ABSTRACTS

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ERYTHROPOIETIN AND ERYTHROPOIETIN RECEPTOR IN BREAST CANCER: EVIDENCE FOR A NOVEL AUTOCRINE LOOP INDUCED BY HYPOXIA.

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Background: Erythropoietin (Epo), a glycoprotein hormone induced by tissue hypoxia, is normally produced by the kidney and acts via Epo receptors (EpoR) to stimulate growth, prevent apoptosis and induce differentiation of red blood cell precursors. Expression of Epo and EpoR has recently been demonstrated in several non-hematopoietic tissues, suggesting a broader role for Epo signaling in regulating cell growth, cell survival and angiogenesis. Hypoxia is a prominent feature of solid tumors and is thought to select for aggressive cancer phenotypes and promote neovascularization. Aim: To investigate whether Epo signaling may play a role in the development and hypoxic adaptation of breast cancers. Methods: We studied the expression, activation and hypoxic induction of Epo and EpoR mRNA and protein in MCF-7 and BT549 human breast cancer cells using RT-PCR, Western blot and immunocytochemistry. Results: We found that human breast cancer cells express both Epo and EpoR and their expression by the tumor cells is stimulated by hypoxia. Epo stimulated tyrosine phosphorylation, DNA synthesis and proliferation in the tumor cells suggesting that Epo signaling is biologically active. Conclusion: Our findings have significant implications for theories regarding multistage carcinogenesis, as well as for the diagnosis, treatment and prevention of cancer. Our data suggest that autocrine/ paracrine Epo signaling may play a prominent role in the survival of hypoxic tumors. The hypoxic upregulation of Epo and EpoR suggests novel ways in which hypoxia may promote cancer.

EXPRESSION OF ERYTHROPOIETIN AND ERYTHROPOIETIN RECEPTOR IN BREAST TISSUE AND ITS BIOLOGICAL IMPLICATION.

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Background: Erythropoietin (Epo), induced by tissue hypoxia, controls the survival, proliferation and differentiation of Epo receptor (EpoR) bearing erythroid progenitors and plays a role in protection of neurons from invasion, neovascularization, metastasis, resistance to chemo- and radiation therapy and the selection of cells with diminished apoptotic potential. Aim: In the present study we wished to characterize the expression of Epo and EpoR in a large series of mammary carcinomas. Methods: The expression of Epo and EpoR was studied by immunohistochemistry in 184 invasive and 158 in situ mammary carcinomas and benign mammary epithelium. The correlation of protein expression with various clinicopathologic features of the tumors was analyzed. Results: We found weak to moderate expression of Epo and EpoR in benign mammary epithelial cells. Epo expression was significantly increased in carcinomas compared to benign epithelium in non-smokers, but not in smokers. Epo staining was heterogeneous in the tumors with prominent expression in tumor cells adjacent to necrotic areas and at the infiltrating edge of tumors. EpoR expression was significantly increased in carcinomas compared to benign epithelium both in non-smokers and smokers. EpoR expression was homogenous in the tumors, although higher expression was seen adjacent to necrotic areas. EpoR, but not Epo expression was significantly higher in tumors showing high combined histologic grade, tumor necrosis, lymphovascular invasion, lymph node metastases and loss of hormone receptor expression. Conclusions: Our findings suggest that increased Epo signaling may play an important role in breast carcinogenesis and may represent a novel autocrine or paracrine mechanism by which hypoxia, including that caused by smoking, can promote breast cancer.

EXPERIMENTS IN SEARCH OF LOCAL ANTI-INFLAMMATORY AGENTS: STUDIES ON L-SELECTIN AND IL-2 RECEPTORS.

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Migration of peripheral lymphocytes to inflammation sites starts with the engagement of the L-selectin cell surface molecule. We have found that L-selectin is in close proximity to the T cell receptor in the plasma membrane of human peripheral lymphocytes. This fact was demonstrated by proliferation and fluorescence based flow cytometric studies and by the biophysical energy transfer method. The energy transfer method established that L-selectin is within the distance of 170 angstrom to the T cell receptor. In the course of these studies, we have found that certain compounds disengage mAb to the main epitope of L-selectin. Some of these compounds showed selectivity for this L-selectin epitope. Such compounds could block the initial attachment and the migration of these immune cells out of blood circulation. Interestingly, the very same type of compounds could block the attachment of IL-2 to its receptor. This blockage could be demonstrated by cell culture, membrane potential, electron spin resonance and lateral diffusion of surface protein studies. On the atomic scale, electron density simulation method differentiated between compounds able and unable to block L-selectin and the IL-2 receptors.

OBESITY-INDUCED UPREGULATION OF UNCOUPLING PROTEIN-2 IS NOT LINKED TO THE SEVERITY OF FATTY LIVER DISEASE. **GyÛrgy Baffy, M.D., Ph.D.[1,2], Chen-Yu Zhang, M.D.[1], Jonathan N. Glickman, M.D.[3] and Bradford B. Lowell, M.D., Ph.D.[1], Div. of Endocrinology, Beth Israel Deaconess Medical Center[1] and Div. of Gastro-enterology[2] and Pathology[3], Brigham & Women's Hospital, Harvard Medical School, Boston, MA.**

Background: Uncoupling protein-2 (UCP2) is a mitochondrial inner membrane protein that mediates proton leak, uncouples ATP synthesis from fuel oxidation, and negatively regulates reactive oxygen species (ROS) production in the mitochondria. Expression of hepatic UCP2 is markedly increased in various animal models of obesity. Evidence is accumulating that ROS greatly contribute to the progression of steatohepatitis. It has been speculated that increased UCP2 expression may compromise cellular ATP levels and contribute to liver damage. Alternatively, UCP2 may exert a protective role by diminishing oxidative stress in fatty liver disease. Aims: In the present study, gene knockout mice were used to definitively evaluate the role of UCP2 upregulation in obesity-induced fatty liver. Methods and results: UCP2 knockout mice were crossed with *ob/ob* mice, a leptin-deficient strain that develops massive fatty liver. UCP2 deficiency had no effect on the obesity of *ob/ob* mice. Serum ALT levels were measured to assess hepatocellular injury. ALT levels were 2-to-3 fold higher in *ob/ob* mice compared to wild-type mice as expected, but UCP2 deficiency had no significant effect on ALT elevation. Mice were sacrificed at 25 weeks of age and the steatohepatitis score was determined. Steatohepatitis in crossbred mice showed no difference from *ob/ob* mice (males, 4.7±0.2 vs. 4.8±0.7, N.S.; females, 3.7±0.6 vs. 3.8±0.6, N.S.). To avoid confounding effects of the absence of leptin, an adipose-derived hormone with pro-inflammatory properties, steatosis was also induced in UCP2 knockout mice by high-fat diet. Male UCP2 knockout mice were fed with a high-caloric diet rich in coconut oil (DK12330, Research Diet, Inc., New Brunswick, NJ) for 8 months. Again, UCP2 deficiency had no effect on diet-induced weight gain. Serum ALT levels remained normal and the steatohepatitis score in UCP2 knockout mice was the same as in wild-type controls (3.8+1.3 vs. 3.8±1.3). Conclusion: Contrary to expectations, increased expression of UCP2 in the liver of mice with genetically or diet-induced obesity exerts neither protective nor deleterious effect on the severity of fatty liver disease. Other, possibly metabolic roles of UCP2 upregulation in obesity will be discussed.

THE BRITISH NATIONAL HEALTH SERVICE - STILL THE PRIDE OF BRITAIN AND THE ENVY OF THE WORLD? **Andras Barabas, M.D., Medical School, Cambridge University and the Department of Surgery, West Suffolk Hospital, Bury St Edmunds, United Kingdom.**

Soon after the Second World War, on July 1, 1948, the Labor Government introduced a free comprehensive health care system in Britain, the National Health Service (NHS). The NHS was supposed to look after the health of all British citizens "from cradle to grave". The NHS was financed entirely from general taxation and was totally "free at the point of delivery". For the first 30-40 years of its existence the great majority of British people regarded the NHS as "the pride of Britain and the envy of the world". In the past decade, however, the NHS lost some of its popularity and there is general agreement that it requires urgent improvement. In this talk I shall discuss the failings and successes of the NHS and I shall summarize the numerous proposals currently debated in Britain about the changes needed to bring the NHS up to date.

ALZHEIMER'S DISEASE: HISTORY OF THE FIRST CENTURY. **J. Paul Binette, M.D., VA**

WNYHCS, Buffalo and Department of Medicine and Biomedical Sciences, State University of New York at Buffalo, NY.

Mrs. Auguste D was admitted to hospital in Frankfurt, Germany under the care of Dr. Alois Alzheimer on November 25, 1901 and died there on April 8, 1906. The brain pathology was reported by Dr. Alzheimer on November 4, 1906 and published the following year. The description of the characteristic lesions, plaques and tangles, accords with the lesions as described at the present time, as does the clinical presentation of memory loss, disorientation and psychosocial impairment. The eponym was bestowed on presenile dementia by Dr. Kraepelin in 1910. It has subsequently been found that the same pathology encompasses senile dementia; that familial and sporadic forms of the disease burden the human race; that the plaques harbor many proteins including the amyloid fibril forming Aβ peptide derived from the cleavage of the normal amyloid precursor protein; that the tangles are examples of tauopathies resulting from hyperphosphorylation of the tau protein. We also know that Alzheimer's disease is the most common cause of dementia in the elderly and is incurable at present, but vast strides have been achieved in our understanding of the disease and a little progress in its treatment.

ESCHERICHIA COLI O157:H7 INFECTIONS IN THE UNITED STATES, WITH SPECIAL ATTENTION TO THE MIDWEST. IS IT SAFE TO BARBECUE? Timea Bor, M.D., West Holt Memorial Hospital, Atkinson, NE.

Enterohemorrhagic E.coli is the cause of more than 20,000 cases of enteral infections as well as 250 deaths in the U.S. each year. Twenty years ago when this new strain of E.coli was first described, the pathogenesis of the disease was not well known yet, but they knew that undercooked hamburgers were the case of infection. The bloody diarrhea caused by E.coli E157:H7 usually is a self-resolving problem, but it may lead to hemolytic uremic syndrome and three to five percent of the H.U.S. cases will die despite hemodialysis and intensive care treatment. Since there is no specific treatment for this infection, the best is to prevent it with proper meat processing and adequate cooking.

NEWCASTLE DISEASE VIRUS VACCINE (MTH-68/H) IN MALIGNANT GLIOMAS.

Laszlo K. Csatary, M.D.[1], Arnold I. Freeman, M.D.[2] and Christine Csatary, M.D.[1], United Cancer Research Institute, Alexandria, VA, USA[1] and Hadassah University Hospital, Jerusalem, Israel[2].

Glioblastoma is a highly malignant brain tumor with a median survival time of one year. Gliomas are very difficult to treat, they are resistant to conventional treatment schedules. In former papers we reported on patients with various malignant tumors successfully treated with Newcastle disease virus (MTH-68/H) vaccine, after all conventional therapies were exhausted. Now we report the strickingly positive outcomes with five patients suffering from malignant glioma. The patients received MTH-68/H vaccine therapy from 2 to 6 years. Oncolytic viruses have gained attention in the treatment of experimental and human malignant tumors. It is of special interest that chemotherapy resistant malignancies often respond very well to the MTH-68/H vaccine, suggesting that NDV causes viral-induced oncolysis, probably through programmed cell death or by other unknown mechanisms. It is important to emphasize that this agent has no toxic effects, including its lack of neurotoxicity and is a promising candidate for further evaluation in patients with malignant gliomas. Presently several cancer research institutes – mainly in in vitro and animal experiments – confirm that different human and animal attenuated viruses are indeed effective in destroying cancer cells, including gliomas.

THYROID GLAND VOLUME AND IODINE EXCRETION IN NEWBORNS.

L. Csáthy, M.D., Ph.D.[1], I. Molnár, M.D., Ph.D.[2], Gy. Szász, M.D.[3] and J. Math, Ph.D.[4], Department of Pediatrics[1], 3[d] Dept. of Internal Medicine[2] and Dept. of Radiology[3], Kenåzy County Hospital and Institute of Psychology[4], Kossõth University, Debrecen, Hungary.

There are only a few data available on the thyroid gland volume of full term newborns and pre-terms. The aim of this study was to obtain data on thyroid gland volume and iodine excretion in the newborn period. The thyroid volumes were determined in 120 full term newborns (gest. age: 39.4±1.0 weeks, birth weight: 3250±740 grams) and 70 pre-terms (gest. age: 35.0±1.3 weeks, birth weight: 2250±260 grams) on the 4-6th day of life with a 10 MHz linear array head. All mothers were euthyroid. The volume of each lobe was calculated separately using the formula of an ovoid (DxWxLxπ/6). The mean volume of the whole gland (SD) was 0.46±0.20 ml in full term newborns, and 0.33± 0.12 ml in pre-terms. The difference is significant ($P<0.05$). A slight difference could be found between the volume of two lobes, and the volumes of boys and girls, but the differences were not significant. The iodine content of drinking water in Hajdu-Bihar

County is low. In our previous study (investigations of 330 pregnant women) it was found, that the urinary iodine excretion was low (less than 10 microgram/ml) in about of 54% of the cases. Urine specimens from 430 full term newborns (gest. age: 38.8±1.3 weeks, birth weight: 3100±710 grams) and 160 pre-terms (gest. age: 35.0±1.3 weeks, birth weight: 2220±320 grams) were investigated on the 4-6th day of life by the Sandell-Kolthoff colorimetric method. The results of the iodine determinations: the urinary iodine excretion was in average 8.08 μg/ml of the full term newborns and 9.66 μg/ml of the pre-terms. There were slight differences between the thyroid volume of full term newborns and pre-terms with low and normal urinary iodine excretion. On the basis of our results iodine supplementation is highly advisable during pregnancy, to reduce the low iodine levels of the newborns.

MORTALITY CHANGE: PERFORMANCE AND PROSPECTS 1950-2050. Paul Demeny, Ph.D., The Population Council, New York

World population during the last five decades of the 20th century grew from 2.52 billion to 6.06 billion, corresponding to an average annual rate of 1.75 percent. This historically unprecedented expansion was generated by high but declining fertility rates combined with an extraordinarily rapid lowering of general levels of mortality. The aim of this presentation is (1) to quantitatively identify the specific effect of changes in mortality on population growth, both globally and by broad geographic regions; (2) to discuss the proximate and the underlying factors generating improvements in health hence indirectly in life expectancy; (3) to consider the prospects for further decreases in mortality rates during the next half century; and (4) to outline the main demographic, social, and economic consequences of the expected mortality trends and the challenges they pose for public policy.

END OF LIFE ISSUES AND THE PSYCHIATRIST. Ede Frecska, M.D., Department of Psychiatry, University of Florida, Gainesville, FL

The presentation will address the current status of Advanced Directives in the US, how it can affect patient care and the doctor-patient relationship. Do Not Resuscitate (DNR) order is conceptualized as medical intervention. Like all medical interventions DNR orders have risks and benefits, therapeutic effects and unintended side effects. The increased risk of unintended effects of DNR is emphasized in an era when medical care providers are under increasing social and financial pressures from outside. Under the cover of mercy and with the use of smart phraseology the same factors promote the practice of euthanasia and assisted suicide. There is some realistic concern that physicians may allow life-ending interventions when treatment of depression may be more appropriate. The slippery slope of gradually dissolving doctor-patient relationship will be displayed with a possible outcome when physicians would no longer be agents of their patients and would not strive to be advocate for their patient's interests. Physicians should be aware of the following dangers: first, the right to die will translate into an obligation on the part of others to kill or help kill; second, there can be no way to confine the practice to those who knowingly and freely request death; third, the medical profession's devotion to healing and refusal to kill - it's ethical center - will be destroyed.

NEWER CONCEPTS IN CORONARY ARTERY DISEASE. William Ganz, M.D., Department of Medicine, the University of California, Los Angeles and Cedars-Sinai Medical Center, Los Angeles, CA.

Stable (or chronic) angina is characterized by episodes of chest pain provoked by exertion or mental stress in persons with severe coronary artery stenosis. Previously, the angina was attributed to increase in coronary blood flow that was inadequate for the increase in myocardial demand for blood flow and 0_2, due to the coronary artery stenosis. However, studies of myocardial perfusion in recent years found that blood flow increased only in the subepicardial half while in the subendocardial half the blood flow fell below the pre-angina level. This so called "endo→epi steal" can be explained by greater workload and greater extravascular compression in the subendocardial myocardium, resulting in significantly reduced vasodilatory reserve. During rising demand the subendocardial arterioles become maximally dilated and hence perfusion pressure dependent. Potent arteriolar dilators such as dipyridamole or adenosine have a similar effect like rising demand. For that reason they can be used interchangeably for "stress testing" of patients for coronary artery disease. Unstable angina is characterized by episodes of chest pain at rest in the absence of increased demand. Ruptured or fissured plaque with a superimposed incompletely occlusive thrombus, intermittently worsening and improving, is the anatomical basis of unstable angina. Complete thrombotic occlusion and acute myocardial infarction frequently complicates unstable angina. Instant collateral blood flow after occlusion of a coronary artery. Collateral channels 40 microns in diameter connect the coronary arteries and their large branches. Under normal conditions they are non-functional because the pressures at their two ends are identical. When one coronary artery becomes occluded,

pressure distal to the site of occlusion falls precipitously and collateral blood begins to flow to the occluded artery. This collateral blood flow attenuates the severity of myocardial ischemia and the rapidity of necrosis. Collateral blood flow to the subendocardium is lowest and therefore necrosis begins from the subendocardiurn and spreads toward the epicardium over several hours. Exertion, mental stress and arteriolar dilators may cause a recipient to donor artery "steal".

THE ORGANIZATION OF DELIVERY OF HEALTH CARE IN THE KOMARNO REGION OF SLOVAKIA. Jïzsef Gaulieder, M.D., Department of Pediatrics, County Hospital, Komarno, Slovak Republic.

The author will describe the organization of delivery of health care in the Komarno region (birthplace of Hans Selye) of Southern Slovakia. Seventy five percent of the population of this region belongs to the Hungarian minority. Except for a few minor differences however, the system for health care delivery in the rest of the Slovak Republic is the same as in Komarno. The soft revolution in 1989 brought radical changes in the health care field also. There was a significant reduction in the number of hospital beds, the size of the County Hospital was reduced from 813 beds to 573. Private practice was re-introduced, especially in primary care but also in some specialties, such as cardiology, surgery etc. The decades old monopoly of state health care insurance was broken and initially there were 13 privately owned insurance companies. Today there are still 5 of them, contracting with hospitals and private physicians. Although there are a few physicians and dentists in the region who offer their services for private pay only, their number is marginal. The majority of health care providers and their patients depend on the insurance companies, despite their poor performance.

THE ROLE OF ENDOTHELINS IN GASTRO-DUODENAL ULCERATION. Zoltan Gombos, M.D[1], Aron Vincze, M.D., Ph.D.[2], Zsuzsa Sandor, M.D., Ph.D.[2], Martin Jadus, Ph.D.[2] and Sandor Szabo, M.D., Ph.D.[2], Departments of Pathology, University of Massachussetts, Worcester and Berkshire Medical Center, Pittsfield, MA[1] and University of California, Irvine and VA Med. Center, Long Beach, CA[2].

This presentation provides insight to the complexity of gastroduodenal mucosal injury emphasizing the importance of endothelin pathway in the natural history of gastroduodenal ulceration. Endothelins (ET) are produced mainly by endothelial cells, which are also regulated via autocrine and paracrine pathways by these peptides. Our results demonstrated a rapid and time-dependent release of ET-1 into the systemic circulation after intragastric administration of ethanol or HCl in rats. The ET-1 release preceded the development of hemorrhagic erosions and might be used as a diagnostic tool to non-invasively quantify acute gastric mucosal lesions. The development of solitary duodenal ulcers in the rat was preceded only by an organ- (involving only the duodenum and not the stomach) and molecule-specific (induced only by cysteamine and not by nonulcerogenic analog ethanol-amine) rapid local release of ET-1. The severity of cysteamine-induced duodenal ulcers was dose depen-dently decreased by pretreatment with ET-1 antibodies or the receptor antagonist bosentan. As we have shown, ET, as endogenous mediators of mucosal injury might have a biphasic role in this pathogenetic process.

NEW DEVELOPMENTS IN THE DIAGNOSIS AND MANAGEMENT OF EARLY PROSTATE CANCER. Gabriel P. Haas, M.D., Department of Urology, Upstate Medical University, Syracuse, NY.

Carcinoma of the prostate gland continues to remain the most common non-skin cancer diagnosed in men and the second leading cause of cancer mortality. During the 1990's major strides have been made in the early detection of prostate cancer and by the onset of the new millennium this appears to have resulted in leveling off and possible decrease in mortality due to this disease. The latest diagnostic approaches, as well as the impact of improved early detection, will be discussed. The treatment of localized prostate cancer continues to be controversial because there are several treatment alternatives available. The role of observation, radical prostatectomy, radiation therapy (including brachytherapy) will be discussed and the potential benefits and risks of each option will be elucidated. At the conclusion of this presentation it is anticipated that the audience will have gained new insight into the epidemiology, diagnosis and management of localized prostate cancer.

ROLE OF TNF-α AND ITS 55 AND 75 kDa RECEPTORS IN BRONCHIAL HYPER-REACTIVITY. Adrienne Halász, M.D.[2], Endre Cserháti, M.D., Ph.D., Sc.D.[1], Lajos, Kïsa, M.D., Ph.D.[2] and Károly Cseh, M.D., Ph.D.[3], 1st Department of Pediatrics, Semmelweis University Faculty of Medicine[1], Children's Hospital Svábhegy[2] and Károlyi Hospital[3], Budapest, Hungary.

The pathophysiological role of the Tumor Necrosis Factor (TNF) system was studied in non-asthmatic offspring of asthmatic parents with and without bronchial hyper-reactivity proved by the methacholine airway challenge

test. There were 80 offspring in the study, 37 of them were of adult age, 43 were children. Serum TNF-α and Soluble Tumor Necrosis Factor Receptor Type 1-55 kDa (sTNF-R1) and Soluble Tumor Necrosis Factor Type 2-75 kDa (sTNF-R2) were determined by an ELISA test. The results are presented as the mean ± Standard Deviation. The findings are as follows:

	TNF-α (pg/ml)	
Hyperreactive:	adults 5.18±0.87	children 5.08±1.78,
Non-hyperreactive	4.12±0.43	3.75±0.68
	p<0.0001	p=0.0084
	sTNF-R1 (ng/ml)	
Hyperreactive	adults 1.44±0.31	children 1.30±0.25
Non-hyperreactive	1.21±0.14	1.13±0.11
	p=0.0305	p=0.0042
	sTNF-R2 (ng/ml)	
Hyperreactive	adults 0.85±0.40	children 0.70±0.46
Non hyperreactive	0.56±0.56	0.33±0.17
	p=0.0084	p=0.0048
	sTNF-R1/R2 ratio	
Hyperreactive	adults 1.96±0.73	children 2.85±2.06
Non hyperreactive	4.82±3.40	4.42±2.30
	p=0.0272	p=0.0167

Provocation dose of methacholine values, resulting in a 20% reduction of forced expiratory volume in one second (PD20 FEV_1) were found to be in significant negative linear correlation with TNF-α, sTNF-R1 and R2 levels in hyperreactive adults and with TNF-α and sTNF-R2 in hyperreactive children. TNF-α correlated significantly with its receptors both in hyperreactive adults and children and with the BMI values of adults. The TNF system may contribute to the pathophysiology of bronchial hyper-reactivity. Alterred shedding of sTNF-R1 seems to occur in hyperreactive patients.

DYSTONIA MUSCULORUM DEFORMANS. EIGHT YEARS EXPERIENCE WITH A PATIENT.

Ágnes Herczegfalvi, M.D., Ph.D.[1] and Dezsð J. Jeszenszky, M.D.[2], Dept. of Neurology, Heim Pál Children's Hospital, Budapest, Hungary[1] and Klinik fur Orthopedische Chirurgie, Kantonspital St. Gallen, Switzerland[2].

The term dystonia was introduced by Oppenheim and Vogt in 1911 to describe the relatively slow, long sustained frequently forceful contorting movements of an uncommon disease, dystonia musculorum deformans. Flatau and Sterling in the same year first suggested that the disease might have hereditary basis and gave it the more accurate name torsion dystonia of childhood. The 1990 epidemiological study of Eldridge, who analyzed all reported primary cases of dystonias, revealed two patterns of inheritance, autosomal recessive and dominant. The recessive form begins in early childhood, and is progressive over a few years. The dominant form begins later, usually in late childhood and adolescence and progresses more slowly. Our patient, A.F. is now 17 years old. His symptoms started in March 1992 with painful spasms on the right part of the neck. He was observed in the hospital, where inflammatory and metabolic disorders were excluded. CT scan and MRI of the head and neck were without any abnormalities. He was treated with several drugs, which temporarily improved his movements. The spasms are intermittent at first, and in free intervals muscular tone and volitional movements are normal. Gradually the spasms became more frequent and in May 1993 they were continuous in the neck and trunk, and the body became grotesquely contorted. The hands were also involved, they were fisted and at times choreoathetitic movements were seen. After administration of Botulinum toxin his condition temporarily improved. Severe torsion kyphoscoliosis developed later. The only solution for this, problem was spinal surgery. It raised lot of problems to perform the spinal surgery and we spent 6 years to find the more suitable methodologies.

HOW MALIGNANT CELLS (MELANOMA; KIDNEY CARCINOMA) ESCAPE APOPTOTIC DEATH AND HOW CAN THEY BE FORCED TO COMMIT DOCTOR-ASSISTED SUICIDE?

Joseph C. Horvath, M.D.[1,3], Pamela G. Brown[1], Michael Sorace[1] and Joseph G. Sinkovics, M.D.[1,2,3,4], Cancer Institute St. Joseph's Hospital[1]; Departments of Medicine[2] and Medical Microbiology & Immunology[3], Univ. of South Florida College of Medicine; HL Moffitt Cancer Center[4], Tampa, FL

Relative interferon-(IFN) resistance of neoplastic cells could be turned against the cancer cell (CML, hairy cell leukemia, kidney carcinoma, melanoma) by the administration of much higher than naturally induced doses of IFNα or by infecting the cancer cell with viruses. Even IFN-sensitive viruses (Cassel's 73T NDV, VSV) could replicate in cancer cells and effect oncolysis. Another unnatural feature of neoplastic cells is apoptosis (A) resistance. Melanoma cells achieve this state of existence by opposing the mitochondrial cytochrome c + Apaf-1 = apoptosome sequence of events as their Apaf-1 gene (12q23) suffers allelic loss (Nature 4O9:207 '01). If VSV achieves its oncolytic effect through the activation of the Apaf-1 system (J Virol 75:3474 '01) how could it be oncolytic in melanoma cells? Probably through unopposed replication of large viral progenies. Other means of A-

resistance in melanoma cells consist of downregulated or *mdm* protein-inhibited p53; upregulated Bcl-2; generation of caspase-inhibitory proteins (IAP); subversion of cell death signals as to rather service than kill the malignant cell by establishing autocrine or paracrine growth loops: FasL→FasR, IL-2→IL2R; and neurotrophins for melanoma cells metastatic to the brain. Melanoma cells produce immunosuppressive cytokines (IL-10, TGFβ), constitutively activate NFκB, a protector against TNFα-induced A; downregulate MHC expression; express decoy receptors and solubilize FasR to bind and preempt FasL away from the cell. CD40 and its ligand CD 154 trigger A in melanoma cells. HLA-A2-restrieted Melan A/MART 1-specific immune T cells expressing the CD40 ligand can kill $CD40^+$ melanoma cells. We endeavor to generate such T cells for adoptive therapy. Kidney carcinoma cells may also coexpress FasR and FasL without inducing their own A. Their FasL can kill $FasR^+$ host T cells. Further a glycosphingolipid of tumor cell origin blocks tumor-reactive immune T cells. Yet memory immune T cell clones with TCR of Vα2O and Vβ22 survive in the host and may be reactivated later. Dendritic cells loaded with autologous tumor cell peptide antigens could readily activate tumor-specific immune T cells that release IFNγ, TNFα and GM-CSF upon encounter with their target tumor cell. Dendritic cell vaccines not prepared properly (undifferentiated dendritic cells devoid of costimulatory molecules) induce host tolerance to the tumor. Differentiated dendritic cells fused with irradiated autologous tumor cells ("dendritomas") by viral agents (Cassel's 73T NDV, VSV, Sendai virus) would induce antitumor immunity capable of rejecting a small tumor burden and are effective not only against dormant micrometastases but also against growing tumors (Internat J Oncol 16:81 '00; Nature Med 6:332 '00; J Immunther 24:99 & 122, '01).

FACTORS PREDISPOSING TO BRACHIAL PLEXUS INJURIES. **Leslie Iffy, M.D.[1] and Valária Váradi, M.D.[2], Department of Obstetrics and Gynecology, UMDNJ - New Jersey Medical School, Newark, NJ[1] and Division of Neonatology, St. Margit Hospital, Budapest, Hungary[2].**

Based on the principle announced in a leading American journal in 1993 that "...most traditional risk factors for shoulder dystocia have no predictive value (and) shoulder dystocia itself is an unpredictable event", numerous articles in the 1990's expressed a defeatist attitude about physicians' ability to prevent or successfully treat this complication. In the same process, the view that injury of the brachial plexus is often a spontaneous 'in utero' event rather than a birth injury, has gained wide acceptance in medical circles recently. Reviewing the literature, including their own relevant publications, the authors conclude that undue emphasis upon "predictability" may have obscured long established medical concepts about the feasibility of "prevention". For centuries, doctors used broad preventive measures in a variety of circumstances rather than restricting them to individuals with predictable afflictions. The contemporary literature lists a large number of factors known to be conducive to arrest of the fetal shoulders during delivery. Many of these are identifiable ante-partum and/or intra-partum. Investigators have made worthwhile efforts to recognize and even quantitate the weights of these factors. They range from unrecognized or uncontrolled gestational diabetes through fetal macrosomia, protraction and arrest disorders during labor, to the use of extraction instruments in the second stage. Utilizing this information prospectively, with due attention to the circumstances, actions and inactions that increase the risk and severity of shoulder dystocia, in the opinion of the writers, many fetal injuries can be avoided without a significant increase in the already very high rate of cesarean sections. The writers' own data indicate that the incidence of brachial plexus injury is exceedingly infrequent among neonates delivered by cesarean section. Since the rate of abdominal deliveries is about 25% in the United States, the rarity of associated Erb's and Klumpke's palsies precludes spontaneous 'in utero' injury as a quantitatively significant etiologic factor in congenital brachial plexus lesions.

HELICAL CT CHOLANGIOGRAPHY (HCTCA): USE AN OLD METHOD IN A NEW WAY!
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Background: Before the ultrasound era cholangiography used to be a conventional method for the imaging of extra-hepatic bile ducts. Endoscopy is too invasive for simple diagnostics. Introduction of helical/spiral CT equipment has opened a new age in noninvasive cholangiography. Since 1996 we investigated more than 160 patients with HCTCA. Methods and Materials: Hepatotropic contrast material was administered in a slow intravenous infusion in order to reach a satisfying opacification of the biliary duct system followed by nephrotropic contrast material for demonstrating the surrounding liver parenchyma, pancreatic head and blood vessels. With a Siemens Sornatom Plus 4 helical scanner transaxial scans were taken, than post-processed and reconstructed by MPR and 3D rendering MIP and SSD

methods. Results: The common bile duct, the cystic duct and the main hepatic ducts have been demonstrated readily. Visualization of the secondary and tertiary intrahepatic ducts depended on the extent of dilation. The bile passage could be followed successfully toward the duodenum. Papilla sclerosis, narrowing of the bile ducts and ductal stones/sludge were demonstrated in the extra- and even in the intrahepatic bile ducts. Causes of external compressions were shown by nephrotropic contrast material. Conclusions: In the diagnostic algorythm ultrasound still has the essential role in the imaging of biliary pathologies. Endoscopy tends to be a therapeutic rather than only diagnostic intervention. HCTCA proved to be a very useful, noninvasive tool for demonstrating the bile ducts simultaneously with their environment: intraductal stones, strictures, compressions and anatomical variants can also be demonstrated.

ETHICAL ISSUES IN MODERN CLINICAL NEUROSCIENCE: IMPACT ON HEALTH CARE DELIVERY. **George Karpati, MD, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada.**

One of the most important ethical issues in modern clinical neuroscience concerns the quality of life as determined by the functional state of the nervous system (NS). Neurological deficits that can significantly impair the quality of like include: a./ reduced level of consciousness, b./ cognitive decline, c./ mental depression and thought disorders, d./ dysphasia, e./ visual failure and deafness, f./ motor paralysis and gait disorders, g./ urinary incontinence and sexual impotence. Diseases that can lead to these impairments include: cerebrovascular disease, NS trauma, degenerative diseases (Parkinson's, Alzheimer's, Huntington's), infections (HIV, syphilis, etc), cerebral palsy and genetic disorders (muscular dystrophies, peripheral neuropathies, ataxias, etc). The normal aging process of the NS can also produce such deficits. Thus, the relative and absolute increase in the number of old people in most industrialized societies accentuate this issue. Several important questions arise in relation to a reduced quality of life due to NS deficits: Should the patient and/or his/her family have the ultimate and decisive role in determining the acceptance or rejection of a certain quality of life? What are the cultural, ethnic, religious and personal factors that can influence the attitude of patients and their families? What is the role of the physician and health care institutions in this matter? (Professionalism vs morality vs legality issues, questions of active or passive euthanasia, etc). What is society's stake in this matter: (compromising of the quantity and quality of overall health care, augmenting the public and private financial burden, etc)? What is the role of lawmakers and governments in this field? The above matters will be highlighted by statistical data and illustrative case reports will be cited to illuminate the complexity and the controversial nature of these issues.

LAPAROSCOPIC TOTAL COLECTOMY FOR SLOW TRANSIT CONSTIPATION.
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Aim of the Study: Total colectomy is the preferred surgical option in the management of slow transit constipation (STC). With advances in technology and instrumentation, laparoscopic total colectomy (LTC) has become feasible. However, it is unknown whether LTC offers the patient any advantages over open total colectomy (OTC). The purpose of this study was to compare the clinical outcomes between all LTC and OTC procedures performed by one department during the same time period. Patients and Methods: During a three-year period, 21 total colectomies were performed for STC and the patients (20 women, 1 man) were placed in groups according to the procedure (13 OTC, 8 LTC). One patient in the OTC group was converted from a laparoscopic operation because of extensive adhesions. The median age was similar in both groups (OTC 39, range 27-67; LTC 43, range 19-67 years). Twenty of the 21 patients had undergone colonic transit studies preoperatively. A telephone survey was conducted to evaluate postoperative bowel function and patient satisfaction in each group. Statistical analyses were performed using a Wilcoxon Rank Sum test with $p \leq 0.05$ considered statistically significant. Results: The median operative time was 30 minutes longer in the LTC group (OTC 180, range 90-300 vs. LTC 210, range 180-310 minutes, p=0.037). The median time to passage of flatus in the LTC group was 2 days shorter (OTC 4 vs. LTC 2 days). Postoperative complications occurred in seven (56 %) and in one (13 %) of the OTC and LTC groups, respectively. The median length of stay (LOS) was 3 days shorter for the LTC patients (LTC 6.5 vs. OTC 9.5, p=0.054). Eighteen patients were available for the telephone survey resulting in a median follow-up of 28 months (range 2-32). There was no difference in postoperative bowel function (bowel frequency, use of laxatives, and bloating). On a scale of 1 to 10, both groups were highly satisfied with the postoperative results (median score: OTC 9, LTC 10). Conclusions: LTC is a safe, feasible operation for STC with short-term post-operative results equivalent to those achieved after OTC. With less time to the return of bowel function, as well as a shorter LOS, we believe LTC may become the preferred surgical approach.

ARTHROSCOPIC TRANSHUMERAL RECONSTRUCTION OF ROTATOR CUFF TEAR.
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In 1990 an arthroscopic transhumeral rotator cuff reconstruction technique was developed and used by the authors to treat all sizes of rotator cuff tears allowing the same type of repair to be performed as the open procedure and therefore have the possibility to achieve the same success rate as open repair with the advantages of the minimally invasive surgery and using the many years of experience of the first 150 repairs. Material: 307 arthroscopic rotator cuff repair procedures done on 304 patients between Dec. 1990 and March 1994 were reviewed. 150 cases were arthroscopic transhumeral fixation and 157 tendon end to end repair. Out of the 150 transhumeral repair cases studied 18 cases were traumatic, 124 were Impingement III tears and 8 defects after calcium removal. There were 42 small, 66 medium and 42 large tears. The average age was 56 years. Method: An anterior acromioplasty and an arthroscopic tendon to bone repair using the bone cutting giant needle was done in all the cases. An AC-Joint plasty was done in 20 cases and tendon transposition in 5. Postoperatively the patients start full passive motion one day after surgery and active motion six weeks later. Results: Out of 150 arthroscopic transhumeral repair cases it was possible to evaluate 132 patients having 133 procedures with an average follow up of 5 years. The results were grouped using Neer's classification. There were 64% excellent, 34% satisfactory and 2% unsatisfactory. The UCLA average score improved from 15.8 preoperative to 31.5 postoperative. Conclusion: Full reconstruction was done in all cases except three. Morbidity is reduced in comparison to open surgery. The procedure can be performed in an outpatient setting and after the learning curve even easier repair of tears compared to the open method with less complications.

INITIATION AND PROGRESSION OF PITUITARY TUMORS.
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The aim of this presentation is to review the causes of pituitary tumor initiation and progression. Methods used were histology, immunohistochemistry, electron microscopy and in-situ hybridization. The following are the results and conclusions: Pituitary tumors can be divided into adenomas and carcinomas. Pituitary adenomas are non-metastatizing, monoclonal cell proliferations arising in and composed of adenohypophysial cells. They are common, represent 10-15 % of intracranial neoplasms. Pituitary carcinomas are very rare; they appear to originate in preexisting adenomas and can be diagnosed only if distant cerebrospinal and/or systemic metastases are documented. The pathogenesis of pituitary tumors is unresolved. Two major theories emerged. One theory emphasized the role of protracted stimulation by hypothalamic hormones causing increased secretion and cell multiplication and the developing hyperplasia subsequently transforms to adenoma. The alternative theory proposed that adenomas result from primary defect of the adenohypophysial cell. According to the two step tumorigenesis theory: tumor initiation and progression should be distinguished. Initiation means that one single adenohypophysial cell transforms to adenoma cell. Tumor progression is defined as the multiplication of the transformed cell leading to the formation of a detectable tumor mass. Recent studies suggest that pituitary tumor formation is due to genetic abnormalities. Several mutations have been demonstrated. The all inclusive genetic abnormality is, however, still obscure. Several factors such as changes in endocrine milieu, growth factors, cytokines, receptor abnormalities, hypothalamic stimulating hormones and loss of inhibiting compounds are involved in tumor progression. Although the evidence that pituitary tumors develop because of genetic abnormalities is overwhelming, it should be noted that proliferation does not depend exclusively on the tumor cells themselves. Extracellular factors, such as angiogenesis, neoformation of vessels, are necessary for tumor growth, invasion and spread. If new vessels are not formed, tumors cannot grow and metastases cannot be formed and without oxygen and other nutrients the tumor cells undergo necrosis. The connective tissue stroma plays also a role in tumor progression. Metalloproteinases can degrade the connective tissue thereby facilitating invasion, penetration of tumor cells to the vessels and tumor dissemination. It is crucial to keep in mind that the adenohypophysis is composed of several distinct cell types which are regulated by diverse mechanisms, function differently and produce specific hormones characteristic of each cell type. The pathogenesis of adenomas arising in different cell types is not the same and a better understanding of pituitary tumor initiation and progression can only be achieved if tumors originating in different cell types are analyzed separately.

PERISACCADIC CHANGES IN HUMAN BRAIN ACTIVITY: A MULTICHANNEL EEG STUDY.
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Wollner, M.D., D.Sc.[1], Department of Neurology, State University of New York, Health Science Center, Brooklyn, NY[1], NINDS, NIH, Bethesda, MD[2] and Department of Medical Physiology, University of Szeged, Hungary[3].

Aim: To study the activation sequence of various cortical areas involved in the control of human saccadic eye movements. Several cortical areas have been shown to participate in saccadic activity in humans including the frontal and parietal eye fields and occipital cortices (OC). The exact activation sequence of various cortical areas in saccades, however, has remained largely unknown because of the poor temporal resolution of functional neuroimaging techniques. Methods: EEG techniques provide temporal resolution in the millisecond range and are spatially accurate enough to detect regional activation if the signal is recorded from a sufficiently high number of electrodes. We measured EEG spectral power in both light and dark (without visual cues) conditions. We used a 64-channel montage in 10 volunteers trained to perform large (14^o) voluntary saccades. Continuous EEG was recorded from 58 (tin) surface electrodes. Data were sampled at 500 Hz. Saccadic onset was marked. Epochs of 2560 msec prior to saccadic onset up to 2048 msec after the saccadic onset were selected for analysis. After off-line digital data processing, spectral power analysis was performed for each 128 msec epoch during the 4608 msec period. Spectral power analysis was performed to monitor changes of cerebral activity time locked to the saccade using the concept of task related desynchronization (TRD) and synchronization (TRS). We used a factorial ANOVA design to assess the significance of spectral power differences between variables (light-dark, subjects, electrodes, time). Only comparisons significant after Bonferroni-correction ($p<0.05$) were accepted. Results: 1) There is activation of the contralateral frontal cortex *prior* to the onset of the saccade. This result was the same in both light and darkness. 2) There is bilateral OC activation *after* the onset of the saccade in both light and dark. Conclusions: The frontal TRD contralateral to the direction of a saccade is likely to represent FEF activation prior to the saccadic onset. The post-saccadic alpha TRD in posterior regions demonstrating occipital/perioccipital neuronal activity, because of its independence of visual input, indicates the effect of non-visual information, e.g. the angle of gaze. The activation of OC and/or parieto-occipital cortex following frontal activity and without overt visual stimuli may be representing neural activity due to the reception of efferent copies of motor commands and/or neuronal reorganization of visual space representation as a corollary of saccadic gaze shift.

CORTICAL WATERSHED MICROINFARCTS CAUSED BY CEREBRAL HYPOPERFUSION FURTHER AGGRAVATE COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE.

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Since Alzheimer disease (AD) is known to be often associated with cerebral hypoperfusion, the risk that it generates not only white matter changes but watershed cortical microinfarcts as well should be increased. Histopathological information about the occurrence of such cortical lesions in AD are missing. In order to analyze if watershed cortical infarcts are present or not in AD, the brains of 184 autopsy cases (105 definite AD and 79 age matched controls) were selected and analyzed using histochemical and immunohistochemical techniques. The results showed a statistically significant association ($p=0.001$) between the occurrence of watershed cortical infarcts and AD (25% versus 2.5% in controls). The three-dimensional (3-D) reconstruction of whole brains of 6 AD cases using 3 mm spaced serial brain sections was performed to analyze the distribution of the cortical microinfarcts. The microinfarcts were restricted to the watershed cortical zones, indicating that cerebral hypoperfusion is the determinant factor in the genesis of these vascular border zone infarcts. The results also indicate the important role of congophilic angiopathy and perturbed hemodynamic factors (e.g. decreased blood pressure). In conclusion, in AD cerebral hypoperfusion induces not only white matter changes but cortical border zone infarcts as well, further aggravating the degenerative process and worsening dementia. It is important to consider that neuroleptic treatment, frequently employed in AD, will accentuate cerebral hypo-perfusion by decreasing blood pressure. Therefore, to treat and prevent arterial hypotension in AD is essential.

THE "FOR HEALTHY NATION" PUBLIC HEALTH PROGRAM, 2001 - 2010.

István Mikola, M.D., Minister of Health, Hungary.

The fact that Hungary has a lag of several years in life expectancy behind the developed industrial societies called for a comprehensive public health reform. Some issues of top priority in the reform: 1. Prevention of diseases, such as myocardial infarction, neoplasms, mental disorders and musculosceletal diseases. 2. Providing a healthy beginning for life and childhood, developing healthy environment and educating and training in health promotion. 3. Improving the safety of sanitary and food systems, promoting healthy nutrition. 4. Controlling the

abuse of certain hazardous consumer goods such as alcohol, nicotine and drugs. 5. Eliminating the disadvantageous public health situation of minorities. The Ministry of Health, - involving other sectors - prepared a strategy that can provide an opportunity for closing the gap in relation of the public health situation up to the level of developed industrial societies in the coming decade. The program is based on primary prevention and on the restructuring of the medical infrastructure that developed in Hungary in an unbalanced way and based on - among others - the adaptation of up to date information systems and on the preventive programs with high priority.

HUMAN CAROTID ARTERY IMPLANTATION INTO THE CANINE: A NEW ACUTE ANIMAL MODEL OF HUMAN CAROTID ARTERY DISEASE. **Laszlo Miskolczi, M.D., Matthew J. Gounis, Ph.D., Baruch B. Lieber, Ph.D. and L. Nelson Hopkins, M.D., Toshiba Stroke Research Center, University of Buffalo, Buffalo, NY.**

Aim of study: A reliable, easy to construct animal model of human carotid artery disease for training or device testing purposes does not exist. We created such a model by implanting formalin-fixed human carotid arteries, taken from cadavers, into the canine carotid circulation. Methods: Carotid arteries of human cadavers are harvested and pressure fixed with formalin. An 8 cm long segment, involving the distal CCA and the proximal ICA is mounted on plastic connectors that allow devices up to 7 French size to pass. The ECA is ligated except the Superior Thyroid Artery (STA). The specimen is thoroughly flushed with saline and pressure-tested. The animal is anesthetized and a 10 cm long segment of the right CCA is accessed, cleaned and clipped proximally and distally. A 4 cm segment of the dog artery is replaced with the human artery using plastic connectors on both sides. After the air is removed via the STA by releasing first the distal then the proximal clip, the branch is ligated. Finally, angioplasty/stenting of the human ICA can be performed via femoral access. The dog is sacrificed after the study. On one animal we performed flow test for 3 hours with a sonic flowmeter. The vital parameters of the animal were also constantly monitored throughout the experiment. Findings: Surgery time is about an hour. Human arteries can be quickly connected and disconnected. In our flow test animal blood flow in the implanted artery slightly varied between 120 and 140 ml/min, the vital parameters of the dog were also unchanged. The implanted human artery showed disturbed flow at the carotid bifurcation. Navigation of an angioplasty balloon to the human artery was easy via the plastic connectors. The 4 mm ICA remained intact after the inflation of a 4.5 mm balloon at 6 atmospheres. Conclusion: Our animal model of human carotid disease is easy to prepare and it very closely resembles human patients. We intend to use the model for physician training and to test devices such as stents, balloons or distal protection devices. The acute nature, use of a formalin-fixed arteries and reliance on properly fixed diseased cadaver arteries are the weaknesses of the model.

MANAGEMENT OF CHRONIC RENAL DISEASE: ENFORCING SPEED LIMITS ON THE ROAD TO DIALYSIS. **Andras Mogyorosi, M.D., Ph.D., Division of Nephrology, Department of Medicine, Virginia Common-wealth University/Medical College of Virginia and McGuire VAMC, Richmond, VA.**

According to the US Renal Data System and its European and Japanese counterparts, the incidence of end stage renal disease is increasing relentlessly. Clearly, chronic renal disease puts tremendous burden on patients, their families, and society as a whole. The significance of retarding the relentless process of decline in renal function is obvious and it is now appropriately emphasized in professional as well as in lay circles. Based on the findings of recent landmark trials, slowing the progression of kidney disease is possible but requires a concerted effort of all health care providers that follow the individual patient. This update summarizes available therapeutic options that were shown to or are suspected to slow the progression of chronic renal disease. New developments in the field will also be discussed. Specifically, blood pressure control, the use of angiotensin converting enzyme inhibitors, anemia management, smoking cessation and the treatment of hyperlipidemia will be critically analyzed in terms of their capability of slowing the progression of kidney disease. The importance of other non-specific measures such as the avoidance of non-steroid anti-inflammatory drugs, and the prevention of contrast nephropathy among patients with pre-existing renal disease will be emphasized.

PERCUTANEOUS ANGIOPLASTY AND STENTING IN OCCLUSIVE ILIAC ARTERY DISEASE. **Balázs Nemes, M.D.[1,2], Árpád Simonffy, M.D.[1], Viktor Berczi, M.D., Ph.D.[1] and Kálmán Hutti, M.D., Ph.D.[1], Department of Cardiovascular Surgery, Semmelweis University Faculty of Medicine, Budapest, Hungary[1] and Toshiba Stroke Research Center, University at Buffalo, NY[2].**

Iliac artery stenoses respond well to simple angioplasty, the long-term results are comparable with reconstructive surgery. Stents can eliminate most of the local complications and improve the technical success rate. We

performed 253 iliac angioplasties in 226 patients: 77 female (34%), 149 male (66%). The average age was 58.6 years (34-92). The technical success rate was 97.2% (246/253). There were 7 unsuccessful cases, in 6 cases we were unable to cross the stenotic segment with the guide wire and in one case we stopped the procedure due to seizure of an epileptic patient. Early re-occlusion (<24 h) occurred in 3 cases (1.1%). We used endovascular stents in 32 cases (12.6%). We do not use primary stenting; our indications for stenting were the followings: severe dissection (10 cases), 40%> residual stenosis (22 cases). Minor complications occurred in 10 cases (4%), there were 8 major complications (3%) that required surgery (6 bleeding, 1 rupture, 1 dissection). There were no lethal complications. Our results confirm that iliac artery angioplasty is a simple and fast method, with very good results and low risk for complications compared to surgery.

HEALTH AND DEMOGRAPHIC SITUATION IN SLOVENIA. A COMPARATIVE DESCRIPTION.
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Slovenia is a newborn Central-European state, bordering Croatia, Austria, Italy and Hungary. A small ethnic Hungarian community is settled around the town of Lendva, in the Prekmurje (Murántúl) region. Our aim is to present the main health- and demography related data in a historical context. Our data cover the general and regional birth- and lethality rate but also the mortality rate during the last 30 years. Analyzing these data we found, that instead of rapid and successful economic development, the Slovene demographic growth shows a very negative tendency. The situation in the Prekmurje (Murántúl) region is the worst in Slovenia. We would like to point out some psychosocial and psychotraumatological aspects of the health and demographic situation, presented above. Namely, we would like to point out, that the constant political changes (during the 20th Century) significantly influenced the general health and demographic situation in the Prekmurje (Murántúl) region and especially in the town of Lendva. A successful preventive health related program has to consider also the sociopsychological and psychotraumatological roots of the above presented situation.

PURIFICATION, MOLECULAR AND FUNCTIONAL ANALYSIS OF INTERSTITIAL CELLS OF CAJAL.
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Interstitial cells of Cajal (ICC), a mesenchymal cell type residing in the myenteric region and within smooth muscle layers of the GI tract, have been identified as pacemakers and mediators of neurotransmission. Depletion of these key components of the GI motor apparatus has been implicated in the pathogenesis of various GI motor disorders including diabetic gastroparesis (Ordog et al., Diabetes 49:1731, 2000). Molecular- and cellular-level analysis of ICC in health and disease has been hampered by their paucity and limited accessibility. The purpose of the present work was to develop techniques to purify ICC from murine GI muscles and demonstrate the utility of the purified cells in quantitative molecular and functional studies. ICC were identified in live GI muscles or in their primary cell cultures with fluorescent monoclonal antibodies against the ICC marker Kit. After dispersion, Kit^+ cells were tagged with a secondary antibody conjugated to paramagnetic beads and sorted on magnetic columns. Enrichment of ICC was assessed by flow cytometry. In freshly dispersed cell suspensions and cultured cells magnetic selection resulted in a 3-9- and 20-53- fold enrichment of Kit^+ cells, respectively. The resultant cultures frequently contained extensive networks of multipolar ICC that displayed regular oscillations in membrane potential (slow waves) or in mitochondrial $[Ca^{2+}]$ as monitored by tetramethylrhodamine or rhod-2 fluorescence and confocal line scanning microscopy. Since nonspecific uptake of the ICC label by some resident macrophages appeared unavoidable in our paradigm, in another set of experiments we also labeled the latter cells with a fluorescent monoclonal anti-F4/80 antibody and purified ICC (i.e. $Kit^+F4/80^-$ cells) by fluorescence-activated cell sorting. Enrichment of ICC was assessed by quantitative RT-PCR detection of *c-kit.* This approach resulted in a 160±47-fold (mean±SEM) enrichment of *c-kit* mRNA in the $Kit^+F4/80^-$ population relative to unsorted, dissociated cells. We conclude that immunolabeling and magnetic sorting of ICC can be used to obtain relatively pure, functional pacemaker cell networks. However, molecular analysis of ICC requires fluorescent sorting and the simultaneous identification of resident macrophages. Supported by a Seed Grant from the UNR Sanford Center for Aging and by NIH Grants DK-40569 and DK-41315.

HEALTH CARE DELIVERY AND THE HEALTH OF THE POPULATION IN TRANSCARPATHIA.
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Transcarpathia, the westernmost region of the Ukraine has not undergone an overall reform of health care delivery. The old, Soviet type health care system is still in existence. The economic problems of the last 10 years are reflected in the health services as well as in the population indexes. Transcarpathia, like the other regions in this area had a negative growth in the population. This was brought about by a quantum leap in emigration and by decreasing natural growth. The decreasing number of births and a higher mortality are more characteristic of districts populated by the Hungarian minority. Beside cardiac and circulatory diseases and malignant tumors, mortality from infectious diseases showed a prominent, 40% increase since 1995. Mortality from tuberculosis shows an even higher, 70% increase since 1995. This is even more pronounced in people over 35 years of age. Mortality from tuberculosis is seven times higher among men than women, malignant tumors are 1.7 times and accidents are 3.7 times more frequent among men.

BACK-TO-SLEEP CAMPAIGN BENEFITS PHYSICIANS AND NURSES IN HUNGARY.

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Background: Following many Sudden Infant Death Syndrome (SIDS) initiatives in the US, most physicians believe that these methods are effective. However, the effectiveness of' medical education initiatives may be even broader, benefiting countries still without such programs. Objective: To determine if physicians and nurses in a country with no SIDS risk reduction program have nevertheless been influenced by the Back-to-Sleep initiatives. Design and Methods: At a conference for Hungarian neonatologists, pediatricians and nurses in October of 2000, attendees were asked whether prone, supine or lateral sleep should be recommended for infants and whether smoking, prone sleep, soft bedding or overheating were considered risk factors for mortality. Results: All attendees (n=67) completed the survey. Twenty-seven were physicians, 38 were nurses. Two did not specify profession and were eliminated. Overall, 56 (86%) of the responders identified prone sleep as a risk factor for SIDS, with no difference between physicians, 25 (92%), and nurses, 31 (82%). However, physicians were more likely than nurses to recommend supine sleep rather than lateral ($p<0.01$), as noted in the table, and none recommended prone.

Recommended sleep position	Nurses (n=38)	Physicians (n=27)
Back	16 (59%)	10(26%)
Side	11 (41%)	27 (71%)
Prone	0	1 (3%)

Eighty-eight percent of responders identified soft bedding as a risk factor, with nurses more likely to do so ($p<0.05$), 63% identified smoking and 62% identified overheating as risk factors, with physicians more likely to do so ($p<0.05$). Conclusions: SIDS risk reduction campaigns appear to benefit countries that have not yet undertaken these initiatives, possibly through global continuing education and access to medical journals. However, nurses' awareness, critical because of their contact with and influence on parental behavior, was not as current regarding optimal sleep position, and we speculate that international nursing journals need to provide an additional forum for this information.

PATHOPHYSIOLOGY OF HYPERTENSION.

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Essential hypertension underlies most cases of high blood pressure, affecting 15-20% of the adult population in developed countries. The exact mechanism of abnormal elevation of blood pressure is still poorly understood. Experimental data and human observations from kidney transplantation suggest that the kidney is not only a victim, but also a cause of the disease. Great efforts have been made to establish a pathophysiological concept of pressure dysregulation, leading to the identification of two primary mechanisms, namely, general vasoconstriction and plasma volume expansion due to increased sodium retention. While the results to date point to a combination of these mechanisms in causing essential hypertension, it seems that compensatory adaptation of various regulatory systems may mask the primary pathological process. Recent genetic studies have provided a new approach to determine the primary cause of hypertension, raising the possibility of intervention via correcting the genetic defect. Four major genetic methods have been employed in this study. The animal model studies included the development and analysis of hypertensive strains and manipulation of the expression of specific genes by transgenic methods. Genetic approaches in humans included molecular investigations of rare inherited

syndromes of human hypertension and direct analysis of essential hypertension. A review of the latest information in this area also reveals that beside clear advantages, the modern molecular biological approaches have numerous limitations and methodical pitfalls. There is a long way ahead before we will be able to treat or prevent hypertension by eliminating its primary cause, which is certainly heterogenous.

NUTRITIONAL HABITS OF THE ELDERLY.
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Life style and nutritional habits have an important role in the control of body weight and in the occurrence and outcome of some diseases. To analyze this relationship we studied 150 elderly people. The women in this group were over 60 years of age, the men over 65. The participants received a very detailed, seven page questionnaire. This extended to many aspects of their eating habits: the timing of meals, the preferred items, their body weight in every decade of the their life as well as many aspects of their social and economic circumstances. The data gathered by the questionnaire were then compared to their physical examinations, laboratory tests, anthropologic parameters and to former and recent morbidity. The results of this wide ranging evaluation are the subject of this presentation. Our results indicate, that the eating habits of overweight people are in strong correlation to their body weight and to the occurrence of obesity in their families.

PROGRAMMED CELL DEATH (APOPTOSIS): ESSENTIAL BIOLOGICAL LAW IN THE ONTO-GENESIS, MATURE LIFE AND SENESCENCE OF CELL COMMUNITIES COUNTERACTED IN NEOPLASIA AND SUPPRESSED OR PROMOTED IN VIRALLY INFECTED CELLS.
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While the initiating events of apoptosis (A) may vary (extrinsic through receptors for ligands TNFα, TRAIL, Fas etc. or intrinsic through cytochrome c of mitochondria+ Apaf-1 = apoptosomes), the end result is always the same: caspase-mediated slicing of genomic DNA strands between integers of 180 bp (the "DNA ladder"). The phenomenon has been observed for decades (1940s: in the CNS of the chicken embryo; 1960s: in the metamorphosis of insects and ontogenesis of nematode worms; 1970s: in the healthy, neoplastic and virally infected mammalian cells), but its fundamental biological importance has only been recognized recently. Here we show protection of CLL cells from A by fibroblast-like host cells and their molecular mediators; and bidirectional A in malignant lymphomas as immune T cells kill lymphoma cells and vice versa lymphoma cells trigger A in defensive host lymphocytes. Review similar events in the case of several solid tumors. Propose mechanisms by which tumor cells may be forced to undergo A (with examples): chemotherapeutic agents; hormone withdrawal or antihormones for hormone-dependent tumors; deprivation of growth factors; gene therapy with *wt* p53 and other tumor suppressor genes; Bcl-2 antagonists or bcl-2 antisense oligonucleotides, antimycins; Fas or TRAIL ligands; cFLIP inhibitors; certain oncolytic viruses; antitumor immunity generated by tumor vaccines and adoptive immunotherapy. Tabulate pro- and antiapoptotic events in the host cell-virus relationship in cases of adeno-, dengue- and baculoviruses; HIV-1 and HTLV-1, 2; HSV-1 and EBV; hepatitis C virus; polio-rhinovirus recombinant; NDV, VSV and Sendai virus. From these data we deduce the attributes of the ideal oncolytic virus whether it has evolved and can be found in Nature or rather it is engendered by genetic engineering in the laboratory. Arch ges Virusforsch 7:403-411 1957; Die Grundlagen der Virusforschung (Verlag Ung Akad Wissenschaft, Budapest) pp. 98-103, 1956; The Immunology of Malignant Disease (CV Mosby, St.Louis, 2nd ed.) pp. 180-2, 1976; Intervirology 36:193-214 1993; Medic Hypothes 44:359-368,1995; J Clin Virol 16:1-15, 2001; Acta Microbiol Immunol Hung in print 2001. Newer information on VSV and reovirus oncolytic to human glial neoplasms in Sinkovics & Horvath: Internat J Oncol vol 19 2001 (in print).

MRI EVIDENCE OF VOLUME LOSS IN SUBCORTICAL GRAY MATTER STRUCTURES IN PARTIAL EPILEPSY.
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Rationale*:* Hippocampal and amygdalar volume loss has been described in temporal lobe epilepsy. Patterns of subcortical volume loss involving the thalamus, caudate, and cerebellum may also lateralize or localize the seizure onset zone. Methods*:* MRI volumetric measurements were performed on 48 patients who underwent surgery for medically refractory epilepsy. These included 20 patients

undergoing right temporal lobectomy (RTLE), 20 with left temporal lobectomy (LTLE) and 8 with left frontal lobe resections (LFLE). Duration of epilepsy was about 20 years. Preoperative MRI scans were acquired using a three-dimensional T1 gradient echo sequence (TE6, TR24, $FA25^0$). Hippocampus, amygdala, thalamus, cerebellar hemispheres and caudate heads were measured bilaterally on an SGI workstation following spatial normalization. Results*:* The right-to-left hippocampal, amygdalar, thalamic, cerebellar and caudate volume ratios (VR) were 0.72, 0.92, 0.92, 0.98 and 0.97 for RTLE, 1.43, 1.18, 1.08, 0.99, and 0.99 for LTLE, and 1.06, 1.06, 1.01, 0.95, and 1.01 for LFLE, respectively. Hippocampal volume ratio differed statistically between the three groups, while amygdalar and thalamic volumes differed between the right and left temporal lobe groups. Cerebellar volume ratios significantly differed between the LFLE and temporal lobe groups. In TLE patients with hippocampal atrophy, there was a significant correlation in the degree of asymmetry between amygdalar and thalamic structures, but not for the hippocampal volume ratios, suggesting progressive injury to these structures in chronic temporal lobe epilepsy. Furthermore, right-to-left volume ratios were correlated for all structures with frequency of generalized tonic-clonic seizures (GTCs). Conclusions: These data suggested that hippocampal, amygdalar, and thalamic VR can lateralize a temporal lobe seizure focus. It also indicated more specific atrophy of the contralateral cerebellum in patients with left frontal lobe epilepsy. Finally, there was evidence for progressive injury to the amygdala and thalamus ipsilateral to the atrophied hippocampus, which, in part, may be due GTCS.

COMPLEMENT ACTIVATION UNDERLYING A RANGE OF PSEUDO-ALLERGIC REACTIONS TO DRUGS AND RADIOCONTRAST AGENTS.

Janos Szebeni, M.D., Ph.D., Department of Membrane Biochemistry, Walter Reed Army Institute of Research, Silver Spring, MD. There is growing awareness of the fact that numerous drug-induced immediate hypersensitivity reactions do not fit in Gell and Coombs' Type I category of drug allergies, characterized by the pivotal pathogenic role of allergen-specific IgE. Such non-IgE-mediated or "pseudo-allergic" reactions are caused by numerous i.v. drugs whose clinical formulations contain particulate matter, such as micelles, liposomes or other self-aggregating components. Examples for such drug formulations include the anticancer drugs Taxol and Doxil, and certain iodinated radiocontrast media. Common features of these "pseudoallergens" include the capability to activate the complement (C) system, and the fact that the symptoms they cause are typical manifestations of excessive anaphylatoxin generation in blood. Hence, these reactions were called recently "C activation-related pseudoallergy" (CARPA). The presentation will focus on the experimental and clinical results suggesting a causal role of C activation in the above pseudoallergies, along with the mechanism of C activation, the animal models, risk factors, laboratory predictive tests and possible pharmacological prevention of these reactions.

NEWCASTLE DISEASE VIRUS INDUCED APOPTOSIS IN PC12 PHEOCHROMOCYTOMA CELLS.

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The avian paramyxovirus Newcastle disease virus (NDV) causes severe infections in birds. It is essentially nonpathogenic in rodents and humans, but was found to have an oncolytic potential against certain types of human malignancies. An attenuated NDV vaccine (designated MTH-68/H) was found to cause regression of various human tumors, but the mechanism of its oncolytic action and its selectivity toward malignant cells remain poorly understood. Wild-type NDV was reported to cause apoptotic death in several avian cultured cell types. Programmed cell death may thus be the basis for the oncolytic effect of NDV vaccines. To test this possibility we chose the PC12 rat pheochromocytoma cell line, a widely used model system for apoptosis. The MTH-68/H vaccine was found to cause apoptotic death of PC12 cells in a dose-dependent manner. A very brief exposure of cells to the virus was found to trigger the apoptotic response. Apoptotic DNA fragmentation was not affected by stimulating growth factor pathways or signaling mechanisms mediated by protein kinase C or the second messenger calcium. In contrast, stimulation of protein kinase A by cAMP analogs gave partial protection against the virus. PC12 cells thus provide a useful model system to study the effects of NDV on cell survival at the molecular level.

RECENT TRENDS OF TUBERCULOSIS EPIDEMIOLOGY.

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The epidemiology and its current trends behind the recent fears about the resurgence of tuberculosis are discussed in this report. Data collected by the World Health Organization (WHO) shows that about one third of the

world's population is infected, and about 2 million people die from the disease annually. The number of newly infected people is still rising; the estimates were 8 million for 1997 and 8.4 million for 1999, defying the previous belief that tuberculosis (TB) was a well controlled disease. The most significant factors influencing the recent epidemiological trend of TB are HIV-TB co-infection, migration from low to high prevalence areas and the deterioration of national TB programs over the last decade. The influence of these individual factors vary among different geographical areas, HIV-TB being the most challenging in Africa and SE Asia, migration in the developed countries, while poorly managed TB programs are primarily responsible for the increased TB burden in the former Soviet Union. In addition, inconsistent or partial treatment leads to the development of drug-resistant (MDR) strains that pose a frightening threat to our ability to control TB. However evidence suggests that the appearance of MDR-TB has not been responsible for the observed increase of TB incidence as yet. The WHO recommends the global implementation of DOTS - directly observed therapy, short course - to find, treat and achieve sputum conversion of the infectious cases, as well as to stop the emergence of resistant strains. DOTS was adopted in 127 countries by 1999, in principle reaching 45% of the world's population. By year 2000 well established programs have achieved 91-96% cure rates among new cases, proving the success and the potential of DOTS.