and in vivo increased their sensitivity to IL-13PE cytotoxin consisting of IL-13 and a truncated form of Pseudomonas exotoxin. Immunodeficient mice with established prostate tumors transfected with AM or treated with AM peptide showed reduction in tumor size by intratumoral administration of IL-13PE in a dose-dependent manner. At the highest dose (three 100 μg/kg/d every alternate day), >70% reduction of tumor size was observed compared with controls (P < or = 0.01). These results indicate that two completely unrelated hormones (AM and IL-13) are closely related to each other and that we have identified a novel role of AM in sensitizing certain types of prostate tumors to IL-13R-directed therapeutic agent.

**Editorial Comment:** In this study the authors have investigated the effect of purified recombinant adrenomedullin, synthetic adrenomedullin peptide or gene transfection of adrenomedullin on IL-13Rα2 in prostate cancer cells in vitro and in vivo in a mouse model. The biological function of up-regulated IL-13Rα2 protein was examined in a xenograft model of human prostate cancer. Adrenomedullin gene transfected prostate carcinoma cells formed tumors in athymic nude mice, which were subsequently treated with IL-13 Pseudomonas exotoxin immunotoxin, and tumor growth was measured. A dramatic decrease in tumor size was observed. The authors identified adrenomedullin, a new class of tumor sensitizer for IL-13 targeted anticancer therapy, in certain types of prostate cancers. IL-13R directed therapy may be useful in prostate cancers with low expression of IL-13Rα2 after adrenomedullin treatment followed by IL-13 Pseudomonas exotoxin cytotoxin based therapy. Since recent studies have identified IL-13Rα2 chain as a tumor rejection antigen, adrenomedullin may also be useful as a sensitizer for cancer vaccines for localized cancers.

Anthony Atala, M.D.

Infection and Inflammation of the Genitourinary Tract

**Cystitis is Associated With TRPV1b-Downregulation in Rat Dorsal Root Ganglia**

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**Editorial Comment:** Patients diagnosed with interstitial cystitis often report that symptoms started with a bladder infection but later persisted. This study provides a possible mechanism for sensitization during acute inflammation of the bladder related neurons. This sensitization takes place on a central level in the spinal cord and could result in hypersensitivity to preexisting or later developing endogenous or exogenous stimuli in the particular patient. This model does not address whether early treatment or symptomatic relief could alter or forestall these spinal cord changes, but the results are intriguing.

Richard E. Berger, M.D.

**Serotonergic and Noradrenergic Facilitation of the Visceromotor Reflex Evoked by Urinary Bladder Distension in Rats With Inflamed Bladders**

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Bladder inflammation resulting from intravesical administration of zymosan significantly enhances the visceromotor reflex (VMR) evoked by urinary bladder distension (UBD). The present study
examined whether intrathecal (i.t.) administration of receptor antagonists to either norepinephrine (NE) or serotonin (5-HT) altered this enhancement effect. I.t. administration of the non-specific 5-HT receptor antagonist methysergide (30 microg), the 5-HT(3) receptor antagonist ondansetron, or the 5-HT(1A) receptor antagonist WAY 100635 eliminated the enhancement effect produced by intravesical zymosan and also tended to reduce electromyographic (EMG) responses to UBD in non-inflamed rats. I.t. administration of either the non-specific NE receptor antagonist phentolamine (30 microg) or the alpha(1) antagonist WB 4101 also eliminated the enhancement effect, whereas i.t. administration of the alpha(2) antagonist yohimbine failed to significantly affect the enhancement effect. The effects of phentolamine and methysergide were not mediated by changes in bladder compliance. This is the first study to demonstrate that bladder hypersensitivity resulting from bladder inflammation is partly mediated by 5-HT and NE facilitatory effects. Based on these and previous findings we conclude that the net nociceptive response to bladder distension under conditions of bladder inflammation represents a complex interaction of facilitatory influences of spinal 5-HT and NE, and inhibitory influences of spinal opioids.

Editorial Comment: Most clinical studies concerning the treatment of pelvic pain and bladder pain syndromes have been empirical because we have had little understanding of the organ specifics and neuropathology of the disorders. This study documents the 5-HT and NE facilitatory central effects on the visceromotor reflexes involved in bladder inflammation. Studies such as this will be important in developing rational single agent and combination trials in the future.

Richard E. Berger, M.D.

Laparoscopy/New Technology

Does Topical Haemostatic Agent Have an Adverse Effect on the Function of the Prostatic Neurovascular Bundle?

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Objective: To assess the functional and histological effects of a bovine thrombin topical haemostatic agent used clinically to aid in surgical haemostasis (FloSeal(TM), Baxter International Inc., Deerfield, IL, USA) on the cavernous nerves in a canine model of survival, as there are concerns that the fibrotic/inflammatory response to this product could affect neural function. Materials and Methods: In phase I, nine adult male dogs had the bilateral neurovascular bundles (NVBs) dissected. A small intravenous catheter placed directly into the erectile bodies of the penis was used to record the intracorporal pressure (ICP). Erection was induced by electrical stimulation of the NVB on each side. After intraoperative randomization to treatment or control, 5 mL of FloSeal was unilaterally applied along the NVB on the treatment side. In phase II, after 2 weeks of survival, both control and treatment NVB were again dissected and re-stimulated to produce an erectile response. The mean arterial pressure and ICP were recorded. The prostate and the NVBs were then removed for histological analysis. Results: All dogs achieved erections after electrical stimulation on both the control and treatment side. There was no statistically significant difference in absolute ICP, pressure increase from baseline or systemic pressure after stimulating the NVB on the treatment side between phases I and II. Histological analysis showed a giant-cell reaction around the FloSeal granules and mild focal perineural oedema, but the cavernous nerves were otherwise normal in appearance. Conclusion: In this short-term functional study, FloSeal did not adversely affect cavernous nerve function, measured as the erectile response to electrical stimulation. We found no evidence contraindicating its use during radical prostatectomy.

Editorial Comment: This animal study adds to the favorable clinical and animal experience supporting the safety of bovine thrombin topical hemostatic agent on the neurovascular bundles during radical prostatectomy.

Jeffrey A. Cadeddu, M.D.