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ABSTRACTS

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MICROGLANDULAR ADENOSIS WITH TRANSITION TO ADENOID CYSTIC CARCINOMA OF THE BREAST. Geza Acs, MD, PhD¹, Jean F. Simpson, MD² and David L. Page, M.D.², Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, PA¹ and Department of Pathology, Vanderbilt University Medical Center, Nashville, TN².

Background: Microglandular adenosis (MGA) is a well recognized, if rare and incompletely characterized entity in which carcinoma is rarely thought to develop. Methods: We reviewed cases from a large consult series and found 14 cases in which patterns of adenoid cystic carcinoma (ACC) coexisted with MGA. Immunohistochemical characterization with beta-catenin, E-cadherin, cytokeratins, S-100, smooth muscle actin (SMA) and vimentin was performed. Results: ACC with its defining dual lumen types appeared to form a transition with characteristic small, gland-like spaces of MGA. MGA stained irregularly and similarly to that seen in myoepithelium with the three markers of myoepithelial cells in the breast: S-100, SMA and vimentin. These three were also positive in the more solid elements of ACC. Most of the cases had areas that were well developed ACC. However, some cases appeared to have expanded glands intermingled within the MGA, a pattern that might be best regarded as transitional to ACC. A similarity to solid pattern adenoid cystic carcinoma was noted.

Conclusions: Adenoid cystic carcinoma may develop in a background of and in continuity with microglandular adenosis. Both entities are known to be expansile and infiltrative without having metastatic capacity. Altered myoepithelial cells appear to be the major element in both entities.

FABLES FROM A FAULTY FAT FACTORY: NONALCOHOLIC STEATOHEPATITIS AND INSULIN RESISTANCE. Gyorgy Baffy, M.D., Ph.D., Liver Research Center, Brown Medical School and Rhode Island Hospital, Providence, RI.

Nonalcoholic steatohepatitis (NASH) was first described in 1980 and reached a remarkable importance since then. The term NASH designates a liver disease that is pathologically indistinguishable from alcoholic steatohepatitis and may progress into end-stage liver disease. The diagnosis is made by liver biopsy and requires a reliable history of insignificant alcohol consumption. Nonalcoholic fatty liver disease (NAFLD) is a broader definition that includes a spectrum from simple steatosis to NASH. Today, NAFLD has the highest prevalence among all liver diseases in the US. It is estimated that 20% of the population have fatty liver and 2% to 3% have NASH. Moreover, NASH appears to be the most likely cause of cryptogenic cirrhosis. There is much to learn about the epidemiology, pathogenesis, natural history, and treatment of NAFLD. NAFLD is most

prevalent among patients with obesity and type II diabetes, essential and increasingly prevalent conditions of the metabolic syndrome that also includes hypertension and hypertriglyceridemia. However, NAFLD also occurs in non-obese, non-diabetic patients. Recent studies showed that many of these patients still exhibit insulin resistance, a major feature of the metabolic syndrome. Predictors of progressing NAFLD include insulin resistance in addition to severe obesity, older age, hypertension, and high transaminase levels. The pathogenesis of NASH is currently viewed as result of a 'second hit' by oxidative stress and cytokines on top of the existing steatosis. NAFLD may also evolve into acute liver failure or hepatocellular carcinoma. There is no satisfactory treatment for NASH and the prevention of progressive NAFLD is therefore unresolved. Currently accepted and experimental treatment options will be reviewed with a special emphasis on the management and potential correction of insulin resistance.

CHANGING THE WAY OF PATIENT CONSENT TO KNOWLEDGE OVER INFORMATION.

Ken Berger, M.D., Department of Sports Medicine, University of Toronto, Ontario, Canada.

A fiduciary relationship should be nurtured between patient and physician. This requires effective communication throughout all aspects of care; especially pertaining to treatment decisions. In the context of illness as experienced by the patient a unique set of circumstances is presented. However, communication in an illness context is fraught with problems. The patient is vulnerable and the situation may be overwhelming. Voluminous amounts of information are available to patients from a host of health care providers, family members, support groups, advocacy centers, books, journals, and the Internet. Often conflicting and confusion, frequently complex, this information may be of greater burden than benefit. Some information is of high validity and reliability while other information is of dubious reliability. The emotional freight of bad news may further inhibit understanding. An overload of information may pose an obstacle in decision-making. To facilitate the transformation of information into knowledge, the health care provider must act on some occasions as a filter, on other occasions as a conduit, and on still other occasions simply as a reservoir. The evolution of patient rights to receive or refuse treatment, the right to know or not to know calls for a change in processing of overwhelming information in our modern era. In this presentation we will discuss the difference between information and knowledge. How can health care providers ensure they have given their patients all necessary and sufficient

information to make an autonomous decision? How can they facilitate the transformation of information into knowledge? The effect of knowledge to consent allows a more focused, relevant and modern approach to choice in health care.

ALZHEIMER'S DISEASE: PROGRESS AND CHALLENGES. J. Paul Binette, M.D., VAWNYHCS and School of Medicine and Biomedical Sciences, State University of New York at Buffalo, NY.

We will consider the above in the diagnosis, etiology and therapy of this devastating disease. The tasks, formal and informal, testing memory are major means of early diagnosis and when combined with imaging refinements achieve a high degree of accuracy. Biomarkers such as the tau and A β levels in cerebro-spinal fluid may also prove useful in establishing the diagnosis. Genetic dissection may eventually sustain an early diagnosis or add to the presence of plaques and tangles, the pathological hallmarks of the disease. The etiology is becoming known as multi-factorial with inheritance making the major contribution in the early age group leaving the door open for further discoveries, particularly in the vast majority of afflicted elderly. Trauma, decreased cerebral blood flow, free radicals, inflammation and specific cytokines have also been incriminated. A candle has begun to shine in the darkness as treatment, although imperfect has become available and intensive research is producing rational therapy such as vaccines, lipid lowering drugs, anti-inflammatory agents and modulators of chemical cascade responsible for the disease.

INVESTIGATION OF POSSIBLE OTO- OR NEPHROTOXIC SIDE EFFECTS OF AMINO-GLYCOSIDE TREATMENT OF URINARY TRACT INFECTIONS IN NEWBORNS.

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The aim of this study was to investigate the possible oto- or nephrotoxic side effects of Gentamicin treatment of urinary tract infections (UTI) in the newborn period. Patients: 20 patients (15 girls, 5 boys) were treated in our Level II neonatal unit. 7 preterms and 13 full term newborns, (birth weight between 1700 and 4200 grams, gestational age: between 35 and 42 weeks). In cases of significant bacteriuria two doses of Gentamicin (5 mg/kg) were given intramuscularly within a week. 80 % of the pathogens were E. coli. The examination for ototoxicity

was carried out with the Echocheck instrument, manufactured by Otodynamics Co, using transient otoacoustic emission. The hearing test was done before and one day after the first injection of Gentamicin and two weeks after completion of the treatment. Urinary N-acetyl-D-glucosaminidase activity was used for the detection of nephrotoxicity. This is a very sensitive indicator of tubular damage. Our patients did not have any other disease that could have led to tubular damage. The enzyme activity was measured before and after treatment, and also at the time of the control examination, two weeks after the completion of treatment. The Gentamicin serum level was determined one hour after the injections. The serum level of the drug was in only one instance higher than 10 µg/ml. Results: During the study period no oto- or nephrotoxic effects were found in this group of newborns. We could not detect hearing loss in any one of the infants. There was no pathological increase in the enzyme activity after treatment that would indicate nephrotoxicity. The UTIs were cured in 19 cases. Conclusion: The sequential Gentamicin treatment in cases of UTI of newborns is a safe, reliable, cost effective method

HIGH-GRADE SOFT TISSUE SARCOMA: A TEN YEAR EXPERIENCE. Andrei A. Czitrom, M.D. and Richard A. Stahr, OPA-C Advanced Surgical Institutes, Medical City Dallas Hospital, Dallas, TX.

The purpose of this prospective study was to evaluate the results of combined modality therapy for high-grade soft tissue sarcomas. From 1992 to 2002 a total of 48 patients (18 males, 30 females, age range 13—89 years, average age 54.8 years) were prospectively followed in a single orthopedic oncology practice. Previous inadvertent excisions with residual positive microscopic margins made up 21 of the 48 patients. Seven patients were seen for recurrent tumors. Combined modality treatment was carried out non-randomly as follows: 1) pre-operative radiation in 29 (combined with postoperative boost in 7 of 29); 2) post-operative radiation in 6; 3) pre-operative chemotherapy and radiation in 4; 4) brachytherapy in 2; and 5) no radiation or chemotherapy in 7 patients. The surgical treatment was wide excision in 44 and amputation in 4 cases. Positive microscopic margins were detected in 5 cases (10.4%), 2 of these were in the no radiation group, 2 in the pre-operative radiation group and 1 in the pre-operative chemotherapy and radiation group. Wound complications developed in 11 patients (22.9%), 7 were major (14.6%) and 4 were minor (8.3%). All 7 of the major wound problems occurred in patients who had pre-operative radiation and had no relationship to the use of tissue transfers. The 3 year actuarial tumor control results in 29 patients were as follows: local control - 89.7% (all 3

local recurrences were in patients who had negative surgical margins and 2 of 3 died); disease free survival - 58.6%; overall survival - 65.5%. We conclude that pre-operative radiation increases the risk for wound complications without a significant improvement in tumor control rates.

DO WE NEED AUTOPSIES IN MODERN MEDICINE? U.G. Prudlo, M.D.¹ and O. Dworak, M.D.², ^{2nd} Department of Internal Medicine¹ and Institute of Pathology², City Hospital, Fürth, Germany.

There is a need for quality control procedures in evidence based modern medicine. Currently autopsies are performed at a decreasing rate. Comparing our clinical and autopsy diagnoses we investigated the usefulness of the autopsies as quality control procedure in our hospital. Methods: Between 1997 and 1999, 823 adult autopsies were carried out in five different hospitals. Pathological diagnoses were compared to clinical diagnoses and when the clinical and pathological diagnoses differed the therapeutic relevance of the difference was assessed. Results: The charts of 429 male and 394 female patients were examined. The mean age at death was 72.0 years (69.1 years for men and 75.0 years for women). 576 necropsies were carried out in the Hospital of the City of Fürth and the remaining autopsies were distributed through four other hospitals. The frequency of autopsies was steadily decreasing during the three years. The clinically established cause of death was the same as the cause of death identified at autopsy in 591 cases (71.8%). In 147 cases the autopsy resulted in change in the cause of death and in 13 out of these cases the change of the diagnosis may have had impact in the management of the patient. The autopsy confirmed the important clinical diagnoses other than the cause of death, in 616 cases (74.9%). In 20 of the 117 cases with incorrect diagnoses other than the cause of death, the patient may have required different therapy. Conclusions: with the introduction of new diagnostic and therapeutic approaches, medicine undergoes rapid evolution. Since studies based on autopsy material indicate that the rate of incorrect clinical diagnoses is stable, pathology still remains one of the best quality control procedures in modern medicine.

IATROGENIC CONSEQUENCES OF PALLIATIVE REPAIR OF CONGENITAL HEART DISEASE.

Peter G. Forbath, M.D., Department of Medicine, University of Toronto and St. Michael's Hospital, Toronto, Canada.

Artificial organs are no longer science fiction in the 21st century. Palliative repair of heart disease started 58 years

ago with benefits to Tetralogy of Fallot patients. Today the available procedures are probably more numerous than the variety of lesions. Palliative repair procedures occasionally may cause (secondary) iatrogenic consequences immediately or years following a given operation. The following palliative repairs will be discussed: a./ repairs needed for left and right ventricular obstruction, b./ total or palliative repairs of Tetralogy and of transposition of the great vessels, c./ conditions following repairs of the atrial and ventricular septa. Additionally such repairs may result in electrophysiological consequences. These results may require sophisticated pacemakers, defibrillators or numerous EP procedures. Normal conditions of life (e.g. pregnancy, dental care) may change after palliation and adds to the iatrogenic scope on patients with repaired heart disease.

THE PAINFUL HEEL SYNDROME.

Thomas Fried, M.D., Member, Canadian Olympic Association, Toronto, Canada.

Pain in the heel is common and quite disabling. It is usually related to the plantar fascia or to the subtalar joint. Therapy, including physical therapy, medication (oral or injected) or even surgery is not helpful, or helps only temporarily. Commercial orthosyses are on the market, but are not very helpful, although some of them offer partial relief. Surgery in case of plantar fascia problem frequently aggravates the condition. According to my experience a good orthopedic technician can do much more to relieve pain than any surgical intervention. We, my orthotist and myself, designed and built an orthosys for the plantar fasciitis problem and a new type of sole-heel unit for pain arising from the subtalar joint. The relief was not only subjective, but also substantiated by pressure transducer measurements. The technical data will be discussed and models demonstrated and circulated.

ACUTE MYOCARDIAL INFARCTION: AN UPDATE. William Ganz, M.D., Cedars-Sinai Medical Center and the Univ. of California at Los Angeles, CA.

Acute myocardial infarction is caused by abrupt occlusion of a coronary artery by a thrombus developed at the site of ruptured atherosclerotic plaque. The fall in intracoronary pressure distal to the site of occlusion leads to instant opening of congenitally preformed collateral channels coming from the other coronary arteries and large branches. The channels initially about 40 microns in diameter are gradually dilated by the effect of pressure and blood flow so that by 24 hours their diameter increases to 100 microns and they become angiographically visible. These collaterals moderate the severity of myocardial ischemia and reduce the occurrence

of ventricular fibrillation. After approximately 20 minutes of myocardial ischemia the myocardial cells begin to die first in the subendocardium and gradually over 4-5 hours the wave front of necrosis progresses to the epicardium. It is obvious that the earlier during the progression of necrosis the coronary artery is reopened the more of the jeopardized myocardium can be salvaged. Not infrequently the total occlusion of the coronary is preceded by hours and days of plaque instability manifested by episodes of chest pain. Recognition of these episodes of chest pain as potential precursors of a heart attack and their treatment can prevent the development of an acute myocardial infarction. When the occlusion persists and signs of an acute myocardial infarction are present the earliest possible reopening is critically important because "time is myocardium". The artery can be reopened either by intravenous administration of fibrinolytic agents injected in boluses or in infusion or mechanically by primary balloon angioplasty or primary stenting. Clinically, acute myocardial infarction is typically manifested by severe substernal pain with or without radiation, typical electrocardiographic changes, myocardial enzyme release into the blood, myocardial wall motion abnormalities in the echocardiogram. Reopening of the coronary artery is signaled by relief of chest pain associated with improvement in the electrocardiogram. Mortality was reduced from 13-15% in 1980 to 5-7% in year 2000. Prevention: low fat diet, cholesterol reducing agents, exercise, no smoking, treatment of high blood pressure, treatment of diabetes, antiplatelet agents, weight control.

INFLUENCE OF OPIATES ON THE DEVELOPMENT OF HIV INFECTION OF THE NERVOUS SYSTEM IN AIDS. Georg Gosztonyi, M.D., Ph.D.², Manfred Sell, M.D.³, A. Julio Martinez, M.D.⁴ and Volkmar Schneider, M.D., Ph.D.¹, Institute of Forensic Medicine¹ and Department of Neuropathology², Freie Universität Berlin, Institut für Pathologie, Auguste Viktoria Klinikum³, Berlin and Department of Pathology (Neuropathology), University of Pittsburgh⁴, USA.

Intravenous drug users beside homosexuals form the second largest risk group of AIDS cases in Europe and North America. In order to assess the influence of opiates on the development of neuropathological syndromes, the central nervous system (CNS) of 450 AIDS cases had been investigated histologically and immunohistochemically. The direct invasion of the CNS by HIV is characterized by perivascular infiltrates of HIV-infected macrophages and multinucleated giant cells, mainly in the white matter of the brain. This form of neural involvement

has been denoted as HIV encephalitis (HIV-E). Besides HIV-E further CNS complications occur in AIDS, such as lymphomas, and the sequels of opportunistic infections, as glial nodular encephalitis, subpial and subependymal necroses, progressive multifocal leukoencephalopathy (PML), toxoplasma- and fungal encephalitides. The most prominent difference between the two largest risk groups was found in the prevalence of HIV-E. The typical picture of HIV-E was present in 51% of the i.v. drug users, but only in 30% of homosexual AIDS patients. An opposite tendency was observed in glial nodular encephalitis, most probably due to CMV- and toxoplasma-infections, and in the subpial and subependymal necroses caused by CMV infection. The ratio of i.v. drug users in the last two syndromes was markedly lower than that of homosexuals. In the remaining neuropathologic syndromes the differences between the ratios of the two risk groups was not so conspicuous. We also examined the possible influence of antiretroviral therapy on the prevalence of neuropathological syndromes. There were no essential differences between AIDS cases with or without antiretroviral therapy. The mean duration of the disease in cases with HIV-E was shorter in the drug users than in the homosexuals at almost identical mean age. These results indicate that the immunosuppressive effect of HIV is potentiated by opiates, so that the drug addict AIDS patients are exposed to a double endangerment.

ERECTILE DYSFUNCTION IN THE AGE OF VIAGRA. Gabriel P. Haas, M.D., Ph.D., Department of Urology, State University of New York Upstate Medical Center, Syracuse, NY.

Erectile dysfunction is a serious consequence of genitourinary malignancies, multiple medical conditions and the aging process. During the last decade novel treatment modalities ranging from medical management, minimally invasive interactions and surgical approaches have been developed. This presentation will reveal the pathophysiology of erectile dysfunction, the contributing medical factors and the treatment algorithm recommended. The pharmacology of sildenafil will be characterized and the specific utilization of this medication, including how to take it, when to take it and possible contraindications will be discussed.

RETROELEMENTS (RE) AND RETROVIRUSES (RV) I. STRUCTURE, MODE OF REPLICATION AND PATHOGENICITY. Joseph C. Horvath, M.D., and Joseph G. Sinkovics, M.D., St. Joseph's Hospital, University of South Florida College of Medicine, Tampa, FL.

Retrovirologists follow the blazing trails of giants. Ellerman and Bang discovered the virus of chicken leukosis (1908) and Rous extracted the causative virus of chicken sarcoma (1911). Barbara McClintock recognized first mobile DNA elements in maize and set the stage for the discovery of transposons from the prokaryotic genomes upward in every living cell. Temin conceived the entity of "provirus" meaning that an RNA viral genome can be inserted into the genome of its host cell where it behaves like a new gene and is vertically transmitted to the cell's progeny in the germline (1970). Lwoff already knew that bacteriophages can exist in this stage and can be activated to replicate and dissolve the host cell: the phenomenon of lysogeny (1950s). Baltimore and Temin independently isolated first the enzyme reverse transcriptase encoded by the retroviral genome that retrotranscribes viral single stranded RNA into dsDNA: the provirus (1970). Bishop and Varmus deciphered that retroviruses in their proviral state of existence can transduce and/or recombine with host cell genes (1976). Frequently these host cell genes are those that encode growth factor receptors and their ligands. Amplifications and constitutive overexpression of these genes lead to uncontrolled replications of the cells harboring them: malignant transformation occurs as the c -protooncogene becomes v -oncogene. Another class of retroviruses induces malignancy by inserting its provirus next to a cellular growth factor gene thus causing its constitutive high expression through the promoter/enhancer of its long terminal repeat (LTR). Bittner's mouse mammary tumor virus is the best example of malignant transformation by proviral insertion next to a host gene encoding neoangiogenesis: the $int \rightarrow bFGF$ system. Gross, Friend, Moloney, Rauscher and others isolated mouse leukemia viruses (1950s). The Gallo team propagated the first human leukemia virus (HTLV-I). The Montagnier and the Gallo teams share credit for the discovery of HIV-1 a retrolentivirus, the cause of AIDS (1983). Antiretroviral immunity in mouse leukemia (immunization with attenuated virus or with photodynamically inactivated viral vaccine, production of virus-neutralizing antibodies, including those deriving from plasma cells fused with lymphoma cells (the first hybridoma) and immune T cells) was described by Sinkovics (1960s). Viruses present in fetal life are accepted as "self" and induce tolerance (Burnet & Medawar). New discoveries in the making are

the AIDS vaccine and the use of retroviral vectors for gene therapy. Budding retroviral particles were observed in human malignant tissues by Dmochowski; Györkey; Szakacs (1960s) and Zucker-Franklin (1995). New diseases of possible retroviral etiology are lupus, multiple sclerosis, certain lymphomas and bronchioalveolar carcinoma. This latter entity resembles jaagziekte of the sheep caused by a retrovirus acting in collusion with a herpesvirus. Certain herpes viruses incorporate genomic sequences of a retrovirus; for example Marek's virus contains a reticuloendotheliosis viral segment. We postulate herpes- and retroviral collusion (EBV or HHV-8) in Reed-Sternberg or Kaposi's sarcoma cells.

LAPAROSCOPIC ONCOLOGIC LOW ANTERIOR RESECTION FOR NEOPLASIA OF THE RECTUM. Hermann Kessler, M.D. and Werner Hohenberger, M.D., Department of Surgery, University of Erlangen, Germany.

Introduction: A 58 year old lady reported repeated transanal bleeding. Rectoscopy and biopsy revealed an ulcerated adenoma located on the anterior wall of the rectum with a diameter of more than 3 cm at 8 cm from the anal verge. It was highly suspicious for carcinoma. **Methods:** The procedure was performed with the patient in the modified lithotomy position using five trocars. The inferior mesenteric artery is divided first at its origin close to the aorta dissecting all lymph nodes located along its trunk. Close to the ligament of Treitz and below the inferior edge of the pancreas, the inferior mesenteric vein is clipped and transected. The sigmoid and the descending colon are freed up laterally. The splenic flexure is mobilized completely with the lesser sac being opened. After bilateral incision of the peritoneum down to the peritoneal reflection, the rectum is mobilized posteriorly down to the pelvic floor, sparing the hypogastric nerves. After further anterior mobilization, the rectum is transected in its middle third using an angulating stapler. The descending colon is also transected. The specimen is saved in a plastic bag that is closed and pulled outside after enlarging the left lower abdominal incision to a length of 5 cm. The colorectal anastomosis is established. **Results:** In 28 months, 92 patients have been operated on by rectosigmoidal resections for various indications. There was one postoperative leak treated by laparoscopic diverting ileostomy. In 3 patients, fibrosis of the double-stapling anastomosis occurred requiring reoperation. There was no postoperative mortality. **Conclusion:** Laparoscopic oncologic anterior rectal resection is safe and feasible according to the principles valid in conventional tumor surgery.

EVALUATION OF THE RESULTS OF 861 ARTHROSCOPIC RECONSTRUCTION OF ROTATOR CUFF TEARS. G. Kovacs, M.D.¹ and J. Ertl, M.D.², Maingau Hospital, Frankfurt, Germany¹ and Kaiser Hospital, Sacramento, CA².

A comparison of the long term results (average 7.1 years) and short term results (average 1.8 years) after arthroscopic transhumeral reconstruction of rotator cuff tears with the same technique. The technique was developed in 1990 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. **Material:** Evaluation of the results in two patient groups: The first one is the long term patient group with an average of 7.1 years after surgery (No: 150.) The second one is the patient group with an average of 1.8 years. (No: 711). **Method:** An anterior acromioplasty and an arthroscopic tendon to bone repair using a bone cutting needle was done in all cases. An AC-Joint plasty was done in 12% of the cases and tendon transposition in 1.4 %. Postoperatively the patients start full passive motion a day after surgery and active motion six weeks later. **Results:** The results were grouped using Neer's classification. In the long term group there were 64% excellent, 34% satisfactory and 2% unsatisfactory results. In the short term group the results were 71% excellent, 24 % satisfactory and 5 % unsatisfactory. The UCLA average score improved from 15.8 preoperative to 31.5 postoperative.

APPLICATION OF MICROARRAY TECHNOLOGY IN STUDIES RELATED TO THE PITUITARY GLAND. Kalman Kovacs M.D., Ph.D. and Eva Horvath, Ph.D., Department of Laboratory Medicine and Pathobiology, St. Michael's Hospital, University of Toronto, Canada.

Aim of Study - Microarray technology is a recently developed novel way of investigating expression of a large number of genes. In this presentation results obtained by microarray technology related to the pituitary gland will be reviewed. **Methods -** Paraffin blocks of archival material can be used. The technique permits large scale screening of candidate genes that may have potential importance in the initiation, progression and morphologic characterization of various pituitary tumor types. **Results -** So far very few studies were undertaken to investigate microarray changes in pituitary glands. The results were published from other laboratories. It was revealed that in rodents pituitary tumor growth and regression were accompanied by characteristic genetic abnormalities. In

human pituitary tumors expression of numerous genes was found to be abnormal. The gene expression profile was different in various pituitary adenoma types. Conclusions - . Microarray technology is a powerful approach to rapidly identify genes that may play an important role in tumor biology. The few studies undertaken so far raise the hope that microarray technology will revolutionize tumor diagnosis and treatment. Further work is needed to correlate the genetic changes with clinical behavior, hormone levels, rate of tumor progression and morphologic features of tumors including immunohistochemistry, transmission electron microscopy and in situ hybridization. We foresee that microarray technology will help substantially to understand better pituitary tumor pathogenesis, growth and pathology. It will also be valuable to develop new and effective treatment modalities. Support - Our studies were supported by the Jarislowsky Foundation, Lloyd Carr Harris Foundation and the St. Michael's Hospital Research Center. We wish to express our sincere thanks for the support.

YELLOWSTONE IN THE WINTER. HEALTH HAZARDS. Thomas Z. Lajos, M.D., Department of Cardio-Thoracic Surgery, Buffalo General Hospital and the School of Medicine and Biomedical Sciences, State University of New York, Buffalo, NY

The purpose of this paper is to discuss and reveal the hazards of winter in the Yellowstone echo center. Our first national park has been established by congressional decree in 1872. This national wonder was created by a volcanic eruption 2 million to 600,000 years ago, scattering the volcanic ashes from Oregon to Kansas. This 40 miles caldera created the world's most unique geothermal and biological atmosphere. The molten rock exists only 3 miles below the surface giving rise to various hydrothermal features. The combination of a harsh winter and erupting hot springs present specific hazards to nature and human life. Yellowstone's counties (Mammoth, Geyser, Lake, Canyon and Roosevelt) have their own microclimate, flora, geothermal eruptions and animal life. Violent death (53), winter (40), traffic accidents (40), hazards of nature (27), poisonous gases (12), geothermal features (115) and wild animals (24) have taken their tolls of more than 300 human lives in the past 130 years. The park is raw nature and it can not only kill but cause serious, unpredictable injuries such as scalding, burns, falls, traffic accidents and wild animal mauling. Each of these will be described in the lecture. We have created this wilderness for our and our children's enjoyments; for the people of our country. If we want to preserve it for the future, we have to accept it and learn to respect it too. In the wilderness one is never very far away from the edge

and if one takes it for granted, it will come up and bite us.

NEW RESULTS IN PREVENTION AND TREATMENT OF CORONARY HEART DISEASES. Stephen Lazarovits M.D., Internist, Toronto, Ontario, Canada.

There has been significant progress in the prevention and treatment of coronary heart diseases during the last few years. The aim of the study is to give a summary and evaluation of these results. Recent observations prove, that atherosclerosis develops as the result of inflammatory response in the vessel wall, caused by infectious agents. C reactive protein, an inflammatory marker, associated with the ischemic events, is better indicator for the diagnosis of coronary heart disease (CHD) than cholesterol. It has been proven, that antibiotic treatment significantly lowers the risk of death in heart attacks. The relatively new statin-niacin treatment is more effective than statins alone and can slash the risk of heart attacks by 70 %. In a combined statin-niacin treatment experiment statins lower the level of LDL, and niacin boosts the level of HDL. According to the angiograms, after combined statin-niacin treatment the plaque build up had actually decreased. It has been statistically proven, that clinical use of antioxidant vitamins E and C, with or without statins, may help to prevent CHD morbidity and mortality. However the study showed, that the antioxidant vitamins A, C, beta carotin and selenium, used in the combined treatment form, blunted the expected rise in HDL cholesterol, and may not be beneficial. Further investigations will have to determine, whether all antioxidant vitamins are responsible for the blunting effect. Experiments were performed using statins for the prevention of strokes, osteoporosis, Alzheimer's and diabetes. Other new observations show, that radiation and new methods in angiography might be useful for the prevention of CHD. The sudden stopping of statin therapy causes the blood nitric acid level to drop below normal and can increase the risk of death. New experimental data are showing benefits of statins for primary prevention of CHD and elevated LDL levels, for strokes, diabetes, osteoporosis and Alzheimer's disease. Another question to be answered is, would statin treatment be beneficial even for patient, having low blood cholesterol.

DIABETIC KIDNEY DISEASE. AN UPDATE AT THE TURN OF THE CENTURY.

Andras Mogyrosi, M.D., Ph.D., Division of Nephrology, Department of Medicine, Commonwealth University/Medical College of Virginia and McGuire VAMC, Richmond, VA.

According to the US Renal Data System as well as its European and Japanese counterparts, the number of patients with end stage renal disease due to diabetic nephropathy is increasing relentlessly. Currently more than 40% of patients needing renal replacement therapy in the United States develop their kidney disease because of Type 1 or 2 Diabetes Mellitus. On a more optimistic note, recent landmark trials indicate that slowing the progression of diabetic kidney disease is possible. This update on diabetic nephropathy will summarize new developments in the field. Therapeutic options that were shown to or suspected to slow the progression of the disease will be discussed. Glucose control, antihypertensive therapy and the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers will be critically analyzed in terms of their efficacy of slowing the progression of diabetic kidney disease. Potential future treatment options derived from the results of basic research studies of the last decade will be entertained.

FOLLOW-UP RESULTS OF OUR PATIENTS OPERATED ON FOR COLO-RECTAL TUMORS.

András P. Nagy, M.D. and Zita Nagy, Semmelweis Hospital, Kiskúnhalas, Hungary.

We operated on 864 patients with colo-rectal tumor between 1993 and 2001. 45% of these were found to be inoperable at the time of the exploration either for technical or for oncological reasons. Those at whom surgery was successfully completed were closely followed. In the first post-surgical year they returned for a follow-up examination that included colonoscopy every 3 months, in the second year every 6 months. As a result we found polyps in 65 cases that were removed through the colonoscope. In 28 cases we found new tumors, 12 of these were second tumors and 16 were recurrences. The 28 patients where new tumors were found were operated on again. All the 12 cases where we found second tumors were operable, while only 11 of the 16 recurrent tumors were. Our results show the importance of close follow-up of these patients. We consider this a "third prevention" that will lengthen the survival of these individuals.

TAMOXIFEN FOR BREAST CARCINOMA PREVENTION IN PREMENOPAUSAL WOMEN. Istvan Nyirjesy, MD. Georgetown University School of Medicine, Washington, DC.

Background: The NSABB P-1 Study concluded that Tamoxifen (Tmx) 20 mg daily for 5 years reduced the risk of invasive cancer by 49% in women who were at greater than 1.66% predicted risk to develop breast cancer within 5 years. The decrease in risk was 44% in women aged 49 or younger. Despite these findings, high-risk premenopausal women often decline Tmx for prevention, because of the unpredictability of its effect on the reproductive system. **Method:** The literature of the endocrine effects of Tmx was reviewed via Medline searches. **Results:** In premenopausal women, mean estradiol levels rise by 2 to 300%, while progesterone levels may or may not increase. FSH increases slightly, while it decreases by about 50% in postmenopausal women. Ovulation usually continues, but menstrual irregularities have been reported in up to 25%. No instance of pregnancy in women on Tmx were reported, but 14 pregnancies followed Tmx induced ovulation. Information on fetal outcomes was not available. The following gynecological adverse reactions have been related to Tmx therapy: increased risk of endometrial cancer (RR=2.53 to 5.6), myometrial hypertrophy, involuntary ovulation induction in a perimenopausal woman with recurrent breast cancer, cystic glandular hyperplasia of the endometrium, endometrial polyps and symptomatic endometriomas. Hot flashes were reported in up to 64%, vaginal discharge in 30% and irregular menses in 25% of women. **Conclusion:** Premenopausal use of Tmx is associated with usually mild adverse effects on the reproductive system. Due to lack of data on fetal outcome, avoidance of pregnancy is advisable. Since the reproductive side effects may reduce the quality of life, each patient's individual risk factors should be evaluated to determine whether delaying Tmx prophylaxis until after the menopause is reasonable.

PREVENTION OF DEATHS FROM CANCERS OF THE CERVIX UTERI AND OF THE BREAST. WESTERN SUCCESSES AND HUNGARIAN PROBLEMS. Istvan Nyirjesy, M.D., Georgetown University School of Medicine, Washington, DC.

In year 2000, Hungary had the highest cancer mortality among 45 countries reporting to the World Health Organization. Specifically, cervical cancer mortality was nearly 2.5 times higher in Hungary than in the USA, where it diminished nearly six fold between 1930 and 2000. Death reduction from cervical cancer results from the diagnosis and treatment of precancerous states, which

can only be accomplished by mass screening. For over 15 years, we studied extensively the cervical cancer issue in Hungary, and identified several problems. These include absence of universal screening, failure to follow abnormal findings and to diagnose and treat precancerous lesions. In the Western countries, screening for cervical cancer is based on Papanicolaou (Pap) smears, and, follow-up by colposcopy of any anomaly that indicates the need for a biopsy. Taking of colposcopically directed biopsies, a relatively inexpensive ambulatory procedure was prohibited in Hungary. Cone biopsies were allowed, but since conization requires major anesthesia and hospitalization, its use was limited. In countries where Pap smears are too expensive, less accurate but still valuable methods can be used, but none of these have been applied in Hungary. One of these is cervicoscopy (speculum examination of the cervix following staining with acetic acid), followed by immediate biopsy of the abnormal areas. An alternative for Pap smear is testing for Human Papillomavirus (HPV), the etiologic agent of cervical cancer. Because of high cost, and, the unpredictable course of HPV infections, such an approach may be confusing. Acceptance of universal screening is hindered by the lack of knowledge about its benefits by the Hungarian public, and also by many GP-s and internists. In the USA, GP-s are often involved in screening examinations, whereas law to do so in Hungary prevents them. In the U.S., reduction of breast cancer deaths (10% between 1990 and 2000) has been successfully accomplished by early diagnosis, with the combination of periodic physical exams combined with mammography (over age 40). Tamoxifen prevention can further reduce breast cancer incidence by 50% in high-risk women. Other approaches, such as exercise, weight reduction, abstinence from alcohol may be of value, and in high risk patients, preventive Tamoxifen therapy should be considered. It has been estimated that about 80% of American women have a mammogram at least every two years, while in 2000, there were only 5 dedicated mammography units in Hungary, and few surgeons are trained in biopsies of x-ray detected nonpalpable tumors. To conclude, Hungary should educate the public and physicians, and, should apply modern cancer death prevention approaches that were found to be successful in other countries.

TRENDS IN PEDIATRIC EMS UTILIZATION IN A RURAL STATE. Sean M. Stone, M.D., Tamas R. Peredy, M.D. and John H. Burton, M.D., Main Medical Center, Portland, ME.

Introduction: Little data exists in the literature regarding the characterization of trends in pediatric EMS utilization. Key to the understanding of the epidemiology of EMS activation, this information would allow administrators to anticipate additional resource needs in high growth areas and would impact EMS educator curricula development. We hypothesized that patients in their late teens would represent a group with high EMS utilization rates due to increased risk taking behavior and interpersonal violence-related emergencies. 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 the five most recently completed 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. Results: From 1996-2000, 907,150 total records were generated (see Table 1).

Table 1. Database Totals.

	EMS calls total	EMS calls ages 10-20	EMS scene calls ages 10-20
1996	158,638	13,994	8,920
1997	173,871	14,718	9,105
1998	187,354	15,940	9,901
1999	189,401	16,671	10,000
2000	197,886	17,581	10,493
% change	4.9 (1.1-9.6)	5.1 (4.6-8.3)	3.5 (2.0-7.6)

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. While EMS encounters for the late teen group related to high risk behavior (see Table 2) saw dramatic rises during the study period in (alcohol related 30%, drug overdoses 50%, behavioral emergencies 60% and risk for suicide 200%) their respective totals contributed little to the overall EMS call increases.

Table 2. Age Group Sub-analysis
(% change over 5 years)

	Age 6-10	Age 11-15	Age 16-20
EtOH	0	0	+33
OD's	0	0	+49
Behavioral	+74	+87	+62
Suicide*	0	+12	+117
MVA	+5	+2	+15
Non-MVA trauma	+9 (46)	+19 (179)	+43 (433)

*Suicide data field collected 1998-present.

EMS utilization for the late teen group was impacted greatly by an increased incidence of non-vehicular trauma (i.e.: interpersonal violence, sports related injuries, etc.) which rose by >400 calls during the study period. Conclusions: Pediatric EMS encounters represent a small but growing minority of the total EMS volume. Late teens saw the highest utilization increases, largely due to non-vehicular related injuries. A heightened awareness of and preparation for Pediatric EMS encounters related to behavioral and traumatic emergencies will be important if current trends continue.

THE LIVING AORTIC VALVE. Francis Robicsek, M.D., Ph.D.¹, Mano J. Thubrikar, Ph.D.², Michel Labrosse², Kenton J. Zehr, M.D.³, Department of Thoracic and Cardiovascular Surgery, Carolinas Medical Center, Charlotte, NC¹, The Heineman Medical Research Laboratory, Charlotte, NC² and Division of Cardiovascular Surgery, Mayo Clinic, Rochester, MN³

The authors present an in-depth study of the role of stress in the development of degenerative disease of the tricuspid aortic valve and also examine various factors as how they may act in the presence of different valve-sparing and valve substituting operations. Using in-vitro measurements, computer simulations and clinical observations, a new theory of the cause of degenerative aortic valve disease is presented and a new aortic root prosthesis is introduced which, by its morphological features and compliant nature, is expected to decrease stress on the aortic leaflets, thus improve their function and increase their longevity.

DIFFERENT ACTIVATION IN PPRE BINDING IN FATTY LIVER AFTER LPS AND ALCOHOL STIMULATION. László Romics, M.D., P. Mandrekar, Ph.D., G. Szabo, M.D., Ph.D., University of Massachusetts Medical School, Worcester, MA.

Aim of the study: Dysregulation of inflammatory pathways may contribute to the vulnerability of fatty liver to endotoxin-induced damage. Both TNF and NFkB

activation are increased by chronic alcohol treatment. In contrast, acute alcohol has anti-inflammatory effects in Kupffer cells and monocytes. Peroxisome proliferator activated-receptors (PPAR α and PPAR γ) and PPRE activation can inhibit NFkB activation. Increased PPAR α and PPAR γ mRNA levels were noted in fatty liver. The purpose of this study was to evaluate the relationship between NFkB and PPRE nuclear binding in fatty and lean livers after endotoxin or acute alcohol insults. Methods: Animals: leptin-deficient, ob/ob, mice and their lean littermates (n=3-4/stimulation): saline, alcohol (20% v/v; ob/ob: 350 μ l, lean: 200 μ l, i.p), LPS: (0.5 μ g/g body weight, i.p), alcohol+LPS (LPS given 1 hour after alcohol). Animals were sacrificed 1 - 24 hours after LPS. Nuclear extracts of whole liver homogenates were prepared and evaluated in EMSA for NFkB and PPRE binding. Serum TNF and IL-6 protein were determined by ELISA, RNA by RT-PCR. Results: NFkB activation after LPS stimulation was 2.1-3.2-fold greater in fatty than lean livers at all time points. After alcohol treatment, LPS induced binding of the functionally active NFkB heterodimer (p65/p50) was attenuated in lean (40% decrease @ 1 hour) but augmented in fatty livers (44% increase @ 1 hour; peak differences). Increased NFkB activation in the alcohol+LPS-treated ob/ob mice was mirrored by higher serum TNF α (1505 pg/ml compared to 715 pg/ml) and IL-6 levels compared to the lean littermates. Alcohol and LPS had different effects on PPRE binding between obese and lean livers (Alcohol: ob/ob: 51% increase, lean: 12% decrease; LPS: ob/ob 200% increase, lean: 32% decrease, all @ 2 hours). Finally, alcohol pretreatment decreased LPS-induced PPRE binding in ob/ob (50% @2hours) but not in lean mice at all time points. Conclusion: In contrast to the anti-inflammatory effects of acute alcohol on LPS-induced NFkB in lean mice, alcohol resulted in NFkB hyper-induction in fatty livers of ob/ob mice. This was concomitant to a reduced activation of PPRE binding, a potential inhibitor of inflammation, in LPS plus alcohol treated ob/ob mice. A balance of pro- and anti-inflammatory pathways may be critical to the pathogenesis of fatty liver injury.

RECONSTRUCTION OF THE EDENTULOUS PATIENT IN THE NEW MILLENNIUM.

Tim Silegy, D.D.S., Private Practice in Oral and Maxillofacial Surgery, Long Beach, CA.

Premature loss of teeth leads to progressive resorption of alveolar bone and significant impairment of masticatory function. Traditional management of these patients involves fabricating complete upper and lower prostheses (dentures) that restores only 30 percent of masticatory

function and in some cases accelerates bone loss. Reconstruction of the edentulous maxilla and mandible with dental implants dramatically improves masticatory function and prevents progressive bone loss. This presentation will show how recent advances in surgical and restorative techniques make this the standard when treating the edentulous individual.

RETROELEMENTS (RE) AND RETROVIRUSES (RV) II. ORIGINS AND ROLES IN GENOMIC EVOLUTION. Joseph G. Sinkovics, M.D.* and Joseph C. Horvath, M.D., St Joseph's Hospital and University of South Florida College of Medicine, Tampa FL.

The human genome consists of 3,400,000,000 bp of nucleotides some deriving from ancient prokaryotes and archaea; is sparsely populated with functional genes: we possess less than 50,000 genes. Human chromosome 21 expresses 225 protein-encoding genes and harbors over 2000 endogenous proviral DNA sequences. Genomic lengths of some amebas or plants (fern, lily, rice) exceed that of *Homo*: the C-value paradox. Less than 2% of our genome is encoding working proteins, whereas prokaryotic genomes (already interspersed by mobile insertional DNA sequences: IS; Mu phages etc) are fully operational: cca 95% of their genome encodes proteins. The *Saccharomyces* genome is 12,067,280 bp long with 6340 genes and 70% of it encodes proteins; its P and Ty elements are retrotransposons (R-Tn) and Ty-1 and Ty-3 function as copia and gypsy elements from the *Drosophila* upward. The Tc1 mariner Tn elements extend from the silk moth through flowering plants upward. In addition to our functional genes we possess IS, short and long interspersed elements (SINE-Alu/LINE), Tn and R-Tn, pseudogenes (ψ g) deriving from retrotranscribed mRNA and endogenous proviral DNA sequences up to 44% of our genome. LTR (long terminal repeat) R-Tn can evolve into endogenous or exogenous RV or into functional genes. Our endogenous proviral DNA sequences endowed with *env* appear as RV particles in cells of syncytiotrophoblasts (HERV-E;R;W), teratocarcinomas (HERV-K10), breast carcinomas (HERVK-T47D), lupus (SLE) (HRV-5), multiple sclerosis (MSRV), lymphoma/leukemia (HRV-5) and Kaposi's sarcoma; in this latter tumor we propose endogenous retroviral DNA insertions transactivating autocrine loops of neoangiogenesis (bFGF;VEG-F) and operating in collusion with HHV-8. Our most prominent exogenous retro(lenti)viruses are HTLV-I, II and HIV-1,2 both acquired from simian hosts. Our known functional genes deriving from R-Tn exceed 45 and include those active in placental syncytiotrophoblasts; the RAG/VDJ system of adaptive immunity which were inserted into the genome

of the now extinct *Placoderms* and became fully operational in their descendants the cartilaginous fishes and upward; telomerase which determines longevity vs senescence; and centromere binding proteins essential for orderly cell divisions. The human genome harbors enormous reserves of RE that may evolve into new vertically (endogenous) or horizontally (exogenous) spreading RV or into new genes to direct our future evolution under drastic environmental pressures imposed upon us by deteriorating conditions of the chemically polluted, radioactive and highly carcinogenic Earth; population of the planet Mars; and space travel. The *Homo* genome differs from that of the species *Pan* in 1-2% of their genes. The differing genes are those that directed the evolution of the human brain (Science 296: 233&340 02). It is the speed and quantity of gene expression rather than qualitative genomic changes that characterize the difference between the cerebral cortices of *Pan* and *Homo*. Our currently idle ψ g, SINE-Alu/LINE and LTR-R-Tn may provide for future enlargement and refinement of our cerebral cortical capacities or they may degenerate us into ferocious beasts with large but misguided brains. RE and RV are us! {AACR (New Orleans LA) 01 & ASCO (Orlando FL) 02; Clinical Virology Symposium USF Clearwater FL 02}. *Recipient of the Centenarian Kaposi Award 2002, Kaposi Foundation, Budapest, Hungary; presented Memorial Lecture at the Hungarian Scientific Academy: "Retroviruses R Us".

OPTIMIZING THE IN VITRO ENVIRONMENT WITH AUTOLOGOUS ENDOMETRIAL CO-CULTURE. Istvan Somkuti, M.D., Ph.D., Jay S. Schinfeld M.D., and Larry I. Barmat M.D., Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Abington Memorial Hospital and Jefferson Med. College, Philadelphia, PA

Autologous endometrial coculture involves the growth of embryos on top of a layer of a patient's own uterine lining cells in an effort to provide a more natural environment. Our aim in developing this procedure was to improve embryo quality and pregnancy rates, especially in those patient's with multiple failed attempts. Endometrial biopsy was performed in the luteal phase, cells digested, glands and stroma isolated, and then grown to confluence. Patients underwent standard IVF stimulation and then embryos were plated in conventional media (standard liquid used in IVF) versus on their own uterine lining cells (coculture). Data will be presented suggesting that the embryos grown on the coculture cells were more advanced and less fragmented. Pregnancy rates also increased.

PRIMATE MODELS FOR HUMAN PHOTOSENSITIVE EPILEPSY. C. Akos Szabo, M.D.¹, Michelle Leland, D.V.M.², Laszlo Sztonak, M.D.¹, Santiago Restrepo, M.D.¹, Richard Haines, D.V.M.¹, James J. Elliott, D.V.M.¹, Jeff T. Williams, Ph.D.², University of Texas Health Science Center, San Antonio, Texas¹ and Southwest Foundation for Biomedical Research, San Antonio, Texas².

Primate models for epilepsy have been studied for the past four decades with the objective of defining the biochemical and neurophysiological principles underlying epilepsy. *Papio papio* has been studied extensively and offers an excellent model of human photosensitive epilepsy. Most of the pedigreed baboons at the Southwest Foundation of Biomedical Research in San Antonio belong to related subspecies, such as *Papio anubis*, *cynocephalus* and their hybrids. The goals of the proposed study include a rigorous characterization of the epileptic phenotypes in these subspecies and the demonstration of heritability of the phenotypes. To date, we studied more than twenty seizure baboons and ten controls (asymptomatic baboons least related to the seizure baboons). Almost all of the seizure baboons demonstrated interictal discharges activated by ketamine, and over half of them had myoclonic or absence seizures with ketamine or photic stimulation. Only three (30%) of controls had interictal discharges activated by ketamine, one of which had a myoclonic seizure. The interictal discharges, seizures and photic responses are identical to those associated with idiopathic or inherited generalized photosensitive epilepsy in humans. Further baboons with witnessed seizures and their asymptomatic siblings or parents will be studied to determine the heritability of the epilepsy and EEG phenotypes. Our hope is that this primate model will offer insight into the genetic mechanisms underlying idiopathic generalized photosensitive epilepsy in humans.

THE EFFECT OF HIGH POWER MILLIMETER WAVE IRRADIATION ON EPIDERMAL KERATINOCYTES. Imre Szabo, M.D., Ph.D., Michael R. Manning, M.Sc. and Marvin C. Ziskin, M.D., Center for Biomedical Physics, Temple University School of Medicine, Philadelphia, PA.

Millimeter wave (MW) irradiation (7.1 mm, 42.2 GHz) has been successfully used in the clinical practice for mono- or adjuvant therapy of a wide range of systemic diseases. In addition, direct irradiation of wounds was

reported to induce an accelerated healing process. It is believed that the biological effect of MW irradiation is mediated by the neuro-immuno-endocrine system; however, thermal mechanisms might also be involved. Theoretical data suggest that the majority of energy is absorbed in the epidermis and papillar dermis, the surface layers of skin, where keratinocytes represent the most numerous constituents. In this study we analyzed the effect of high power MW irradiation on HaCaT keratinocyte cultures *in vitro* and on murine skin *in vivo*. The temperature was measured by infrared camera and thermocouples. The effect of irradiation on keratinocyte monolayers was studied by double staining of cells with the vital fluorescent dyes carboxyfluorescein succinimidyl ester and ethidium bromide. MW irradiation at the incident power density (IPD) of 1.85 W/cm² induced a delayed-type cellular damage in the beam area. Dead cells were found TUNEL positive implying the development of apoptosis upon exposure. In contrast, incubation of cells for 1 h at the peak temperature induced by MW irradiation resulted in no significant cell damage in HaCaT monolayers. MW irradiation at lower IPD range (1.2-1.4 W/cm²) was further studied *in vivo* by measuring the superficial and subcutaneous temperature in murine skin. We detected a rapid temperature rise at the beginning of MW irradiation, which was followed by a constant temperature phase. In spite of high peak temperatures in the irradiated skin areas there developed only mild reversible symptoms (e.g. erythema or superficial dryness) or none at all. In addition, no detectable hair damage was found. The subcutaneous temperature measurements show that MW irradiation induced heating can penetrate deep into the skin, and cause a dose-dependent temperature rise in the subcutaneous tissue without a detectable skin injury at IPDs lower than 1.3 W/cm².

MOLECULAR ALTERATIONS OF THE E-CADHERIN GENE IN MELANOMA AND COLORECTAL CARCINOMA CELL LINES.

A.D.Varnai, M.D.^{1,2}, A.Bosserhoff, Ph.D.³, R.Büttner, M.D.⁴, Marienhospital Euskirchen¹, Institute of Pathology, Medical School RWTH, Aachen², Institute of Pathology, Regensburg³ and Institute of Pathology, University of Bonn⁴, Germany

Introduction: Malignant transformation of melanocytes and colon epithelial cells frequently coincides with the loss of E-cadherin expression. We wanted to find out if a mutation in the E-cadherin gene coincides with this loss of E-cadherin expression. Methods: Genomic DNA was isolated from five melanoma and five colorectal carcinoma cell lines. Exons and intron-exon-boundaries of E-cadherin were amplified using PCR. The PCR products

were purified and subsequently direct cycle sequencing reactions were performed and analyzed by capillary electrophoresis. Results: In melanoma cell lines mutations were not detected either in the coding region or in the flanking intron-extron boundaries. In colorectal cell lines we detected a heterozygote frame shift mutation in one of the cell lines. Furthermore all five cell lines showed a polymorphism in exon 13. Three new intronic polymorphisms were detected in both of cell line types, none of which affected a region critical for exon-intron processing. Conclusion: Downregulation of E-cadherin is a frequent event in melanoma cell lines but it does not involve mutations in the E-cadherin gene. In colorectal cell lines there is a coincidence between molecular alterations and downregulation of E-cadherin. This could be important for malignant transformation and metastatic disease.

INHIBITION OF ADENOVIRUS INFECTION AND ADENOVIRUS PROTEASE IN VITRO BY GREEN TEA CATECHINS. Joseph M. Weber, Ph.D., Angeline Ruzindana-Umunyana, Ph.D., and Sucheta Sircar, Ph.D., Departement de Microbiologie et d'Infectiologie, Faculte de Medecine, Universite de Sherbrooke, Sherbrooke, Quebec, Canada,

Green tea catechins have been reported to inhibit proteases involved in cancer metastasis and infection by influenza virus and HIV. To date there are no effective anti-adenoviral therapies. Consequently we studied the effect of green tea catechins, and particularly the predominant component, epigallocatechin 3-gallate (EGCG), on adenovirus infection and the viral proteinase adenain, in cell culture. Adding EGCG (100 μ M) to the medium of infected cells reduced virus yield by two orders of magnitude, giving an IC_{50} of 25 μ M and a therapeutic index of 22 in Hep2 cells. The agent was most effective when added to the cells during the transition from the early to the late phase of viral infection suggesting that EGCG inhibits one or more late steps in virus infection. One of these steps appears to be virus assembly because the titer of infectious virus and the production of physical particles was much more affected than the synthesis of virus proteins. Another step might be the maturation cleavages carried out by adenain. Of the four catechins tested on adenain, EGCG was the most inhibitory with an IC_{50} of 109 μ M, compared with an IC_{50} of 714 μ M for PCMB, a standard cysteine protease inhibitor. EGCG and different green teas inactivated purified adenovirions with IC_{50} of 250 and 245-3095, respectively. We conclude that the anti-adenoviral activity of EGCG manifests itself through several mechanisms, both outside and inside the

cell, but at effective drug concentrations well above that reported in the serum of green tea drinkers.



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