

Henry Ford Health System Publication List May 2008

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Behavioral Services

Ketterer, M. W., W. Knysz, et al. (2008). "Cardiovascular symptoms in coronary-artery disease patients are strongly correlated with emotional distress." *Psychosomatics* **49**(3): 230-4. [Article Request Form/Click for Article Request Form](#)

Department of Behavioral Health and the Heart and Vascular Institute, Henry Ford Hospital, Detroit MI 48202 USA. MarkWKetterer@cs.com

BACKGROUND: The relationship of cardiovascular events and cardiovascular symptoms is unclear, and physical symptoms, including most cardiovascular symptoms, are known to be influenced by emotional distress. **OBJECTIVE:** Authors examined the relative strength of association of multiple measures of emotional distress and accepted cardiac risk factors with five common cardiac symptoms (chest pain, fatigue, palpitations, presyncope, and dyspnea). **METHOD:** The authors tested the association of multiple cardiovascular symptoms with various measures of emotional distress (i.e., the scales of the Symptom Checklist-90-Revised) and the putative risk factors for disease status in 109 patients with documented coronary artery disease. **RESULTS:** Measures of emotional distress were stronger correlates of patient-rated distress due to the symptoms than were traditional risk factors. **CONCLUSION:** Treatment of emotional distress may be a viable strategy for symptom-control in cardiovascular disease.

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Bone & Joint Center

Tchernenko, V., M. Radlinska, et al. (2008). "DNA bending in transcription initiation." *Biochemistry* **47**(7): 1885-95. [Article Request Form/Click for Article Request Form](#)

Molecular Biology Section, Bone and Joint Center, Henry Ford Hospital, Detroit, Michigan 48202, USA.

Electrophoretic mobility shift (bandshift) phasing analysis and rotational variant topological analysis were performed on initiation complexes formed on the bacteriophage lambda PR promoter. Both the open complex and an abortive complex containing a short RNA primer extending to +3 were characterized. The two methods were used to analyze a series of constructs containing tandemly repeated copies of the PR promoter, with the repeat length increased in single base pair increments to progressively change the rotational setting of adjacent copies. The phasing effect observed in bandshift analysis of open complexes formed on this set of constructs provided qualitative evidence for the presence of a bend. Subsequent rotational variant topological analysis confirmed this and quantified the overall bend angle in the open complex as well as in the +3 abortive complex: a bend of 49 degrees +/- 7 degrees was measured for the open complex, while a bend of 47 degrees +/- 11 degrees was measured for the +3 complex, i.e., the two bends are the same. However, the topological results are not consistent with extensive superhelical wrapping of DNA on either complex as has been proposed. The two complexes do differ in the size of the transcription bubble: the open complex contains a 10.4 +/- 0.1 bp bubble, while that of the +3 complex is 12.2 +/- 0.1 bp, a

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result consistent with "DNA scrunching" during the onset of transcription. A model for the overall path of the DNA in the open complex is presented that is consistent with the measured bend angle. Measurement of both bubble size and overall bend angle complements the results of crystal structures in providing an enhanced description of the solution structures of the intact initiation complexes.

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Bone & Joint Center

Yang, M., B. Zhang, et al. (2008). "Contrasting expression of membrane metalloproteinases, MT1-MMP and MT3-MMP, suggests distinct functions in skeletal development." *Cell Tissue Res.* [PDF Full Text](#)

Bone and Joint Center, Henry Ford Hospital, Detroit, MI, 48202, USA.

Membrane-type 1 matrix metalloproteinase (MT1-MMP) is the most ubiquitous and widely studied of the membrane-type metalloproteinases (MT-MMPs). It was thus surprising to find no published data on chicken MT1-MMP. We report here the characterization of the chicken gene. Its low sequence identity with the MT1-MMP genes of other species, high GC content, and divergent catalytic domain explains the absence of data and our difficulties in characterizing the gene. The absence of structural features in the chicken gene that have been suggested to be critical for the activation of MMP-2 by MT1-MMP; for the effect of MT1-MMP on cell migration and for the recycling of MT1-MMP suggest these features are either not essential or that MT1-MMP does not perform these functions in chickens. Comparison of the expression of chicken MT1-MMP with MT3-MMP and with MMP-2 and MMP-13 has confirmed the previously recognized co-expression of MT1-MMP with MMP-2 and MMP-13 in fibrous and vascular tissues, particularly those surrounding the developing long bones in other species. By contrast, MT3-MMP expression differs markedly from that of MT1-MMP and of both MMP-2 and MMP-13. MT3-MMP is expressed by chondrocytes of the developing articular surface. Similar expression patterns of this group of MT-MMPs and MMPs have been observed in mouse embryos and suggest distinct and specific functions for MT1-MMP and MT3-MMP in skeletal development.

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Bone & Joint Center

Yeni, Y. N., E. A. Zelman, et al. (2008). "Trabecular shear stress amplification and variability in human vertebral cancellous bone: relationship with age, gender, spine level and trabecular architecture." *Bone* **42**(3): 591-6. [PDF Full Text](#)

Bone and Joint Center, Henry Ford Hospital, Detroit, MI, USA. yeni@bjc.hfh.edu

Trabecular shear stress magnitude and variability have been implicated in damage formation and reduced bone strength associated with bone loss for human vertebral bone. This study addresses the issue of whether these parameters change with age, gender or anatomical location, and if so whether this is independent of bone mass. Additionally, 3D-stereology-based architectural parameters were examined in order to establish the relationship between stress distribution parameters and trabecular architecture. Eighty cancellous bone specimens were cored from the anterior region of thoracic 12 and donor-matched lumbar 1 vertebrae from a randomly selected population of 40 cadavers. The specimens were scanned at 21-microm voxel size using microcomputed tomography (microCT) and reconstructed at 50microm. Bone volume fraction (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), bone surface-to-volume ratio (BS/BV), degree of anisotropy (MIL1/MIL3), and connectivity density (-#Euler/Vol) were calculated directly from micro-CT images. Large-scale finite element models were constructed and superior-inferior compressive loading was simulated. Apparent cancellous modulus (EFEM) was calculated. The average trabecular von Mises stress generated per uniaxial apparent stress ($\sigma(-)VM / \sigma_{app}$) and coefficient of variation of trabecular von Mises stresses (COV) were calculated as measures of the magnitude and variability of shear stresses in the trabeculae. Mixed-models and regression were used for analysis. $\sigma(-)VM / \sigma_{app}$ and COV were not different between genders and vertebrae. Both $\sigma(-)VM / \sigma_{app}$ and COV increased with age accompanied by a decrease in BV/TV. Strong relationship of $\sigma(-)VM / \sigma_{app}$ with BV/TV was found whereas COV was strongly related to EFEM/(BV/TV). The results from T12 and L1 were not different and highly correlated with each other. The relationship of $\sigma(-)VM / \sigma_{app}$ with COV was observed to be different between males and females. This difference could not be explained by architectural parameters considered in this study. Our results support the relevance of trabecular shear stress amplification and variability in age-related vertebral bone fragility. The relationships

found are expected to help understand the micro-mechanisms by which cancellous bone mass and mechanical properties are modulated through a collection of local stress parameters.

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Bone & Joint Center

Yerramshetty, J. S. and O. Akkus (2008). "The associations between mineral crystallinity and the mechanical properties of human cortical bone." *Bone* **42**(3): 476-82. [PDF Full Text](#)

Bone and Joint Center, Henry Ford Health System, Detroit, MI, USA.

It is well known that the amount of mineralization renders bone its stiffness. However, besides the mere amount of the mineral phase, size and shape of carbonated apatite crystals are postulated to affect the mechanical properties of bone tissue as predicted by composite mechanics models. Despite this predictive evidence, there is little experimental insight on the relation between the characteristics of mineral crystals and hard tissue mechanics. In this study, Raman spectroscopy was used to provide information on the crystallinity of bone's mineral phase, a parameter which is an overall indicator of mineral crystal size and stoichiometric perfection. Raman scans and mechanical tests (monotonic and fatigue; n=64 each) were performed on the anterior, medial, lateral and posterior quadrant sections of 16 human cadaveric femurs (52 y.o.-85 y.o.). The reported coefficient of determination values (R²) were adjusted for the effects of age to bring out the unbiased contribution of crystallinity. Crystallinity was able to explain 6.7% to 48.3% of the variation in monotonic mechanical properties. Results indicated that the tissue-level strength and stiffness increased with increasing crystallinity while the ductility reduced. Crystallinity explained 11.3% to 63.5% of the variation in fatigue properties. Moduli of specimens with greater crystallinity degraded at a slower rate and, also, they had longer fatigue lives. However, not every anatomical quadrant displayed these relationships. In conclusion, these results acknowledge crystal properties as an important bone quality factor and raise the possibility that aberrations in these properties may contribute to senile osteoporotic fractures.

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Cardiology

Brawner, C. A., J. K. Ehrman, et al. (2008). "Quality assurance and cardiopulmonary exercise testing in clinical trials." *J Card Fail* **14**(4): 283-9. **Article Request Form/Click for Article Request Form**

Division of Cardiovascular Medicine, Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA.

BACKGROUND: Peak oxygen uptake (VO₂) measured during cardiopulmonary exercise testing (CPX) is often used as an outcome measure in clinical trials. The purposes of this study are (a) to report the outcomes of a quality assurance (QA) procedure instituted in multisite clinical trials by a CPX data core laboratory and (b) to report a normative VO₂ reference dataset for future use. **METHODS:** The CPX laboratory at each site participating in a multisite clinical trial in which Henry Ford Hospital served as the CPX data core laboratory was required to pass a standardized QA procedure before site activation and regularly thereafter. Data were compared with a VO₂ reference dataset (pilot data) and assessed for test-retest reproducibility. VO₂ data that represented a normal physiologic response were used to develop a final normative VO₂ reference dataset. **RESULTS:** Between 2003 and 2006, 81 laboratories submitted 144 baseline QA tests. Of these, 34% did not initially meet the passing criteria, largely because of poor test-retest reproducibility. Among all QA tests submitted to the core laboratory, 159 unique volunteers had exercise data that met the criteria to be entered into the final normative VO₂ reference dataset. Within this dataset, the mean coefficient of variation for VO₂ between the test and retest was 5.1%. **CONCLUSION:** A standardized QA procedure can be used to identify aberrant data and minimize the variability of VO₂ measured in a clinical trial or the routine evaluation of patients.

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Cardiology

Srivastava, A. V., K. Ananthasubramaniam, et al. (2008). "Prognostic implications of negative dobutamine stress echocardiography in African Americans compared to Caucasians." *Cardiovasc Ultrasound* **6**: 20. [PDF Full Text](#)

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BACKGROUND: African Americans (AA) have higher rates of cardiovascular morbidity and mortality than Caucasians (CA). Despite its excellent negative predictive value, the influence of race on the prognostic implications of negative dobutamine echocardiography in predicting major cardiac problems is largely unknown. METHODS: We studied 387 AA and 340 CA patients with negative dobutamine stress echocardiography (NDSE). Kaplan-Meier survival analysis was used to create freedom-from-event curves for major adverse cardiac events over a 36-month period, and a Cox proportional-hazards multivariable model to examine the influence of race on cardiac outcomes. RESULTS: AA patients were younger (69.4 +/- 12.6 vs. 74.2 +/- 10.7, $p < .001$), had higher incidence of diabetes mellitus (37% vs. 29%, $p = .01$), hypertension (91% vs. 85%, $p = .006$), left ventricular hypertrophy (70% vs. 49%, $p < .001$) and lower incidence of prior coronary artery disease (27% vs. 34%, $p = .05$) compared to CA patients. Ejection fraction $\geq 50\%$ was comparable (81% vs. 82%, $p = .8$). At 3-years, AA patients had a lower freedom from nonfatal myocardial infarction (92% vs. 96%, $p = .006$) and any cardiac event (cardiac death, myocardial infarction) (91% vs. 95%, $p = .005$) compared to CA patients. CONCLUSION: This is the first study to demonstrate that AA patients have higher rates of nonfatal MI and MACE compared to CA patients with a NDSE. These patients require closer follow-up and aggressive preventive and treatment strategies should be employed to help reduce cardiovascular morbidity and mortality despite negative ischemic workup.

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Cardiology

Tita, C., V. Karthikeyan, et al. (2008). "Stress echocardiography for risk stratification in patients with end-stage renal disease undergoing renal transplantation." *J Am Soc Echocardiogr* **21**(4): 321-6. **Article Request Form/Click for Article Request Form**

Heart and Vascular Institute, Henry Ford Hospital, Detroit, Michigan 48202, USA.

BACKGROUND: The predictive accuracy of stress echocardiography (SE) for adverse cardiac events has been variable in the population with end-stage renal disease undergoing renal transplantation (RT). METHODS: We performed a retrospective study of 149 patients who had pretransplant SE before RT between 1997 and 2003. Patients were followed up for a mean of 2.85 years for major adverse cardiovascular events (MACE). RESULTS: Of 149 patients studied, 139 had a negative SE, 65% were African American; 12 underwent cardiac catheterization. Only 1 patient required pre-RT revascularization. Sixteen MACE occurred over the follow-up period. SE had 37.5% sensitivity, 95.3% specificity, 33.3% positive predictive value, and 96.1% negative predictive value for MACE in the first year post-RT. First-year posttransplant event rates were 4.0% versus 30% ($P < .001$) for patients with a negative SE and positive SE, respectively. Multivariate predictors of MACE were positive SE (hazard ratio [HR] 7.64), hemoglobin less than 11 g/dL post-RT (HR 4.44), and calcium channel blocker use posttransplant (HR 2.90). CONCLUSIONS: A negative SE has low incidence of MACE in this intermediate- to high-risk patient subset. A positive SE predicts a sevenfold higher risk of cardiovascular events regardless of the need for revascularization before the transplant.

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Dermatology

Hexsel, C. L., S. D. Bangert, et al. (2008). "Current sunscreen issues: 2007 Food and Drug Administration sunscreen labelling recommendations and combination sunscreen/insect repellent products." *J Am Acad Dermatol*. **Article Request Form/Click for Article Request Form**

Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.

The Food and Drug Administration (FDA) regulates sunscreens as over-the-counter drugs. This article describes sunscreen actives available in the United States, new developments available elsewhere, and the amendment to the FDA 1999 sunscreen monograph, released on August 27, 2007, which proposes a new grading system for ultraviolet B protection, a cap of the sunburn protection factor to 50+, and a 4-star grading of ultraviolet A protection. In addition, current data on combination sunscreen and insect repellent products are discussed. Application of a combination product too frequently poses the risk of insect repellent toxicity, whereas application too infrequently invites photodamage. It may be prudent to follow the same approach of our Canadian colleagues of discontinuing combination products until more investigations are available.

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Dermatology

Mahmoud, B. H., C. L. Hexsel, et al. (2008). "Effects of visible light on the skin." *Photochem Photobiol* **84**(2): 450-62. **Article Request Form/Click for Article Request Form**

Multicultural Dermatology Center, Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA.

Electromagnetic radiation has vast and diverse effects on human skin. Although photobiologic studies of sunlight date back to Sir Isaac Newton in 1671, most available studies focus on the UV radiation part of the spectrum. The effects of visible light and infrared radiation have not been, until recently, clearly elucidated. The goal of this review is to highlight the effects of visible light on the skin. As a result of advances in the understanding of skin optics, and comprehensive studies regarding the absorption spectrum of endogenous and exogenous skin chromophores, various biologic effects have been shown to be exerted by visible light radiation including erythema, pigmentation, thermal damage and free radical production. It has also been shown that visible light can induce indirect DNA damage through the generation of reactive oxygen species. Furthermore, a number of photodermatoses have an action spectrum in the visible light range, even though most of the currently available sunscreens offer, if any, weak protection against visible light. Conversely, because of its cutaneous biologic effects, visible light is used for the treatment of a variety of skin diseases and esthetic conditions in the form of lasers, intense pulsed light and photodynamic therapy.

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Diagnostic Radiology

Babajani-Feremi, A., H. Soltanian-Zadeh, et al. (2008). "Integrated MEG/fMRI Model Validated Using Real Auditory Data." *Brain Topogr.* **Article Request Form/Click for Article Request Form**

Image Analysis Laboratory, Radiology Department, Henry Ford Hospital, One Ford Place, 2F, Detroit, MI, 48202, USA, abbasb@rad.hfh.edu.

The main objective of this paper is to present methods and results for the estimation of parameters of our proposed integrated magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) model. We use real auditory MEG and fMRI datasets from 7 normal subjects to estimate the parameters of the model. The MEG and fMRI data were acquired at different times, but the stimulus profile was the same for both techniques. We use independent component analysis (ICA) to extract activation-related signal from the MEG data. The stimulus-correlated ICA component is used to estimate MEG parameters of the model. The temporal and spatial information of the fMRI datasets are used to estimate fMRI parameters of the model. The estimated parameters have reasonable means and standard deviations for all subjects. Goodness of fit of the real data to our model shows the possibility of using the proposed model to simulate realistic datasets for evaluation of integrated MEG/fMRI analysis methods.

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Diagnostic Radiology

Scher, C., J. Craig, et al. (2008). "Bone marrow edema in the knee in osteoarthritis and association with total knee arthroplasty within a three-year follow-up." *Skeletal Radiol* **37**(7): 609-17. **PDF Full Text**

Henry Ford Macomb Hospital, Michigan State University Osteopathic Radiology Residency, Warren Campus, 13355 West Ten Mile Road, Warren, MI, 48089, USA, cscher1@hfhs.org.

OBJECTIVE: The purpose of this study was to determine if a correlation exists between magnetic resonance imaging (MRI) findings of bone marrow edema (BME) in osteoarthritis (OA) of the knee joint and need for total knee arthroplasty (TKA) within a follow-up period of 3 years. **MATERIALS AND METHODS:** The entire database of knee MR studies over a 3-year period was used to select individuals with knee OA. A chart review was conducted to identify and include only those who had a 3-year follow-up appointment from the time of the initial MR study. There were 25 patients in the OA-only group (four men and 21 women; age range, 28-75; average age, 49.3 years). The OA and BME group had 48 patients (23 men and 25 women; average age, 55.5 years). The MRs were reviewed and interpreted by a musculoskeletal radiologist and were classified into one of four patterns of BME: none, focal, global, or cystic pattern. Meniscal tear and degree of cartilage loss were also assessed. **RESULTS:** Subjects who had BME of any pattern type were 8.95 times as likely to progress rapidly to a TKA when

compared to subjects with no BME ($p = 0.016$). Subjects with a global pattern of BME were 5.45 times as likely to have a TKA compared to subjects with focal, cyst, or no BME ($p < 0.05$). Subjects with a global edema pattern were 13.04 times as likely to have a TKA than subjects with no marrow edema in the knee ($p < 0.01$). There was no correlation of TKA with meniscal tear or cartilage loss. The group of subjects who had a TKA were 12.6 years older than those who did not have a TKA ($p < 0.001$). However, the BME results were still significant after accounting for the age difference. **CONCLUSION:** Our classification of patterns into global, focal, cystic, and absence of BME is an attempt to further define edema in osteoarthritis and how it relates to clinical progression. Patients with BME and OA have an increased risk of TKA as opposed to OA and no marrow edema. The BME pattern with the worst prognosis for the knee is the global pattern.

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Emergency Medicine

Rivers, E. P., V. Coba, et al. (2008). "Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature." *Curr Opin Anaesthesiol* **21**(2): 128-40. [PDF Full Text](#)

Department of Emergency Medicine, Henry Ford Health Systems, Detroit, Michigan 48202, USA. erivers1@hfhs.org

PURPOSE OF REVIEW: Aggressive approaches to acute diseases such as acute myocardial infarction, trauma, and stroke have improved outcomes. Early goal-directed therapy for severe sepsis and septic shock represents a similar approach. An analysis of the literature assessing external validity and generalizability of this intervention is lacking. **RECENT FINDINGS:** Eleven peer-reviewed publications (1569 patients) and 28 abstracts (4429 patients) after the original early goal-directed therapy study were identified from academic, community and international settings. These publications total 5998 patients (3042 before and 2956 after early goal-directed therapy). The mean age, sex, APACHE II scores and mortality were similar across all studies. The mean relative and absolute risk reduction was 0.46 +/- 26% and 20.3 +/- 12.7%, respectively. These findings are superior to the original early goal-directed therapy trial which showed figures of 34% and 16%, respectively. A consistent and similar decrease in healthcare resource consumption was also found. **SUMMARY:** Early goal-directed therapy modulates systemic inflammation and results in significant reductions in morbidity, mortality, and healthcare resource consumption. Early goal-directed therapy has been externally validated and is generalizable across multiple healthcare settings. Because of these robust findings, further emphasis should be placed on overcoming logistical, institutional, and professional barriers to implementation which can save the life of one of every six patients presenting with severe sepsis and septic shock.

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Eye Care Services

Mogk, L., G. R. Watson, et al. (2008). "Speaker's corner. A commentary on the Medicare low vision rehabilitation demonstration project." *Journal of Visual Impairment & Blindness* **102**(2): 69-75. [PDF Full Text](#)

Eye Care Services, Henry Ford Health System

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Hematology, Medical Oncology and Josephine Ford Cancer Center

Sandhu, A., T. J. Yates, et al. (2008). "Pulmonary artery sarcoma mimicking a pulmonary embolism." *Indian J Cancer* **45**(1): 27-9. **Article Request Form/Click for Article Request Form**

Department of Hematology/Oncology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, USA. tyates1@hfhs.org.

Sarcomas involving the lung are a rare occurrence, often a result of metastatic disease from primary malignancies involving the skin, liver, breast or heart. Primary pulmonary artery sarcomas are rarer still, with limited cases reported world-wide and consequently data regarding treatment modalities are sparse and largely experimental. These tumors are often mistaken for a pulmonary embolism and seemingly supported by radiological findings. Patients will often present without symptom resolution despite therapeutic anticoagulation. The following case illustrates how a soft tissue sarcoma of the pulmonary artery can mimic a pulmonary embolism, thus, resulting in both a diagnostic and therapeutic dilemma. A positron emission tomography scan was an invaluable tool in this case, showing increased radiotracer uptake and placing neoplasm at the

top of the differential diagnosis. This ultimately led to a biopsy that was vimentin positive, cytokeratin negative and CD117 negative, thus consistent with soft tissue sarcoma.

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Hypertension and Vascular Research

Li, X. C., T. D. Liao, et al. (2008). "Long-term hyperglucagonaemia induces early metabolic and renal phenotypes of Type 2 diabetes in mice." *Clin Sci (Lond)* **114**(9): 591-601. [Article Request Form/Click for Article Request Form](#)

Laboratory of Receptor and Signal Transduction, Division of Hypertension and Vascular Research, Henry Ford Hospital, Detroit, MI 48202, USA.

Clinical studies have shown that patients with early Type 2 diabetes often have elevated serum glucagon rather than insulin deficiency. Imbalance of insulin and glucagon in favouring the latter may contribute to impaired glucose tolerance, persistent hyperglycaemia, microalbuminuria and glomerular injury. In the present study, we tested the hypothesis that long-term glucagon infusion induces early metabolic and renal phenotypes of Type 2 diabetes in mice by activating glucagon receptors. Five groups of adult male C57BL/6J mice were treated with vehicle, glucagon alone (1 microg/h via an osmotic minipump, intraperitoneally), glucagon plus the glucagon receptor antagonist [Des-His(1)-Glu(9)]glucagon (5 microg/h via an osmotic minipump), [Des-His(1)-Glu(9)]glucagon alone or a high glucose load alone (2% glucose in the drinking water) for 4 weeks. Glucagon infusion increased serum glucagon by 129% (P<0.05), raised systolic BP (blood pressure) by 21 mmHg (P<0.01), elevated fasting blood glucose by 42% (P<0.01), impaired glucose tolerance (P<0.01), increased the kidney weight/body weight ratio (P<0.05) and 24 h urinary albumin excretion by 108% (P<0.01) and induced glomerular mesangial expansion and extracellular matrix deposition. These responses were associated with marked increases in phosphorylated ERK1/2 (extracellular-signal-regulated kinase 1/2) and Akt signalling proteins in the liver and kidney (P<0.01). Serum insulin did not increase proportionally. Concurrent administration of [Des-His(1)-Glu(9)]glucagon with glucagon significantly attenuated glucagon-increased BP, fasting blood glucose, kidney weight/body weight ratio and 24 h urinary albumin excretion. [Des-His(1)-Glu(9)]glucagon also improved glucagon-impaired glucose tolerance, increased serum insulin by 56% (P<0.05) and attenuated glomerular injury. However, [Des-His(1)-Glu(9)]glucagon or high glucose administration alone did not elevate fasting blood glucose levels, impair glucose tolerance or induce renal injury. These results demonstrate for the first time that long-term hyperglucagonaemia in mice induces early metabolic and renal phenotypes of Type 2 diabetes by activating glucagon receptors. This supports the idea that glucagon receptor blockade may be beneficial in treating insulin resistance and Type 2 diabetic renal complications.

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Hypertension and Vascular Research

Ren, Y., J. L. Garvin, et al. (2008). "Cross-talk between arterioles and tubules in the kidney." *Pediatr Nephrol*. [Article Request Form/Click for Article Request Form](#)

Division of Hypertension and Vascular Research, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI, 48202, USA, yren1@hfhs.org.

In hypertension the pressure natriuresis set point is shifted to a higher pressure due to an increase in both renal vascular resistance and sodium (Na) reabsorption. The afferent arterioles (Af-Arts) and efferent arterioles (Ef-Arts) account for most renal vascular resistance; they control glomerular filtration rate (GFR) and peritubular pressure, and, consequently, renal function. Af-Art and Ef-Art resistance is regulated by factors similar to those in other arterioles and also by tubuloglomerular feedback (TGF). TGF operates via the macula densa, which senses increases in sodium chloride (NaCl) and sends a signal that constricts the Af-Art and dilates the Ef-Art. In the outer renal cortex, the connecting tubule (CNT) returns to the glomerular hilus and contacts the Af-Art. This morphology is compatible with cross-talk between the CNT and Af-Art, so-called connecting tubule glomerular feedback (CTGF). Our studies show that increasing NaCl delivery to the CNT results in Af-Art dilatation that can be blocked by inhibitors of Na transport. We believe cross-talk between the CNT and Af-Art is a novel mechanism that may contribute to regulation of renal blood flow and GFR.

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Hypertension and Vascular Research

Sharma, U., N. E. Rhaleb, et al. (2008). "Novel anti-inflammatory mechanisms of N-Acetyl-Ser-Asp-Lys-Pro in hypertension-induced target organ damage." *Am J Physiol Heart Circ Physiol* **294**(3): H1226-32. [PDF Full Text](#)

Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, MI 48202, USA.

High blood pressure (HBP) is an important risk factor for cardiac, renal, and vascular dysfunction. Excess inflammation is the major pathogenic mechanism for HBP-induced target organ damage (TOD). N-acetyl-Ser-Asp-Lys-Pro (Ac-SDKP), a tetrapeptide specifically degraded by angiotensin converting enzyme (ACE), reduces inflammation, fibrosis, and TOD induced by HBP. Our hypothesis is that Ac-SDKP exerts its anti-inflammatory effects by inhibiting: 1) differentiation of bone marrow stem cells (BMSC) to macrophages, 2) activation and migration of macrophages, and 3) release of the proinflammatory cytokine TNF-alpha by activated macrophages. BMSC were freshly isolated and cultured in macrophage growth medium. Differentiation of murine BMSC to macrophages was analyzed by flow cytometry using F4/80 as a marker of macrophage maturation. Macrophage migration was measured in a modified Boyden chamber. TNF-alpha release by activated macrophages in culture was measured by ELISA. Myocardial macrophage activation in mice with ANG II-induced hypertension was studied by Western blotting of Mac-2 (galectin-3) protein. Interstitial collagen deposition was measured by picrosirius red staining. We found that Ac-SDKP (10 nM) reduced differentiation of cultured BMSC to mature macrophages by 24.5% [F4/80 positivity: 14.09 +/- 1.06 mean fluorescent intensity for vehicle and 10.63 +/- 0.35 for Ac-SDKP; P < 0.05]. Ac-SDKP also decreased galectin-3 and macrophage colony-stimulating factor-dependent macrophage migration. In addition, Ac-SDKP decreased secretion of TNF-alpha by macrophages stimulated with bacterial LPS. In mice with ANG II-induced hypertension, Ac-SDKP reduced expression of galectin-3, a protein produced by infiltrating macrophages in the myocardium, and interstitial collagen deposition. In conclusion, this study demonstrates that part of the anti-inflammatory effect of Ac-SDKP is due to its direct effect on BMSC and macrophage, inhibiting their differentiation, activation, and cytokine release. These effects explain some of the anti-inflammatory and antifibrotic properties of Ac-SDKP in hypertension.

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Hypertension and Vascular Research

Zhan, E., T. Keimig, et al. (2008). "Dose-Dependent Cardiac Effect of Estrogen Replacement in Mice Post-Myocardial Infarction." *Exp Physiol*. **Article Request Form/Click for Article Request Form**

Henry Ford Hospital.

Hormonal replacement therapy (HRT) has recently been shown to increase the risk of cardiovascular events in women. However, it is not clear whether the adverse effect of HRT is related to dosage and/or the presence of progestin. Using a mouse model of myocardial infarction (MI), we studied the dose-effect of estrogen replacement on mortality and cardiac remodeling and dysfunction post-MI in the absence of progestin. Six-week-old females were subjected to ovariectomy (ovx). A pellet containing a low, moderate or high dose of 17beta-estradiol (E2, 0.42, 4.2, or 18.8 microg/day) or placebo was implanted subcutaneously on the day of ovx. MI was induced 8 weeks later, and cardiac morphology and function were evaluated 8 weeks after MI. We found that E2 at moderate and high doses adversely affected mortality. A low dose of E2 that restored plasma estrogen close to physiological levels had no significant effect on mortality but tended to improve cardiac function and remodeling, associated with reduced fibrosis and increased capillary density. At an increased dose, E2 exacerbated cardiac fibrosis, hypertrophy, dysfunction and dilatation, associated with liver and kidney enlargement and ascites. PKC and ERK1/2 were enhanced by MI but were not affected by E2. In summary, E2 at a low dose tended to be cardioprotective. At increased doses that raised plasma estrogen far beyond the physiological level, E2 was detrimental to the heart. Our data suggest that dosage should be an important consideration when studying the effect of estrogen replacement on the heart.

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Infectious Diseases

Vazquez, J. A. (2007). "Role of posaconazole in the management of oropharyngeal and esophageal candidiasis." *Ther Clin Risk Manag* **3**(4): 533-42. **Article Request Form/Click for Article Request Form**

Division of Infectious Diseases, Henry Ford Hospital, Microbiology and Infectious Disease Translational Research Center, Wayne State University School of Medicine Detroit, MI, USA.

Mucocutaneous candidiasis (MC) is one of the first signs of human immunodeficiency virus (HIV) infection. Over 90% of patients with AIDS will eventually develop oropharyngeal candidiasis (OPC) at some time during their illness, and an additional 10% will develop esophageal candidiasis (EC). Although numerous antifungal agents are available, azoles, both topical (clotrimazole) and systemic (fluconazole, itraconazole), have replaced older topical antifungals (gentian violet and nystatin) in the management of MC in these patients. The systemic azoles, itraconazole and fluconazole, are generally safe and effective agents in HIV-infected patients with MC. A concern in these patients is the clinical relapse, which appears to be dependent on degree of immunosuppression and is more common following clotrimazole and ketoconazole than with fluconazole or itraconazole. Posaconazole is a new extended-spectrum triazole recently approved for the management of OPC. In vitro, posaconazole possesses potent activity against numerous *Candida* species, including strains that are resistant to fluconazole. Recent clinical trials demonstrate that posaconazole is as efficacious as fluconazole in producing a successful clinical response in HIV-infected patients with OPC/EC. In addition, posaconazole was safe and more effective in sustaining clinical success after treatment was discontinued. Posaconazole appears to be an effective alternative in the management of MC in this difficult- to-treat population.

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Infectious Diseases

Vazquez, J. A. (2008). "Clinical Practice: Combination Antifungal Therapy for Mold Infections: Much Ado about Nothing?" *Clin Infect Dis* **46**(12): 1889-901. [PDF Full Text](#)

Division of Infectious Diseases, Henry Ford Hospital, Wayne State University School of Medicine, Detroit, Michigan.

In general, mortality rates associated with systemic fungal infections have not improved much in more than a decade, although the number of antifungal agents available for the treatment of serious fungal infections has increased in the past few years. A possible approach to decreasing mortality rates associated with fungal infections may be to treat patients with combinations of different classes of antifungals. Recently, in vitro and animal studies evaluating different combinations of antifungal agents have demonstrated important synergistic and/or additive activity against many genera of fungi. However, prudence is required, because some antifungal combinations have demonstrated antagonistic activity. Well-controlled clinical trials are still necessary to define the most efficacious antifungal combination. In addition, these clinical trials should evaluate the adverse event profile of the combination regimens, as well as their pharmaco-economic impact.

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Internal Medicine

Alhakeem, M., A. Arabi, et al. (2008). "Unusual sites of metastatic involvement: intracardiac metastasis from laryngeal carcinoma." *Eur J Echocardiogr* **9**(2): 323-5.

Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA.

Cardiac metastatic squamous cell laryngeal carcinoma is rare. We report the case of a 49-year-old man with recurrent squamous laryngeal carcinoma presenting with right leg acute ischaemia and large mobile right and left cardiac masses. The patient has history of laryngeal squamous cell cancer surgically treated with total laryngectomy, thyroidectomy, and tracheostomy 2 years ago. He was admitted to our intensive care unit with acute right leg pain, left sided chest pain, hypotension 92/55, and tachycardia 112 bpm. On physical exam, he had a faint pulse of his right Posterior Tibial artery with a cold foot, but no discoloration. Heart sounds were normal with no murmur. Initial workup showed a Troponin of 0.27. An electrocardiogram showed sinus tachycardia, with inverted T waves in the Infero-lateral leads. Emergent surgical thrombectomy was done on his right leg with restoration of arterial blood flow to the affected limb. An echocardiogram showed a preserved left ventricular function with multiple areas of echogenic masses in all four cardiac chambers located at the annulus of the tricuspid valve, the right ventricular free wall and along the inter-ventricular septum. No intracardiac shunt was detected by contrast study. Computed tomography scan of the heart confirmed the presence of multiple exophytic intracardiac masses within the left atrium, the right ventricle, interventricular septum, and lateral free wall of the left ventricle. Immunohistochemical staining with cytokeratin of the emboli was consistent with malignant squamous cell carcinoma consistent with metastases of his known laryngeal squamous cell cancer.

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Medical Genetics

Gross, S. J., B. A. Pletcher, et al. (2008). "Reply to letter from Michael L. Begleiter." Genet Med. **Article Request Form/Click for Article Request Form**

Albert Einstein College of Medicine, Bronx, New York (Gross) New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey (Pletcher) Henry Ford Hospital, Detroit, Michigan (Monaghan).

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Medical Genetics

Gross, S. J., B. A. Pletcher, et al. (2008). "Response to Levy-Lahad letter." Genet Med. **Article Request Form/Click for Article Request Form**

Albert Einstein College of Medicine, Bronx, New York (Gross) New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey (Pletcher) Henry Ford Hospital, Detroit, Michigan (Monaghan).

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Nephrology

Besarab, A. (2008). "The erythropoietin controversy: Where does iron fit in?" Nephrology News & Issues **22**(3): 4-6. **Article Request Form/Click for Article Request Form**

Department of Nephrology, Henry Ford Hospital

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Neurology

Cerghet, M., D. Tapos, et al. (2008). "Homozygous Myotonic Dystrophy With Craniosynostosis." J Child Neurol. **Article Request Form/Click for Article Request Form**

Departments of Pediatrics and Neurology, Wayne State University, and the Department of Neurology, Henry Ford Hospital, Detroit, Michigan.

Myotonic dystrophy is considered a true dominant condition with no difference in the phenotype between heterozygous and homozygous cases. The homozygous state is very rare and only a few patients have been reported in the literature. We report a 2.5-year-old boy from a nonconsanguineous marriage, with a unique combination of clinical and radiological findings: hypotonia, motor and language developmental delay, ventriculomegaly, subcortical white matter lesions, and craniosynostosis. Mutation analysis revealed 2 copies of expansion mutation of 1260 and 60 cytosine-thymine-guanine repeats in the myotonic dystrophy protein kinase gene. Both the mildly symptomatic (434 repeats) mother and the asymptomatic (37 repeats) father are heterozygous. Craniosynostosis has not been reported previously in myotonic dystrophy. This homozygous case expands the clinical spectrum of myotonic dystrophy type 1 and provides support to the hypothesis that myotonic dystrophy type 1 pathophysiology could be, in part, due to the loss of normal function of the wild-type protein.

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Neurology

Santra, M., S. Santra, et al. (2008). "Ectopic decorin expression up-regulates VEGF expression in mouse cerebral endothelial cells via activation of the transcription factors Sp1, HIF1alpha, and Stat3." J Neurochem **105**(2): 324-37. **PDF Full Text**

Department of Neurology, Henry Ford Hospital, Detroit, Michigan 48202, USA.

We demonstrate that a proteoglycan decorin (DCN) up-regulates the vascular endothelial growth factor (VEGF) expression with activation of VEGF regulating transcription factors Sp1, hypoxia-inducible factor 1alpha (HIF1alpha), and signal transducer and activator of transcription 3 (Stat3) via epidermal growth factor receptor (EGFR), mitogen-activated protein kinase extracellular signal-regulated kinase 1/2 (ERK1/2), and protein kinase B (AKT) pathways in DCN transfected mouse cerebral endothelial (MCE) cells. Treatment with pharmacological inhibitors and small interfering RNAs reveal that induction and activation of Sp1, HIF1alpha, and Stat3 facilitate their nuclear localization and binding to their specific motifs of the VEGF promoter and induce VEGF expression via two independent pathways, DCN/EGFR/phosphoinositide-3 kinase/AKT and DCN/EGFR/ERK1/2, respectively, in DCN synthesizing MCE cells. The cell type specific glycosylation protects Sp1 and HIF1alpha from proteasome degradation and plays an important and novel role in the regulation of VEGF in DCN transfected MCE cells. Induction of gelatinases (matrix metalloproteinase 2 and 9), the serine protease tissue plasminogen activator and plasmin by DCN transfection in MCE cells leads to extracellular proteolysis and to release of matrix-bound VEGF and activation of angiogenesis. In this study, we demonstrate that two independent downstream signal pathways, DCN/EGFR/ERK1/2 and DCN/EGFR/phosphoinositide-3 kinase/AKT, mediate up-regulation and activation of transcription factors of VEGF such as HIF1alpha, Stat3, and Sp1 and increase VEGF transcription and angiogenesis in MCE cells.

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Neurology

Schuh, L., D. E. Burdette, et al. (2008). "Learning Clinical Neurophysiology: Gaming is Better than Lectures." *J Clin Neurophysiol* **25**(3): 167-169. [PDF Full Text](#)

From the Departments of *Neurology and daggerBiostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, Michigan.

We sought to find evidence for generalizability of a game and team oriented educational intervention in clinical neurophysiology in a neurology residency program. A prospective educational intervention was studied in a single neurology residency program and compared with a historical control. Seventeen PGY 2-4 residents studied neurophysiology in 2004-2005. The historical control was 20 PGY 2-4 residents from 1998 to 2002. The neurophysiology educational intervention consisted of weekly presentations, followed by a game show-type oral quiz which was team-based and required all residents to participate. The control group attended faculty-prepared didactic lectures. Outcome measures were percent correct subset neurophysiology Residency Inservice Training Examination scores. United States Medical Licensing Examination step 1 scores were also compared between the groups. Data were analyzed with analysis of variance methods accounting for multiple measurements. The mean +/- standard error neurophysiology subset percent correct Residency Inservice Training Examination score was 63.6 +/- 4.12 for the intervention group and 49.4 +/- 2.35 for the control (P = 0.002). There was no difference in United States Medical Licensing Examination step 1 scores between the two groups (P = 0.11). We found evidence for generalizability of the effectiveness of a team-oriented educational intervention in clinical neurophysiology with gaming and oral quizzing in improving subset Residency Inservice Training Examination performance compared with faculty prepared didactics.

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Neurology

Silver, B., M. Lu, et al. (2008). "Blood pressure declines and less favorable outcomes in the NINDS tPA stroke study." *J Neurol Sci*. [PDF Full Text](#)

Henry Ford Hospital, Detroit, MI, United States.

BACKGROUND AND PURPOSE: Hypertension is the most important modifiable risk factor for secondary stroke prevention but the immediate management of blood pressure after stroke is uncertain. We evaluated outcomes in the NINDS tPA stroke study in relation to blood pressure declines during the first 24 h after randomization. METHODS: Declines in blood pressure compared to baseline and preceding time points were analyzed in relationship to favorable outcomes (by a global test), poor outcomes (Rankin scale >3) and death at 3 months. RESULTS: 551 patients did not receive immediate pre-randomization anti-hypertensive treatment and had available blood pressures. Multivariate analysis showed significantly and progressively reducing likelihoods of a favorable outcome with each 10 mmHg decline in systolic blood pressure (SBP) >50 mmHg compared to any preceding measurement. Poor outcomes were significantly more likely in patients with >50 mmHg SBP reduction (or >30 mmHg compared to any immediately preceding measurement). There was an increased risk

of death with blood pressure declines >60 mmHg. tPA treatment still produced favorable outcomes compared with placebo even with blood pressure declines. The median largest SBP reduction from baseline in patients treated with tPA was 35 mmHg compared to 30 mmHg in placebo-treated patients (p<0.01). CONCLUSIONS: In this post hoc analysis, progressively reducing likelihoods of a favorable outcome were seen with increasing declines in SBP. Despite a greater likelihood of favorable outcomes, tPA treatment was associated with a greater reduction in blood pressure than placebo. Randomized trials of blood pressure management are needed.

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Neurology

Zhang, R. L., Z. G. Zhang, et al. (2008). "Lengthening the G(1) phase of neural progenitor cells is concurrent with an increase of symmetric neuron generating division after stroke." *J Cereb Blood Flow Metab* **28**(3): 602-11.

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Department of Neurology, Henry Ford Health System, Detroit, MI 48202, USA.

The proportion of neural progenitors that remain in (P fraction) and exit from (Q fraction) the cell cycle determines the degree of neurogenesis. Using S-phase labeling with 5-bromo-2'-deoxyuridine and a double nucleoside analog-labeling scheme, we measured the cell-cycle kinetics of neural progenitors and estimated the proportion of P and Q fractions in the subventricular zone (SVZ) of adult rats subjected to stroke. Stroke increased SVZ cell proliferation, starting 2 days, reaching a maximum 4 and 7 days after stroke. The cell-cycle length (T(C)) of SVZ cells changed dynamically over a period of 2 to 14 days after stroke, with the shortest length of 11 h at 2 days after stroke. The reduction of the T(C) resulted from a decrease of the G(1) phase because the G(2), M, and S phases were unchanged. In addition, during this period, reduction of the G(1) phase was concomitant with an increase in the P fraction, whereas an augmentation of the Q fraction was associated with lengthening of the G(1) phase. Furthermore, approximately 90% of cells that exited the cell cycle were neurons and the population of a pair of dividing daughter cells with a neuronal marker increased from 9% at 2 days to 26% at 14 days after stroke. These data suggest that stroke triggers early expansion of the progenitor pool via shortening the cell-cycle length and retaining daughter cells within the cell cycle, and the lengthening of G(1) leads to daughter cells exiting the cell cycle and differentiating into neurons.

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Neurosurgery

Golembieski, W. A., S. L. Thomas, et al. (2008). "HSP27 mediates SPARC-induced changes in glioma morphology, migration, and invasion." *Glia* **56**(10): 1061-1075. [PDF Full Text](#)

Barbara Jane Levy Laboratory of Molecular Neuro-Oncology, Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan.

Secreted protein acidic and rich in cysteine (SPARC) regulates cell-extracellular matrix interactions that influence cell adhesion and migration. We have demonstrated that SPARC is highly expressed in human gliomas, and it promotes brain tumor invasion in vitro and in vivo. To further our understanding regarding SPARC function in glioma migration, we transfected SPARC-green fluorescent protein (GFP) and control GFP vectors into U87MG cells, and assessed the effects of SPARC on cell morphology, migration, and invasion after 24 h. The expression of SPARC was associated with elongated cell morphology, and increased migration and invasion. The effects of SPARC on downstream signaling were assessed from 0 to 6 h and 24 h. SPARC increased the levels of total and phosphorylated HSP27; the latter was preceded by activation of p38 MAPK and inhibited by the p38 MAPK inhibitor SB203580. Augmented expression of SPARC was correlated with increased levels of HSP27 mRNA. In a panel of glioma cell lines, increasing levels of SPARC correlated with increasing total and phosphorylated HSP27. SPARC and HSP27 were colocalized to invading cells in vivo. Inhibition of HSP27 mRNA reversed the SPARC-induced changes in cell morphology, migration, and invasion in vitro. These data indicate that HSP27, a protein that regulates actin polymerization, cell contraction, and migration, is a novel downstream effector of SPARC-regulated cell morphology and migration. As such, it is a potential therapeutic target to inhibit SPARC-induced glioma invasion. (c) 2008 Wiley-Liss, Inc.

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Other

Bulgarelli, N. (2007). "The PDCA of SFX." *Journal of Hospital Librarianship*. 7(3): 85-9. [Article Request Form/Click for Article Request Form](#)

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Pathology

Stark, A., A. Kapke, et al. (2008). "Advanced stages and poorly differentiated grade are associated with an increased risk of HER2/neu positive breast carcinoma only in White women: findings from a prospective cohort study of African-American and White-American women." *Breast Cancer Res Treat* 107(3): 405-14. [PDF Full Text](#)

Department of Pathology and Laboratory Medicine, Henry Ford Health System, K-6, Main Hospital Campus, 2799 West Grand Blvd, Detroit, MI 48202, USA. Astark1@hfhs.org

OBJECTIVE: The primary objective of this study was to evaluate the race-specific risk associated with HER2/neu positive breast carcinoma in a prospective cohort design. Our secondary objectives were to assess prevalence of different breast cancer phenotypes between African-American and White women and to determine if race was associated with the risk of basal-like breast carcinoma phenotype in this cohort. METHODS: Demographic, clinical and pathologic data were collected from existing databases. The status of HER2/neu and hormone receptors was dichotomized as either positive or negative. Immunohistochemistry taxonomy was used to assess prevalence of different breast carcinoma phenotypes. Risk estimates were calculated using the multivariable logistic regression statistics. CONCLUSIONS: The risk of HER2/neu positive breast carcinoma differs between African-American and White women. For White women only, this risk was statistically significant and increased almost linearly within each TNM stage with grade dedifferentiation. The statistically significantly higher prevalence of "ER(-)/PR(-), HER2(-)" phenotype in African American women potentially is the attributing factor to observed lack of an association between the risk of HER2/neu positive breast carcinoma with advanced stages and poorly differentiated grade. Among women diagnosed with "ER(-)/PR(-), HER2(-)" phenotype the odds ratios of being African-American and pre-menopausal was 1.72 (95% CI 1.17-2.54, P = 0.006) and 1.94 (95% CI 1.27-2.96, P = 0.002), respectively. The histologic features of basal-like and ER(-)/HER2(+)carcinomas overlaps. Differences in the biology of breast carcinoma between African American and White women are partially attributed to the disparity in more adverse pathologic prognostic indicators at the initial clinical presentation of this disease.

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Radiation Oncology

Brown, S. L., A. Kolozsvary, et al. (2008). "Histone deacetylase inhibitors protect against and mitigate the lethality of total-body irradiation in mice." *Radiat Res* 169(4): 474-8. [Article Request Form/Click for Article Request Form](#)

Department of Radiation Oncology, Henry Ford Hospital, Detroit, Michigan 48202, USA. sbrown1@hfhs.org

It was hypothesized that histone deacetylase (HDAC) inhibitors may increase survival after total-body irradiation (TBI) based on previous reports demonstrating that HDAC inhibitors stimulate the proliferation of bone marrow stem cells. Using the time for mice to lose 20% or more of their weight as the end point, two HDAC inhibitors, valproic acid and trichostatin-A, were found to reduce lethality in a dose-dependent manner. HDAC inhibitors were effective at reducing lethality when given either 24 h before or 1 h after TBI. The results indicate that HDAC inhibitors have potential for protecting against and mitigating radiation-induced lethality.

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Radiation Oncology

Jin, J. Y., F. F. Yin, et al. (2008). "Use of the BrainLAB ExacTrac X-Ray 6D System in Image-Guided Radiotherapy." *Med Dosim* 33(2): 124-134. [Article Request Form/Click for Article Request Form](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI; Department of Radiation Oncology, Duke University Medical Center, Durham, NC; Department of Radiation Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA; and Department of Radiation Oncology, University of Nebraska, Nebraska Medical Center, Omaha, NE.

The ExacTrac X-Ray 6D image-guided radiotherapy (IGRT) system will be described and its performance evaluated. The system is mainly an integration of 2 subsystems: (1) an infrared (IR)-based optical positioning system (ExacTrac) and (2) a radiographic kV x-ray imaging system (X-Ray 6D). The infrared system consists of 2 IR cameras, which are used to monitor reflective body markers placed on the patient's skin to assist in patient initial setup, and an IR reflective reference star, which is attached to the treatment couch and can assist in couch movement with spatial resolution to better than 0.3 mm. The radiographic kV devices consist of 2 oblique x-ray imagers to obtain high-quality radiographs for patient position verification and adjustment. The position verification is made by fusing the radiographs with the simulation CT images using either 3 degree-of-freedom (3D) or 6 degree-of-freedom (6D) fusion algorithms. The position adjustment is performed using the infrared system according to the verification results. The reliability of the fusion algorithm will be described based on phantom and patient studies. The results indicated that the 6D fusion method is better compared to the 3D method if there are rotational deviations between the simulation and setup positions. Recently, the system has been augmented with the capabilities for image-guided positioning of targets in motion due to respiration and for gated treatment of those targets. The infrared markers provide a respiratory signal for tracking and gating of the treatment beam, with the x-ray system providing periodic confirmation of patient position relative to the gating window throughout the duration of the gated delivery.

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Sleep Medicine

Richardson, G. S. (2007). "Human physiological models of insomnia." *Sleep Med* 8 Suppl 4: S9-14. [PDF Full Text](#)

Sleep Research Laboratory, Henry Ford Hospital, Detroit, MI, USA. grichar1@hfhs.org

Despite the wide prevalence and important consequences of insomnia, remarkably little is known about its pathophysiology. Available models exist primarily in the psychological domain and derive from the demonstrated efficacy of behavioral treatment approaches to insomnia management. However, these models offer little specific prediction about the anatomic or physiological foundation of chronic primary insomnia. On the other hand, a growing body of data on the physiology of sleep supports a reasonably circumscribed overview of possible pathophysiological mechanisms, as well as the development of physiological models of insomnia to guide future research. As a pragmatic step, these models focus on primary insomnia, as opposed to comorbid insomnias, because the latter is by its nature a much more heterogeneous presentation, reflecting the effects of the distinct comorbid condition. Current understanding of the regulation of sleep and wakefulness in mammalian brain supports four broad candidate areas: 1) disruption of the sleep homeostat; 2) disruption of the circadian clock; 3) disruption of intrinsic systems responsible for the expression of sleep states; or 4) disruption (hyperactivity) of extrinsic systems capable of over-riding normal sleep-wake regulation. This review examines each of the four candidate pathophysiological mechanisms and the available data in support of each. While studies that directly test the viability of each model are not yet available, descriptive data on primary insomnia favor the involvement of dysfunctional extrinsic stress-response systems in the pathology of primary chronic insomnia.

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Surgery

Deeb, D., X. Gao, et al. (2008). "CDDO-Me inhibits proliferation, induces apoptosis, down-regulates Akt, mTOR, NF-kappaB and NF-kappaB-regulated antiapoptotic and proangiogenic proteins in TRAMP prostate cancer cells." *J Exp Ther Oncol* 7(1): 31-9. [Article Request Form/Click for Article Request Form](#)

Department of Surgery, Henry Ford Health System, Detroit, MI 48202, USA.

Chemoprevention represents a promising strategy to reducing the incidence of prostate cancer which afflicts more than 240,000 males annually in the U.S. 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and its C-28 methyl ester (CCDO-Me) and C-28 imidazole (CDDO-Im) derivatives are synthetic oleanane triterpenoids that exhibit several-fold more potent antiinflammatory activity than naturally occurring oleanolic acid, but have not been investigated for prevention

of the prostate. In order to evaluate the anticancer activity of CDDOs for prostate cancer, we have investigated the effect of synthetic oleanane triterpenoids on molecular targets relevant to the chemoprevention and treatment of prostate cancer in vitro in TRAMPC-1 cells derived from the primary tumor in the prostate of a transgenic adenocarcinoma of the mouse prostate (TRAMP) mouse. Data demonstrate that CDDOs strongly inhibit the proliferation of TRAMPC-1 cells with a potency order of CDDO-Me>CDDO-Im>CDDO. Because CDDO-Me showed the most growth inhibitory activity it was further analyzed for the anticancer activity. CDDO-Me induced apoptosis in TRAMPC-1 cells as shown by the increased binding of annexin V-FITC and cleavage of procaspases 3, -8, and -9. It effectively inhibited the molecular targets such as p-Akt, NF-kappaB, and p-mTOR and downstream effectors of mTOR (p-S6K1, cyclin-D1, and cdk4). Further, CDDO-Me inhibited NF-kappaB-regulated antiapoptotic Bcl-2, Bcl-xL, and XIAP and proangiogenic VEGF. Taken together, these data demonstrate that CDDO-Me is potentially a potent chemopreventive agent that inhibits several molecular targets that are known to play critical roles in the development and progression of prostate cancer.

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Surgery

Haurani, M. J., M. E. Cifuentes, et al. (2008). "Nox4 Oxidase Overexpression Specifically Decreases Endogenous Nox4 mRNA and Inhibits Angiotensin II-Induced Adventitial Myofibroblast Migration." *Hypertension*. **Article Request Form/Click for Article Request Form**

Department of General Surgery, and Hypertension and Vascular Research Division, Henry Ford Health System, Detroit, Mich.

The vascular adventitia is emerging as an important modulator of vessel remodeling. Adventitial myofibroblasts migrate to the neointima after balloon angioplasty, contributing to restenosis. We postulated that angiotensin II (Ang II) enhances adventitial myofibroblast migration in vitro via reduced nicotinamide-adenine dinucleotide phosphate oxidase-derived H₂O₂ and that Nox4-based oxidase promotes migration. Ang II increased myofibroblast migration in a concentration-dependent manner, with a peak increase of 1023±83%. Rat adventitial myofibroblasts were cotransfected with human Nox4 and human p22-phox plasmids or an empty vector. PCR showed an 8-fold increase in human Nox4 and human p22-phox plasmid expression. Using RT-PCR with primers specifically designed for rat reduced nicotinamide-adenine dinucleotide phosphate oxidases, endogenous Nox levels were determined. Ang II decreased endogenous Nox4 and Nox1 mRNA to 41% and 27% of control, respectively, but had no effect on Nox2. Cotransfection with human Nox4 and human p22-phox plasmids combined with Ang II reduced endogenous Nox4 mRNA levels (37±5% of control; P<0.05), whereas it had no significant effect on Nox1 or Nox2. In empty vector-transfected cells, Ang II increased myofibroblast migration by 192±32% versus vehicle (P<0.01) while increasing H₂O₂ (473±22% versus control; P<0.001). Cotransfection with human Nox4 and human p22-phox plasmids decreased Ang II-induced migration (46±6%; P<0.001) in parallel with attenuation of H₂O₂ production (23±8% versus empty vector; P<0.05). Our data suggest that Nox4 promotes Ang II-induced myofibroblast migration via an H₂O₂-dependent pathway. The data also suggest that Nox4 causes feedback inhibition of its own expression in adventitial myofibroblasts.

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Surgery

Kakkos, S. K., G. K. Haddad, et al. (2008). "Percutaneous rheolytic thrombectomy for thrombosed autogenous fistulae and prosthetic arteriovenous grafts: outcome after aggressive surveillance and endovascular management." *J Endovasc Ther* **15**(1): 91-102. **Article Request Form/Click for Article Request Form**

Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, USA.

PURPOSE: To study the outcome of rheolytic thrombectomy for hemodialysis access occlusion. **METHODS:** A prospective study was conducted of 187 patients (88 men; median age 63 years, range 21-89) with end-stage renal disease treated with the AngioJet rheolytic thrombectomy catheter followed by angioplasty (+/- stenting) of the culprit lesions in 285 episodes of arteriovenous graft (n = 261) or fistula (n = 24) thrombosis. Clinical success was defined as at least one successful subsequent hemodialysis session. Graft monitoring and surveillance included clinical and hemodialysis parameters, respectively, to detect a failing/failed access. **RESULTS:** Rheolytic thrombectomy had a technical (immediate) success rate of 98.2% and a clinical success rate of 95.1%. Technical and clinical success for patients presenting within 2 days of the thrombosis was

99.6% and 96.6%, respectively, compared to 91.8% ($p = 0.003$, odds ratio 20.8) and 87.8% ($p = 0.019$, odds ratio 4) for later presentation. The number of stenoses that was managed (median, interquartile range) was significantly higher in grafts (4, 3-4) compared to fistulae (2, 2-3; $p < 0.001$) and in accesses that had been treated for dysfunction or thrombosis in the past (4, 3-4) compared to accesses that had not (3, 3-4; $p = 0.07$). During follow-up, 95 (36.6%) accesses had no further thrombotic events, 23 (9%) accesses became dysfunctional and were treated with endovascular techniques, 137 (52.3%) developed recurrent thrombosis for which rheolytic thrombectomy was attempted, and 30 (11.5%) were abandoned or removed for infection. Functional assisted primary patency at 1, 6, 12, and 18 months was 72.4%, 45.1%, 30.3%, and 22.4%, respectively. Reintervention and venous outflow stenosis were associated with better and worse outcomes, respectively; multivariate analysis identified patient age, central vein stenosis, and stenting as additional independent predictors of improved patency. CONCLUSION: Rheolytic thrombectomy is a highly successful procedure, with acceptable long-term assisted primary patency. Early referral for thrombectomy should be encouraged.

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Urology

Krane, L. S., A. Shrivastava, et al. (2008). "A four-step technique of robotic right adrenalectomy: initial experience." *BJU Int* **101**(10): 1289-92. [Article Request Form/Click for Article Request Form](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

OBJECTIVE: To report a safe, quick and reproducible technique of robotically assisted right adrenalectomy (RRA), developed by assessing the surgical anatomy of the right adrenal gland, its vascularity, and the surrounding structures, through a high definition, magnified three-dimensional view of the operating field provided by the da Vinci surgical system (Intuitive Surgical, Sunnyville CA, USA). PATIENTS AND METHODS: Four patients had RRA between January and July 2007 at the Vattikuti Urology Institute, for varied indications. We extensively reviewed published anatomical and surgical reports of the anatomy of the region to plan the surgical steps for RRA, careful reconfirming recognized anatomical facts and their probable significance. The surgical steps involved: (i) complete division of the hepatocolic ligament; (ii) definition of the right adreno-caval junction (ACJ); (iii) division of the right adrenal vein; (iv) dissection and removal of the adrenal gland circumferentially. The surgery was digitally recorded and reviewed. RESULTS: All the adrenalectomies were done transperitoneally through five ports, replicating predetermined surgical steps. There were no anaesthesia or surgery related events and no patient required conversion to open surgery. All the patients had an uneventful recovery and were discharged home 0-3 days after RRA. With increasing experience it was possible to reach the ACJ with minimal peripheral dissection. From a lateral approach, we visualized the adrenal vein travelling along the anterior portion of the gland before terminating at the inferior vena cava and the retrocaval location of the medial edge of the adrenal gland. The right adrenal vein (singular or duplicate) was the only surgically significant vessel, as the other vessels encountered were controlled with bipolar diathermy. CONCLUSIONS: Robotic assistance facilitated microdissection of fine anatomical planes around the right adrenal gland and provided direct access to the crucial ACJ. This technique permits ligation of the adrenal vein as an initial step, with no need to handle the adrenal gland. In the initial experience with four patients this technique was reproducible, regardless of indication or anatomical variance.

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