

Henry Ford Health System Publication List June 2006

This is a bibliography of journal articles published by Henry Ford Health System personnel. A search was compiled in [PubMed](#) during the month of June 2006, and then imported into [EndNote](#) for formatting.

We will be compiling this bibliography on a monthly basis. Please [contact us](#) if you would like to receive this publication list via email. If the full-text of the article is not available, you can request it from the Sladen Library by clicking on the [Article Request Form](#) or calling us at (313) 916-2550.

You can access this page at http://www.henryford.com/body_nologin.cfm?id=46638.

Abbud, C., V. Gowda, C. Ma, A. Ormsby and M. Lee (2006). "Quantitative evaluation of langerhans cells in the epidermis in mycosis fungoides and inflammatory dermatoses: not a useful diagnostic adjunct." *Am J Dermatopathol* **28**(3): 233-4. [PDF Full-Text](#)

Ades, P. A., P. D. Savage, C. A. Brawner, C. E. Lyon, J. K. Ehrman, J. Y. Bunn and S. J. Keteyian (2006). "Aerobic capacity in patients entering cardiac rehabilitation." *Circulation* **113**(23): 2706-12. [PDF Full-Text](#)

BACKGROUND: Symptom-limited treadmill testing is commonly performed on entry to cardiac rehabilitation (CR) for its prognostic value and to design a safe and effective exercise program. Normative values for this evaluation are not available. The primary goals of this study were to establish normative values for peak aerobic capacity (peak V(O₂)) for patients entering CR and to create nomograms for conversion of peak V(O₂) to a percentage of predicted exercise capacity, stratified by age, gender, and diagnosis. METHODS AND RESULTS: Peak V(O₂) was measured in 2896 patients entering CR from 1996 to 2004. Peak V(O₂) was higher in men than in women: 19.3 +/- 6.1 mL.kg(-1).min(-1) (range, 5.2 to 49.7 mL.kg(-1).min(-1)) versus 14.5 +/- 3.9 mL.kg(-1).min(-1) (range, 3.8 to 29.8 mL.kg(-1).min(-1)) (P < 0.0001). Peak V(O₂) decreased steadily with age with a greater rate of decline in men than women (0.242 versus 0.116 mL.kg(-1).min(-1) per year) (P < 0.01). Factors associated with lower peak V(O₂) include coronary artery bypass grafting (CABG), angina at stress testing, hypertension, and, in women, beta-blocking medications. Nomograms are presented for individual values to be compared with mean values by age, gender, and cardiac diagnosis. These include a nomogram to convert estimated maximal metabolic equivalents to actual peak V(O₂) for patients who do not undergo direct measurement of peak V(O₂). CONCLUSIONS: Values of peak V(O₂) on entry to CR are extremely low, particularly in women, approaching values seen with severe chronic heart failure. This underscores the importance of CR after a major cardiac event to improve physical function and long-term prognosis.

Anh, D., S. Krishnan and F. Bogun (2006). "Accuracy of electrocardiogram interpretation by cardiologists in the setting of incorrect computer analysis." *J Electrocardiol* **39**(3): 343-5. **Full-Text Not Available** / [Click for Article Request Form](#)

BACKGROUND: Overreading of 12 lead electrocardiograms (ECGs) is required to circumvent errors of computerized ECG interpretation. The accuracy of the overreading physician's interpretation of ECGs that were incorrectly read as atrial fibrillation by a computer algorithm has not been systematically examined.

METHODS: A total of 2298 ECGs with the computerized interpretation of atrial fibrillation from 1085 patients were analyzed by 2 electrophysiologists, who identified 442 ECGs (19%) from 382 patients (35%) that were incorrectly interpreted as atrial fibrillation. Charts were reviewed to determine the interpretation of the ECG by the ordering physician (primary reader) and the overreading cardiologist. **RESULTS:** Cardiologists as primary readers more often corrected the misinterpreted ECGs as compared with internists, emergency physicians, or other specialists (94% vs 71%, $P < .001$). Surprisingly, interpretations by cardiologists as primary readers were more accurate than the interpretation provided by overreading cardiologists (94% vs 72%, $P < .001$). **CONCLUSION:** Knowledge of an individual patient on whom an ECG is ordered may result in a more critical rhythm assessment and might account for the higher accuracy of rhythm interpretation by the cardiologist as compared with the interpretation by the overreading cardiologist who is lacking relevant clinical information.

Anton, T., J. Gutierrez and J. Rock (2006). "Tentorial schwannoma: a case report and review of the literature." *J Neurooncol* **76**(3): 307-11. [PDF Full-Text](#)

INTRODUCTION: Schwannomas are most often found in association with the eighth cranial nerve, but may also arise from any other cranial nerve. They are rarely found in an intra-parenchymal location. Unusual locations for intracranial schwannomas have also been reported in association with neurofibromatosis. **CLINICAL PRESENTATION:** A 23-year-old male without von Recklinghausen's disease presented with intermittent dizziness and difficulty swallowing. Past medical history was significant for a motor vehicle accident (MVA) without loss of consciousness 6 months prior. Magnetic resonance imaging revealed a large tentorial-based tumor. At surgery the origin of the tumor was clearly the tentorium, and while the trigeminal nerve was displaced, it easily separated from the mass. There was no attachment to any other cranial nerve in the immediate vicinity and postoperative cranial nerve examination was unremarkable. Pathological review was consistent with schwannoma. **CONCLUSION:** While there are few reported cases of tentorial-based schwannoma, these tumors have been noted in unusual locations within the intracranial vault, and clinicians should be aware of this diversity of origin.

Arbab, A. S., S. D. Pandit, S. A. Anderson, G. T. Yocum, M. Bur, V. Frenkel, H. M. Khuu, E. J. Read and J. A. Frank (2006). "Magnetic resonance imaging and confocal microscopy studies of magnetically labeled endothelial progenitor cells trafficking to sites of tumor angiogenesis." *Stem Cells* **24**(3): 671-8. **Full-Text Not Available / [Click for Article Request Form](#)**

AC133 cells, a subpopulation of CD34+ hematopoietic stem cells, can transform into endothelial cells that may integrate into the neovasculature of tumors or ischemic tissue. Most current imaging modalities do not allow monitoring of early migration and incorporation of endothelial progenitor cells (EPCs) into tumor neovasculature. The goals of this study were to use magnetic resonance imaging (MRI) to track the migration and incorporation of intravenously injected, magnetically labeled EPCs into the blood vessels in a rapidly growing flank tumor model and to determine whether the pattern of EPC incorporation is related to the time of injection or tumor size. **MATERIALS AND METHODS:** EPCs labeled with ferumoxide-protamine sulfate (FePro) complexes were injected into mice bearing xenografted glioma, and MRI was obtained at different stages of tumor development and size. **RESULTS:** Migration and incorporation of labeled EPCs into tumor neovasculature were detected as low signal intensity on MRI at the tumor periphery as early as 3 days after EPC administration in preformed tumors. However, low signal intensities were not observed in tumors implanted at the time of EPC administration until tumor size reached 1 cm at 12 to 14 days. Prussian blue staining showed iron-positive cells at the sites corresponding to low signal intensity on MRI. Confocal microscopy showed incorporation into the neovasculature, and immunohistochemistry clearly demonstrated the transformation of the administered EPCs into endothelial cells. **CONCLUSION:** MRI demonstrated the incorporation of FePro-labeled human CD34+/AC133+ EPCs into the neovasculature of implanted flank tumors.

Badani, K. K., A. K. Hemal, M. Fumo, S. Kaul, A. Shrivastava, A. K. Rajendram, N. A. Yusoff, M. Sundram, S. Woo, J. O. Peabody, S. R. Mohamed and M. Menon (2006). "Robotic extended pyelolithotomy for treatment of renal calculi: a feasibility study." *World J Urol* **24**(2): 198-201. [PDF Full-Text](#)

Percutaneous nephrolithotomy (PCNL) remains the treatment of choice for staghorn renal calculi. Many reports suggest that laparoscopy can be an alternative treatment for large renal stones. We wished to evaluate the role and feasibility of laparoscopic extended pyelolithotomy (REP) for treatment of staghorn calculi. Thirteen patients underwent REP for treatment of staghorn calculi over a 12-day period. Twelve patients had partial staghorn stones and one had a complete staghorn stone. All patients had pre-operative and post-operative imaging including KUB and computed tomography. All procedures were completed robotically without conversion to laparoscopy or open surgery. Mean operative time was 158 min and mean robotic console time was 108 min. Complete stone removal was accomplished in all patients except the one with a complete staghorn calculus. Estimated blood loss was 100 cc, and no patient required post-operative transfusion. REP is an effective treatment alternative to PCNL in some patients with staghorn calculi. However, patients with complete staghorn stones are not suitable candidates for this particular technique.

Bansal, I., H. Kerr, J. J. Janiga, H. S. Qureshi, M. Chaffins, H. W. Lim and A. Ormsby (2006). "Pinpoint papular variant of polymorphous light eruption: clinical and pathological correlation." *J Eur Acad Dermatol Venereol* **20**(4): 406-10. **Full-Text Not Available / [Click for Article Request Form](#)**

BACKGROUND: Polymorphous light eruption (PMLE) is the most common chronic idiopathic photodermatosis usually manifesting as a papular eruption along with several other morphological variants including a pinpoint papular variant. **METHODS AND MATERIALS:** Between June 1998 and August 2003, 10 PMLE patients presented to the Department of Dermatology at Henry Ford Hospital with complaints of a pruritic pinpoint papular eruption associated with sun exposure. In six patients skin biopsies were performed along with a detailed history and complete skin examination. We correlated the histology with the clinical course of disease corresponding to acute and subacute disease presentation. We also performed immunohistochemistry on three cases to study the immunophenotype in PMLE. **RESULTS:** The clinical, histologic and immunostain findings are summarized. Acute: Clinically pinpoint papules and vesicles, some with erythematous base, were seen. Histology showed focal vesicle formation, spongiosis, oedema, red blood cells extravasation, and superficial and deep perivascular and interstitial lymphocytic infiltrate with occasional eosinophils. Subacute: Clinically pinpoint papules with or without erythema were seen. Histology of the pinpoint lesion showed a nodular collection of lymphocytes and histiocytes with claw-like extension of epidermal rete ridges at the lateral boundaries of the lesion. Overlying epidermal atrophy with adjacent spongiosis, exocytosis, oedema and a superficial perivascular lymphocytic infiltrate and parakeratosis was also observed. The histologic differential diagnosis included lichen nitidus. Immunohistochemical stains revealed the following results: CD8, CD68 positive, CD4 variable (strongly positive to negative) and S-100 negative. **CONCLUSION:** (i) Pinpoint papular variant of PMLE is a distinct entity, which shows characteristic histology corresponding to the clinical course of the disease (acute and subacute). (ii) The histologic and immunophenotypic differential diagnosis of this variant during the subacute phase includes lichen nitidus.

Barton, K. N., H. Stricker, A. Kolozsvary, R. Kohl, G. Heisey, T. N. Nagaraja, G. Zhu, M. Lu, J. H. Kim, S. O. Freytag and S. L. Brown (2006). "Polyethylene glycol (molecular weight 400 DA) vehicle improves gene expression of adenovirus mediated gene therapy." *J Urol* **175**(5): 1921-5. **[PDF Full-Text](#)**

PURPOSE: A significant limitation of adenoviral mediated suicide gene therapy is poor gene distribution in vivo. The choice of vehicle has been demonstrated to affect the level of adenoviral delivered gene transduction. We examined the hypotheses that 1) adenovirus suspended in PEG400 improves gene expression in the naive canine prostate model, 2) improved transgene expression with PEG400 results in improved tumor control and 3) vehicle affects the initial adenoviral spread from a single intratumor injection. **MATERIALS AND METHODS:** The magnitude and volume of gene expression were measured 24 hours following intraprostatic injection of adenovirus suspended in PEG400 (12.5% weight per volume) or saline as vehicle. Tumor growth delay was measured in mice bearing human tumor xenografts following the injection of adenovirus in PEG400 and saline. The initial spread of adenovirus was measured by confocal microscopy following a single injection of fluorescently labeled adenoviral particles in human tumor xenografts using each vehicle. **RESULTS:** Adenovirus suspended in PEG400 provided an average of twice the level of gene expression in the canine prostate and significantly better tumor control relative to

saline in preclinical tumor models ($p = 0.046$ and 0.036 , respectively). The initial spread of adenovirus with PEG400 was superior to that of adenovirus in saline and the latter was largely limited to the needle tract. CONCLUSIONS: Adenoviral gene therapy vectors suspended in PEG400 results in improved tumor control because of greater initial adenoviral spread, and the increased volume and magnitude of gene expression in vivo.

Beierwaltes, W. H. (2006). "cGMP stimulates renin secretion in vivo by inhibiting phosphodiesterase-3." *Am J Physiol Renal Physiol* **290**(6): F1376-81. [PDF Full-Text](#)

The interaction between renin, nitric oxide (NO), and its second messenger cGMP is controversial. cAMP is the stimulatory second messenger for renin but is degraded by phosphodiesterases (PDEs). We previously reported that increasing endogenous cGMP in rats by inhibiting its breakdown by PDE-5 stimulated renin secretion rate (RSR). This could be reversed by selective inhibition of neuronal nitric oxide synthase (nNOS). PDE-3 metabolizes cAMP, but this can be inhibited by cGMP, suggesting that renal cGMP could stimulate RSR by diminishing PDE-3 degradation of cAMP. Rats were anesthetized with Inactin before determination of blood pressure (BP), renal blood flow (RBF), and sampling of renal venous and arterial blood to determine RSR. In 13 rats, basal BP was 104 ± 2 mmHg, RBF was $6.1 \text{ ml} \times \text{min}^{-1} \times \text{g kidney wt}^{-1}$ and RSR was $2.9 \pm 1.4 \text{ ng ANG I} \times \text{h}^{-1} \times \text{min}^{-1}$. Inhibiting PDE-5 with 20 mg/kg body wt i.p. Zaprinast did not change hemodynamic parameters but increased RSR fivefold to $12.2 \pm 4.9 \text{ ng ANG I} \times \text{h}^{-1} \times \text{min}^{-1}$ ($P < 0.05$). Renal venous cAMP was increased by Zaprinast from 93.8 ± 27.9 to $149.2 \pm 36.0 \text{ pM} \times \text{min}^{-1} \times \text{g kidney wt}^{-1}$ ($P < 0.05$). When another 10 rats were treated with the PDE-3 inhibitor Milrinone (0.4 microg/min over 30 min, which did not affect hemodynamics), RSR was elevated to $10.4 \pm 4.4 \text{ ng ANG I} \times \text{h}^{-1} \times \text{min}^{-1}$. Milrinone also increased renal venous cAMP from 212 ± 29 to $304 \pm 29 \text{ pM} \times \text{min}^{-1} \times \text{g kidney wt}^{-1}$ ($P < 0.025$). Administration of Zaprinast to rats pretreated with Milrinone ($n = 10$) did not further increase in RSR ($7.5 \pm 3.3 \text{ ng ANG I} \times \text{h}^{-1} \times \text{min}^{-1}$). These results are consistent with endogenous renal cGMP inhibiting PDE-3, which diminishes renal metabolism of cAMP. The resulting increase in cAMP serves as an endogenous stimulus for renin secretion. This suggests a pathway by which NO can indirectly stimulate RSR through its second messenger cGMP.

Cankovic, M., A. R. Gaba, F. Meier, W. Kim and R. J. Zarbo (2006). "Detection of non-maternal components of gestational choriocarcinoma by PCR-based microsatellite DNA assay." *Gynecol Oncol*. [PDF Full-Text](#)

OBJECTIVE.: Gestational and non-gestational choriocarcinomas have distinctly different tissues of origin, parental genotypes, natural histories, and responses to therapy. Our objective was to develop a convenient, fast, and reliable assay that would, using only patient tissue, allow separation of gestational from non-gestational choriocarcinomas. METHOD.: Benign and malignant tissues, preserved in paraffin blocks and separated by microdissection, were examined using a commercial PCR-based tissue identity assay (ABI AmpFISTR Profiler Plus Kit and ABI 377 DNA sequencer) to detect genetic profiles of 9 microsatellite markers, along with X and Y chromosome markers. Cases included 6 choriocarcinomas. Controls included eight non-germ cell reproductive tract tumors and two hydatidiform moles. RESULTS.: The microsatellite markers identified the five choriocarcinomas diagnosed on clinical and histological grounds as gestational, to be of genetically non-maternal (androgenic) origin. The neoplasm previously classified as a non-gestational choriocarcinoma was demonstrated to be of maternal origin, as were the non-germ cell reproductive tract tumors. Samples from hydatidiform moles contained either androgenic markers only or a mix of maternal and androgenic markers, as previously seen in complete and partial moles, respectively. CONCLUSION.: A commercially available microsatellite DNA diagnostic assay is a quick and convenient way to discriminate between gestational and non-gestational choriocarcinoma.

Cavasin, M. A., Z. Y. Tao, A. L. Yu and X. P. Yang (2006). "Testosterone enhances early cardiac remodeling after myocardial infarction, causing rupture and degrading cardiac function." *Am J Physiol Heart Circ Physiol* **290**(5): H2043-50. [PDF Full-Text](#)

Cardiac rupture can be fatal after myocardial infarction (MI). Experiments in animals revealed gender differences in rupture rate; however, patient data are controversial. We found a significantly higher rupture rate in testosterone-treated female mice within 1 wk after MI, whereas castration in males significantly

reduced rupture. We hypothesized that testosterone may adversely affect remodeling after MI, exaggerating the inflammatory response and increasing cardiac rupture, whereas estrogen may be cardioprotective, attenuating early remodeling and reducing rupture rate. We studied the effect of gender and hormone manipulation on morphological and histological changes during early remodeling after MI in 4-wk-old male and female C57BL/6J mice and how these events could affect cardiac function. Females were randomly divided into 1) sham ovariectomy + placebo (s-ovx + P), 2) s-ovx + testosterone (T), 3) ovx + P, and 4) ovx + T; males were divided into 1) sham castration + P (s-cas + P), 2) s-cas + 17beta-estradiol (E), 3) cas + P, and 4) cas + E. At 6 wk after gonadectomy and hormone manipulation, MI was induced. Mice were randomly killed 1, 2, 4, 7, and 14 days after MI. The left ventricle was weighed and sectioned for evaluation of MI size, infarct expansion index (IEI), and neutrophil infiltration. Transthoracic echocardiography was performed in conscious mice in the 14-day group before organ harvest. Cardiac rupture rate and IEI were significantly higher in testosterone-treated females and noncastrated males than in controls; these effects were accompanied by enhanced neutrophil infiltration and pronounced deterioration of cardiac function and left ventricular dilatation. Ovariectomy in females and estrogen supplementation in males did not confer significant protection from cardiac rupture, IEI, or neutrophil infiltration. We concluded that, in mice, high testosterone levels enhance acute myocardial inflammation, adversely affecting myocardial healing and early remodeling, as indicated by increased cardiac rupture, and possibly causing deterioration of cardiac function after MI, and, conversely, estrogen seems to have no significant protective effect in the acute phase after MI.

Chen, J., A. Zacharek, A. Li, C. Zhang, J. Ding, C. Roberts, M. Lu, A. Kapke and M. Chopp (2006). "Vascular endothelial growth factor mediates atorvastatin-induced mammalian achaete-scute homologue-1 gene expression and neuronal differentiation after stroke in retired breeder rats." *Neuroscience*. [PDF Full-Text](#)

Neurogenesis declines with advancing age. The mammalian achaete-scute homologue-1 encodes a basic helix-loop-helix transcription factor, which controls neuronal differentiation. In this study, we first tested whether atorvastatin treatment enhances neurological functional outcome and neuronal differentiation after stroke in retired breeder 12 month rats. Rats were subjected to middle cerebral artery occlusion and treated with or without atorvastatin (3 mg/kg) for 7 days. Atorvastatin significantly increased expression of mammalian achaete-scute homologue-1, beta-tubulin III, and vascular endothelial growth factor in the ischemic brain, and concomitantly improved functional outcome compared with middle cerebral artery occlusion control rats. Increased neurogenesis significantly correlated with functional recovery after stroke. To further investigate the mechanisms of atorvastatin-induced neuronal differentiation, experiments were performed on neurospheres derived from retired breeder rat subventricular zone cells. Atorvastatin increased neuronal differentiation and upregulated vascular endothelial growth factor and mammalian achaete-scute homologue-1 gene expression in cultured neurospheres. Vascular endothelial growth factor-treated neurospheres significantly increased mammalian achaete-scute homologue-1 and beta-tubulin III expression. Inhibition of vascular endothelial growth factor decreased atorvastatin-induced mammalian achaete-scute homologue-1 and beta-tubulin III expression. These data indicate that atorvastatin increases neuronal differentiation in retired breeder rats. In addition, atorvastatin upregulation of vascular endothelial growth factor expression, influences mammalian achaete-scute homologue-1 transcription factor, which in turn, facilitates an increase in subventricular zone neuronal differentiation. These atorvastatin-mediated molecular events may contribute to the improved functional outcome in retired breeder rats subjected to stroke.

Davis, R.M., Reviewer. (2006). *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, 2006. [PDF Full-Text](#)

Davis, S. and A. Affatato (2006). "Blunt chest trauma: utility of radiological evaluation and effect on treatment patterns." *Am J Emerg Med* **24**(4): 482-6. [PDF Full-Text](#)

Minor chest wall trauma is a common complaint in the emergency department (ED) (Barnea Y, Kashtan H, Skornick Y, Werbin N. Isolated rib fractures in elderly patients: mortality and morbidity. *Can J of Surgery*

2002;45(1):43-6; Lee RB, Bass SM, Morris JA, Mackenzie EJ. Three or more rib fractures as an indicator for transfer to a level I trauma center. *J Trauma* 1990;30:689-94; Dubinsky I, Low A. Non-life-threatening blunt chest trauma: Appropriate investigation and treatment. *Am J Emerg Med* 1997;15(3):240-3). Up to 50% of rib fractures may be missed on standard x-ray (Ziegler DW, Agarwal NN. The morbidity and mortality of rib fractures. *J Trauma* 1994;37:975-9; Palvanen M, Kannus P, Niemi S, Parkkari J. Hospital-treated minimal-trauma rib fractures in elderly Finns: long-term trends and projections for the future. *Osteoporosis International*). Little consensus exists among emergency physicians with respect to the workup of minor blunt chest trauma. The purpose of this study was to evaluate the accuracy of emergency physicians in interpreting rib radiographs and to determine if that interpretation resulted in any variance in treatment patterns. Our study is a retrospective study of 271 charts from a community-based teaching hospital from August 2000 to August 2002. Patients were excluded if they suffered major trauma. The treatment rendered was categorized. Categories included over-the-counter medication, nonsteroidal anti-inflammatory drugs, narcotics, and muscle relaxants. The overall chi(2) calculation showed no differences between the fractured group and the no fracture group ($P = .072$). From this, it can be concluded that there were no between-group differences in drugs prescribed based on whether a fracture was diagnosed by the ED physician. Indicating that the interpretation of the rib series does not influence the physicians treatment plan.

Ehrman, J.K., C.A. Brawner, B. Czerska, W.D. Weaver, G. Jacobsen, and S.J. Keteyian (2006). "Oxygen uptake efficiency slope and survival in patients with systolic heart failure." *J Am Coll Cardiol* 47(4): 155A, Suppl A. **Full-Text Not Available / [Click for Article Request Form](#)**

Ewing, J. R., S. L. Brown, M. Lu, S. Panda, G. Ding, R. A. Knight, Y. Cao, Q. Jiang, T. N. Nagaraja, J. L. Churchman and J. D. Fenstermacher (2006). "Model selection in magnetic resonance imaging measurements of vascular permeability: Gadomer in a 9L model of rat cerebral tumor." *J Cereb Blood Flow Metab* 26(3): 310-20. **Full-Text Not Available / [Click for Article Request Form](#)**

Vasculature in and around the cerebral tumor exhibits a wide range of permeabilities, from normal capillaries with essentially no blood-brain barrier (BBB) leakage to a tumor vasculature that freely passes even such large molecules as albumin. In measuring BBB permeability by magnetic resonance imaging (MRI), various contrast agents, sampling intervals, and contrast distribution models can be selected, each with its effect on the measurement's outcome. Using Gadomer, a large paramagnetic contrast agent, and MRI measures of T(1) over a 25-min period, BBB permeability was estimated in 15 Fischer rats with day-16 9L cerebral gliomas. Three vascular models were developed: (1) impermeable (normal BBB); (2) moderate influx (leakage without efflux); and (3) fast leakage with bidirectional exchange. For data analysis, these form nested models. Model 1 estimates only vascular plasma volume, v(D), Model 2 (the Patlak graphical approach) v(D) and the influx transfer constant K(i). Model 3 estimates v(D), K(i), and the reverse transfer constant, k(b), through which the extravascular distribution space, v(e), is calculated. For this contrast agent and experimental duration, Model 3 proved the best model, yielding the following central tumor means (+/-s.d.; n = 15): v(D) = 0.07 +/- 0.03 for K(i) = 0.0105 +/- 0.005 min(-1) and v(e) = 0.10 +/- 0.04. Model 2 K(i) estimates were approximately 30% of Model 3, but highly correlated (r = 0.80, P < 0.0003). Sizable inhomogeneity in v(D), K(i), and k(b) appeared within each tumor. We conclude that employing nested models enables accurate assessment of transfer constants among areas where BBB permeability, contrast agent distribution volumes, and signal-to-noise vary.

Fumo, M. J. and G. A. McLorie (2006). "Management of the valve-bladder syndrome and congenital bladder obstruction: the role of nocturnal bladder drainage." *Nat Clin Pract Urol* 3(6): 323-6. **Full-Text Not Available / [Click for Article Request Form](#)**

Valve-bladder syndrome often develops after the resolution of posterior urethral valves, but is also found after the resolution of congenital bladder obstruction. The features of this syndrome include the persistent dilation of the upper urinary tracts, a thick-walled, noncompliant urinary bladder, urinary incontinence, and polyuria secondary to nephrogenic diabetes insipidus. Nocturnal bladder management, which involves timed emptying of the bladder or continuous drainage, has been recommended in conjunction with diurnal

timed voiding therapy as an adjunct to the treatment of valve-bladder syndrome. This treatment is derived from the hypothesis that valve-bladder syndrome is caused by congenital obstruction, and that the resultant changes in detrusor muscle are associated with a persistent bladder dysfunction characterized by chronic overdistention of the urinary bladder. Such overdistention is exacerbated by polyuria, and can be a cause of secondary hydronephrosis. Bladder dysfunction and overdistention is usually treated during waking time, but occasionally this is not effective on its own, and nocturnal therapy is used as well. To date, there are a few sets of data that suggest overnight bladder drainage can bring about profound improvements in the degree of upper-tract hydronephrosis, renal function, or bladder function. Nocturnal bladder drainage seems, in these initial reports, to be a simple and safe therapeutic maneuver. This review discusses the etiology of valve-bladder syndrome and examines each of the studies which have investigated nocturnal bladder drainage in its treatment.

Ganger, L. K. and I. H. Hamzavi (2006). "Excess salt and pepper hair treated with a combination of laser hair removal and topical eflornithine HCl." *J Drugs Dermatol* 5(6): 544-5. [PDF Full-Text](#)

A common problem among aging women, salt and pepper facial hair poses a significant psychosocial impact as well as a challenge for treatment. Various laser therapies or topical eflornithine HCl 13.9% cream are commonly used to reduce the rate of hair growth. We report a case of a woman with salt and pepper hair in the beard distribution. A combination of laser hair removal with concurrent use of topical eflornithine was used in the treatment.

Halash, C., B. McLellan, S. Patten, G. Brown, M. Mlynarek, K. Corpus, N. Price, L. Phillips, H. Hoff, and D. Smith (2006). "How sweet it is – implementing a tight glycemic control protocol in an urban tertiary medical ICU." *Crit Care Nurse* 26(2): S7-8. **Full-Text Not Available** / [Click for Article Request Form](#)

Harding, P., L. Balasubramanian, J. Swegan, A. Stevens and W. F. Glass, 2nd (2006). "Transforming growth factor beta regulates cyclooxygenase-2 in glomerular mesangial cells." *Kidney Int* 69(9): 1578-85. [PDF Full-Text](#)

This study examines the hypothesis that transforming growth factor beta (TGFbeta) regulates cyclooxygenase-2 (COX-2) and induces prostaglandin E synthase (mPGES-1) in rat mesangial cells. COX-2 expression was determined by Northern blot analysis after treatment with either TGFbeta1 or the selective COX-2 inhibitor, NS398. mPGES-1 expression was determined by real-time polymerase chain reaction. The effect of TGFbeta1 on COX-2 gene transcription was assessed using a luciferase reporter assay, and mRNA stability was also determined. To determine whether TGFbeta1 activates elements of the COX-2 promoter, we performed gel shift analyses to examine activation of activator protein-1 (AP-1) and nuclear factor kappaB (NF-kappaB). Prostaglandin E(2) (PGE(2)) and thromboxane B2 (TxB2) production was assayed by enzyme immunoassay. Finally, the pathophysiological relevance of COX-2 inhibition on the downstream effects of TGFbeta was assessed by examining collagen type I mRNA and net collagen production. COX-2 mRNA and mPGES-1 were induced after treatment with TGFbeta1 for 4 h, and this rise was accompanied by a three-fold increase in PGE(2) production that could be antagonized by selective inhibition of COX-2 with NS398. TGFbeta1 increased transcription by approximately 50% and activated both AP-1 and NF-kappaB. These effects were antagonized by co-treatment with NS398. Treatment with TGFbeta1 also doubled the half-life of COX-2 mRNA. Neither collagen type I mRNA nor net collagen production were altered by co-treatment with NS398. In conclusion, these results indicate that TGFbeta stimulates COX-2 and mPGES-1, with additional effects on transcription and stability of COX-2 mRNA.

Jenrow, K. A., A. E. Ratkewicz, D. N. Zalinski, K. M. Roszka, N. W. Lemke and K. V. Elisevich (2006). "Influence of ionizing radiation on the course of kindled epileptogenesis." *Brain Res* 1094(1): 207-16. [PDF Full-Text](#)

Several clinical and experimental reports suggest that low-dose irradiation of an established epileptic focus can reduce the occurrence of spontaneous seizures. Conversely, some recent reports suggest that under

some conditions low-dose irradiation may have disinhibitory effects on seizure expression. Here, we have investigated mechanistic aspects of this phenomenon in the kindling model of epilepsy by applying focal irradiation at various points during kindling development. Rats were kindled to stage 5 by afterdischarge-threshold electrostimulation of the left amygdala. Treatment groups were irradiated using a collimated X-ray beam (18 MV) either prior to kindling, at kindling stage 3, or at kindling stage 5, by exposure of the left amygdala to a single-fraction central-axis dose of 25 Gy. Generalized seizure thresholds (GSTs) were subsequently assayed at weekly intervals for 10 weeks and at monthly intervals for an additional 3 months, along with the severity of the evoked seizures. Irradiation produced no significant effects on seizure threshold, but did produce persistent changes in seizure severity which varied as a function of the timing of irradiation. Relative to sham irradiated controls, the occurrence of stage 6 seizures was significantly increased by irradiation prior to kindling, but was unaffected by irradiation at kindling stage 3, and significantly reduced by irradiation at kindling stage 5. Quantitative immunohistochemical assays for neuron and astrocyte densities within the amygdala and hippocampus revealed only subtle changes in neuronal density within the dentate granule cell layer. These results are discussed in relation to mechanisms of seizure- and radiation-induced plasticity.

Kaszala, K., D. N. Kenigsberg and S. C. Krishnan (2006). "Drug-induced T wave alternans." *J Cardiovasc Electrophysiol* **17**(3): 332. **Full-Text Not Available** / [Click for Article Request Form](#)

Ketterer, M.W., C.A. Brawner, M. VanZant, S.J. Keteyian, J.K. Ehrman, W. Knysz, A. Farha, S. Deveshwar, and L. Wulsin (2006). "Psychometric screening in coronary artery disease patients." *Circulation* **113**(21): E810. **Full-Text Not Available** / [Click for Article Request Form](#)

Kruger, D. F., C. L. Martin and C. E. Sadler (2006). "New insights into glucose regulation." *Diabetes Educ* **32**(2): 221-8. **Full-Text Not Available** / [Click for Article Request Form](#)

This review article describes the regulation of glucose homeostasis in subjects with and without diabetes based on the emergence of new information and discusses modes of action, attributes, and limitations of current diabetes therapies. In normal physiology, glucose homeostasis is tightly controlled by the interaction of pancreatic and gut hormones. Since the 1920s, diabetes has been viewed as a disease caused by deficient secretion of insulin, resulting in reduced glucose uptake and subsequent hyperglycemia. The discovery in the 1950s of the pancreatic hormone glucagon, which opposes insulin by increasing glucose appearance in the circulation, resulted in a bihormonal model of glucose homeostasis. More recently, with the discovery of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) in the 1970s and the pancreatic hormone amylin in the 1980s, it is now understood that several organs and hormones play roles in maintaining glucose homeostasis. Therapies for diabetes have focused on compensation for deficient insulin action through stimulation of insulin secretion, administration of insulin itself, reduction of peripheral insulin resistance, or decreased glucose absorption from the intestine. The discoveries of amylin and GLP-1 have furthered our understanding of the abnormalities involved in diabetes, enabling the development of additional therapeutic options.

Lamerato, L., S. Havstad, S. Gandhi, D. Jones and D. Nathanson (2006). "Economic burden associated with breast cancer recurrence: findings from a retrospective analysis of health system data." *Cancer* **106**(9): 1875-82. [PDF Full-Text](#)

BACKGROUND: The economics of breast cancer recurrence are poorly understood. For this retrospective cohort study, the authors evaluated the economic burden of breast cancer recurrence by using data from a large Midwestern healthcare system. **METHODS:** Women with Stage I or II breast cancer (according to the American Joint Commission on Cancer staging criteria) were identified from the tumor registry of the Henry Ford Health System. The economic burden of breast cancer recurrence was estimated from patient charges (adjusted to 2003 U.S. dollars). **RESULTS:** From 1996 to 2002, 1616 patients with early breast cancer were identified, including 192 patients who had recurrent tumors. Patients with recurrence had significantly greater charges in the 6-month and 12-month postrecurrence periods (45,855 U.S. dollars and 79,253 U.S. dollars, respectively) compared with the 6-month and 12-month prerecurrence periods (10,715

U.S. dollars and 12,344 U.S. dollars, respectively; both $P < .001$). This was evident for all recurrence types (locoregional, contralateral breast, and distant), but it was most evident for distant recurrences. In a regression analysis that was adjusted for baseline characteristics, the mean monthly charges were significantly greater for patients with recurrence versus patients without recurrence ($P < .001$), and this was true for each recurrence type. For women with recurrence ($n = 74$ patients), the mean charges during the 6-month postrecurrence period were significantly greater than mean charges during the initial 6-month period after diagnosis (50,355 U.S. dollars vs. 38,254 U.S. dollars; $P < .01$). Quarterly charges for continuing care postrecurrence were significantly greater than prerecurrence charges (4934 U.S. dollars vs. 1825 U.S. dollars; $P < .001$). The mean charges for terminal care were significantly greater ($P < .01$) for women with recurrence ($n = 27$ patients, 63,434 U.S. dollars) versus women without recurrence ($n = 65$ patients, 53,872 U.S. dollars). **CONCLUSIONS:** Patients with early breast cancer who experienced recurrence required more costly care than patients who did not develop recurrent disease. Therapies that reduce the risk of recurrence may reduce costs significantly.

Lee, J. J. and T. F. Downham, 2nd (2006). "Furosemide-induced bullous pemphigoid: case report and review of literature." *J Drugs Dermatol* **5**(6): 562-4. [PDF Full-Text](#)

Bullous pemphigoid (BP) is an acquired autoimmune disease characterized by subepidermal vesicles and bullae. The etiology for BP is mostly idiopathic with the highest occurrence in elderly patients; however, it is now well-accepted that BP has been triggered by or associated with drug therapy. We present a case of furosemide-induced bullous pemphigoid and review the literature of drug-induced bullous pemphigoid (DIBP).

Lewis, T. G. and E. D. Nydorf (2006). "Intralesional bleomycin for warts: a review." *J Drugs Dermatol* **5**(6): 499-504. [PDF Full-Text](#)

Intralesional bleomycin has been used for the treatment of warts since the 1970s. Currently, there is a limited amount of evidence from randomized placebo-controlled trials comparing intralesional bleomycin with other local treatments for warts. Numerous reports have been published on the use of intralesional bleomycin for the treatment of recalcitrant warts with cure rates ranging from 14% to 99%. The majority of the data suggests that bleomycin is effective in over two-thirds of the reported cases with minimal side effects. In this paper, we review the mechanism of action, pharmacokinetics, safety profile, supply and storage, dosage scheme, techniques for administration, and efficacy of intralesional bleomycin for the treatment of warts.

Lewis, T. G., C. Tuchinda, H. W. Lim and H. K. Wong (2006). "Life-threatening pustular and erythrodermic psoriasis responding to infliximab." *J Drugs Dermatol* **5**(6): 546-8. [PDF Full-Text](#)

Pustular and erythrodermic psoriasis can be a debilitating and recalcitrant disease which may result in secondary complications such as sepsis, electrolyte imbalance, renal failure, and heart failure. We report a case of a 46-year-old patient with life-threatening erythrodermic psoriasis who responded rapidly to intravenous infliximab.

Li, Y., K. McIntosh, J. Chen, C. Zhang, Q. Gao, J. Borneman, K. Raginski, J. Mitchell, L. Shen, J. Zhang, D. Lu and M. Chopp (2006). "Allogeneic bone marrow stromal cells promote glial-axonal remodeling without immunologic sensitization after stroke in rats." *Exp Neurol* **198**(2): 313-25. **Full-Text Not Available / [Click for Article Request Form](#)**

We evaluated the effects of allogeneic bone marrow stromal cell treatment of stroke on functional outcome, glial-axonal architecture, and immune reaction. Female Wistar rats were subjected to 2 h of middle cerebral artery occlusion. Rats were injected intravenously with PBS, male allogeneic ACI- or syngeneic Wistar- bone marrow stromal cells at 24 h after ischemia and sacrificed at 28 days. Significant functional recovery was found in both cell-treated groups compared to stroke rats that did not receive BMSCs, but no difference was detected between allogeneic and syngeneic cell-treated rats. No evidence of T cell priming or humoral antibody production to marrow stromal cells was found in recipient rats after treatment with allogeneic cells. Similar numbers of Y-chromosome+ cells were detected in the female rat brains in both

groups. Significantly increased thickness of individual axons and myelin, and areas of the corpus callosum and the numbers of white matter bundles in the striatum were detected in the ischemic boundary zone of cell-treated rats compared to stroked rats. The areas of the contralateral corpus callosum significantly increased after cell treatment compared to normal rats. Processes of astrocytes remodeled from hypertrophic star-like to tadpole-like shape and oriented parallel to the ischemic regions after cell treatment. Axonal projections emanating from individual parenchymal neurons exhibited an overall orientation parallel to elongated radial processes of reactive astrocytes of the cell-treated rats. Allogeneic and syngeneic bone marrow stromal cell treatment after stroke in rats improved neurological recovery and enhanced reactive oligodendrocyte and astrocyte related axonal remodeling with no indication of immunologic sensitization in adult rat brain.

McFarlin, K., A. E. Sargsyan, S. Melton, D. R. Hamilton and S. A. Dulchavsky (2006). "A surgeon's guide to the universe." *Surgery* **139**(5): 587-90. [PDF Full-Text](#)

Morita, H., S. Khanal, S. Rastogi, G. Suzuki, M. Imai, A. Todor, V. G. Sharov, S. Goldstein, T. P. O'Neill and H. N. Sabbah (2006). "Selective matrix metalloproteinase inhibition attenuates progression of left ventricular dysfunction and remodeling in dogs with chronic heart failure." *Am J Physiol Heart Circ Physiol* **290**(6): H2522-7. [PDF Full-Text](#)

Matrix metalloproteinases (MMPs) contribute to the progression of left ventricular (LV) dysfunction and remodeling associated with heart failure (HF). The present study examined the long-term effects of a selective MMP inhibitor PG-530742 (PG) on the progression of LV dysfunction and remodeling in dogs with HF. Chronic HF [LV ejection fraction (LVEF), $\leq 36\%$] was produced by multiple sequential intracoronary microembolizations in 24 dogs. Two weeks after the last embolization, dogs were randomized to 3 mo of therapy with either high-dose (HD) PG (3.5 mg/kg, n = 8), low-dose (LD) PG (0.2 mg/kg, n = 8), or to a matched placebo (PL, n = 8). PG has been shown to produce complete inhibition of MMP-2, -3, -9, and -13, while sparing MMPs-1 and -7. Hemodynamic and echocardiographic measurements were made before and 3 mo after initiating therapy. In PL and LD dogs, LVEF decreased significantly, and LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) increased significantly during the 3-mo follow-up period. Whereas in HD dogs ejection fraction increased from 36 ± 1 to $40 \pm 1\%$ ($P = 0.003$), EDV and ESV decreased (59 ± 4 vs. 57 ± 4 ml, $P = 0.02$; and 38 ± 2 vs. 34 ± 2 ml, $P = 0.00001$, respectively). When compared with controls, HD-treated dogs showed 30% reduction in replacement fibrosis, 29% reduction in interstitial fibrosis, and 28% reduction in myocyte cross-sectional area. mRNA expression of selective MMPs was also reduced in LV tissue in HD- but not LD-treated dogs. In conclusion, in dogs with moderate HF, long-term monotherapy with HD selective MMP inhibitor PG prevents LV remodeling and the progression of global LV dysfunction.

Nagaraja, T. N., R. L. Croxen, S. Panda, R. A. Knight, K. A. Keenan, S. L. Brown, J. D. Fenstermacher and J. R. Ewing (2006). "Application of arsenazo III in the preparation and characterization of an albumin-linked, gadolinium-based macromolecular magnetic resonance contrast agent." *J Neurosci Methods*. **Full-Text Not Available** / [Click for Article Request Form](#)

A macromolecular magnetic resonance contrast agent (MMCA) was prepared by linking bovine serum albumin (BSA) to gadolinium (Gd) via a chelating agent, diethylenetriaminepentaacetic acid (DTPA). Colorimetric testing with 2,7-bis(o-arsenophenylazo)-1,8-dihydroxynaphthalene-3,6-disulfonic acid (arsenazo III) was performed to check for the appearance of free gadolinium during preparation and to quantify the Gd content in the final product. The complex was purified by dialysis, concentrated by lyophilization and characterized by magnetic resonance (MR) proton relaxation times. The resultant product had a molecular weight of about 90kDa, Gd:BSA ratio of 14:1, and T(1) and T(2) relaxation times of 128.3 and 48.9ms, respectively, at a field strength of 7Tesla (T) and at 20% concentration. Contrast enhancement of Gadomer-17 (a dendritic MMCA) and Gd-linked to BSA (Gd-BSA) was sequentially evaluated in a rat brain gliosarcoma model (n=5) by MR imaging (MRI). Following intravenous injection, the blood concentration of Gadomer-17 fell rapidly, whereas that of Gd-BSA was almost constant for the duration of imaging. The areas of enhancement of both MMCAs were comparable. The spatial distribution

of Gd-BSA showed good agreement with Evans blue-tagged albumin. Treatment with dexamethasone decreased Gd-BSA enhancement in the tumor. These results suggest that the arsenazo III method is applicable in preparing Gd-BSA to image brain tumors and their response to treatment. This simple method may also be useful for preparing other gadolinium-linked MMCAs.

Qian, J. Y., A. Leung, P. Harding and M. C. LaPointe (2006). "PGE2 stimulates human brain natriuretic peptide expression via EP4 and p42/44 MAPK." Am J Physiol Heart Circ Physiol **290**(5): H1740-6. [PDF Full-Text](#)

Brain natriuretic peptide (BNP) produced by cardiac myocytes has antifibrotic and antigrowth properties and is a marker of cardiac hypertrophy. We previously showed that prostaglandin E2 (PGE2) is the main prostaglandin produced in myocytes treated with proinflammatory stimuli and stimulates protein synthesis by binding to its EP4 receptor. We hypothesized that PGE2, acting through EP4, also regulates BNP gene expression. We transfected neonatal ventricular myocytes with a plasmid encoding the human BNP (hBNP) promoter driving expression of a luciferase reporter gene. PGE2 increased hBNP promoter activity 3.5-fold. An EP4 antagonist reduced the stimulatory effect of PGE2 but not an EP1 antagonist. Because EP4 signaling can involve adenylate cyclase, cAMP, and protein kinase A (PKA), we tested the effect of H-89, a PKA inhibitor, on PGE2 stimulation of the hBNP promoter. H-89 at 5 μ M decreased PGE2 stimulation of BNP promoter activity by 100%. Because p42/44 MAPK mediates the effect of PGE2 on protein synthesis, we also examined the role of MAPKs in the regulation of BNP promoter activity. PGE2 stimulation of the hBNP promoter was inhibited by a MEK1/2 inhibitor and a dominant-negative mutant of Raf, indicating that p42/44 MAPK was involved. In contrast, neither a p38 MAPK inhibitor nor a JNK inhibitor reduced the stimulatory effect of PGE2. Involvement of small GTPases was also studied. Dominant-negative Rap inhibited PGE2 stimulation of the hBNP promoter, but dominant-negative Ras did not. We concluded that PGE2 stimulates the BNP promoter mainly via EP4, PKA, Rap, and p42/44 MAPK.

Rivard, J., J. Janiga and H. W. Lim (2006). "Tacrolimus ointment 0.1% alone and in combination with medium-dose UVA1 in the treatment of palmar or plantar psoriasis." J Drugs Dermatol **5**(6): 505-10. [PDF Full-Text](#)

Psoriasis is a common skin condition affecting approximately 2.6% of the population in the US. The most effective current therapies for psoriasis have suppressive activity against T lymphocytes directly or by modulating the biologic effects of inflammatory cytokines. Tacrolimus has been used successfully to treat a number of T cell-mediated diseases. UVA1 has been shown to induce T lymphocyte apoptosis. Combination treatment is commonly used in the management of psoriasis. Therefore, this pilot study was performed to evaluate if the combination of medium-dose UVA1 (50 J/cm²) and tacrolimus ointment is effective for the treatment of palmar plantar psoriasis. A total of 5 patients completed the study of 30 UVA1 treatments, and another patient completed half of the treatments. No dramatic changes in plaque thickness or scaling were seen with either tacrolimus alone or with the combination of tacrolimus and medium dose UVA1 on palmar or plantar psoriasis.

Rivard, J. and H. W. Lim (2006). "The use of 308-nm excimer laser for dermatoses: experience with 34 patients." J Drugs Dermatol **5**(6): 550-4. [PDF Full-Text](#)

Targeted phototherapy has been utilized in the past few years for the treatment of various dermatoses. In this article, we summarize the experience of using 308-nm excimer laser at Henry Ford Hospital, Detroit, MI, for the treatment of psoriasis, vitiligo, palmoplantar psoriasis, and hand dermatitis. A total of 34 patients were treated between January 2003 and February 2005. Of the 28 patients with psoriasis, over 80% had greater than 75% improvement after an average of 12 treatments. While the number of patients was small, excimer laser showed promising results for palmoplantar psoriasis. Possibly due to patient selection bias, we have not had the same success as other studies for the treatment of vitiligo with this modality.

Rivard, J. and D. Ozog (2006). "Henry Ford Hospital dermatology experience with Levulan Kerastick and blue light photodynamic therapy." J Drugs Dermatol **5**(6): 556-61. [PDF Full-Text](#)

Photodynamic therapy (PDT) takes advantage of our understanding of the cutaneous response to topically applied porphyrins to selectively destroy malignant or premalignant cells. This type of therapy has been used to treat a variety of cutaneous diseases, including actinic keratoses, basal cell carcinoma, acne, and others. The treatment protocols are not standardized across institutions. We present the Henry Ford Dermatology protocol and early results of our first 150 treatments with PDT.

Rivers, E (2006). "Implementation of an evidence-based "standard operating procedure" and outcome in septic shock: What a sepsis pilot must consider before taking flight with your next patient." *Crit Care Med* **34**(4): 1247. [PDF Full-Text](#)

Roehrs, T., M. Hyde, B. Blaisdell, M. Greenwald and T. Roth (2006). "Sleep loss and REM sleep loss are hyperalgesic." *Sleep* **29**(2): 145-51. [PDF Full-Text](#)

STUDY OBJECTIVES: Disturbed sleep is observed in association with acute and chronic pain, and some data suggest that disturbed and shortened sleep enhances pain. We report the first data showing, in healthy, pain-free, individuals, that modest reductions of sleep time and specific loss of rapid eye movement (REM) sleep produces hyperalgesia the following morning. **DESIGN:** Two repeated-measures design protocols were conducted: (1) a sleep-loss protocol with 8 hours time-in-bed, 4 hours time-in-bed, and 0 hours time-in-bed conditions and (2) a REM sleep-loss protocol with 8 hours time-in-bed, 2 hours time-in-bed, REM deprivation, and non-REM yoked-control conditions. **SETTING:** The studies were conducted in an academic hospital sleep laboratory. **PARTICIPANTS:** Healthy pain-free normal sleepers, 7 in the sleep-loss protocol and 6 in the REM sleep-loss protocol, participated. **MEASUREMENTS:** Finger-withdrawal latency to a radiant heat stimulus tested at 10:30 AM and 2:30 PM and the Multiple Sleep Latency Test conducted at 10:00 AM, noon, 2:00 PM, and 4:00 PM were measured. **RESULTS:** Finger-withdrawal latency was shortened by 25% after 4 hours of time in bed the previous night relative to 8 hours of time in bed ($p < .05$), and REM sleep deprivation relative to a non-REM yoked-control sleep-interruption condition shortened finger-withdrawal latency by 32% ($p < .02$). **CONCLUSION:** These studies showed that the loss of 4 hours of sleep and specific REM sleep loss are hyperalgesic the following day. These findings imply that pharmacologic treatments and clinical conditions that reduce sleep and REM sleep time may increase pain.

Roehrs, T., A. Kapke, T. Roth and N. Breslau (2006). "Sex differences in the polysomnographic sleep of young adults: a community-based study." *Sleep Med* **7**(1): 49-53. **Full-Text Not Available** / [Click for Article Request Form](#)

BACKGROUND AND PURPOSE: In small, clinical samples, men have reduced slow wave sleep compared to women. Given the higher prevalence of sleep-related breathing disturbance in men, this study assessed sex differences in sleep in a large, non-clinical sample of adults and controlled for primary sleep disorders. **PATIENTS AND METHODS:** Men and women, 31-40 years old, drawn from a longitudinal sample representative of southeast Michigan served as subjects. Each underwent a sleep study consisting of two consecutive 8-h nights of standard polysomnography (NPSG) and a multiple sleep latency test (MSLT) the intervening day. **RESULTS:** Of the 439 eligible participants, 292 (66.5%) agreed to spend two consecutive nights and the intervening day in the sleep laboratory. Standard polysomnograms that monitored respiration and leg movements were collected each night, and on the intervening day the MSLT was performed. Men had more sleep-related breathing disturbance than women. After adjusting for this higher prevalence of respiratory disturbance, men still had a lower mean sleep efficiency (i.e. increased wake time) and a higher percentage of stage 1 sleep. Men and women did not differ in most other sleep parameters and did not differ in level of daytime sleepiness on the MSLT. **CONCLUSIONS:** Sleep-related respiratory disturbance accounted for some of the sex differences in sleep. After correcting for respiratory disturbance, men still had lighter and less efficient sleep, but this was not associated with greater daytime sleepiness. Whether this reflects a sex difference in the functioning of the sleep homeostat will require further study.

Rosenthal, L. S., S. Garzon, S. Setty and M. Yao (2006). "Left-sided facial mass. Spindle cell lipoma of the parotid gland." *Arch Pathol Lab Med* **130**(6): 875-6. [PDF Full-Text](#)

Schuger, C., K. A. Ellenbogen, M. Faddis, B. P. Knight, P. Yong and R. Sample (2006). "Defibrillation energy requirements in an ICD population receiving cardiac resynchronization therapy." *J Cardiovasc Electrophysiol* **17**(3): 247-50. **Full-Text Not Available** / [Click for Article Request Form](#)

OBJECTIVES: While defibrillation energy requirements (DERs) have been extensively studied in patients receiving conventional defibrillators, the DERs of patients receiving cardiac resynchronization therapy with defibrillation capability (CRT-D) devices have not been well described. The purpose of this analysis was to characterize DERs (defined as true threshold or the presence of appropriate safety margins) in patients undergoing implant of a CRT-D and to determine whether DERs in this population were similar to those reported for patients undergoing implantation of conventional defibrillators. **METHODS:** Data were analyzed retrospectively from the VENTAK CHF/CONTAK CD biventricular pacing study. An appropriate safety margin of at least 10 J was verified with at least two successful conversions with 21 J or less. Multivariate logistic regression was performed to determine baseline predictors of failed DER testing. **RESULTS:** Of 501 patients enrolled, 444 (89%) had successful DER test outcomes. Of the remaining 57 patients, 34 converted with energies \geq 21J, and 23 had their testing terminated prematurely or were not tested, primarily due to patient condition. Larger left ventricular internal dimension in diastole ($P = 0.003$) and prolonged procedure time ($P = 0.01$) were significant predictors of higher energy requirements. Few significant complications arose from DER testing. **CONCLUSIONS:** DER testing can be accomplished safely and successfully in the majority of CRT-D patients. However, safety margins cannot be ascertained in a significant number of these patients. Left ventricular inner diameter in diastole (LVIDd) and prolonged procedure time may predict higher DERs, and could be used to anticipate the need for a high-energy device or inclusion of a subcutaneous array.

Sheibani-Rad, S. and V. Velanovich (2006). "Effects of depression on the survival of pancreatic adenocarcinoma." *Pancreas* **32**(1): 58-61. [PDF Full-Text](#)

OBJECTIVES: Depression frequently predates the diagnosis of pancreatic adenocarcinoma. In other malignancies, depression has been shown to adversely affect survival. The purpose of this study was to assess whether survival after resection for pancreatic cancer is shortened by the pretreatment presence of depression. **METHODS:** A database of all patients diagnosed with pancreatic cancer was retrospectively reviewed for depression, resection, and chemotherapy and/or radiation therapy. A total of 258 patients were studied; 21% had depression, 19% had surgical resection of the tumor, and 42% were treated with chemotherapy and/or radiation therapy. Survival data was analyzed using Cox proportional hazard regression and life table analysis. **RESULTS:** The median survival time for all depressed patients with pancreatic cancer was 5 months compared with 4 months for all nondepressed patients with pancreatic cancer ($P < 0.9$). There was no difference in stage, rate of surgical resection, rate of chemotherapy administration, or rate of radiation therapy use between depressed and nondepressed patients. **CONCLUSION:** Patients who had undergone surgical resection or chemotherapy and/or radiation therapy had longer survival times than those who did not. Depression, although common among patients with pancreatic cancer, does not affect survival.

Silver, B., K. M. Grover, X. Arcila, P. D. Mitsias, S. M. Bowyer and M. Chopp (2006). "Recovery in a patient with locked-in syndrome." *Can J Neurol Sci* **33**(2): 246-9. **Full-Text Not Available** / [Click for Article Request Form](#)

BACKGROUND AND PURPOSE: Sildenafil citrate has been shown to enhance neurogenesis, angiogenesis, synaptogenesis, and neurological outcome by augmentation of cyclic guanosine monophosphate (cGMP) levels in animal models of ischemic stroke. Whether sildenafil citrate may be helpful for recovery in human stroke is unknown at this time. **METHODS:** A 41-year-old woman with locked-in syndrome due to pontine infarction began receiving 150 mg of oral sildenafil citrate daily on a compassionate use basis in August 2003 and continues treatment at this time. Magneto-encephalography (MEG) was performed at 12 and 17 months after stroke. **RESULTS:** No serious adverse events have occurred. Significant milestone recoveries including standing, use of both arms, talking, and full return of swallowing have occurred, particularly after nine months of treatment. The MEG showed a significantly

increased amplitude in the somatosensory cortex. CONCLUSION: Daily use of high dose sildenafil citrate appears to be safe in this patient with stroke resulting in locked-in syndrome. Further studies will be required to establish safety and efficacy.

Tuchinda, C. and H. K. Wong (2006). "Etanercept for chronic progressive cutaneous sarcoidosis." *J Drugs Dermatol* **5**(6): 538-40. [PDF Full-Text](#)

Sarcoidosis is a chronic, multisystem, granulomatous disease that has various cutaneous manifestations. Chronic cutaneous sarcoidosis can be difficult to manage. Patients often need systemic corticosteroids as well as other immunosuppressive agents, which may be associated with side effects and long-term complications. We report a 43-year-old patient with chronic progressive cutaneous sarcoidosis unsuccessfully treated with systemic steroid and immunosuppressive agents whose cutaneous lesions responded significantly to etanercept as monotherapy.

van Buskirk, C., E. M. Burd and M. Lee (2006). "A painful, draining black lesion on the right heel. Tungiasis." *Clin Infect Dis* **43**(1): 65-6, 106-8. **Full-Text Not Available / [Click for Article Request Form](#)**

Varelas, P., A. Helms, G. Sinson, M. Spanaki and L. Hacein-Bey (2006). "Clipping or coiling of ruptured cerebral aneurysms and shunt-dependent hydrocephalus." *Neurocrit Care* **4**(3): 223-8. **Full-Text Not Available / [Click for Article Request Form](#)**

BACKGROUND: Hydrocephalus may develop either early in the course of aneurysmal subarachnoid hemorrhage (SAH) or after the first 2 weeks. Because the amount of SAH is a predictor of hydrocephalus, the two available aneurysmal treatments, clipping or coiling, may lead to differences in the need for cerebrospinal fluid (CSF) diversion, as only surgery permits clot removal. METHODS: Hospital and University Hospitals Consortium (UHC) databases were used to retrieve data on all patients admitted to our hospital with aneurysmal SAH during the last 4 years. The incidence of permanent ventricular shunt (VS) according to treatment modality used was evaluated. RESULTS: One hundred eighty-eight patients were admitted with aneurysmal SAH. Coiling was performed on 48 (26%) and clipping on 135 (73.8%) patients. Fifty-six (31%) patients required CSF diversion. External ventricular drain was placed in 30 (22.2%) clipped and 13 (27.1%) coiled patients ($p = 0.5$), and VS in 6 patients of the two treatment groups (4.4 versus 12.5%, respectively; $p = 0.08$). Patients requiring VS had longer UHC-expected hospital length of stay (LOS), as well as observed ICU and hospital LOS, compared to patients with temporary or no CSF diversion (24 +/- 14 versus 15 +/- 8, 20.5 +/- 9 versus 11 +/- 7, and 30 +/- 13 versus 16 +/- 11 days, respectively; $p < 0.01$). In a logistic regression model, VS was independently associated with rebleeding, external ventricular drain placement, coiling, and UHC-expected LOS (odds ratios, 95% confidence interval 12.1, 2.3 - 62.6, 6.9, 1.6 - 30, 6.25, 1.3 - 29, and 1.1, 1.02 - 1.14, respectively). CONCLUSIONS: One-third of patients admitted with aneurysmal SAH require temporary or permanent CSF diversion. Permanent shunting was found to be associated with coiling in our patient population.

Varelas, P. N., D. Eastwood, H. J. Yun, M. V. Spanaki, L. Hacein Bey, C. Kessarlis and T. A. Gennarelli (2006). "Impact of a neurointensivist on outcomes in patients with head trauma treated in a neurosciences intensive care unit." *J Neurosurg* **104**(5): 713-9. [PDF Full-Text](#) (ID = sladen / Password = library1)

OBJECT: The aim of this study was to evaluate the impact of a newly appointed neurointensivist on outcomes in head-injured patients in the neurological/neurosurgical intensive care unit (NICU). METHODS: The mortality rate, length of stay (LOS), and discharge disposition of all patients with head trauma who had been admitted to a 10-bed tertiary care university hospital NICU were compared between two 19-month periods, before and after the appointment of a neurointensivist. Data regarding these patients were collected using the hospital database and the University HealthSystem Consortium (UHC) database. Samples of medical records were reviewed for Glasgow Coma Scale (GCS) score documentation. The authors analyzed data pertaining to 328 patients before and 264 after the neurointensivist's appointment. The unadjusted mean in-hospital mortality rate increased 1.1% in the after period, but this increase was significantly lower compared with the UHC-based expected increase of 8.1% in the mortality rate during

the same period ($p < 0.0001$). The unadjusted mean mortality rate in the NICU decreased from 13.4 to 12.9% (relative mortality rate reduction 4%) and the mean NICU LOS increased from 3.1 to 3.6 days (relative NICU LOS increase 16%), both nonsignificantly. A 51% reduction in the NICU-associated mortality rate ($p = 0.01$), a 12% shorter hospital LOS ($p = 0.026$), and 57% greater odds of being discharged to home or to rehabilitation ($p = 0.009$) were found in the after period in multivariate models after controlling for baseline differences between the two time periods. Better documentation of the GCS score by the NICU team was also found in the after period (from 60.4 to 82%, $p = 0.02$). **CONCLUSIONS:** The institution of a neurointensivist-led team model had an independent, positive impact on patient outcomes, including a lower NICU-associated mortality rate and hospital LOS, improved disposition, and better chart documentation.

Vazquez, J. A. (2005). "Anidulafungin: a new echinocandin with a novel profile." *Clin Ther* **27**(6): 657-73. **Full-Text Not Available / [Click for Article Request Form](#)**

BACKGROUND: Until recently, available treatment for serious fungal infections comprised amphotericin B and azoles, which have limitations. Renal toxicity is a major concern with amphotericin B, while drug-drug interactions, hepatotoxicity, and skin rashes are the primary concerns with the azole medications. The development of the echinocandins, including caspofungin, has helped to fill the need for more efficacious antifungals that are useful across different patient populations and have a good safety profile. Anidulafungin is an echinocandin being developed to treat mucosal and invasive fungal infections. **OBJECTIVE:** The aim of this report was to describe the pharmacodynamic and pharmacokinetic (PK) properties of anidulafungin. **METHODS:** Data were identified using MEDLINE and National Library of Medicine Gateway searches for English-language literature (key words: anidulafungin, esophageal candidiasis, echinocandin, caspofungin, ravuconazole, voriconazole, posaconazole, micafungin, and fluconazole; years: 1996-2004), and from meeting abstracts of the American Society for Blood and Marrow Transplantation (Arlington Heights, Illinois), European Congress of Clinical Microbiology and Infectious Diseases (Basel, Switzerland), International Conference on Antimicrobial Agents and Chemotherapy (Washington, DC), and Infectious Diseases Society of America (Arlington, Virginia). **RESULTS:** Anidulafungin has potent in vitro activity against *Aspergillus* and *Candida* spp, including those resistant to either fluconazole or amphotericin B. Results of several clinical trials imply that anidulafungin is effective in treating esophageal candidiasis (EC), candidemia, and invasive candidiasis (IC). In a Phase III, randomized, blinded clinical trial evaluating anidulafungin (50 mg/d) versus fluconazole (100 mg/d) for the treatment of EC, 97.2% and 98.9% of patients who received anidulafungin and fluconazole, respectively, showed evidence of cure or improvement (treatment difference, -1.6%; 95% CI, -4.1 to 0.8). In a Phase II study of candidiasis and candidemia, anidulafungin showed success rates of 72%, 85%, and 83% in patients receiving the drug at dosages of 50, 75, or 100 mg/d, respectively. Studies evaluating the concomitant use of anidulafungin and either amphotericin, voriconazole, or cyclosporine did not show clinically significant drug-drug interactions or altered adverse-event (AE) profiles ($P < 0.05$). A population PK analysis showed no significant effect of age, race, concomitant medications, or renal or hepatic insufficiency on the PK properties of anidulafungin ($P < 0.05$). **CONCLUSIONS:** Anidulafungin may offer a new option to treat serious fungal infections, such as EC,azole-refractory EC, candidemia, and IC. In addition, anidulafungin has been associated with no clinically significant drug-drug interactions and few treatment-related AEs. Anidulafungin may offer a new option in the management of serious and difficult-to-treat invasive fungal infections.

Vazquez, J. A. and J. D. Sobel (2006). "Anidulafungin: a novel echinocandin." *Clin Infect Dis* **43**(2): 215-22. **[PDF Full-Text](#)**

Until recently, the treatment available for serious fungal infections was composed of amphotericin B and azoles, and each class demonstrated significant limitations. Echinocandins are a new class of drugs that have shown promising results in treating a variety of fungal infections. Of these, anidulafungin is a novel echinocandin that appears to have several advantages over existing antifungals. It is unique because it slowly degrades in humans, undergoing a process of biotransformation rather than being metabolized. It has potent in vitro activity against *Aspergillus* and *Candida* species, including those resistant to fluconazole or amphotericin B. Results of several clinical trials indicate that anidulafungin is effective in treating esophageal candidiasis, including azole-refractory disease. The results of a recent study comparing fluconazole versus anidulafungin demonstrated the superiority of anidulafungin in the treatment of

candidemia and invasive candidiasis (IC). Studies evaluating the concomitant use of anidulafungin and either amphotericin B, voriconazole, or cyclosporine did not demonstrate significant drug-drug interactions or adverse events. To date, anidulafungin appears to have an excellent safety profile. On the basis of early clinical experience, it appears that anidulafungin will be a valuable asset in the management of serious and difficult-to-treat fungal infections.

Wang, L., Z. G. Zhang, R. L. Zhang, S. R. Gregg, A. Hozeska-Solgot, Y. LeTourneau, Y. Wang and M. Chopp (2006). "Matrix metalloproteinase 2 (MMP2) and MMP9 secreted by erythropoietin-activated endothelial cells promote neural progenitor cell migration." *J Neurosci* **26**(22): 5996-6003. [PDF Full-Text](#)

We investigated the hypothesis that endothelial cells activated by erythropoietin (EPO) promote the migration of neuroblasts. This hypothesis is based on observations in vivo that treatment of focal cerebral ischemia with EPO enhances the migration of neuroblasts to the ischemic boundary, a site containing activated endothelial cells and angiogenic microvasculature. To model the microenvironment within the ischemic boundary zone, we used a coculture system of mouse brain endothelial cells (MBECs) and neural progenitor cells derived from the subventricular zone of the adult mouse. Treatment of MBECs with recombinant human EPO (rhEPO) significantly increased secretion of matrix metalloproteinase 2 (MMP2) and MMP9. rhEPO-treated MBEC supernatant as conditioned medium significantly increased the migration of neural progenitor cells. Application of an MMP inhibitor abolished the supernatant-enhanced migration. Incubation of neurospheres alone with rhEPO failed to increase progenitor cell migration. rhEPO activated phosphatidylinositol 3-kinase/Akt (PI3K/Akt) and extracellular signal-regulated kinase (ERK1/2) in MBECs. Selective inhibition of the PI3K/Akt and ERK1/2 pathways significantly attenuated the rhEPO-induced MMP2 and MMP9, which suppressed neural progenitor cell migration promoted by the rhEPO-activated MBECs. Collectively, our data show that rhEPO-activated endothelial cells enhance neural progenitor cell migration by secreting MMP2 and MMP9 via the PI3K/Akt and ERK1/2 signaling pathways. These data demonstrate that activated endothelial cells can promote neural progenitor cell migration, and provide insight into the molecular mechanisms underlying the attraction of newly generated neurons to injured areas in brain.

Wang, L., Z. G. Zhang, R. L. Zhang, Z. X. Jiao, Y. Wang, D. S. Pourabdollah-Nejad, Y. LeTourneau, S. R. Gregg and M. Chopp (2006). "Neurogenin 1 mediates erythropoietin enhanced differentiation of adult neural progenitor cells." *J Cereb Blood Flow Metab* **26**(4): 556-64. **Full-Text Not Available** / [Click for Article Request Form](#)

Proneuronal basic helix-loop-helix (bHLH) transcription factor, neurogenin 1 (Ngn1), regulates neuronal differentiation during development of the cerebral cortex. Akt mediates proneuronal bHLH protein function to promote neuronal differentiation. Here, we show that recombinant human erythropoietin (rhEPO) significantly increased Akt activity and Ngn1 mRNA levels in neural progenitor cells derived from the subventricular zone (SVZ) of adult rat, which was coincident with increases of neural progenitor cell proliferation, differentiation, and neurite outgrowth. Inhibition of Akt activity by the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) inhibitor, LY294002, abolished rhEPO-increased Ngn1 mRNA levels and the effects of rhEPO on neural progenitor cells. In addition, reducing expression of endogenous Ngn1 by means of short-interfering RNA (siRNA) blocked rhEPO-enhanced neuronal differentiation and neurite outgrowth but not rhEPO-increased proliferation. Furthermore, treatment of stroke rat with rhEPO significantly increased Ngn1 mRNA levels in SVZ cells. These data suggest that rhEPO acts as an extracellular molecule that activates the PI3K/Akt pathway, which enhances adult neural progenitor cell proliferation, differentiation, and neurite outgrowth, and Ngn1 is required for Akt-mediated neuronal differentiation and neurite outgrowth.

Warnick, S. J., Jr. and V. Velanovich (2006). "Correlation of patient-derived utility values and quality of life after pancreaticoduodenectomy for pancreatic cancer." *J Am Coll Surg* **202**(6): 906-11. [PDF Full-Text](#)

BACKGROUND: Utility value (UV) represents the "value" that a patient places on a given health state and can be closely associated with quality of life. The purpose of this study was to determine if UV and quality

of life are correlated after pancreaticoduodenectomy for pancreatic adenocarcinoma and to assess quality of life after pancreaticoduodenectomy. **STUDY DESIGN:** Patients who underwent pancreaticoduodenectomy for pancreatic cancer were interviewed using the 36-item Short Form Health Survey, which measures 8 domains of quality of life. Patients assessed their current health state by rating their present health from 0 (which was equivalent to death) to 100 (which was equivalent to perfect health), and by a time-exchange (TE) method that asked how many years of their present life they would be willing to exchange for perfect health. Statistical analysis consisted of linear regression analysis and Mann-Whitney U test. **RESULTS:** Twenty patients were interviewed. The UVs correlated with the TE ($p = 0.003$, $r = -0.63$), and 6 of 8 36-item Short Form Health Survey domains: physical functioning ($p < 0.00001$, $r = 0.82$), role-physical ($p = 0.005$, $r = 0.61$), bodily pain ($p = 0.003$, $r = 0.63$), general health ($p = 0.00001$, $r = 0.81$), vitality ($p = 0.01$, $r = 0.54$), and mental health ($p = 0.03$, $r = 0.5$). The TE score correlated with the physical functioning ($p = 0.06$, $r = -0.59$) and bodily pain ($p = 0.05$, $r = -0.44$) domains. There were significant differences in the UV, TE, physical functioning, role-physical, and role-emotional between patients less than 1 year and more than 1 year postoperative. **CONCLUSIONS:** These data imply that patient-perceived health status and quality of life are linked and that quality-of-life scores after pancreaticoduodenectomy are better in patients more than 1 year postoperative.

Weaver, M., J. Liu, D. Pimentel, D. J. Reddy, P. Harding, E. L. Peterson and P. J. Pagano (2006). "Adventitial delivery of dominant-negative p67phox attenuates neointimal hyperplasia of the rat carotid artery." *Am J Physiol Heart Circ Physiol* **290**(5): H1933-41. [PDF Full-Text](#)

Several essential components of NADPH oxidase, including p22phox, gp91phox (nox2) and its homologs nox1 and nox4, p47phox, p67phox, and rac1, are present in the vasculature. We previously reported that p67phox is essential for adventitial fibroblast NADPH oxidase O₂- production. Thus we postulated that inhibition of adventitial p67phox activity would attenuate angioplasty-induced hyperplasia. To test this hypothesis, we treated the adventitia of carotid arteries with a control adenovirus (Ad-control), a virus expressing dominant-negative p67phox (Ad-p67dn), or a virus expressing a competitive peptide (gp91ds) targeting the p47phox-gp91phox interaction (Ad-gp91ds). Common carotid arteries (CCAs) from male Sprague-Dawley rats were transfected with Ad-control, Ad-p67dn, or Ad-gp91ds in pluronic gel. After 2 days, a 2-F (Fogarty) catheter was used to injure CCAs in vivo. After 14 days, CCAs were perfusion-fixed and analyzed. In 13 experiments, digital morphometry suggested a reduction of neointimal hyperplasia with Ad-p67dn compared with Ad-control; however, the reduction did not reach statistical significance ($P = 0.058$). In contrast, a significant reduction was achieved with Ad-gp91ds ($P = 0.006$). No changes in medial area or remodeling were observed with either treatment. Moreover, adventitial fibroblast proliferation in vitro was inhibited by Ad-gp91ds but not by Ad-p67dn, despite confirmation that Ad-p67dn inhibits NADPH oxidase in fibroblasts. These data appear to suggest that a multicomponent vascular NADPH oxidase plays a role in neointimal hyperplasia. However, inhibition of p47phox may be more effective than inhibition of p67phox at attenuating neointimal growth.

Wong, H. K. and G. C. Tsokos (2006). "Fas (CD95) ligation inhibits activation of NF-kappaB by targeting p65-Rel A in a caspase-dependent manner." *Clin Immunol*. **Full-Text Not Available / [Click for Article Request Form](#)**

Apoptosis is an important mechanism in T cell regulation. Initiation of apoptosis can be activated through two signaling pathways via proteins that bind the death domain, the MAPK-JNK pathway mediated by DAXX and the caspase pathway mediated by FADD. T cell proliferation is initiated by ligation of the T cell receptor (TCR) and activation of NF-kappaB, a transcription factor that has antiapoptotic functions. These pathways however are not isolated, and potential crosstalk between elements of the apoptotic pathway and growth pathway may be essential in determining cell survival. We studied the interaction between Fas- and the TCR-initiated pathways in Jurkat T cell as these pathways lead to opposing consequences. We show that Fas activation can inhibit TCR- and PMA/ionophore-initiated activation of NF-kappaB activity. The inhibition is caspase-dependent since an inhibitor of caspase activation, DEVD, can block the suppression of NF-kappaB activity following crosslinking of Fas. Analysis of the expression of the subunits of NF-kappaB revealed that the levels of p50 remained constant, whereas the levels of p65 were markedly decreased by crosslinking of Fas. These findings suggest that the Fas-ligation-mediated

suppression preferentially targets p65 protein expression as a mechanism for suppression of antiapoptotic activities of NF-kappaB during apoptosis.

Zacharek, A., J. Chen, C. Zhang, X. Cui, C. Roberts, H. Jiang, H. Teng and M. Chopp (2006). "Nitric oxide regulates Angiopoietin1/Tie2 expression after stroke." *Neurosci Lett.* [PDF Full-Text](#)

We tested whether the nitric oxide donor, (Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl) aminio] diazen-1-ium-1,2-diolate (DETA-NONOate), increases expression of Angiopoietin (Ang1)/Tie2, which may play a role in regulating angiogenesis and vascular integrity after stroke in rats. Wistar rats were subjected to middle cerebral artery occlusion and treated with or without DETA-NONOate. Stroke rats treated with DETA-NONOate show significantly increased Ang1, Tie2 and Occludin expression in the ischemic border compared with control stroke animals ($p < 0.05$). Consistent with in vivo data, DETA-NONOate promotes capillary tube formation in cultured brain endothelial cells. Neutralizing Ang1 antibody attenuates DETA-NONOate-induced capillary tube formation. The data suggest that the Ang1/Tie2 axis promotes DETA-NONOate-induced angiogenesis and stabilizes of angiogenic vessels after stroke.

Zhang, C., Y. Li, J. Chen, Q. Gao, A. Zacharek, A. Kapke and M. Chopp (2006). "Bone marrow stromal cells upregulate expression of bone morphogenetic proteins 2 and 4, gap junction protein connexin-43 and synaptophysin after stroke in rats." *Neuroscience.* [PDF Full-Text](#)

Bone morphogenetic proteins play a key role in astrocytic differentiation. Astrocytes express the gap junctional protein connexin-43, which permits exchange of small molecules in brain and enhances synaptic efficacy. Bone marrow stromal cells produce soluble factors including bone morphogenetic protein 2 and bone morphogenetic protein 4 (bone morphogenetic protein 2/4) in ischemic brain. Here, we tested whether intra-carotid infusion of bone marrow stromal cells promotes synaptophysin expression and neurological functional recovery after stroke in rats. Adult male Wistar rats were subjected to 2 h of right middle cerebral artery occlusion. Rats were treated with or without bone marrow stromal cells at 24 h after middle cerebral artery occlusion via intra-arterial injection ($n=8$ /group). A battery of functional tests was performed. Immunostaining of 5-bromo-2-deoxyuridine, Ki67, bone morphogenetic protein 2/4, connexin-43, synaptophysin, glial fibrillary acidic protein, neuronal nuclear antigen, and double staining of 5-bromo-2-deoxyuridine/glial fibrillary acidic protein, 5-bromo-2-deoxyuridine/neuronal nuclear antigen, glial fibrillary acidic protein/bone morphogenetic protein 2/4 and glial fibrillary acidic protein/connexin-43 were employed. Rats treated with bone marrow stromal cells significantly ($P < 0.05$) improved functional recovery compared with the controls. 5-Bromo-2-deoxyuridine and Ki67 positive cells in the ipsilateral subventricular zone were significantly ($P < 0.05$) increased in bone marrow stromal cell treatment group compared with the controls, respectively. Administration of bone marrow stromal cells significantly ($P < 0.05$) promoted the proliferating cell astrocytic differentiation, and increased bone morphogenetic protein 2/4, connexin-43 and synaptophysin expression in the ischemic boundary zone compared with the controls, respectively. Bone morphogenetic protein 2/4 expression correlated with the expression of connexin-43 ($r=0.84$, $P < 0.05$) and connexin-43 expression correlated with the expression of synaptophysin ($r=0.73$, $P < 0.05$) in the ischemic boundary zone, respectively. Administration of bone marrow stromal cells via an intra-carotid route increases endogenous brain bone morphogenetic protein 2/4 and connexin-43 expression in astrocytes and promotes synaptophysin expression, which may benefit functional recovery after stroke in rats.

Zhang, J., Y. Li, M. Lu, Y. Cui, J. Chen, L. Noffsinger, S. B. Elias and M. Chopp (2006). "Bone marrow stromal cells reduce axonal loss in experimental autoimmune encephalomyelitis mice." *J Neurosci Res.* [PDF Full-Text](#)

We investigated the ability of human bone marrow stromal cell (hBMSC) treatment to reduce axonal loss in experimental autoimmune encephalomyelitis (EAE) mice. EAE was induced in SJL/J mice by injection with proteolipid protein (PLP). Mice were injected intravenously with hBMSCs or PBS on the day of clinical onset, and neurological function was measured daily (score 0-5) until 45 weeks after onset. Mice were sacrificed at week 1, 10, 20, 34, and 45 after clinical onset. Bielschowsky silver was used to identify axons. Immunohistochemistry was performed to measure the expression of nerve growth factor (NGF) and

MAB1281, a marker of hBMSCs. hBMSC treatment significantly reduced the mortality, the disease severity, and the number of relapses in EAE mice compared with PBS treatment. Axonal density and NGF(+) cells in the EAE brain were significantly increased in the hBMSC group compared with the PBS group at 1, 10, 20, 34, and 45 weeks. Disease severity was significantly correlated with decreased axonal density and decreased NGF, and increased axonal density was significantly correlated with reduced loss of NGF expression after hBMSC treatment. Most of the NGF(+) cells are brain parenchymal cells. Under 5% of MAB1281(+) cells colocalized with NG2(+), a marker of oligodendrocyte progenitor cells. Nearly 10% of MAB1281(+) cells colocalized with GFAP, a marker of astrocytes, and MAP-2, a marker of neurons. Our findings indicate that hBMSCs improve functional recovery and may provide a potential therapy aimed at axonal protection in EAE mice, in which NGF may play a vital role. (c) 2006 Wiley-Liss, Inc.

Zhuo, J. L., X. C. Li, J. L. Garvin, L. G. Navar and O. A. Carretero (2006). "Intracellular ANG II induces cytosolic Ca²⁺ mobilization by stimulating intracellular AT1 receptors in proximal tubule cells." *Am J Physiol Renal Physiol* **290**(6): F1382-90. [PDF Full-Text](#)

Intracellular ANG II induces biological effects in nonrenal cells, but it is not known whether it plays a physiological role in renal proximal tubule cells (PTCs). PTCs express angiotensinogen, renin, and angiotensin-converting enzyme mRNAs, suggesting the presence of high levels of intracellular ANG II. We determined if microinjection of ANG II directly in single PTCs increases intracellular calcium concentration ([Ca²⁺]_i) and, if so, elucidated the cellular mechanisms involved. Changes in [Ca²⁺]_i responses were studied by fluorescence imaging using the Ca²⁺ indicator fluo 3. ANG II (1 nM) was microinjected directly in the cells, whereas cell-surface angiotensin type 1 (AT1) receptors were blocked by losartan (10 microM). When ANG II (1 nM) was added to the perfusate, there was a marked increase in [Ca²⁺]_i that was blocked by extracellular losartan. With losartan in the perfusate, intracellular microinjection of ANG II elicited a robust increase in cytoplasmic [Ca²⁺]_i that peaked at 30 s (basal: 2.2 +/- 0.3 vs. ANG II: 14.9 +/- 0.4 relative fluorescence units; P < 0.01). Chelation of extracellular Ca²⁺ with EGTA (2 mM) did not alter microinjected ANG II-induced [Ca²⁺]_i responses (Ca²⁺ free + ANG II: 12.3 +/- 2.6 relative fluorescence units, not significant vs. ANG II); however, pretreatment with thapsigargin to deplete intracellular Ca²⁺ stores or with U-73122 to inhibit phospholipase C (1 microM each) markedly attenuated microinjected ANG II-induced [Ca²⁺]_i responses. Combined microinjection of ANG II and losartan abolished [Ca²⁺]_i responses, whereas a combination of ANG II and PD-123319 had no effect. These data demonstrate for the first time that direct microinjection of ANG II in single PTCs increases [Ca²⁺]_i by stimulating intracellular AT1 receptors and releases Ca²⁺ from intracellular stores, suggesting that intracellular ANG II may play a physiological role in PTC function.

**HFHS Publication List
Sladen Library**

http://www.henryford.com/body_nologin.cfm?id=46638

If you are interested in receiving this list of HFHS Publications on a monthly basis, please fill out the following information:

Name _____

Department _____

Phone Number _____

Email _____

Do you want to receive it:

_____ **Via email (Recommended format – includes links to full-text if available)**

_____ **Via interdepartmental mail**

Please return to:

**Valerie Reid
HFH Sladen Library, K-17
(313) 916-2550
(313) 874-4730 Fax
vreid1@sladen.hfhs.org**