TTF-1 negative, suggestive of stromal cell metaplasia. The presence of lipomatous change did not correlate with clinical hyper- or hypothyroidism nor with patient sex. Although benign neoplasms contained fatty metaplasia (14 of 79) more frequently than did malignant neoplasms (1 of 20), this was not statistically significant ($p = 0.14$).
Conclusion: Our findings suggest that there are two possible pathways for lipomatous change within thyroid nodules. Some oncocytic-type follicular adenomas demonstrate focal lipidization of tumor cells in association with areas of mature intratumoral fat, suggesting that follicular tumor cells, not stromal cells, are undergoing fatty metaplasia. This is in contrast to our observations of "true" adipose tissue deposition in the stroma of adenomatous nodules. The increased incidence of lipomatous change in oncocytic neoplasms and in adenomatous nodules arising in multinodular hyperplasia is a novel observation and may be related to altered metabolic activity in these lesions. Additional studies are warranted to establish a molecular basis for these observations.

219 GALECTIN-3: A USEFUL MARKER IN DISTINGUISHING SILENT CORTICOTROPH ADENOMAS OF THE PITUITARY GLAND
Eleni Thodou; Theodore Argyrakos; George Kontogeorgos, G. Gennimatas Athens General Hospital, Athens, Hellas, Athens, Greece
Background: Functioning corticotroph adenomas are indistinguishable from silent ones. Particularly, silent corticotroph adenomas type 1 are morphologically identical to their functioning counterparts in terms of their histology, histochemistry, immunohistochemistry and ultrastructure. No specific markers to separate them are available so far. Therefore, the necessity for a specific marker is crucial. Galectin-3 (Gal-3) belongs to the family of carbohydrate-binding proteins with high affinity for b-galactoside and it is involved in many biological processes including cell growth and differentiation, cell adhesion, tumor progression, apoptosis and metastasis.
Design: We studied by immunohistochemistry the expression of Gal-3 in 30 ACTH positive corticotroph pituitary adenomas (19 functioning and 11 silent) using a monoclonal antibody specific for Gal-3. All functioning adenomas were removed from patients associated with Cushing's disease. The independent variables t-test was used for comparing the mean percentages of Gal-3 in the two different subgroups. |
Results: Eighteen of the functioning corticotroph adenomas (94.73%) expressed Gal-3 with diffuse cytoplasmic reactivity and focal tendency to membranous enhancement. The mean percentage of Gal-3 positive adenoma cells was 77%. Among the silent corticotroph adenomas, 9 (81.81%) were negative, while the remaining two showed Gal-3 immunoreactivity in 15% and 80% of their adenoma cell population (mean percentage: 8.72%). The statistical differences between functioning and silent adenomas were highly significant ($p=0.001$).
Conclusion: Gal-3 is highly expressed in functioning corticotroph adenomas whereas, the substantial majority of silent adenomas are negative for Gal-3. These observations indicate that Gal-3 may serve as a useful marker in distinguishing silent corticotroph adenomas of the pituitary gland.

220 CORRELATION OF HISTOPATHOLOGY USING THE PASS SYSTEM AND PROLIFERATIVE INDEX IN PHEOCHROMOCYTOMAS AND APPLICATION TO EXTRA-ADRENAL PARAGANGLIOMAS
David Wu; Elizabeth A. Bundock; Vânia Nosé, Brigham and Women`s Hospital, Boston, MA, United States
Background: Adrenal pheochromocytomas are challenging lesions to morphologically classify into those with likely malignant versus benign clinical behavior in a prospective fashion. A scoring system, designated Pheochromocytoma Adrenal Scaled Score, PASS, was recently proposed to aid in this categorization effort. Thus far, no validation studies have been performed assessing the robustness of this system, especially in correlating morphological parameters with tumor proliferative index, as assessed by MIB-1/Ki-67 staining, which has been most consistently correlated with malignancy in independent studies. In the original report, staining for MIB-1 was remarkably variable, ranging from 0-52% of nuclei, and did not correlate with adverse clinical outcome. We sought to further compare MIB-1 staining versus PASS scores in a cohort of adrenal pheochromocytomas using a tissue microarray platform in consideration of this proposed scoring system. In addition, we evaluated the application of this scoring system to extra-adrenal paragangliomas, as these lesions likely result from similar underlying pathobiological mechanisms.
Design: Sixty-six adrenal pheochromocytomas and 61 extra-adrenal paragangliomas from patients of 42.6±17.4 years mean age (44% male) were retrieved from the archive files of the Departments of Pathology of Brigham and Women's Hospital and Children's Hospital, Boston, MA from the period of 1981 to 2005, and included primary and recurrent/metastatic lesions in both syndromic and sporadic patients. A representative slide of each case was reviewed to score PASS, with three representative areas selected for tissue-microarray analysis. MIB-1 staining intensity was subsequently categorized as high, moderate, weak, or none and the number of nuclei stained per unit area was quantified. The number of MIB-1 staining nuclei was then correlated with PASS score as a function of staining intensity.
Results: Our data reveal all adrenal pheochromocytomas studied had a PASS score greater than 4, suggesting potential biologically aggressive behavior, according to the proposed scoring system. Of note, there was a broad range of PASS scores for which there was weak to no MIB-1 staining, including cases with high PASS scores. In contrast, several cases with lower PASS scores showed relatively increased MIB-1 staining. Extension and application of the PASS to extra-adrenal paragangliomas demonstrated similar variability, showing no- to weak staining in higher PASS score cases and increased staining in some lower PASS scores.
Conclusion: Prospective implementation of the PASS likely results in a high false positive rate with low positive predictive value, as all of our cases were designated as being histologically malignant using PASS. Correlation of PASS with MIB-1 showed significant variability in this cohort, similar to the original findings of the PASS. Taken together, we caution that additional information and insight is needed before widespread adaptation of this scoring method, and suggest that more discriminative parameters, including possibly genetic-molecular markers, be considered for optimal stratification of benign versus malignant potential.

Environmental

221 ALTERATIONS OF CELL CYCLE REGULATORS IN CONVENTIONAL RENAL-CELL CARCINOMAS AFTER THE CHERNOBYL ACCIDENT. COMPARISON WITH SPANISH CASES
Antonio Llombart-Bosch, Department of Pathology, Medical School, University of Valencia, Valencia, Spain; *Alina Romanenko,* Department of Pathology, Academy of Medical Sciences of Ukraine, Kiev, Ukraine; *Luisa Morell-Quadreny,* Department of Pathology, Medical School, University of Valencia, Valencia, Spain; *José Antonio López-Guerrero,* Unit of Molecular Biology. Fundación Instituto Valenciano de Oncología, Valencia, Spain; *David Ramos,* Department of Pathology, University of Valencia, Valencia, Spain; *Alexander Vozianov,* Department of Urology, Academy of Medical Sciences of Ukraine, Kiev, Ukraine
Background: There is hypothesized evidence that chronic long-term, low-dose ionising radiation (IR) effects cell cycle regulatory molecules and influences renal-cell carcinogenesis.
Design: The aim of our study was to assess by immunohistochemistry (IHC), using a tissue microarray technique, p53, mdm2, p21WAF1/CIP1, p16INK4a, p14ARF and Ki-67 protein expression in 78 conventional renal cell carcinomas (cRCCs) from Ukrainian patients with different degrees of radiation exposure after the Chernobyl accident, in comparison with analogue Spanish tumors.
Results: Highly significant differences between the Ukrainian and Spanish groups were found in the elevated levels of p53, Ki-67, p21WAF1/CIP1, cyclin D1 and especially p14ARF expression with no relationships with tumor stage or nuclear grade.
Conclusion: Our present findings suggest that chronic long-term, low-dose IR exposure leads to activation and alteration of both p53/mdm2/ p21WAF1/CIP1 protein expression as well as p16INK4a/p14ARF locus proteins which could lead to disruptions and loss of cell cycle checkpoints and, thereby, to enhanced tumor progression and aggressivity.

222 CANCER: AN EMERGING HEALTH PROBLEM IN NORTH CENTRAL NIGERIA
Barnabas Mafala Mandong, Jos University Teaching Hospital, Jos, Nigeria
Background: Cancer as non-communicable disease is now emerging as a major public health problem in the tropics competing with infections like tuberclosis, malaria, HIV and others. There are no complete data on cancer statistics in most developing countries of the tropics.
Design: A retrospective review of cancer daignoses from the cancer registry of regional histopathology laboratory collected over twenty years [1985-2004] at Jos University teaching hospital, Jos.
Results: There were a total of 5606 cancers diagnosed between 1985 and 2004. This figure represents 14.6% of all diagnosed specimens within the same period. There were 3503 cases of cancer in females and 2103 in males giving a 1:0.6 ratio. Contributary factors to high mortality were poverty,with most people living below a dollar per day, and a high cost of screening for cancers,for example that of cervical cancer is between $100-$150.
Conclusion: Cancer which was believed to be rare in north central Nigeria is now a major public health problem competing with infectious diseases.

223 TOXIC ELEMENTS, ENVIRONMENTAL EXPOSURE IN CEARA, BRAZIL
Dary Oliveira, Federal University of Ceara, Fortaleza, Brazil
Background: Introduction of the industrial process of development exposes populations to toxic elements and this will be progressively an important public health problem. Aims of this study are to identify the presence of environmental toxic elements: Al (Aluminum), As (Arsenic), Be (Beryllium), Cd (Cadmium), Hg (Mercury) and Pb (Lead) in a population from Ceara, a northeastern state of Brazil.
Design: Methods include coupled mass spectrometry (ICP-MS) used for the determination of toxic elements in scalp hair samples from a population group (N=2000) over 30 years old and under 80 years. The reference intervals for normal parameters were calculated by Miekeley et al, PUC-Rio, 1998.
Results: Results were considered as toxic levels when more than two standard deviations above mean in parts per million (ppm). Al was found in 38 per cent of the patients, 27 per cent presented Pb, 22 per cent revealed Hg, 11 per cent presented Cd, in 5 per cent we detected As and Be was present in 4 per cent of the patients investigated.
Conclusion: This study reveals that the environmental exposure of toxic elements may be more than we could imagine in the general population. The health effects of such chronic, high level exposures are unknown and the influence of this in other disease raises good questions for further study.

224 PATHOLOGICAL STUDIES OF ALL HUMAN AUTOPSY CASES CONCERNED WITH MINAMATA DISEASE IN JAPAN COMPARED WITH THOSE OF OTHER COUNTRIES UNTIL 2005
Akira Yasutake, National Institute for Minamata Disease, Minamata, Japan; *Hitoshi Takahashi; Akiyoshi Kakita,* Brain Research Institute, Niigata University, Niigata, Japan; *Masumi Sawada,* National Institute for Minamata Disease, Minamata, Kumamoto, Japan; *Hidehiro Tokunaga,* Kumamoto University School of Medicine Kumamoto, Kumamoto, Japan
Background: Minamata disease (MD), a classic example of pollution-related health damage in Japan, was first discovered in 1956 around Minamata Bay in Kumamoto

Prefecture, and again in 1965, in the Agano River basin of Niigata Prefecture.
Design: The autopsy cases concerned with MD are stored in Kumamoto University (KU) School of Medicine and Brain Research Institute and Niigata University (NU), numbering 450 and 30 case, respectively. These cases were again reexamined at the National Institute for MD.
Results: There are four types of pathological changes in the KU cases: 1) acute adult cases, 2) chronic adult cases, 3) infantile cases, and 4) fetal cases. There are three types of NU cases but no fetal cases. Acute cases showed severe damage to the central nervous system, but the peripheral sensory nerves were not observed in detail. Chronic adult cases showed mild lesions of both the central nervous system and the peripheral sensory nerves. Infantile cases displayed the most severe lesions not only in the central nervous system (spongy state), but also in the peripheral sensory nerves. Hypoplasia was characteristic in the central nervous system of fetal cases, while the peripheral nerves showed only mild lesions. Mercury histochemistry revealed the levels of inorganic mercury in the tissues of autopsy cases to be around 0.2 ppm.
Conclusions: Autopsy cases have been reported around the world, from pharmaceutical methylmercury (MeHg) poisoning in England, to MeHg-contaminated bread in Iraq, to pigs poisoned by MeHg in New Mexico (U.S.A.). Though the autopsy cases outside of Japan showed no lesions of peripheral sensory nerves, the characteristic lesions of central nervous system were still present. This discrepancy may possibly arise due to variance in the duration of MeHg-contaminated fish or shellfish intake and also the dose of MeHg. It should also be noted that the peripheral sensory nerves of MD patients showed regeneration over a long time following the injuries. Sensory disturbance in MD patients is one important characteristic symptom, and both the central and peripheral nervous system show signs of damage. It is thus important to clinically confirm the sensory disturbance in patients with MeHg poisoning from fish or shellfish through lesions of the central nervous system.

Experimental Pathology

225 HISTOPATHOLOGICAL INJURY IN THE HEART, INTESTINE AND KIDNEY ASSOCIATED WITH 18%, 21% AND 100% OXYGEN IN THE RESUSCITATION OF HYPOXIC NEWBORN PIGLETS

Yann Brierley, University of Alberta Hospital, Edmonton, AB, Canada

Background: Controversy exists over the optimal oxygen concentration to administer in the resuscitation of hypoxic newborns. Using a hypoxic newborn animal model, our goal was to elucidate the optimal oxygen concentration to be administered during resuscitation, which best minimizes oxygen-derived free radical injury to individual organs.
Design: Newborn piglets (1-3 days old, 1.7-2.5 kg) were anesthetized and instrumented for continuous monitoring. After 2 h of normocapnic alveolar hypoxia with 15% oxygen, piglets were block-randomized to receive 1 h of reoxygenation with 18%, 21%, or 100% oxygen (n=6 per group), followed by 2 h at 21% oxygen. A sham, non-oxygen deprived, group receiving 21% oxygen was also included (n=5). Four days after the initial hypoxic-reoxygenation event, tissue samples of left ventricle, small intestine and right kidney were obtained for histological examination from all four groups. The histologic tissues were independently assessed by two pathologists, who were blinded to the group assignment. Established grading criteria were utilized to stratify the degree of reoxygenation-induced tissue damage.
Results: Hypoxic piglets showed moderate hypoxemia (PaO_2 27-33 mmHg), mild metabolic acidosis (pH 7.20-7.24), tachycardia and hypotension (44-50 mmHg) compared to the sham piglets ($p<0.05$, ANOVA). Fourteen of the 18 hypoxic-reoxygenated piglets survived. One piglet died of cardiopulmonary arrest in the 18% reoxygenated group. Three piglets died (1 in the 21% and 2 in the 100% reoxygenated group) secondary to severe necrotizing enterocolitis, which occurred over 1 to 3 days following the hypoxia-reoxygenation event. Those hypoxic piglets resuscitated with 100% oxygen showed the most cardiac reoxygenation-induced injury, in the form of marked architectural disruption and overt myocardial necrosis. Myocardial injury in the 100% reoxygenated group was worse than that observed in the sham ($p<0.05$), the 18% ($p<0.05$), and the 21% ($p=0.21$) reoxygenated groups (myocardial necrosis in 75%, 0%, 0% and 20% of 100%, sham, 18% and 21% groups, respectively, $p<0.05$, Chi Square test). No statistically significant difference was found in the degree of tissue injury to the small intestines (including the severe necrotizing enterocolitis associated deaths) and kidneys in the sham or in any of the hypoxic-reoxygenated groups.
Conclusion: Among the organs assessed histologically for evidence of reoxygenation damage following a period of moderate normocapnic hypoxia, the heart was the organ most affected. Myocardial injury was most striking in the 100% reoxygenated group. Therefore, our results indicate that resuscitation with 100% oxygen, in the setting of neonatal hypoxia, appears sub-optimal as the first line therapy, given the degree of myocardial injury observed.

226 ONTARIO TUMOUR BANK INITIATIVE AT HAMILTON HEALTH SCIENCES AND THE JURAVINSKI CANCER CENTRE

Leela Elavathil, Hamilton Health Sciences, Hamilton, ON, Canada; *Nanci Howatt; Hal Hirte; Gurmit Singh*, Juravinski Cancer Centre, Hamilton, ON, Canada; *Brent Zanke,* Cancer Care Ontario, Toronto, ON, Canada; *Sugy Kodeeswaran,* Ontario Cancer Research Network, Toronto, ON, Canada; *Amrita Mishra; Alice Lytwyn,* Hamilton Health Sciences, Hamilton, ON Canada

Background: The Ontario Cancer Research Network (OCRN) is a program of the Ontario Institute for Cancer Research (OICR). OICR is a not-for-profit organization mandated to support research in developing and testing new cancer therapies. Funding for OICR comes from the Government of Ontario. The Ontario Tumour Bank (OTB) was initiated in September 2004 as a collaborative initiative between the OCRN and 5 leading Ontario healthcare institutions. The OTB is a repository of neoplastic tumour tissue, peripheral blood, and associated clinical information. The contents of the OTB are accessible by academic and industry researchers for translational research focusing on development of diagnostic tools and novel drug therapies. Hamilton Health Sciences (HHS) joined the OTB consortium in February 2005. We report our experience with the program and the results to date.
Design: Representatives from Anatomical Pathology, Surgery, and Nursing formed the local HHS management committee. OCRN provided funding for capital equipment purchases and salary support for a Clinical Research Coordinator (CRC) and Pathologists' Assistant (PA). Operating costs are recovered from OCRN funding per banked specimen. Anatomical Pathology supervises the tissue and data collection. The CRC reviews the pre-operative list of patients from participating surgeons, and obtains consent and a blood sample in the pre-operative clinic. The CRC reviews the patient chart and completes the OTB clinical data collection forms. On the day of surgery, the PA informs the operating room (OR) of consenting patients, and the OR pages the PA when the tissue is resected. The PA has been trained by the pathologist to collect representative fresh tumour tissue, and to request pathologist assistance when needed. Tissue is placed into 2 ml cryovials and frozen in liquid nitrogen within 30 minutes of devitalization. When available, normal adjacent tissue is also sampled. Two formalin fixed paraffin embedded blocks are made for each case. Tissue is not collected if it may compromise pathology assessment. Representative tissue is tested at a central laboratory for DNA and RNA integrity.
Results: Since the inception of OTB, the HHS site has contributed tissue samples, blood and clinical information from 406 (26.2%) of the 1551 consented donors. The top three tumour sites in the OTB are gynecological, lung and breast. Seventy seven percent (312/406) of tumours from HHS are gynecological cancers, breast cancers and central nervous system tumors. The mean size of tumour sample in OTB is 250 mg. Quality assurance testing has shown that RNA quality from tissue samples, and the DNA quality from buffy coat blood samples, is very good or acceptable in 83% and 85%, respectively. The website for the OTB was launched in March 2006 (www. ontariotumourbank. ca) with an ongoing call for proposals.
Conclusion: OTB has successfully completed 18 months of tissue and data collection. HHS has substantially contributed to the provincial totals. Surgeons, pathologists and basic scientists at HHS have come together in support of this valuable resource. Opportunities for collaboration and pathology involvement in translation research have increased.

227 RAPAMYCIN INHIBITS THE SPONTANEOUS FORMATION OF DE NOVO CANCER IN P53 KNOCKOUT MICE

Andreas Gaumann; Gudrun Koehl; Anna Hoehn; Manuela Kovacs; Hans Schlitt; Edward Geissler, University of Regensburg, Regensburg, Germany

Background: Cancer is a major problem in transplant recipients. Recent data suggest that immunosuppressive drugs like rapamycin (RAPA), or possibly mycophenolate mofetil (MMF), may be capable of reducing the growth of existing tumors. However, little experimental data exists regarding cancer prevention. Here we tested the effects of long-term RAPA, MMF or cyclosporine (CsA) use on spontaneous tumor formation in p53 knock-out (KO) mice.
Design: p53 KO mice received either no treatment, or were treated with RAPA, MMF or CsA at therapeutic levels starting on week 10 after birth. Drugs were fed via custom-made mouse-chow formulations to attain typical immunosuppressive doses. Mice were monitored daily and were sacrificed when clinical signs of disease occurred. The experimental endpoint was at week 28. Tissues from major organs and masses were taken for histologic analysis. Immunohistochemistry confirmed the diagnosis of lymphomas and sarcomas.
Results: All (9/9) untreated mice developed clinically evident tumors by week 28 (mean: 19.7±5.3), as confirmed by histology (6 lymphomas, 3 sarcomas). All CsA-treated mice (9/9) also developed clinical tumors by week 28 (mean: 20.2±5.3; 8 lymphomas, 1 sarcoma). With MMF treatment, 7/10 mice showed clinical evidence of tumor by week 28 (mean: 18.4±3.7; 3 lymphomas, 4 sarcomas), however, histology of the lymphatic organs revealed that the remaining 3 mice had subclinical cancer (3 lymphomas). In contrast, RAPA treatment resulted in only 3 clinically evident tumors before the experimental endpoint (week 12, 18, 26; all lymphomas), with histology revealing subclinical lymphomas in 3 additional mice, but no evidence of tumor in any of the major organs in 4 animals. Log-rank analysis shows a significant decrease in cancer occurrence in the RAPA group ($P=0.02$ vs. controls); tumor occurrence was not significantly altered in either the CsA or MMF groups.
Conclusions: Our results show that de novo development of cancer is reduced in p53 KO mice under RAPA immunosuppression. Although MMF may reduce de novo tumors appearance slightly, the effect is not significant, and CsA does not affect de novo tumor development in this model. These results are the first to show spontaneous cancers in mice arising from p53-mutations can be reduced by RAPA immunosuppression.

228 HLB BLOOD TEST TO EVALUATE THE OXIDATIVE STRESS IN CRONIC DISEASE

Dary Oliveira, Federal University of Ceara, Fortaleza, Brazil

Background: Pathology caused by, associated with or adjunctive to, reactive oxygen species (ROS) plays a role in virtually all disease states and metabolic dysfunctions. Biochemical interactions of these species cause particular "biological markers" which leave characteristic patterns in blood, observed by microscopy.
Design: The aim of this study is to identify the correlation of HLB Blood test (for Heitan-LaGarde-Bradford) and other biochemical parameters. Methods include a review of 1000 patients who had a HLB Blood test performed according Bradford Research Institute, admitted to Pathology Institute of Ceara, between 1998 and 2003. A drop of capillary blood was expressed from the tip of the finger and transferred to a glass slide in a series of drops to produce a desired diminishing thickness. The typical morphological stages are shown in the microphotographs (eclipse E-400, Y-Fl-Epi-Fluorescence attachment).
Results: Results revealed good correlation between the HLB test in 82 per cent of cancer