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The Journal of UROLOGY

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Number 5

CLINICAL UROLOGY

State of Art Article

- Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Evolving Role of Surgery. *H. W. Herr, W. F. Whitmore, Jr., M. J. Morse, P. C. Sogani, P. Russo, J. Sheinfeld and W. R. Fair* 1083

Original Articles

- Anatomical Relationship Between Renal Venous Arrangement and Kidney Collecting System. *F. J. B. Sampaio and A. H. M. Aragão* 1089
- Surgical Treatment of Renal Artery Stenosis After Failed Percutaneous Transluminal Angioplasty. *A. G. Martinez, A. C. Novick and J. M. Hayes* 1094
- Incidence and Properties of Renal Masses and Asymptomatic Renal Cell Carcinoma Detected by Abdominal Ultrasonography. *A. Tosaka, K. Ohya, K. Yamada, H. Ohashi, S. Kitahara, H. Sekine, Y. Takehara and K. Oka* 1097
- Magnetic Resonance Imaging for Assessment of Vena Caval Tumor Thrombi: Comparative Study With Venacavography and Computerized Tomography Scanning. *D. A. Goldfarb, A. C. Novick, R. Lorig, P. N. Bretan, J. E. Montie, J. E. Pontes, S. B. Stroom and S. W. Siegel* (Editorial Comments by J. B. deKernion and B. L. McClennan) 1100
- Extravesical Versus Leadbetter-Politano Ureteroneocystostomy: Comparison of Urological Complications in 320 Renal Transplants. *J. B. Thrasher, D. R. Temple and E. K. Spees* 1105
- Ureterosigmoidostomy: Long-Term Results, Risk of Carcinoma and Etiological Factors for Carcinogenesis. *T. Kälble, A. R. Tricker, P. Friedl, R. Waldherr, J. Hoang, G. Staehler and K. Möhring* 1110
- Primary Adenocarcinoma of Bladder: Favorable Prognostic Significance of Deoxyribonucleic Acid Diploidy Measured by Flow Cytometry. *J. Song, G. M. Farrow and M. M. Lieber* 1115
- Randomized Phase II Evaluation of Carboplatin and CHIP in Advanced Transitional Cell Carcinoma of Urothelium. *D. L. Trump, P. Elson, S. Madajewicz, S. H. Dickman, R. G. Hahn, J. E. Harris, S. E. Vogl and Eastern Cooperative Oncology Group* 1119
- Perioperative Methotrexate, Vinblastine, Doxorubicin and Cisplatin (M-VAC) for Poor Risk Transitional Cell Carcinoma: Eastern Cooperative Oncology Group Pilot Study. *R. Dreicer, E. M. Messing, P. J. Loehrer and D. L. Trump* (Editorial Comments by M. J. Droller, N. J. Vogelzang and A. Yagoda) 1123
- Preliminary Results in Invasive Bladder Cancer With Transurethral Resection, Neoadjuvant Chemotherapy and Combined Pelvic Irradiation Plus Cisplatin Chemotherapy. *G. R. Prout, Jr., W. U. Shipley, D. S. Kaufman, N. M. Heney, P. P. Griffin, A. F. Althausen, B. Bassil, B. N. Nocks, E. C. Parkhurst and H. H. Young, II* (Editorial Comments by M. A. Bagshaw, D. G. Skinner, M. J. Droller and M. B. Garnick) 1128
- Local Recurrence and Survival Following Nerve-Sparing Radical Cystoprostatectomy. *C. B. Brendler, G. D. Steinberg, F. F. Marshall, J. L. Mostwin and P. C. Walsh* (Editorial Comments by J. Garnett and G. Lieskovsky) 1137
- Recurrent Urethral Stricture Disease Managed by Clean Intermittent Self-Catheterization. *L. H. Newman, N. N. Stone, J. H. Chircus and H. C. Kramer* 1142
- Microarchitecture of Intracavernosal Smooth Muscle and Cavernosal Fibrous Skeleton. *A. M. B. Goldstein and H. Padma-Nathan* 1144
- Arteriographically Determined Occlusive Disease Within Hypogastric-Cavernous Bed in Impotent Patients Following Blunt Perineal and Pelvic Trauma. *F. J. Levine, A. J. Greenfield and I. Goldstein* 1147
- Patient Acceptance of and Satisfaction With External Negative Pressure Device for Impotence. *A. A. Sidi, E. F. Becher, G. Zhang and J. H. Lewis* 1154
- Testicular Carcinoma in Patients Positive and at Risk for Human Immunodeficiency Virus. *M. Wilkinson and P. R. Carroll* 1157
- Clinical Stage 1 Testicular Cancer: Role of Modified Retroperitoneal Lymphadenectomy. *J. P. Richie* 1160
- Erythrocyte Polyamine Levels in Human Prostatic Carcinoma. *B. Cipolla, J.-P. Moulinoux, V. Quemener, R. Havouis, L.-A. Martin, F. Guille and B. Lobel* 1164
- Relationship of Prostate Specific Antigen Levels and Residual Tumor Volume in Stage A Prostate Cancer. *H. B. Carter, A. W. Partin, J. I. Epstein, D. W. Chan and P. C. Walsh* (Editorial Comments by D. F. Paulson and W. J. Catalona) 1167
- Prostate Specific Antigen After Irradiation for Prostatic Carcinoma. *I. Kaplan, B. R. Prestidge, R. S. Cox and M. A. Bagshaw* (Editorial Comments by W. J. Catalona, P. H. Lange and W. U. Shipley) 1172
- Prostate Specific Antigen for Assessing Response to Ketoconazole and Prednisone in Patients With Hormone Refractory Metastatic Prostate Cancer. *G. S. Gerber and G. W. Chodak* 1177

Contents continued on page A12

Radical Prostatectomy for Clinical Stage T1-2N0M0 Prostatic Adenocarcinoma: Long-Term Results. <i>D. F. Paulson, J. W. Moul and P. J. Walther</i>	1180
Urinary Excretion of Tamm-Horsfall Protein in Women With Recurrent Urinary Tract Infections. <i>H. Reinhart, N. Obedeanu, T. Hooton, W. Stamm and J. Sobel</i>	1185
Urologists At Work	
Improved Technique for Creation of Ileal Conduit Stoma. <i>J. K. Burgers, D. M. Quinlan and C. B. Brendler</i> (Editorial Comments by F. S. Freiha and W. F. Whitmore, Jr.)	1188
New Technique for Ileal Nipple Fixation: Preliminary Report. <i>M. A. Atta</i> (Editorial Comments by R. G. Rowland and L. R. King)	1192
Enveloping Bladder With Displacement of Flap of Rectus Abdominis Muscle for Treatment of Neurogenic Bladder. <i>Z. Yu-Hai, S. Qiang and W. Jin-Ming</i>	1194
Mohan's Urethral Valvotome: New Instrument. <i>M. K. Abraham</i>	1196
Urethral Plug: New Treatment Modality for Genuine Urinary Stress Incontinence in Women. <i>K. K. Nielsen, B. Kromann-Andersen, H. Jacobsen, E. M. Nielsen, J. Nordling, H. H. Holm and J. F. Larsen</i>	1199
Uncircumcision: Technique for Plastic Reconstruction of Prepuce After Circumcision. <i>W. E. Goodwin</i>	1203
Urological Neurology and Urodynamics	
Urinary Retention Due to Sacral Myeloradiculitis: Clinical and Neurophysiological Study. <i>A. G. Herbaut, M. C. Nogueira and E. Wespes</i>	1206
Pediatric Articles	
Long-Term Urinary Continence and Renal Function in Neonates With Posterior Urethral Valves. <i>J. P. Connor and K. A. Burbige</i>	1209
Management of Posterior Urethral Valves by Initial Vesicostomy and Delayed Valve Ablation. <i>R. D. Walker and M. Padron</i>	1212
Laparoscopy for Nonpalpable Testis: How to Interpret Endoscopic Findings. <i>L. N. Castilho</i>	1215
Pheochromocytoma in Pediatric Age Group: Prostate—Unusual Location. <i>G. E. Voges, F. Wippermann, C. Düber and R. Hohenfellner</i>	1219
Nuclear Morphometry as Prognostic Indicator for Genitourinary Rhabdomyosarcoma: Preliminary Investigation. <i>M. P. Leonard, A. W. Partin, J. I. Epstein, R. D. Jeffs and J. P. Gearhart</i>	1222
Case Reports	
Embolization of Giant Renal Arterial Aneurysm. <i>A. A. Saltiel, T. A. S. Matalon and S. K. Patel</i>	1227
Massive Hemorrhage From Arterioureteral Fistula Associated With Chronic Renal Transplant Failure. <i>A. List, J. Collins and M. MacCormick</i>	1229
Cyclophosphamide-Induced Hemorrhagic Pyelitis and Ureteritis Associated With Cystitis in Marrow Transplantation. <i>M. Efros, T. Ahmed and M. Choudhury</i>	1231
De Novo Carcinoma of Lower Urinary Tract in Renal Allograft Recipients. <i>M. J. Lemmers and J. M. Barry</i>	1233
Polyarteritis Nodosa Masquerading as Primary Testicular Neoplasm: Case Report and Review of Literature. <i>T. K. Huisman, W. T. Collins, Jr. and G. R. Voulgarakis</i>	1236
Burkitt's Lymphoma of Testicle: Report of 2 Cases Occurring in Elderly Patients. <i>M. Root, T. Y. Wang, H. Hescock, M. Parker, P. Hudson and L. Balducci</i>	1239
Retroperitoneal Lymph Node Dissection in Malignant Mesothelioma of Tunica Vaginalis Testis. <i>J. J. Smith, III, M. J. Malone, J. Geffin, M. L. Silverman and J. A. Libertino</i>	1242
Letters to the Editor	
Re: Adrenal Hemorrhage in Newborn With Evidence of Bleeding in Utero, by T. Gotoh, Y. Adachi, O. Nounaka, T. Mori and T. Koyanagi. <i>Y. Reinberg</i>	1244
Re: Prostatic Specific Antigen: Immunoreactivity in Urachal Remnants, by R. Golz and G. E. Schubert. <i>H. D. Flood and E. F. Gaffney</i>	1244
Re: Prostatic Needle Biopsy: Simple Technique for Increasing Accuracy, by S. Marshall. <i>D. W. Bussmann</i>	1244

INVESTIGATIVE UROLOGY

This Month in Investigative Urology: The Production of Lymphokines Following BCG Therapy. <i>A. Morales</i>	1246
Radio-Immunoassay Detection of Interferon-Gamma in Urine After Intravesical Evans BCG Therapy. <i>S. Prescott, K. James, T. B. Hargreave, G. D. Chisholm and J. F. Smyth</i>	1248
Synchronized Electrical Stimulation of the Sympathetic and Parasympathetic Innervation of Bladder: Facilitation of Initiation of Micturition in Dog. <i>R. J. L. H. Bosch, S. R. Aboseif, F. Benard, C. G. Stief, R. A. Schmidt and E. A. Tanagho</i>	1252
Mechanical Properties of Urethra in Healthy and Stress Incontinent Females: Dynamic Measurements in Resting Urethra. <i>G. Lose and H. Colstrup</i>	1258
Determination of Norepinephrine Levels in Adult Human Prostate. <i>H. Lepor, E. Shapiro, R. R. Bowsher and D. P. Henry</i>	1263
Influence of Chondroitin Sulfate, Heparin Sulfate, and Citrate on Proteus Mirabilis-Induced Struvite Crystallization In Vitro. <i>R. J. C. McLean, J. Downey, L. Clapham and J. C. Nickel</i>	1267
Time-Course of Alterations of Bladder Function Following Acetone-Induced Cystitis. <i>K. Kato, S. Kitada, P.</i>	

<i>A. Longhurst, A. J. Wein and R. M. Levin</i>	1272
Effects of Intracavernosal Trazodone Hydrochloride: Animal and Human Studies. <i>K. M. Azadzi, T. Payton, R. J. Krane and I. Goldstein</i>	1277
Long-Term Effects of Gastrocystoplasty in Rats. <i>L. W. Klee, D. M. Hoover, M. E. Mitchell and R. C. Rink</i>	1283
Comparison of Antigen Expression on Normal Urothelial Cells in Tissue Section and Tissue Culture. <i>M. Liebert, G. Wedemeyer, J. H. C. Chang, J. A. Stein, P. E. McKeever, T. E. Carey, A. Flint, Z. Steplewski, D. J. Buchsbaum, R. L. Wahl and H. B. Grossman</i>	1288
Guinea Pig Model for Study of Bladder Mast Cell Function: Histamine Release and Smooth Muscle Contraction. <i>M. M. Christensen, I. Keith, P. R. Rhodes, F. M. Graziano, P. O. Madsen, R. C. Bruskevitz and R. Saban</i>	1293

UROLOGICAL SURVEY

Principles of Oncology and Immunology, and Tumors of Bladder, Penis and Urethra	1302
Male Infertility	1306
Sexual Function and Dysfunction	1309
Renal Calculi	1314
Renal Tumors, Retroperitoneum, Ureter, and Urinary Diversion and Reconstruction	1316
Book Reviews	1319
News and Announcements	1321

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2) Response by the Editorial Staff with identification of a specific individual to work with the Editorial Committee of the sponsors.

3) Agree to a deadline for submission of the papers, number of papers and so forth.

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8) Publication.

SYNCHRONIZED ELECTRICAL STIMULATION OF THE SYMPATHETIC AND PARASYMPATHETIC INNERVATION OF THE BLADDER: FACILITATION OF THE INITIATION OF MICTURITION IN THE DOG

RUUD J. L. H. BOSCH, SHERIF R. ABOSEIF, FRANCOIS BENARD, CHRISTIAN G. STIEF, RICHARD A. SCHMIDT AND EMIL A. TANAGHO*

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ABSTRACT

To improve the quality of bladder contractions induced by parasympathetic stimulation and to facilitate the initiation of voiding, we investigated the effect of sympathetic stimulation on the parasympathetic innervation of the bladder in 12 dogs. For the sympathetic system, the lumbar sympathetic trunks were electrically stimulated; for the parasympathetic system, either the pelvic nerve or the ventral root of S₂ was stimulated.

With voltages at or just above the threshold for achieving a measurable effect on bladder pressure, stimulation of the sympathetic system or the pelvic nerve alone did not lead to voiding, and sacral root stimulation alone elicited voiding in only 7.4 per cent of stimulations. However, when the same stimulus parameters were used for synchronous stimulation, the voiding process was facilitated when sympathetic stimulation was begun five to 10 seconds before parasympathetic stimulation. When the pelvic nerve was used, voiding resulted in 77.7 per cent of stimulations and the bladder was emptied by a mean of 68.7 per cent; with S₂ ventral root stimulation, voiding resulted in 83.3 per cent of stimulations and the bladder was emptied by 59.7 per cent. The facilitory effect of sympathetic stimulation was not abolished when the sympathetic trunks were cut centrally to the point of stimulation, but was absent when the hypogastric nerves were transected.

We feel that sympathetic stimulation modulates the parasympathetic innervation of the bladder. (*J. Urol.*, 144: 1252-1257, 1990)

Many studies have been undertaken to elucidate the role of the sympathetic nervous system in bladder and urethral function, but the question of how the autonomic nervous system initiates voiding remains unclear. The sympathetic nervous system exhibits its action on smooth muscle cells through two different types of adrenergic receptors. Stimulation of alpha-adrenergic receptors generally results in excitation, producing a contraction of the smooth muscles, whereas stimulation of the beta-receptors results in an inhibitory or muscle-relaxing effect. Previous studies¹ have shown that adrenergic receptors are present throughout the bladder: beta-adrenergic receptors predominate in the body and dome; and alpha-adrenergic receptors in the base and bladder neck. In the urethra, alpha receptors predominate.²

The effects of sympathetic stimulation on bladder function can be summarized. Its most powerful effect is a direct inhibition, mediated by beta-adrenergic receptors, of bladder smooth muscle cells.³ A less powerful, alpha-receptor-mediated inhibition of the parasympathetic transmission in bladder ganglia has been described in the cat, although this inhibition varied among animals in the series and among different postganglionic fibers in the same animal, and was apparent only when the excitatory input to the parasympathetic ganglia was at a low level.³ In contrast, others have claimed a consistent, marked facilitation of the parasympathetic postganglionic potential in the same species.⁴ Histochemical^{5,6} and ultrastructural evidence⁶ for a sympathetic action on the parasympathetic bladder ganglia is now well established.

During hypogastric nerve stimulation, an initial contractile

bladder response followed by relaxation was found in the cat^{3,7,8} and dog.⁹⁻¹¹ This response was elicited whether the pelvic nerves were intact or transected. The relaxation phase was abolished by β -blockers.^{3,10} The initial bladder contraction was not blocked by phentolamine^{8,12} (or was so only partially¹⁰) and was inconsistently influenced by phenoxybenzamine.^{3,7,8,11-13} This initial contractile response is not confined to the bladder base¹¹ and is not in accord with the prevailing theories of facilitation of storage by the sympathetic system. Pharmacologic studies have ascribed its origin variously: mediated via the parasympathetic postganglionic pathway,⁸ non-adrenergic,¹⁰ and possibly alpha-adrenergic, but mediated by receptors that must have pharmacologic characteristics different from those involved in ganglionic transmission.³

Apart from the initial non-reflexive contractile response, singular responses in the trigonal area have been noted. These probably represent a threshold effect or a greater preponderance of adrenergic receptor sites.¹¹ Also, a forceful excitation at multiple points in the bladder wall has been obtained, possibly due to a secondary alpha-adrenergic positive feedback mechanism that excites parasympathetic neurons in the sacral spinal cord.¹¹ In agreement with these findings, electrophysiologic studies have shown that hypogastric nerve stimulation often elicits reflex firing in the parasympathetic fibers to the bladder—an effect that can be abolished by transection of the pelvic nerves.³

On anatomical grounds, Feher et al.¹⁴ have argued that bladder contractions are initiated in the trigone, as its innervation is three times greater than that of the dome. Furthermore, they argue that local nerve processes and numerous nexal (desmosome-like) contacts between smooth muscle cells have a role in the activation of other parts of the bladder wall. Thus, evidence exists for a modulatory role of the sympathetic nervous system

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in the initiation of micturition through its action on the bladder base and its non-reflexive and reflexive excitation of the bladder wall. This study was undertaken to investigate this role further by means of well times and synchronous stimulation of the sympathetic and parasympathetic nerve supply of the bladder in the dog. In our experiments the lumbar sympathetic trunks were used for sympathetic stimulation, rather than the hypogastric nerves, because there is electrophysiologic and morphologic evidence that a second sympathetic pathway from the sacral sympathetic chain passes to pelvic organs through the pelvic nerve.¹⁵⁻¹⁷ As the pelvic nerve contains a certain number of sympathetic fibers,¹⁵⁻¹⁷ the ventral root of S_2 was used in some animals for parasympathetic stimulation. The S_2 root in the dog is equivalent to the S_3 root in man, and it carries most parasympathetic fibers involved in bladder contraction. Selective stimulation of the ventral component of the root diminishes the number of reflex pathways available to sphincteric control.¹⁸

MATERIALS AND METHODS

Twelve mongrel dogs (nine male, three female), weighing 21 to 52 kg. (mean 33 kg.), were studied. The three female dogs were used to investigate the influence of sympathetic stimulation on the bladder base. The nine male dogs were used for the synchronized stimulation experiments. In six of the nine, the pelvic nerve and lumbar sympathetic trunks were stimulated synchronously; in the remaining three, the ventral root of S_2 was used in place of the pelvic nerve.

Anesthesia was induced with acepromazine (0.1 mg./kg.) and ketamine (five mg./kg.) and maintained with 45- to 60-mg. intravenous boluses of pentobarbital as needed. The animals breathed spontaneously. They were placed on a heating pad to maintain body temperature and received an intravenous drip of normal saline (two ml./kg./hr.). Blood pressure was monitored through an 18-gauge angiocath in the right femoral artery connected to a Statham transducer.

Through a midline abdominal incision, the bladder was exposed and a 5F catheter with an open end was inserted in the bladder dome via a small stab wound and secured with a pursestring suture. The catheter was connected to a Statham transducer via a three-way stopcock and fluid-filled lines. The stopcock allowed for bladder filling and emptying.

To study the effects of stimulations on the bladder base, one ureter was freed about 10 cm. above the ureterovesical junction. It was transected and tied proximally; the distal end was cannulated with a 3.5F catheter with an end-hole. This catheter was advanced until its tip reached a point about four cm. proximal to the ureterovesical junction and tied in place. Warm normal saline was then perfused at the rate of 0.76 ml./min. with a Harvard perfusion pump; the ureteral catheter was connected to a Statham transducer via a sidearm.

Both sympathetic trunks (fig. 1A) were isolated posterolaterally to the aorta at the level of L_5 , and platinum cuff electrodes (Avery Labs) were placed around them for stimulation. If the pelvic nerve was to be used for parasympathetic stimulation, it was identified on one side (fig. 1B) lateral to the rectum and a platinum cuff electrode was placed around it. If the ventral root of S_2 was to be used, the dog was turned on its abdomen after closure and a laminectomy was performed extending from L_6 to S_4 , giving a wide exposure of the sacral roots in their extradural course. The S_2 root was identified and a good bladder response was confirmed by stimulation with a needle electrode. Under magnification, the dorsal and ventral components were carefully separated and the integrity of the ventral component was verified by neurostimulation and a platinum cuff electrode placed around it. The dog was then turned to the supine position again and the abdomen was reopened.

The voided volume was measured in a calibrated container connected to a Statham transducer via an opening in the bottom. The urine was guided into the container via a trans-

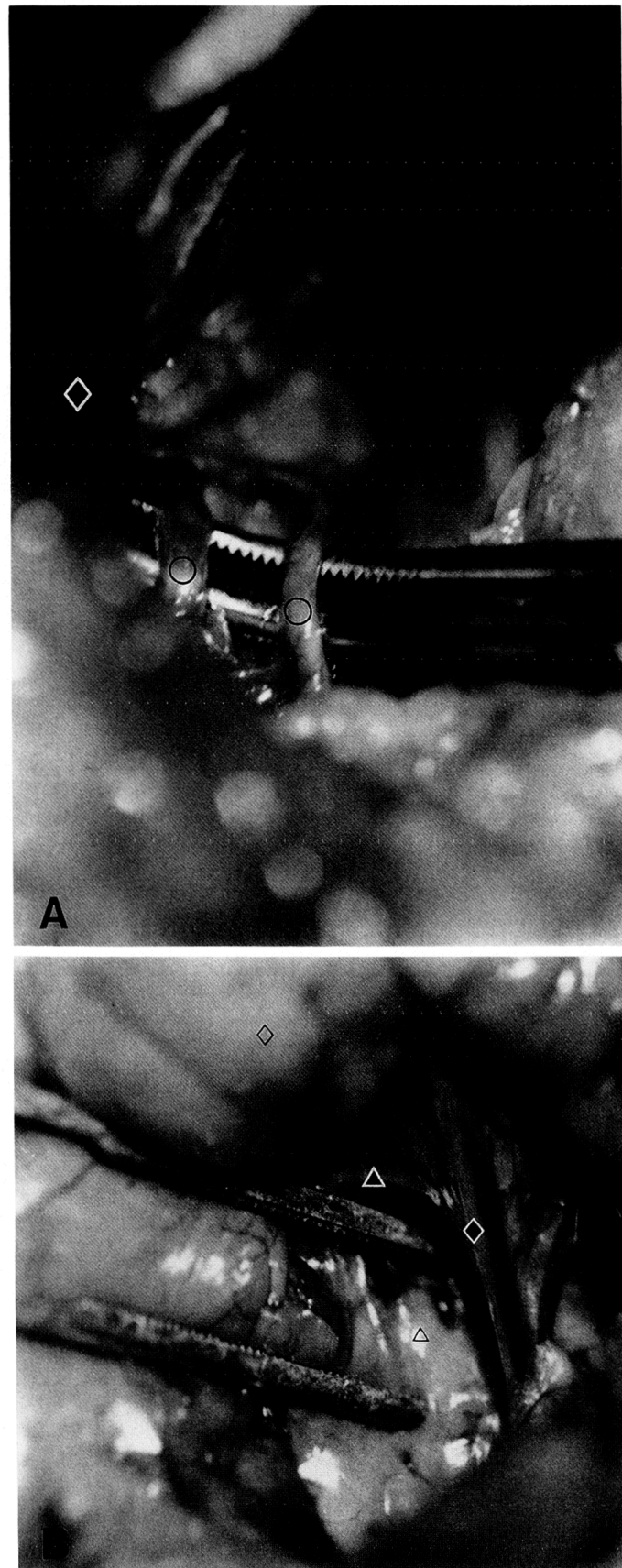


FIG. 1. A, sympathetic trunks isolated via an approach posterolateral to aorta (sympathetic trunks = open circles; aorta displaced to right by retractor = open diamond). B, anatomy of pelvic plexus (pelvic nerve = closed diamond; hypogastric nerve = closed triangle; perivesical fat = open diamond; rectum = open triangle).

parent cylinder with a delay of approximately two seconds. Bladder capacity was determined cystometrically. All stimulations were done with the bladder filled to one third of capacity and with an open abdomen. Stimulation parameters were: 20 Hz frequency; 200 μ s pulsewidth.

In five of the nine male dogs, bladder and urethral responses to stimulation were first recorded with a 7F 2- or 3-membrane catheter placed in the urethra. The membranes were connected to Statham transducers. With the 2-membrane catheter, bladder and mid-urethral responses (from the area of the external sphincter) were recorded; with the 3-membrane catheter, proximal urethral responses (from the area of the bladder neck) were recorded as well. After establishment of the responses, the membrane catheter was removed and the 5F catheter in the bladder dome was used for pressure recording (the urethra was unobstructed).

Control simulations of the lumbar sympathetic trunks alone were performed to determine the lowest voltage that resulted in an initial contractile response of the bladder but no voiding. Control stimulations were similarly performed of the pelvic nerve or the S₂ ventral root alone to determine the threshold voltage that elicited a bladder response of at least 10 cm. H₂O but no voiding. With the same stimulus parameters as in the control stimulations, variously timed combined stimulations were performed: stimulation of both systems simultaneously; sympathetic stimulation begun 5 to 10 sec. before parasympathetic stimulation and continued concurrently; and sympathetic stimulation begun five to 10 sec. before parasympathetic stimulation, but stopped at its onset. Not all combinations were tried in all dogs as it became apparent that the second was the most successful. At least four control stimulations of the sympathetic or parasympathetic system alone and four synchronized stimulations with the most successful timing were performed.

Initially, the intact sympathetic trunks were stimulated, but later in the experiment they were transected and the distal ends stimulated. In three animals the hypogastric nerves were cut at the end of the experiment, and sympathetic trunk and synchronized stimulations were repeated.

The ureteral perfusion pressure was recorded in eight of the nine male dogs, during sympathetic trunk stimulation (in eight) and during pelvic nerve stimulation (in five).

In the female dogs, electrodes were placed around the S₂ ventral root and the lumbar sympathetic trunks and a catheter was placed for measurement of the ureteral perfusion pressure. The bladder was opened anteriorly to abolish the effect of an increase in bladder pressure, and the ureteral perfusion pressure was measured in the presence and absence of stimulation. The bladder was then excised, leaving only the bladder base intact, and stimulations were repeated as before. Lastly, the ureter was freed from the bladder base and divided at the ureterovesical junction and stimulations were again repeated.

All responses recorded by Statham transducers (Model 23 BC) were written on a Grass polygraph (Model 7). In the final analysis of results, the values for each individual dog repre-

sented means of the series of control or synchronized stimulations. Statistical analysis was done with Student's *t* test.

RESULTS

Sympathetic stimulation alone. Stimulation of the sympathetic trunks alone resulted in an initial increase in bladder pressure ranging from three to 14 cm. H₂O (mean 6.9) in nine dogs (table 1). The voltage used to elicit this effect ranged from 0.1 to 6 V (mean 2.7). Even with prolonged stimulation, the bladder response was generally not sustained for more than 10 seconds and no voiding occurred with sympathetic stimulation alone.

In the five dogs in which recordings were first made with a transurethral membrane catheter, two types of responses were seen; in two dogs, sympathetic stimulation led to a small increase in bladder pressure and, surprisingly, to a slight decrease in proximal and mid-urethral pressure (fig. 2A); in three dogs, both bladder and urethral pressure increased. The dog whose response is depicted in fig. 2B exhibited a particularly high increase in proximal and mid-urethral pressure, which was slightly delayed compared with the increase in bladder pressure and was highest at that point where bladder pressure decreased.

Parasympathetic stimulation alone. The increases in bladder pressure with pelvic nerve stimulation in six dogs ranged from 12 to 21 cm. H₂O (see table 1) and were better sustained than those with sympathetic stimulation (fig. 2A), yet voiding still did not occur. With S₂ ventral root stimulation in three dogs, the increases ranged from 13 to 17 cm. H₂O. One dog voided in response to 22.2 per cent of the stimulations, even with the threshold voltage (for an average occurrence of voiding of 7.4 per cent in the three dogs). Fig. 2B shows that the increase in bladder pressure was also accompanied by an increase in proximal and mid-urethral pressure.

Synchronized sympathetic and parasympathetic stimulation. Stimulation of the sympathetic system shortly before parasympathetic stimulation did not decrease the response to the latter (fig. 3). This was seen in all dogs whether or not voiding occurred with synchronized stimulation. When stimulation of both systems was begun simultaneously, voiding did not occur, nor did it occur when sympathetic stimulation was begun five to 10 sec. before parasympathetic stimulation and stopped before it was started. However, when sympathetic stimulation was begun five to 10 sec. before parasympathetic stimulation and continued during at least the first part of it, voiding occurred during a considerable number of stimulations. Synchronized stimulation of the sympathetic trunks and the pelvic nerve on average led to voiding during 77.7 per cent of the stimulations, and the bladder was emptied by an average of 68.7 per cent (range 25 to 100 per cent). Synchronized stimulation with the S₂ ventral root on average led to voiding during 83.3 per cent of the stimulations and the bladder was emptied by an average of 59.7 per cent (range 10 to 86 per cent).

When the distal ends of the transected sympathetic trunks were stimulated, the voiding process was still facilitated (fig. 4). However, when the hypogastric nerves were cut, the effect of sympathetic trunk stimulation was abolished.

TABLE 1. Maximal bladder pressure increase, occurrence of voiding, and percentage of bladder emptying with sympathetic stimulation alone, parasympathetic stimulation alone, and synchronized stimulation

	Sympathetic Trunks			Parasympathetic			Synchronized		
	Voltage	↑ Pressure* (cm. H ₂ O)	% Void	Voltage	↑ Pressure (cm. H ₂ O)	% Void	↑ Pressure (cm. H ₂ O)	% Void	% Emptying
Pelvic nerve (N = 6)	3.2†	6.3	0	2.6	17.2	0	41.8	77.7	68.7
	(0.1-6)	(3-9)		(0.5-5)	(12-21)		(21-61)	(25-100)	(25-100)
S ₂ Ventral root (N = 3)	1.7	8	0	0.9	15	7.4	33.3	83.3	59.7
	(0.1-2.5)	(3-14)		(0.1-2.5)	(13-17)	(0-22.2)	(21-50)	(50-100)	(10-86)

* Measured via catheter in the bladder dome (see Methods).

† Values are means, with the range in parentheses.

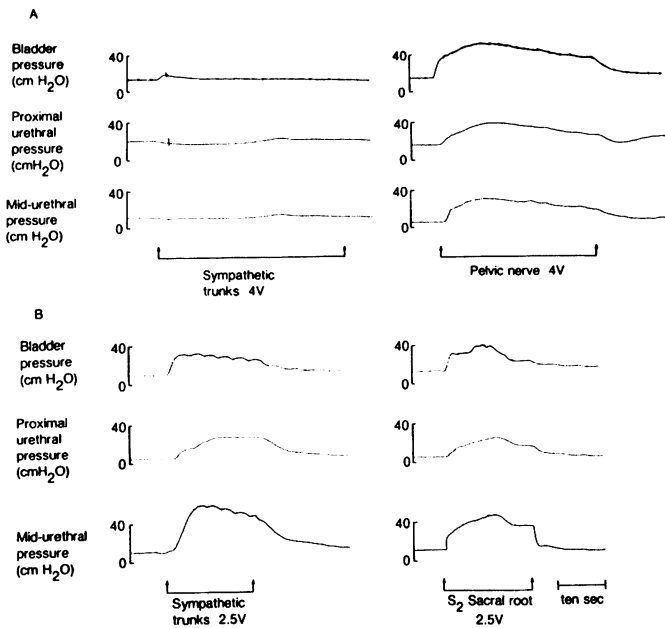


FIG. 2. Recordings of bladder pressure and proximal and mid-urethral pressures in two different dogs. A, sympathetic stimulation results in initial slight increase in bladder pressure and slight drop in proximal and mid-urethral pressure. Pelvic nerve stimulation results in increases in bladder and proximal and mid-urethral pressures. B, in second dog, sympathetic stimulation leads to increases in bladder, proximal and midurethral pressures. Increase in urethral pressure is slightly delayed vis a vis bladder pressure and is highest when bladder pressure decreases. S₂ ventral root stimulation also elicits increases in bladder, proximal and mid-urethral pressures.

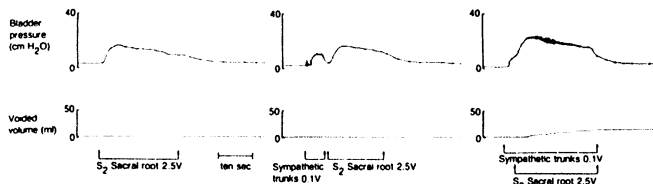


FIG. 3. Recordings of bladder pressure and voided volume. Left: Stimulation of S₂ ventral root increases bladder pressure but does not result in voiding. Middle: Stimulation of sympathetic trunks increases the bladder pressure. S₂ ventral root stimulation, begun after sympathetic stimulation is stopped, does not modify bladder response. Right: When S₂ ventral root stimulation is begun three seconds after sympathetic stimulation, increases in bladder pressure appear to augment each other and voiding results.

In one dog (fig. 3), the increases in bladder pressure obtained with sympathetic or parasympathetic stimulation alone simply augmented each other during synchronized stimulation, and voiding occurred. However, in eight of the nine dogs the bladder pressure during synchronized stimulation was much higher than the sum of the pressure increases obtained with single-system stimulation (figs. 4-6).

Figure 6 demonstrates the recordings of two different dogs during pelvic nerve stimulation alone and during synchronized stimulation. The dog in fig. 6A showed a slight decrease in mid-urethral pressure at the start of sympathetic stimulation, whereas the dog in fig. 6B exhibited a slight increase. In both cases, synchronized stimulation led to voiding.

Effects of sympathetic stimulation on the bladder base. Pelvic nerve stimulation in five dogs led to an average increase in ureteral perfusion pressure of 17.2 cm. H₂O, which reflects the increase in bladder pressure of 16.8 cm. H₂O (table 2). Sympathetic trunk stimulation in eight dogs led to an average increase in ureteral perfusion pressure of 11.9 cm. H₂O. On average, the bladder pressure was 43% less (6.8 cm. H₂O), which reflects the greater impact of sympathetic stimulation on the bladder base.¹⁹⁻²¹

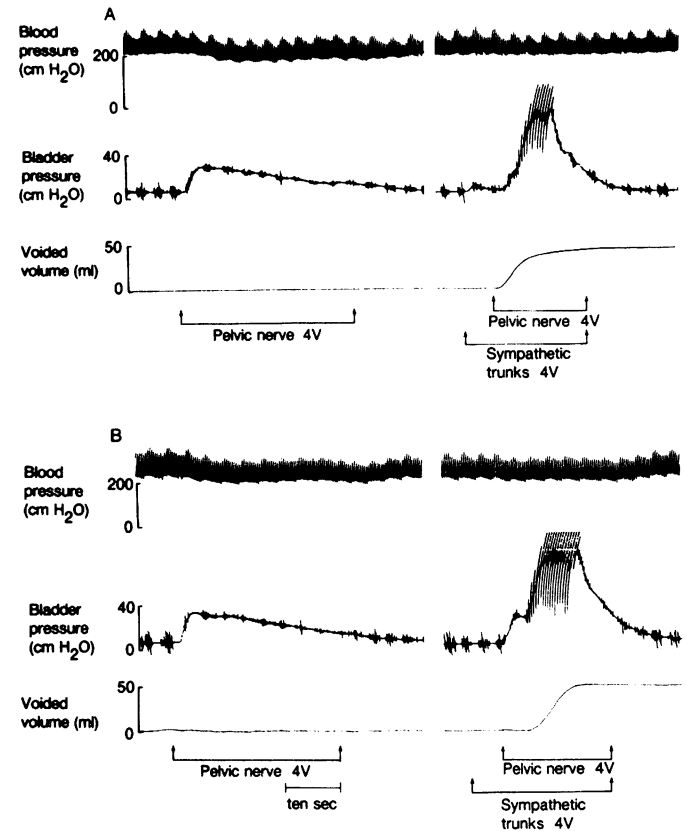


FIG. 4. Recordings of blood pressure, bladder pressure and voided volume with pelvic nerve stimulation alone and with synchronized stimulation: A, stimulation with sympathetic trunks intact; B, stimulation of distal ends of transected sympathetic trunks. Synchronized stimulation leads to voiding in both situations.

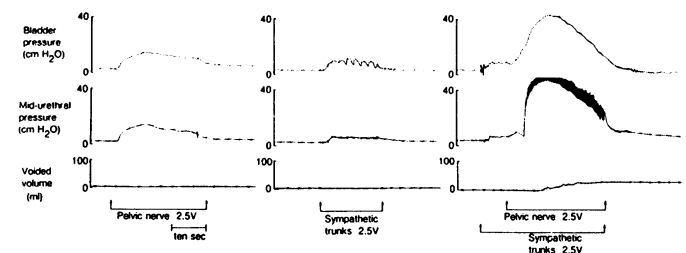


FIG. 5. Recordings of bladder pressure, mid-urethral pressure, and voided volume with pelvic nerve stimulation alone (left), sympathetic stimulation alone (middle), and synchronized stimulation (right). Synchronized stimulation leads to voiding. Mid-urethral pressure tracing shows urethral contractions typical of dog during voiding.

The experiments in the three female dogs had been undertaken to confirm that the increase in ureteral perfusion pressure during sympathetic stimulation is due mainly to contraction of the bladder base and not to a bladder pressure increase or to contraction of the distal ureter itself (fig. 7). In the preparation with an anteriorly opened bladder and with only the bladder base left intact, sympathetic stimulation (2.5-4V) resulted in ureteral perfusion pressure increases ranging from seven to 17.5 cm. H₂O; with S₂ ventral root stimulation (2.5-4V), the increases ranged from 15 to 30 cm. H₂O. This greater effect of parasympathetic stimulation was evident in all three dogs. Distal transection of the ureter abolished the ureteral perfusion pressure increase during both sympathetic trunk and sacral root stimulation.

DISCUSSION

In the present study, the fact that sympathetic stimulation had to overlap parasympathetic stimulation, at least until mic-

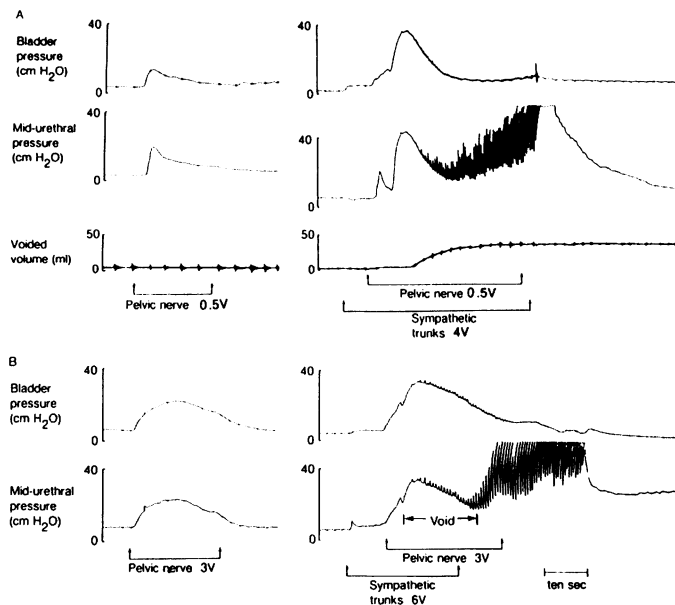


FIG. 6. Recording of bladder, mid-urethral pressure, and voided volume with pelvic nerve stimulation alone and synchronized stimulation in two different dogs. A, pelvic nerve stimulation does not lead to voiding. Sympathetic stimulation begun just before pelvic nerve stimulation leads to slight increase in bladder pressure and slight drop in mid-urethral pressure. During synchronized stimulation, voiding occurs. B, in the second dog, pelvic nerve stimulation does not lead to voiding. Sympathetic stimulation leads to slight increase in both bladder and mid-urethral pressure. During synchronized stimulation, voiding occurs (visual observation). Arrowheads indicate period of voiding. During pulsatile urethral contractions, only small spurts were seen.

TABLE 2. Ureteral perfusion pressure and bladder pressure increases during sympathetic trunk or pelvic nerve stimulation

Sympathetic Trunk Stimulation (N = 8)		Pelvic Nerve Stimulation (N = 5)	
Ureter	Bladder	Ureter	Bladder
11.9 (6.5-25)*	6.8 (3-14)	17.2 (13-29)	16.8 (13-27)
p = 0.07		p = 0.58	

* Values are means in cm. H₂O; the range is in parentheses.

turition actually occurred, suggests that the initiation of voiding is facilitated by a modulatory effect on the parasympathetic system. Overall, synchronized stimulation resulted in a mean bladder pressure increase that was much higher than the sum of the mean pressure increases obtained with sympathetic or parasympathetic stimulation alone. In only one dog was the pressure increase simply a reflection of the sum of the bladder pressure increases in response to single-system stimulation.

It is likely that the facilitation of micturition is due either to a direct effect of the sympathetic system on the bladder ganglia⁴ or to a secondary reflex mechanism. De Groat and Saum³ found that hypogastric nerve stimulation elicited reflex firing in post-ganglionic parasympathetic fibers, which they explained by activation of vesical afferents during the initial contractile phase. La Grange¹¹ described a positive feedback mechanism, with afferent and efferent limbs in the pelvic nerve, as being responsible for the forceful excitation at multiple points in the bladder wall during hypogastric nerve stimulation. The increase in bladder contraction pressure during synchronized stimulation is most probably the most important reason for the facilitation of the initiation of voiding. Further studies with a different protocol are necessary to determine whether and to what extent a change in urethral resistance contributes to the facilitatory effect during synchronized stimulation. Nishizawa et al.,²² in experiments with pressure-flow-EMG studies during micturition in dogs before and after sympathectomy, found that sympathectomy significantly decreased the contraction pres-

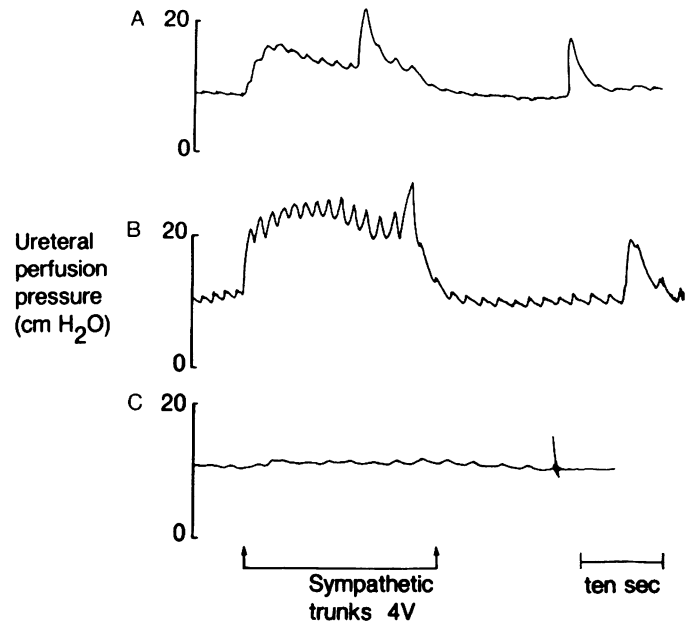


FIG. 7. Recordings of ureteral perfusion pressure during sympathetic stimulation: A, with bladder opened anteriorly; B, with bladder removed, leaving only bladder base and ureterovesical junction intact; and C, with ureter cut about four cm. distal to perfusion catheter. Sympathetic stimulation contracts bladder base.

sure of the bladder during voiding, whereas the intraurethral resistance remained unchanged. They attributed this result to decreased alpha-adrenergic innervation of the bladder.

Sympathetic activity usually leads to an excitatory action on the urethral smooth muscle cells,^{10, 23-25} although inconsistent²⁶ and excitatory as well as inhibitory²⁷ effects have been obtained. If, however, the hypogastric nerves are stimulated when the bladder is full, a urethral pressure increase will not occur, inasmuch as afferent and efferent discharge in the pelvic nerve seems to be able to exert a modulatory effect on the urethral response to sympathetic stimulation.²⁵ In our study, the slight decrease in urethral pressure seen in two dogs during sympathetic stimulation remains difficult to explain.

The initial contraction of the bladder during sympathetic stimulation was accompanied by an increase in ureteral perfusion pressure that averaged 43% more than the simultaneous increase in bladder pressure. Although the number of animals was small, this difference still nearly attained statistical significance ($p = 0.07$). As this increase in perfusion pressure is due to contraction of the bladder base (fig. 7), it is tempting to assume that the initial increase in bladder pressure is mainly, although not exclusively,¹¹ also due to bladder base contraction.

Studies with urodynamics and cineradiography have established that micturition is initiated by relaxation of the pelvic floor, leading to a descent of the bladder base, the start of funneling of the bladder outlet, and an accompanying drop in intraurethral pressure. Contraction of the trigonal area and the detrusor inner longitudinal coat then help to open the proximal urethra and add to the funneling of the bladder outlet.²⁸ The necessary period of sympathetic prestimulation of five to 10 seconds that was found in this study correlates with a similar delay in bladder pressure increase after the intraurethral pressure drop (about five seconds).^{28, 29} Furthermore, this concept is in agreement with the reported finding with simultaneous electromyographic and bladder pressure recordings taken during canine micturition that spiking in the urethrovesical junction precedes a larger and sustained increase in bladder pressure.³⁰

A modulatory relationship between the sympathetic and parasympathetic nervous system can help to explain the phenomena occurring during the initiation of micturition. The

initial contraction of the bladder (mainly the bladder base) during sympathetic stimulation leads to afferent parasympathetic activity and reflex efferent firing of parasympathetic postganglionic fibers via a positive feedback mechanism. The efferent parasympathetic activity then modulates the urethral response to sympathetic stimulation.²⁵

The modulatory effect of the sympathetic nervous system in this study was not mediated via a central sympathetic effect, inasmuch as stimulation of the distal ends of the transected sympathetic trunks did not abolish the facilitation.

This study shows that synchronized sympathetic and parasympathetic stimulation, correctly timed, can facilitate the initiation of micturition. It also demonstrates the importance of continued, detailed analysis of the neural processes involved in micturition. Eventually this could provide us with the necessary knowledge to mimic the physiologic voiding process as closely as possible by the strategic placement of electrodes and the exact timing of the necessary stimuli in patients with certain neurologic voiding disorders.

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