissues. Rarely, pituitary tumors, called carcinomas, give rise to distant cerebrospinal and/or systemic metastases. Some pituitary tumors, called microadenomas, are small, whereas others, termed macroadenomas, are large. Some patients are cured after adenectomy whereas in others the tumor recurs following surgical removal. In recent years many morphologic studies were undertaken to find reliable prognostic indicators that could predict the fate of the patients. The number of mitoses, tumor cellularity, invasiveness, nuclear and cellular pleomorphism, ploidy status can be analyzed. Immunohistochemical investigation appears to be very promising. Immunohistochemical expression of KI-67 antigen, a cell proliferation marker; P-27, a cell cycle inhibitor; P53 oncoprotein, a tumor suppressor gene; vascular endothelial growth factor, hypoxia inducible factor, topoisomerase, telomerase, galectin and cyclooxygenase may uncover the biologic behavior of pituitary tumor cells and may be valuable indicator of prognosis. Recent evidence indicates that formation of new blood vessels, called angiogenesis, plays a crucial role in tumor progression. Blood supply is needed to deliver oxygen and nutrients to the tumor cells and remove waste products. If vascularization is insufficient, tumors can not grow and tumor cells undergo necrosis. Well vascularized tumors in the lung, colon, prostate, breast, etc grow more rapidly

and give rise to metastases more frequently than poorly vascularized tumors. Microvessel density can be quantified by immunohistochemistry using the CD-34 antibody that selectively stains endothelial cells. We have found that microvessel density in benign pituitary adenomas is lower whereas in rapidly growing invasive adenomas and carcinomas is higher than in the non-tumorous adeno-hypophysis. We conclude that angiogenesis is an important prognostic indicator in patients harboring pituitary tumors. (This work was supported by the Jariskowsky Foundation, the Lloyd Carr-Harris Foundation and the St. Michael's Hospital Research Centre).

DISEASES OF THE PERICARDIUM

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The treatment of pericardial diseases has significantly changed in the past decades. Many years ago surgical approaches focused primarily in the treatment of effusions and constrictions. Today the presentation and etiology of pericardial disease have greatly changed.

50 years ago:

- A. Infectious: Tuberculosis, Rheumatic (pancarditis), Pyogenic (bacterial), Viral
- B. Non-infectious: Uremic, Ischemic, Neoplastic, Collagen diseases (polyarteritis, diss. lupus).

Today:

Postoperative 20, Clear (viral?) 10, Malignant 10, Chronic pericarditis (viral) 9, Atypical 8, Bloody 4, Renal 4, CHF 1, Acute MI 1, Purulent 1, Rheumatic 1, Unknown 20.

Today's surgical approaches include: Classical window, Pericardiostomy and minimally invasive pericardiostomy, Classical pericardectomy

Diagnostic methods include: 2D echocardiogram, TEE, CT scan, Fluoroscopy

The author has treated surgically 97 cases of pericardial involvement between 1988 and 2001. Fifty-nine patients had pericardial window. Thirty-eight patients had minimally invasive pericardiostomy. Pericardectomy is indicated in less than 5% of chronic pericarditis, of either viral and/or unknown etiology. Viral pericarditis is not unusual and may be epidemic at times but definite diagnosis is difficult. With our present diagnostic and treatment methods recurrence should be avoided.

WE CAN EXCEED OUR „STRESS TOLERANCE”: CONSEQUENCES AND TREATMENT

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We investigated the alterations in the human body that may have the propensity to cause symptoms. Our aim in detecting these kinds of symptoms is to arrive at an appropriate and relevant diagnosis, to provide timely and effective therapy, to avoid reoccurrence of symptoms (“recidiva”) and to improve functional capacity. Our study aimed at increasing physical performance has been carried out on top athletes and chronic patients at the Semmelweis University, at the National Institute for Sports Medicine and among members of the Hungarian Olympic Team.

Diagnostic tests included methods of clinical and manual medicine, computerized dynamometer Kintrex-1000, and thermo-vision of the skin surface.

Treatment consisted of VIOFOR-, manual-, and AQUAFIT-therapy.

We observed that factors usually considered etiologically unimportant can in fact cause relatively grave consequences in the function of various organ systems. The first step is dysfunction, which can lead to a „degenerative chain reaction”. Normalization of dysfunction by selective (manual, sauna-, and AQUAFIT-therapy) stimuli complemented with augmentation of local and systemic resting energy levels by VIOFOR THERAPY can drive this chain reaction in the regenerative direction. The method is useful for prevention, therapy, and rehabilitation, as well as for performance enhancement.

„VIOFOR” is an English mosaic word for „Very Important Organizer For Organ Regeneration” caused by „Cyclotron Electron Magnetic Resonance Stimulation (CeMeReS)”. Dysfunction of the organ systems is often provoked by decreased local and systemic resting energy levels, consequently, the increase in energy levels is a very important goal in the management of „overuse symptoms”.

FURTHER RESULTS IN PREVENTION AND TREATMENT OF CORONARY HEART DISEASES

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There has been further progress in the prevention and treatment of coronary heart diseases. The aim of the study is to give a summary of the latest results. Further observations prove that atherosclerosis is the consequence

of a process caused by infection. There is increasing recognition that atherosclerosis involves chronic inflammation. C-reactive protein (CRP) predicts future risk of cardiovascular events even in apparently healthy individuals, as it does among those with coronary heart disease (CHD). High-sensitivity CRP tests (hsCRP) detect levels within a range that has been shown to be associated with increased CHD risk. Homocystein lowering treatment (folic acid plus vitamin B6) has been shown to decrease the progress of subclinical atherosclerosis. Evidence suggests that statin therapy may provide a cardioprotective effect even in patients with normal lipid levels. Clinical data predict further increase in the use of statins in the future for several other indications. Researchers from Oxford University, England demand the use of statin therapy for diabetics, even if cholesterol levels are not elevated. According to an article by the American Thoracic Society, statins have immunomodulating and antiinflammatory effects as well. If given to lung transplant patients, statins were shown to reduce tissue rejection and improve pulmonary function. New studies show that statins decreased the incidence of cancer events by a significant percentage. FDA decision expands the use of clopidogrel (Plavix) to the acute coronary syndrome (ACS). A new study found that one-year treatment with a combination of Plavix and aspirin reduced the risk of heart attack, stroke and death by 27 percent in patients who had undergone procedures to clear coronary blockage.

COOPERATIVE EFFORT IN THE DEVELOPMENT OF EMERGENCY MEDICINE IN HUNGARY BETWEEN THE UNIVERSITY OF MASSACHUSETTS AND HUNGARIAN INSTITUTIONS

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This short presentation summarizes the relationship between the University of Massachusetts and the Hungarian Medical Schools as well as the Ministry of Health since 1999 when a memorandum of understanding was signed in Budapest to undertake this joint project. In Hungary, prehospital care is well-developed but emergency medicine as an organized discipline is in its infancy when it takes place within the hospital system. In the last few years, members of the University of Massachusetts faculty have traveled on multiple occasions

to Hungary to contribute to this process. This joint undertaking has raised the interest of the Hungarian Government as well as the Hungarian Universities and hospitals to do more in this important field.

TRANSPLANTED BONE MARROW GENERATES NEW NEURONS IN HUMAN BRAINS

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Adult bone marrow stem cells appear to differentiate into muscle, skin, liver, lung and neuronal cells in rodents. Furthermore, transplanted bone marrow cells have been shown to regenerate myocardial cells, hepatocytes, and epithelium of skin and gastrointestinal tract in humans. Since we have previously demonstrated that transplanted bone marrow cells can enter the brain of mice and differentiate into neurons there, we decided to examine postmortem brain samples from females who had received bone marrow transplants from male donors. The underlying diseases of the patients were lymphocytic leukaemia and genetic deficiency of the immune system and the patients survived between 1-9 months after transplant. We used a combination of immunocytochemistry (to identify neurons using NeuN and Kv2.1 as specific markers) and fluorescent in situ hybridization histochemistry (FISH) to search for Y chromosome-positive cells. In all four patients studied we found cells containing Y-chromosomes in several brain regions. Most of these were non-neuronal, but in addition to endothelial cells and cells in the white matter, neurons were certainly labeled, especially in the hippocampus and cerebral cortex. The youngest patient (a three year old child) who also lived the longest time following transplantation had the greatest number of donor-derived neurons (7 donor derived neurons among 10000). The distribution of the labeled neurons in the sections examined was not homogeneous. There were clusters of Y-positive cells in areas that were otherwise negative suggesting that single progenitor cells underwent clonal expansion and differentiation. We conclude that adult human bone marrow cells have the capacity to enter the brain and generate neurons just as rodent cells do. Perhaps this phenomenon could be exploited to prevent the development or progression of neurodegenerative diseases or to repair tissue damaged by infarction or trauma.

TREATMENT OF HYPERTENSION: AN UPDATE

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Recent landmark trials indicate that slowing the progression of kidney disease and reducing target organ damage in hypertension is possible. This update on hypertension focuses on the role of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in kidney disease and hypertension. New developments in the field will be summarized.

ACEIs are the mainstay of therapy in a whole host of disease processes where the renin-angiotensin axis is upregulated. A new class of drugs, the non-peptide ARBs prevent angiotensin II binding to its AT1 receptor. Consequently, ARBs represent an alternative to ACEIs in blocking the renin-angiotensin system, and the spectrum of their clinical indications may be similar to those of ACEIs. Based on the available evidence, the use of ACEIs and ARBs will be critically analyzed in terms of their efficacy of slowing the progression of kidney disease and reducing target organ damage in hypertension.

Relevant studies from the cardiology literature will also be reviewed. Implications of the ALLHAT, ABCD, IDNT, IRMA, RENAAL, HOPE, LIFE, ELITE, VALHEFT, OPTIMAAL, COOPERATE studies will be discussed.

THE EFFECT OF NaCl ON LINGUAL SURFACE POTENTIALS AND THE ROLE OF AMILORIDE

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The description of electrophysiological principles of human salt taste could represent a major advance in influencing salt intake, a crucial determinant of care of patients with hypertension, renal failure and congestive heart failure. In animals, salt sensing by the tongue shows a positive correlation to the concentration of salts applied to the tongue, and it is decreased by amiloride (a blocker of the epithelial sodium channel [ENaC]). To investigate whether human lingual electrophysiology exhibits similar characteristics we utilized a chamber to measure the lingual surface potential (LSP) while different solutions were applied to the surface of the tongue.

In volunteers (n=13) changing the superfusion solution from rinse solution (30 mM KCl) to 300 mM NaCl for 30

seconds hyperpolarized the LSP by -10.1 ± 0.7 mV. The magnitude of the salt evoked potential ranged between -6.8 to -14.1 mV, indicating inter-individual variability. When solutions of 100 mM and 600 mM NaCl were applied separated by two minutes of rinse solution, the more concentrated solution consistently elicited a more electronegative potential in all subjects ($35 \pm 4.8\%$, $p < 0.001$), demonstrating a dose response relationship between salt concentration and the LSP. To assess whether the activity of ENaC contributes to the human LSP evoked by salt, amiloride-free solutions were applied to the lingual surface (in sequence, rinse for 2 minute, 300 mM NaCl for 30 seconds, rinse for 2 minute) and then similar solutions to which 100 μ M amiloride had been added. Amiloride reduced the LSP by $18.5 \pm 4.3\%$ ($p < 0.005$, $n=11$); it inhibited the salt evoked hyperpolarization in 5 subjects, had a modest effect in 1 subject and had no effect in 5 subjects, whereas all subjects exhibited an amiloride-insensitive component. Subsequently, we varied the amiloride concentration from 10^{-8} to 10^{-4} M while the salt concentration remained 150 mM in an individual who had exhibited amiloride sensitivity. Increasing the amiloride concentration progressively affected the LSP. Amiloride exerted 50% of its inhibitory effect at 1 μ M.

In summary, we showed that LSP hyperpolarizes in response to sodium and there is a dose-response relationship between LSP and the Na-concentration. Amiloride, a blocker of ENaC, inhibits Na induced hyperpolarization. This inhibition varies interindividually and we speculate that it may change in different physiologic and pathophysiologic conditions.

IN VITRO EVALUATION OF TRANSCATHETER FIBRIN GEL INJECTION FOR ANEURYSM TREATMENT

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Rupture of an intracranial aneurysm can result in serious permanent neurological deficit or death. Conventional treatment of an intracranial aneurysm has been by open craniotomy and clipping of the neck. Endovascular treatment was developed as a safer alternative to surgery. The standard endovascular treatment is coiling using detachable coils; however coiling has several limitations as migration, coil compaction, compression of the surrounding brain tissue.

Liquid embolic has a great potential to treat giant or wide neck aneurysms that are difficult to treat using coils. Several synthetic polymers were tested but concerns have been raised regarding the toxicity of the agents used. Distal embolization or parent artery occlusion is a possible complication that is difficult to manage.

Endovascular fibrin gel injection imitates natural thrombosis in the aneurysm which is independent of the patient's own coagulation process. Fibrin gel is currently used for numerous applications such as wound healing, drug delivery and sealant during surgery.

In our in vitro experiments we tested the fibrin gel embolization using aneurysm phantoms and microcatheters for the delivery. Different concentrations of the two components were tested first to determine the optimal gel formation. Further studies were performed in a flow system that allowed us to simulate a more realistic environment and test the stability of the gel and the feasibility of safe embolization. We tested methods for delivery and different materials for making the gel Radiopaque.

The results illustrated that fibrin gel potentially an effective treatment for occluding intracranial aneurysms. Further research is necessary using in vivo aneurysm model to evaluate the safety and efficacy of this treatment method.

AN UPDATE ON POSTMENOPAUSAL HORMONE REPLACEMENT

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The aim of this presentation is the reassessment of hormone replacement therapy (HRT) following the premature discontinuation of the Conjugated Equine Estrogen (CEE) plus Medroxyprogesterone Acetate (MPA) arm of the Women's Health Initiative's (WHI) prospective, double-blind study. On the negative side, WHI found 7 additional cases of nonfatal myocardial infarction, 8 more cases of stroke and of pulmonary emboli, and 8 additional cases of breast cancer per 10,000 hormone users. Benefits were a significant decrease in the risk of hip fracture (36%), of vertebral fracture (40%), of colorectal cancer (37%), as well as a reduction of endometrial cancer (17%). The WHI authors concluded that CEE+MPA produces more risks than benefits, and they essentially recommended against its use. The slight rise of breast cancer incidence (mortality was not increased) was consistent with several previous publications, the lack of protection from cardiovascular

diseases was uncertain because of the advanced age of the subjects. In an additional article, the authors, mainly psychologists and epidemiologists, concluded that HRT did not improve meaningfully the quality of life. Clinicians who have patient contacts cannot share this view. In our practice, following the initial WHI publication of the data by non-medical media, 51% of CEE+MPA users discontinued HRT prior to counseling; 69% of these requested to restart HRT because of severe hot flushes, insomnia and depression. The WHI study has many flaws, which makes the meaning of the published results questionable. Some of these are the following: 1. Exclusion from the study of women who had severe menopausal symptoms; 2. Focus on the 60+-year age group (the majority of women were 10+ years postmenopausal when HRT was initiated); 3. The conclusions on breast cancer incidence are not justified because of lack of significance of the reported 95% confidence intervals; 4. Inclusion in the study of women with prior cardiovascular disease. The CEE only arm of the WHI study continues for lack of important adverse effects, suggesting that the complications reported in the discontinued CEE+MPA arm may have been due to daily exposure to progesterone. We believe that HRT will continue to play a meaningful role in the postmenopausal quality of life since it suppresses flushes, insomnia and depression and helps prevent osteoporosis, colon cancer deaths, urogenital atrophy, as well as Alzheimer Disease.

THE EFFECT OF EXPANDING UNITED STATES EMERGENCY MEDICINE TRAINING CAPACITY ON EMERGENCY PHYSICIAN SUPPLY

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Introduction: Emergency Medicine (EM) in the United States will soon celebrate its 25th year as a primary board of the American Board of Medical Specialties (ABMS). In ¼ century, EM has seen rapid growth of training programs and, subsequently, increasing numbers of certified practicing Emergency Physicians. A number of factors continue to support the expansion of EM including increasing # of ED patient visits, % of Americans without health insurance/primary care and medical student interest/academic acceptance. Factors that threaten long-term growth include: competition by other specialties and non-physician providers for acute care, governmental and third-party payor efforts to divert patient to non-

Emergency Room (ER) settings and caps placed upon funding for physician training.

Methods: A Medline literature review was performed. Additional sources included relevant web material from: AAEM, AAMC, ABEM, ABMS, ACEP, ACGME, AMA, AMSA and SAEM. This met criteria for IRB exemption.

Results: From 1975 to 2002, the number of accredited EM training programs increased from 5 to 125. A majority of those programs are Post Graduate Year (PGY) 1-3 format. Growth occurred through the addition of new programs and expansion of existing programs corresponding to the 1073 currently available National Resident Matching Program (NRMP) entry positions annually. Approximately 7% of graduating American medical students filled 80% these positions. The remaining 18% are filled by American resident transfers, Osteopathic graduates and International medical graduates (IMG). While American graduates enjoy a 90% fill rate for EM, IMGs match at less than 50% except in high concentration areas such as New York or New Jersey. Despite a decline in the estimated number of US hospitals with ERs to 5064, national patient census rose by 7% to more than 102 million visits. The number of practicing EPs remained steady at approximately 32,000 physicians with increasing % being either boarded or residency trained.

Conclusions: Within the dynamic US health care industry no factors have slowed the growth of Emergency Medicine. Despite hospital consolidation, EP supplies are matched by the expanding national training capacity.

MONITORING CELL MEMBRANE ELECTRIC POTENTIAL DURING INTRACYTOPLASMIC SPERM INJECTION FACILITATES THE PROCEDURE AND MAY PROVIDE INFORMATION ABOUT OOCYTE PHYSIOLOGY

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Objective: To evaluate electrophysiologic techniques and possible applications of transmembrane potential measurement during intracytoplasmic sperm injection (ICSI).

Design: Experimental animal studies. Mature mouse oocytes were subjected to intracellular measurements of membrane potential using conventional techniques and modifications of the technique for use with sham ICSI.

During the procedure, the actual penetration of membrane was determined subjectively or objectively with or without monitoring membrane potential. Membrane potential was correlated with oocyte degeneration on the day after ICSI.

Setting: Reproductive research lab.

Animal(s): Mature female B6C3F1 mice at seven to twelve weeks old.

Intervention(s): Measurement of oocyte membrane potential. Sham ICSI.

Main Outcome Measures: Transmembrane electric potential using different electrodes; comparison of subjective and objective determination of membrane penetration.

Result: Measurement of the membrane potential with the same glass pipettes used in ICSI means compromise between signal amplitude and compatibility with the conventional ICSI setup. Signal quality is inversely related to the diameter of the injection pipette, and its amplitude decreases as the concentrated electrode filling solution is replaced by physiologic solutions used in ICSI. When successful membrane penetration is suspected by visualization, measuring the potential at the tip of the injection pipette often proves otherwise. Conversely, when membrane penetration is confirmed by detection of transmembrane potential the procedure may subjectively appear unsuccessful. Low transmembrane electric potential measured with conventional electrode at the time of ICSI predicted oocyte degeneration observed on the following day.

Conclusion: Monitoring of transmembrane potential can be done successfully in conjunction with standard ICSI and may predict oocyte viability.

(Key Words: Oocyte, membrane potential, intracytoplasmic sperm injection)

ASSESSMENT OF GLYCAEMIC COMPENSATION IN DIABETIC PATIENTS ACCORDING TO A SIMPLE MODEL OF HAEMOGLOBIN GLYCATION

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Introduction. Regular use of blood glucose self-monitoring (SMBG) and the introduction of glycated haemoglobin (GHb) assays were revolutionary events in diabetes management. They provided better insight into

situations that in the past were hidden before doctor and patient. However, shortly after introduction of GHb assays two misunderstandings about its role arose: „Glycated haemoglobin reflects the average blood glucose of the patients during the preceding 4 months” and „Glycated haemoglobin measurements can replace assays of blood glucose”.

The model of haemoglobin glycation. Glycated haemoglobin concentration in diabetic

patients depends on two processes with different kinetics:

1. The binding of glucose to haemoglobin in red blood cells follows a 1st order kinetics – it depends mainly on glucose concentration in the blood.

2. The replacement of the oldest red blood cells with the youngest ones occurs at a constant rate (approximately 0,8% of all red blood cells daily – zero order kinetics).

The mathematical equation describing the combined kinetics is complicated but it is possible to understand it without mathematical models: In human blood there are old and young red blood cells approximately in the same amount but the "glycaemic memory" of the old and young cells is different. Therefore GHb values reflect preceding blood glucose values but in a distorted way resembling perspective view. Hyperglycaemic episodes which occurred shortly before GHb assay have a greater effect on GHb concentration as compared with those that occurred long ago (within the 120 day range of red blood cell life span).

Testing the model. The validity of the model was tested in 272 patients treated in 3 diabetes outpatient clinics. GHb was measured by Unimate Hb A1c kits on Cobas Mira analyzer (Roche, Switzerland). In all clinics the best fit between blood glucose values and GHb was found in patients using SMBG (nonlinear correlations; $r = 0,54 - 0,65$).

Conclusions for diabetes management .

1. Near-normal GHb values reflect very probably good blood sugar control but they do not rule out short-term hyperglycaemic excursions or frequent hypoglycaemic episodes.

2. Very high GHb values certainly reflect bad compensation but they do not rule out frequent hypoglycaemic episodes.

3. Intermediate values of GHb do not reflect "intermediate" or "fairly good" compensation because such GHb values can arise from very different combinations of recent and past hyperglycaemic episodes. Our results confirm that assessment of glycaemic compensation is possible only through simultaneous evaluation of blood glucose values (profiles, SMBG, continuous monitoring) and GHb (an integrated marker of blood glucose levels in the past 2 – 3 months).

FOLIC ACID AND PREVENTION OF MAJOR HUMAN DISEASES?

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Randomized controlled trials including the Hungarian trial showed that folic acid supplementation could prevent a substantial proportion (approximately 75%) of neural tube defects, one of the most common and severe groups of congenital malformations. The results prompted several countries in the 1990s to make recommendations to women of reproductive age to consume 0,4-0,8 mg of folic acid to prevent birth defects. Periconceptional supplementation and food fortification have been proved to be two efficient ways to increase blood folate level and lower plasma homocysteine concentration. Some studies suggested that supplementation with higher dose of folic acid may reduce the risk of other types of birth defects, such as orofacial clefts and limb deficiencies. Recent evidence indicates that food fortification with folic acid might have further beneficial role in the general population: 1) folate deficiency anemia among adults may disappear, 2) reduction in mortality of strokes and heart attacks has been observed, thus, increased consumption of folic acid may prevent certain cardiovascular diseases, and 3) folic acid assists DNA repair mechanisms that could lead to reduce the risk of different types of cancer. Folic acid supplementation and food fortification, an inexpensive and effective intervention can be a unique opportunity to prevent major human diseases. Why is there a delay in implementation?

HOW THE PLACENTA COMPROMISES INNATE AND ADAPTIVE MATERNAL IMMUNITY? HOW MALIGNANT TUMORS IMITATE THE PLACENTA? HOW MATERNAL NATURAL KILLER (NK) CELLS RESTRAIN THE TROPHOBLAST? HOW NK CELLS OF THE TUMOR-BEARING HOST CONTROL THE TUMOR?

II. NKT CELLS MEDIATE THE ACCEPTANCE OR REJECTION OF THE FETUS OR THE MALIGNANT TUMOR.

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Rejection of incompatible and "non-self" transplants in the urochordate *Botryllus schlosseri* is carried out by blood cells expressing a receptor BsCD94-1 that is closely related to a receptor of mammalian and human NK cells. Human NK cells were first observed in the blood of the senior author (JS) in 1968-9 (*J Medicine* 1: 15 & 313 '70; in *Leukemia-Lymphoma, Yearbook, Chicago* pp 53-92 '70; *Oncology Times* 18: July & Nov '96) and were referred to as "lymphoid cells practicing immune surveillance". The well-established innate and adaptive immune system of the mammalian host is readily compromised by the placenta of the fetus and by malignant tumors. Adaptive immunity established itself 450 million years ago in cartilaginous fishes (gnatostomata; chondrichthyes). The first (unsuccessful) attempts at placentation occurred also in fishes (Poeciliopsis) and continued in viviparous salamanders. The successful mammalian placenta produces HCG β , TGF β , PIGF and Fas ligand; and the trophoblast conceals its MHC antigens. Tumor cells suppress their MHC expression; release the tolerogen HCG β ; produce TGF β to inhibit clonal expansion of immune T cells of the host; and PIGF with VEGF to induce neoangiogenesis. Cytotrophoblasts express a fusigen endogenous retrovirus to create syncytiotrophoblasts. Tumor cells frequently express their own endogenous retroviruses (Orvosi *Hetilap* 142: 1352 '01; 144: 588 '03). Maternal CD1d-restricted invariant NKT cells are activated to invade the placenta and restrain the invasion-prone trophoblast, while they may induce Th1 or Th2 type immune reactions to the fetus. Th1 (IFN γ , TNF α , IL-2 and immune T cells) reactions kill the fetus; Th2 (IL-4, 5, 6, 10, 13 and antibodies) reactions promote survival of the fetus to term. Tumor-bearing hosts mobilize NKT cells; in the case of Th1 reaction tumor rejection may be accomplished, while in Th2-reactive hosts the tumor prevails. The primordial NK cells with their archaic past emerge as crucial mediators of the feto-maternal relationship and arbitrators of pro- or antitumor immune reactions. Statisticians now search for data if multiparous women whose innate and adaptive immune systems were repeatedly compromised by the placenta displayed increased susceptibility to malignant tumors; or if women who habitually aborted their fetuses practiced a higher level of antitumor surveillance? And how males whose immune system is not compromised by this basic biological event of the species respond to their tumors? If it is old age that takes its toll on our immune surveillance toward cancers of epithelial organs (*Nature* 408: 248 '00) how do we explain the incidence of mesenchymal tumors (leukemias; sarcomas) of children?

**THE BAD GENE STOPS HERE:
PREIMPLANTATION GENETIC DIAGNOSIS IN
ASSISTED REPRODUCTIVE TECHNOLOGIES.**

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Preimplantation genetic Diagnosis (PGD) represents the cutting edge of reproductive technology. It provides the ability to prediagnose many common chromosomal aneuploidies as well as some genetically based diseases. PGD has been developed as a method to help couples who choose IVF to identify chromosomal abnormalities prior to embryo implantation. PGD has also been developed for couples who have a family history of a specific genetic disease. In IVF pregnancies in women 35 years or older, research has shown that aneuploidies (refers to blastomeres in an embryo having one less or one extra chromosome) and other genetic abnormalities of the embryo will increase the risk of spontaneous miscarriage or the development of an abnormal fetus. Thus, performing genetic analysis prior to embryo implantation could prevent the initiation of abnormal pregnancies. PGD may increase the chance for a successful pregnancy and the delivery of a healthy and disease free newborn. This technique may very well revolutionize the way reproductive medicine is practiced.

**ELECTRICAL STIMULATION OF THE VISUAL
CORTICES IN EPILEPSY SURGERY
CANDIDATES**

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Functional neuroimaging, transcortical magnetic stimulation, evoked potentials and electrocortical stimulation have been used to better understand visual processing and the functional relationship of the visual areas. Understanding the location and connectivity of visual functions may help to minimize deficits caused by occipital lobe resections in patients with medically refractory localization-related epilepsy. Methods for mapping the visual cortices in this clinical setting will be reviewed. Examples of electrocortical stimulation in 5 patients with extensive medial, basal and lateral occipital lobe subdural electrode coverage will be presented and the impact of stimulation on their clinical outcome discussed.

Finally, these findings will be complemented by experimental data from primates and functional imaging in humans to better elucidate our current understanding of the visual areas and their connectivity.

**THE ROLE OF THE COMPLEMENT SYSTEM IN
HEALT AND DISEASE: AN UPDATE**

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The complement (C) system represents a group of some 30 plasma and membrane glycoproteins that provides immediate defense against microbial infections. Because of this role, C is traditionally considered as part of the immune system, namely, the nonspecific arm of humoral immunity. Recent progress in C research, however, highlighted numerous additional roles of this system in health and disease. Just to mention a few newly recognized homeostatic functions, C activation turns out to be pivotal in initiating the adaptive (specific) immune response, in plays a key role in the regulation of cardiovascular response to inflammation, as well as in conception, tissue development and repair, and in apoptotic cell clearance. On the other hand, excessive C activation has been recognized to play a critical role in some 30 diseases or adverse conditions, including myocardial infarction, SLE, rheumatoid arthritis and a range of other autoimmune diseases, transplant rejection, abortion, trauma, sepsis, shock, CNS injuries and diseases, HIV infection, allergy and pseudo-allergic reactions to drugs. These recent revelations propel intense industrial efforts to develop C inhibitor drugs, and in fact, a few are very close to clinical use. My presentation will summarize the essentials of the C system, its recently recognized roles in the above-mentioned physiological functions and disease states, and the C inhibitor drugs that are available or are in advanced clinical trials. I will present in detail our own research on the role of C activation in pseudo-allergic reactions to drugs, and in hemorrhagic shock. The goal is to provide a comprehensive update on C research that may be useful for clinicians and basic researchers alike.

PRACTICAL PHARMACOGENETICS

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Pharmacogenetics tests the hypothesis that inter-individual differences in the observed response to a drug (efficacy, safety or tolerability) might be associated with the presence or absence of individual-specific biological markers, thus allowing the prediction of drug response. One approach is to consider the drug effect being an environmental factor, which interacts with the inborn predisposition. Drug response (including side effect) depends on both pharmacokinetics and pharmacodynamics. The pharmacokinetics of a drug is difficult to foretell since many drugs are subject to complex, parallel metabolizing pathways. Nevertheless, pharmacogenetic differences can be overcome by dose-adjustment and by small changes in the structure of the molecule. Unrecognized and undiagnosed disease heterogeneity at the molecular level makes the prediction of pharmacodynamics even harder. Current practical applications of pharmacogenetics to limit an adverse event are mainly restricted to common diseases with dire prognosis (such as cancer and AIDS), where the side effect is both relatively common and tolerated in favor of the beneficial effects of the drug. The use of pharmacogenetics for enhanced efficacy by the identification of non-responders is under way, as well.

This presentation summarizes the most frequently studied genetic polymorphisms and haplotype-associations causing differences in individual drug response, and the scope of their potential use in the future.

HUMANIZATION OF HOSPITALS WORLDWIDE: THE FIRST MODEL FOR A NEEDLE-FREE, INFECTION-FREE AND PAIN-FREE HOSPITAL IS THE UNIVERSITY OF ILLINOIS HOSPITAL

Elemer K Zsigmond, MD, DSc, FCP, Professor Emeritus of Anesthesiology, Medical Director for the NFIFPF UICH Project, UICMC, Chicago, IL 60612 USA

The concept for the humanization of hospitals worldwide has been initiated by the successful campaign of mass-immunization against smallpox, polio, yellow fever, etc. by Robert H Hingson, MD and associates. It was evident that the Med-E-Jet injector (Peace Gun) caused no pain or discomfort, since billions of illiterate, tribal people voluntarily underwent immunization without any evidence of fear or discomfort in thirty years. Therefore, Dr.

Hingson and I hoped that children could be anesthetized by the Med-E-Jet injector without fear of needles and any unpleasant recall for surgery. Indeed, Drs. Kovacs, Fekete and I were able to induce anesthesia with midazolam and/or ketamine fast and safely at the Semmelweis Medical University (1,2). Based on these favorable results, I started the campaign to eliminate needles altogether from daily medical practice by the use of jet-injection (ji) for drug delivery, thereby halting the worldwide epidemic of needle-stick injuries resulting in one million death annually.

Since the two most common adverse experiences reported by patients are 1/ the pain on intravenous injection/catheterization and 2/ the pain experienced during phlebotomy, we first wanted to provide painless local anesthesia for these procedures. ZERO pain scores were recorded with the Med-E-Jet or Biojector jet injections in contrast to the conventional needle/syringe (3). A new Hospital Policy had to be proposed, voted on and approved by the medical staff which mandated the use of local anesthesia with buffered lidocaine given by a jet-injector in order to reduce pain to ZERO. Slowly but surely, all units in the hospital complied with the new policy. Starting in the Surgicenter and Emergency Department with outpatients, we were able to collect from the insurers for the added cost of the technique (30-40cents). The positive financial balance created by the ji local anesthesia allowed us to convert to the use of ji technology for all the sc. and im. injections after new policies for drug administration were approved by the medical staff.

At present, the UICH serves as a model hospital to other hospitals, which wish to convert into a needle-free, infection-free and pain-free hospital which is mandated by Federal Law, the OSHA and JCAHO. The prime task for the WHO in the battle to combat the worldwide epidemic of needle-stick injuries can be accomplished only by the use of ji technology with elimination of needles.

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EDITOR'S NOTE

All abstracts available to the Editorial Office as of September 30, 2003 are included in this Abstract edition of the Archives of the Hungarian Medical Association of America.

The help of Istvan Stadler, Ph.D. (Program Committee Chairman) in forwarding all the abstracts he received is appreciated. I'd like to thank Kamill Gal, M.D. (Past Editor of the Archives) for his valuable comments.

It is of note that some abstracts had to be modified to fit the classic format of the Archives. No alterations pertaining to the scientific content of the abstracts were carried out.

With questions or suggestions please contact the Editor at amogyoro@vcu.edu.

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