

## Best of the 2004 AUA Annual Meeting

*Highlights from the 2004 Annual Meeting of the American Urological Association,  
May 8–13, 2004, San Francisco, CA*

[*Rev Urol.* 2004;6(3):128-160]

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**Key words:** Basic science • Benign prostatic hyperplasia • Bladder cancer • Chronic prostatitis • Erectile dysfunction • Incontinence • Kidney stones • Laparoscopy • Lower urinary tract symptoms • Male infertility • Obesity • Oncology • Overactive bladder • Pediatric urology • Prostate cancer • Prostate-specific antigen • Radical prostatectomy • Renal cell carcinoma • Robotic surgery • Tumor markers • Urolithiasis

The Contributing and Medical Editors of *Reviews in Urology* were among the more than 15,000 attendees of the 2004 American Urological Association (AUA) Annual Meeting in San Francisco. Here, they present the latest developments in their respective areas of expertise.

### Outcomes, Practice Patterns, Quality of Life, and Cost Effectiveness

At this year's AUA meeting, abstracts were chosen for 2 discussed poster sessions in the areas of outcomes, practice patterns, quality of life, and cost effectiveness. Topics included patterns of care and utilization in bladder and prostate cancer, the eco-

nomic impact of urolithiasis and incontinence, robotics, sexual health and behavior, data from the Urologic Disease in America Project, benign prostatic hyperplasia, and neonatal circumcision. Here, I highlight 13 abstracts that I think are noteworthy.

The Urologic Diseases in America Project is a National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)-sponsored effort to better define the patterns of utilization and the economic impact of genitourinary illness in the United States. Data from this study were evaluated in 2 abstracts<sup>1,2</sup> on urolithiasis and male urinary incontinence, respectively. Using claims and absentee data for large private employers, mean annual expenditures for adults

with stones were \$4472 higher than for similar adults without stones. In the second study, using Medicare and Medicaid databases, the Los Angeles-based research team noted that more than 50% of men in nursing homes report incontinence and that overall, nearly \$19 billion in direct costs (1998/1999 dollars) are expended annually. Two parallel studies on stones and incontinence documented similar significant cost burdens. Pearle and associates,<sup>3</sup> analyzing a number of reliable national data sets, calculated the annual cost of urolithiasis in the United States at over \$2 billion, whereas a Kaiser California study<sup>4</sup> estimated that community-dwelling women with incontinence pay more than \$275 a year in out-of-pocket expenses for

pads and other incontinence supplies. These 4 studies clearly document that both stones and incontinence have a major impact on the US health economy.

In studies on prostate cancer, Tewari and colleagues<sup>5</sup> analyzed data from the Prostate Outcomes Consortium, concluding that African Americans do not experience worse overall survival than whites, and both radical prostatectomy and radiation therapy significantly reduce risk of dying from prostate cancer. Krupski and colleagues,<sup>6</sup> however, analyzing data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database documented significant variations in primary treatment rates, with overall rates for less invasive therapies, radiation, and no treatment higher in African American men. In another study, Litwin and colleagues<sup>7</sup> adapted the Total Illness Burden Index for prostate cancer, and it has the potential to be a useful objective assessment

*Tewari and colleagues concluded that African Americans do not experience worse overall survival than whites from prostate cancer, and both radical prostatectomy and radiation therapy significantly reduce risk of dying from prostate cancer.*

tool to evaluate comorbidity in men with prostate cancer.

The Global Study of Sexual Attitudes and Behaviors evaluated more than 7000 men and women in 29 countries.<sup>8</sup> Surprisingly, the most common sexual problem in men was early ejaculation rather than erectile dysfunction, whereas the most common complaint in women was lack of sexual interest.

Nelson and colleagues<sup>9</sup> examined the National Inpatient Survey database, a 20% sample of US community hospitals (including specialty hospitals), to determine the prevalence of newborn circumcision. Their data indi-

% fPSA-Category	Risk by Age Group (%)				
	≤ 55	56-60	61-65	66-70	> 70
≤ 15	35.2	44.4	43.5	47.3	50
16-25	7.1	11.3	12.3	21.7	31.7
> 25	4.1	3.7	5.8	13.9	7.8

% fPSA, free prostate-specific antigen.  
Data from Haese et al.<sup>14</sup>

cate that there has been an increase across all racial/ethnic groups in newborn male circumcision, in spite of the lack of any clear evidence to support a medical indication.

Robotics and similar technologies will likely play an increasingly important role in urologic surgery in the future. Ong and associates<sup>10</sup> presented a study utilizing an interactive video conferencing robot guided by a

was 10.8% among women and 6.2% among men. Remarkably, over 70% of these reported never having sought treatment. Waetjen and associates<sup>12</sup> evaluated 7731 elderly women in a community-based population in an attempt to determine modifiable risk factors for stress and urge incontinence. They concluded that women who were overweight or were taking estrogen were at significantly greater risk of having both types of incontinence, leaving us to conclude that weight loss and cessation of estrogen may improve continence in elderly women.

Finally, in what may be one of the most interesting papers of the sessions, Breau and associates<sup>13</sup> searched the urologic literature between 1982 and 2002 to determine the prevalence of studies with inadequate statistical power to draw a negative conclusion. They identified 112 studies (from *Journal of Urology*, *Urology*, and *BJU International*) containing enough information to do a power calculation. Only 29.5% of these studies had adequate power to substantiate a claim of no difference between groups; therefore, over 70% of negative studies have led to false conclusions. We need to carefully analyze our literature before drawing conclusions.

[Michael P. O'Leary, MD, MPH]

remote physician for daily rounds in postoperative patients. More than half the study patients reported they were comfortable with this type of system, giving it high ratings for physicians' accessibility and personal attention.

A large number of posters focused on urinary incontinence, with several being particularly noteworthy. Link and colleagues<sup>11</sup> presented the Boston Area Community Health Survey (BACH), a population-based community sample of 6000 adults aged 30-79 years, with wide minority representation. They found that the overall prevalence of urinary incontinence

### Prostate Tumor Markers

Once again, prostate cancer tumor markers were a major component of the AUA meeting. Although it was difficult to select from all the excellent presentations made, the following review highlights some of the most important papers.

More and more clinicians are lowering the serum prostate-specific antigen (PSA) cutoff point for biopsy. Haese and colleagues<sup>14</sup> demonstrated high cancer yield in men with PSA between 2 and 4 ng/mL, especially when stratified by age and percent free PSA. The percent free PSA enhances the specificity in this PSA range, with relatively lower prevalence of prostate cancer (Table 1). Men 55 years or younger with a percent free PSA > 25% had only a 4.1% incidence of prostate cancer as opposed to 1 out of 2 men who were over age 70 and had a percent free PSA < 15%.

Another paper that addressed the issue of lower PSA cutoff was presented by Nadler and associates.<sup>15</sup> They evaluated 181 men undergoing ultrasound-guided prostate biopsy who had a total PSA between 2.6 and 4.0 ng/mL and a negative digital rectal examination (DRE). They demonstrat-

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*Data confirm that in widely disparate patient populations, complexed PSA is the preferred analyte.*

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ed that the risk for prostate cancer in men with this lower PSA range increased with age (33% positive biopsy in men younger than 60 years vs 40% in men older than 70). The incidence of clinically insignificant cancers was not greater in the older cohort. The authors concluded that lowering the PSA cutoff should be done for all age groups.

Numerous studies have demonstrated the superiority of a complexed PSA (cPSA) compared with total PSA

	Published Cut Points (%)			Sensitivity at Fixed Values (%)					
	Cut Point	Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
tPSA	4.0	85.2	34.2	85.0	34.3	90.0	27.4	95.0	22.2
cPSA	3.4	84.2	37.3	85.0	35.8	90.0	30.7	95.0	24.3
% cPSA	74.0	93.1	19.2	85.0	37.3	90.0	27.9	95.0	15.3
% fPSA	25.0	92.3	20.4	85.0	36.7	90.0	24.1	95.0	13.0

cPSA, complexed prostate-specific antigen; fPSA, free prostate-specific antigen; Sens, sensitivity; Spec, specificity; tPSA, total prostate-specific antigen.  
Data from Trock et al.<sup>16</sup>

(tPSA) for initial testing. Trock and associates<sup>16</sup> performed a meta-analysis of several international studies comparing these 2 analytes along with the percent free PSA. The study cohort consisted of 5437 men, including 1944 with cancer. Table 2, taken from this abstract, demonstrates the significant findings—namely, clinically relevant sensitivity level cPSA and percent cPSA outperformed tPSA and performed equally to or better than percent free PSA. These data confirm

the doubling time on the first 3 PSA determinations following radical prostatectomy. They compared these results with doubling time obtained from all PSA determination levels following treatment. Of the 1162 men evaluated, the doubling time was < 1 year in 23% of the patients, between 1 and 4.9 years in 69%, and > 5 years in 8% of the patients. There was a tendency for the doubling time calculated from the first 3 determinations to overestimate the eventual PSA doubling time (PSADT). The authors concluded that the sensitivity of the doubling time based on the 3 determinations to detect an eventual doubling time of < 12 months was 86%. PSADT was < 12 months in 67% of the men who were shown to have systemic progression, 26% in those with local recurrence, and 2% in those with no clinical recurrence.

Shen and associates<sup>18</sup> evaluated an ultrasensitive serum PSA nadir and assessed whether it accurately predicted outcome after radical prostatectomy. The authors studied 906 men after radical prostatectomy by measuring serum PSA by the DPC Immulite Ultrasensitive Assay (DPC, Los Angeles, CA) with a low-end

sensitivity level < 0.01 ng/mL. The mean follow-up was 3.2 years; mean time to PSA nadir was 10.1 months, reflecting, undoubtedly, some assay-to-assay and noise variability in this very low range. The authors demonstrated that patients with a PSA nadir < 0.01 ng/mL had a significantly lower rate of biochemical relapse than did patients with a higher nadir. They concluded that the ultrasensitive PSA nadir accurately predicts the risk of early biochemical failure following radical prostatectomy. Men who demonstrate an elevated nadir may be excellent candidates for early adjuvant or salvage therapy.

A number of investigators continue to search for novel prostate markers. Pro-PSA, the proenzyme form of PSA, has been demonstrated to be more associated with carcinoma than tPSA. Raaijmakers and colleagues<sup>19</sup> evaluated 723 men undergoing ultrasound-guided prostate biopsy who were part of a large screening trial. They measured pro-PSA and percent free PSA in these patients. The authors demonstrated that the ratio of pro-PSA to free PSA was significantly higher in men without prostate cancer ( $P < .01$ ). These findings are intriguing and may demonstrate an improved methodology for selecting patients for biopsy. However, the need to measure 3 analytes (tPSA, free PSA, and pro-PSA) will likely render this economically unfeasible.

Insulin-like growth factor has been widely debated as a useful prostate tumor marker. Inman and associates<sup>20</sup> evaluated 144 men undergoing radical prostatectomy for levels of insulin-like growth factor-1 and insulin-like growth factor-binding proteins (IGFBP)-1, -2, and -3. Average patient follow-up was 6.92 years, and 34.8% of the patients experienced PSA failure. IGFBP-2 was a significant predictor of PSA failure in the post-radical prostatectomy population. Moreover,

this was independent of clinical stage, biopsy, Gleason score, and preoperative PSA. An intriguing observation was that IGFBP-2 was a predictor of better biochemical-free survival in men who received neoadjuvant androgen deprivation therapy but of worse survival in those who did not.

Prostate stem cell antigen (PSCA) was evaluated by Han and associates.<sup>21</sup> In their study, PSCA monoclonal antibody testing was performed on tissue microarrays from 256 radical prostatectomy specimens. PSCA intensity staining was associated with adverse prognostic features, including Gleason score  $\geq 7$ , seminal vesicular invasion, and capsular involvement. A PSCA intensity of 3 was associated with a high risk of biochemical failure ( $P < .031$ ). PSCA may represent an important novel marker worthy of further investigation.

Human carcinoma antigen (HCA) has been evaluated in a number of organ sites. Devanney and colleagues<sup>22</sup> studied HCA in the ejaculate of subjects prior to prostate needle biopsy. They compared this with normal age-matched men undergoing fertility evaluation. Nine of the biopsy patients had cancer, and 75 revealed benign findings. Sensitivity of the analysis was 100%; specificity was amazingly high at 83%. HCA was unrelated to serum PSA or age. This may represent a marker worthy of additional study.

It has been well recognized that PSA rises as men age. The long-term longitudinal changes in PSA have been poorly evaluated. Jacobsen and associates,<sup>23</sup> in the Olmsted County study, followed 2115 men. Among these, 475 had a detailed clinical examination including serum PSA determination, DRE, and transrectal sonographic imaging of the prostate. In more than 3846 person-years of follow-up, the average annual change in serum PSA was 3.5%. This was slightly higher after age 50. PSA rose

4.5%, 4.2%, and 4.7% for men in the sixth, seventh, and eighth decades of life, respectively, as compared with 2.5% for men in their 40s. Approximately 75% of the men experienced 2-year rises in PSA of as much as 0.7 ng/mL. About 5% of the men without prostate cancer had a 2-year rise > 1.0 ng/mL. These findings should help us in following serial PSA changes as an indication for biopsy.

Correlation of serum PSA with cancer parameters was given serious questioning by the group from Stanford in a study published in 2002.<sup>24</sup> Stamey and associates<sup>25</sup> followed 1317 men who underwent radical prostatectomy. The authors evaluated the relationship of serum PSA to largest "index" cancer in four 5-year intervals, beginning in 1983. Palpable cancers decreased from 91% in the first 5-year interval to 17% in the last. The mean age decreased from 64 years to 59 years, and mean serum PSA decreased from 25 to 8 ng/mL. The index cancer volume decreased from 5.3 mL to 2.4 mL. Percent Gleason grades 4/5 of the largest cancer averaged 27% to 35%. All cancer histologic parameters had a significant correlation of serum PSA in the first 5-year interval. In the final 5-year period, serum PSA correlated only with prostate size. This paper suggests that with the historically significant stage of migration, the ability of PSA to correlate with findings of radical prostatectomy and by extension outcome may be decreasing.

In an effort to corroborate these findings, Bunde and colleagues<sup>26</sup> evaluated 348 men undergoing radical prostatectomy at a single institution. They demonstrated significant correlations between serum PSA and prostate weight, tumor volume, and Gleason score. PSA was also associated with surgical margin status and pathologic stage. Using multivariate logistic regression analysis control-

ling for stage, surgical margins, and Gleason score, the investigators demonstrated that preoperative PSA was a significant predictor of biochemical recurrence ( $P = .027$ ). These data represent a significant departure from the conclusions of the Stanford group and indicate the need for further investigation.

The relationship of serum PSA to testosterone level has been of increased interest. San Francisco and associates<sup>27</sup> examined 279 men who had a free testosterone level available prior to radical retropubic prostatectomy. Hypogonadal men were considered to be those with free testosterone

phadenectomy for transitional cell carcinoma (TCC). Mean total number of lymph nodes removed was  $19 \pm 15$ , mean number of positive nodes was  $5 \pm 8$ , and mean percent of positive lymph nodes was  $25\% \pm 24\%$ . The authors concluded that the percent of positive lymph nodes, lymphovascular invasion, and tumor stage were associated with disease recurrence and cancer-specific survival. In a subset analysis, this group also reported that lymphovascular invasion, defined as the presence of tumor cells within an endothelium-lined space, was an independent predictor of distant recurrence and

temporal groups and into 2 clinical groups (organ confined and non-organ confined). There was no difference in pathologic findings between groups for either stage or node status.

#### *Detection and Treatment of Bladder Cancer*

Several abstracts were presented on new technologies to improve the detection of bladder cancer. Sarosdy and colleagues<sup>33</sup> reported on a multicenter, prospective, blinded trial that evaluated a multitarget fluorescent in situ hybridization (FISH) assay for the detection of bladder cancer in 497 patients with gross or microscopic hematuria and no prior history of bladder cancer. In patients undergoing evaluation for hematuria, there was a direct correlation of smoking history, positive FISH assay, and detection of bladder cancer. The multitarget FISH assay detected bladder cancer in patients with hematuria better than did cytology. Hedgepeth and associates<sup>34</sup> from the Cleveland Clinic reported that the multitarget FISH assay was a useful indicator in predicting TCC recurrence and was capable of detecting recurrent TCC in patients with atypical and negative urine cytology. A multi-institutional study on the use of hexyl 5-aminoolevulinate (Hexvix; PhotoCure ASA, Oslo, Norway) and fluorescence cystoscopy as an adjunct in the diagnosis of stage Ta/T1 TCC reported that Hexvix instillation was safe and capable of complementing standard endoscopic identification of stage Ta and T1 disease, allowing for a more thorough excision of these lesions.<sup>35</sup> In addition, the use of Hexvix and fluorescence cystoscopy may aid in the detection of carcinoma in situ that may not be visible under standard white light.<sup>36</sup> A European multicenter study compared Hexvix-based fluorescence cystoscopy to standard

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levels  $< 1.5$  ng/dL. Men with lower free testosterone levels tended to have lower PSA levels ( $P = .07$ ). Patients with low free testosterone were diagnosed with prostate cancer at a later age (60 vs 57 years, respectively;  $P < .001$ ). Eighty-seven percent of men with a Gleason score  $\geq 8$  had low free testosterone levels, whereas 55% of those with a Gleason score  $\leq 7$  had low free testosterone levels. The authors concluded that hypogonadal men may have lower PSA levels at the time of prostate cancer diagnosis and may have higher-grade cancers.

[Michael K. Brawer, MD]

## **Urologic Oncology**

### *Staging and Prognostication of Bladder Cancer*

Several interesting abstracts were presented on prognostic indicators following radical cystectomy. Vazina and colleagues<sup>28</sup> reported on a multi-institutional study consisting of 850 patients who underwent radical cystectomy and bilateral pelvic lym-

phadenectomy.<sup>29</sup> They also concluded that nodal involvement was a predictor of distant and local recurrence, whereas lymphovascular invasion and pathologic stage were predictors of distant recurrence only.<sup>30</sup> Shariat and associates<sup>31</sup> developed several nomograms to predict bladder cancer recurrence according to grade and stage from a multi-institutional cohort of 2681 patients. A nomogram incorporating age, gender, cytology, and nuclear matrix protein 22 (NMP-22) allowed for the greatest predictive accuracy for bladder cancer recurrence. The authors suggest that nomogram-based predictions may be used to modify the frequency of cystoscopy follow-up of patients at risk for recurrence. Levinson and colleagues<sup>32</sup> from Columbia University reported on the lack of unfavorable pathologic stage migration over time for bladder cancer in 389 patients who underwent cystectomy from 1990 to 2003. This cohort was divided into 3

cystoscopy in 146 patients with known or suspected bladder cancer.<sup>37</sup> The sensitivity for the detection of bladder cancer for all tumor types was 96% for Hexvix and 79% for standard cystoscopy. In addition, 24% more tumor lesions were visualized by the use of Hexvix cystoscopy.

Sylvester and colleagues<sup>38</sup> reported a meta-analysis on the published results of randomized clinical trials comparing transurethral resection (TUR) alone to TUR plus one immediate postoperative instillation of chemotherapy. Seven randomized trials with recurrence information on 1476 patients were identified. Based on a median follow-up of 3.4 years, 36.7% of patients with stage Ta/T1 bladder cancer who received one postoperative instillation of epirubicin, mitomycin C, thiotepa, or pirarubicin had a recurrence of disease compared with 48.4% of those undergoing TUR alone, which was a reduction of 39% in the odds of recurrence with chemotherapy (OR = 0.61,  $P < .0001$ ). Coen and associates<sup>39</sup> from the Massachusetts General Hospital presented their updated data on the outcomes of bladder preservation for muscle-invasive bladder cancer treated with TUR and concurrent chemoradiation. The 5- and 10-year disease-specific survival rates were 64% and 61%, respectively. The rate of invasive recurrence was near 20% at 5 and 10 years for patients with complete response to chemoradiation. One-third of the patients treated ultimately required a cystectomy either for an incomplete response or recurrence. For patients requiring a cystectomy, the 5- and 10-year disease-specific survival was 50% and 44%, respectively.

#### *Renal Surgery for Kidney Cancer*

Although elective nephron-sparing surgery (NSS) is generally performed in patients with tumors  $\leq 4$  cm in

diameter, emerging data from several abstracts suggest that NSS may be performed on patients with larger tumors that are anatomically amenable, provided an adequate surgical margin can be safely obtained. Patard and colleagues<sup>40</sup> reported on an international multicenter experience on the safety and efficacy of partial nephrectomy for T1 tumors. A total of 1454 patients with T1N0M0 renal tumors were included in the study. Partial and radical nephrectomies were performed in 379 (26.1%) and 1075 (73.9%) patients, respectively,

$\leq 4$  cm. Cho and colleagues<sup>42</sup> reported on the Memorial Sloan-Kettering surgical experience for renal cortical tumors  $< 7$  cm. A cohort of 354 partial nephrectomies was compared with a cohort of patients undergoing radical nephrectomy. No difference in disease-specific survival was noted. In addition, patients who underwent radical nephrectomy had significantly higher serum creatinine than did patients who underwent partial nephrectomy.

Laparoscopic partial nephrectomy is a technically challenging procedure; however, many groups are now

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with a mean follow-up of 62.5 months. Recurrence-free rates between partial and radical nephrectomy were not significantly different. There was no difference in cancer-specific survival between patients with T1a ( $\leq 4$  cm) or T1b ( $> 4-7$  cm) tumors undergoing partial or radical nephrectomy, suggesting that it may be safe to expand the indications of partial nephrectomy to include T1b tumors. Lam and associates<sup>41</sup> from the University of California-Los Angeles reported their institutional NSS experience. A total of 317 patients had undergone NSS. This cohort was divided into an older group (1980-1997) and a contemporary group (1998-2003). There was no difference in the complication rates between the 2 groups, and the contemporary group had a shorter hospital stay and less blood loss. Moreover, there was no difference in disease-specific survival between patients undergoing NSS and the cohort of patients undergoing radical nephrectomy for clinical T1 disease for both tumors  $> 4$  cm and those

reporting their results using this technique. The Cleveland Clinic group reported the etiology and management of complications occurring in 200 patients undergoing laparoscopic partial nephrectomy.<sup>43</sup> Intraoperative complications occurred in 6.5% of patients, and postoperative complications occurred in 22.5% of patients. Postoperative complications included hemorrhage (22.5%), pulmonary (5%), urine leak (4.5%), cardiovascular (3%), acute renal insufficiency (2%), port site hernia (1.5%), and gastrointestinal (1%). The authors maintain that laparoscopic partial nephrectomy is an advanced procedure with potential for complications and that complications are more likely to occur in the presence of central, infiltrating tumors. Finelli and associates<sup>44</sup> from the Cleveland Clinic reported their experience on laparoscopic heminephrectomy, defined as an excision of  $> 30\%$  of renal parenchyma. Compared with laparoscopic partial nephrectomy ( $< 30\%$  excision), laparoscopic heminephrectomy was associated with

longer warm ischemia and total operative times. However, both procedures resulted in similar outcomes.

#### *Minimally Invasive Therapies for Renal Tumors*

A great emphasis on minimally invasive approaches to management of genitourinary malignancies was evident at this year's AUA meeting. One particular procedure that garnered attention was minimally invasive cryotherapy for the management of localized renal cell carcinoma (RCC). Harmon and colleagues<sup>45</sup> presented a multicenter study of 120 patients undergoing renal cryoablation in the United States and Europe. The authors reported that 5% of patients had a persistent lesion following cryotherapy whereas 2.5% developed a metachronous lesion in the same kidney. Treatment failures were identified at a median time of 14 months. The authors reported that risk factors for tumor persistence were lesions > 4 cm and evidence of tumor growth following cryoablation. Hasan and colleagues<sup>46</sup> presented their experience with laparoscopic renal cryoablation at the Cleveland Clinic. The authors reported on 40 patients undergoing the procedure for the treatment of 44 renal tumors with a mean tumor size of 2.4 cm. All patients were followed for a minimum of 4 years. The renal tumors were measured postoperatively after cryotherapy with magnetic resonance imaging (MRI) scans and demonstrated a mean reduction in size of 23%, 33%, 49%, 67%, 80%, and 95% at 3, 6, 12, 24, 36, and 48 months, respectively. The authors also reported that 43% of the renal tumors disappeared completely whereas 5% of patients manifested recurrent or persistent tumors as demonstrated by needle biopsy. Taking cryotherapy to an even less invasive level, Shingleton and Sewell<sup>47</sup> presented their experience

with 90 patients undergoing percutaneous renal cryotherapy for tumors with a mean size of 3 cm. The authors treated a total of 111 tumors using mostly MRI guidance. The procedures were carried out in a mean time of 79 minutes and resulted in 1 major and 8 minor complications. The authors reported a 92% success rate at a median follow-up of 30 months.

Minimally invasive therapies for upper tract TCC were also presented at this year's meeting. Sandhu and colleagues<sup>48</sup> from the United Kingdom presented a percutaneous approach as an alternative to nephroureterectomy for patients with upper tract TCC. The authors described their technique of percutaneous renal surgery with resection or cauterization of the renal lesions followed by radiotherapy applied to the tract. This procedure was performed on 44 patients, 37 of whom were followed over 4.2 years. The authors reported a recurrence-free survival of 62% and a renal preservation rate of 83%. Percutaneous therapy prevented the need for dialysis in 37% of patients. None of the patients in the series developed seeding or recurrence of tumor in the nephrostomy tracts. Also evaluating minimally invasive therapy of upper tract TCC, El-Hakim and colleagues<sup>49</sup> from the Long Island Jewish Medical Center presented their investigation of adjuvant bacille Calmette-Guérin (BCG) after endoscopic treatment of upper tract tumors. The authors evaluated 72 patients (75 renal units) undergoing ureteroscopic or percutaneous approaches for upper tract TCC lesions. Forty-four renal units underwent weekly adjuvant percutaneous BCG therapy for 6 weeks, whereas 29 served as controls. Although not demonstrating an impact on recurrence rate, progression, or survival overall, adjuvant BCG was found on subanalysis to increase overall survival in grade 1 and uni-

focal tumors and to increase recurrence-free survival in unifocal tumors compared with controls.

#### *Staging and Prognostication of RCC*

Numerous investigations of various prognostic factors and staging algorithms were also presented at this year's AUA meeting. Daneshmand and colleagues<sup>50</sup> from the University of Southern California reported on pathologic factors that predict lymph node involvement by RCC tumors. The authors investigated the role of stage, grade, tumor size, cell type, and number of lymph nodes removed in predicting positive lymph nodes at nephrectomy. According to a multivariate analysis, tumors > 7 cm; high-grade, locally advanced tumors; and tumors for which more than 15 nodes were removed at nephrectomy were all found to be significant predictors of lymph node metastases. Stage T4 tumors were most associated with lymph node disease, demonstrating an odds ratio of 6.7. Blute and colleagues<sup>51</sup> from the Mayo Clinic also evaluated pathologic features of primary nephrectomy specimens to create a protocol for extended lymph node dissection. The authors studied 955 patients who underwent lymph node dissection as part of a radical nephrectomy. Of these patients, 68 demonstrated evidence of lymph node involvement whereas 887 did not. Multivariate analysis demonstrated that high grade, presence of sarcomatoid features, tumor size  $\geq$  10 cm, stage pT3, and histologic tumor necrosis were significant predictors of lymph node-positive disease. The authors also reported that although only 0.6% of patients with none or 1 of these high-risk features were found to have positive lymph nodes, 10% of patients with 2 or more features were found to have node-positive disease. The authors concluded that these high-risk features can be

successfully employed in deciding which patients need to undergo extensive lymph node dissection as part of a radical nephrectomy. Bensalah and colleagues<sup>52</sup> from Rennes, France, evaluated the prognostic value of thrombocytosis in localized and metastatic RCC. Platelet count was strongly correlated with tumor stage, Fuhrman grade, tumor size, renal vein or perinephric fat invasion, nodal involvement, and presence of distant metastasis. TNM (tumor, node, metastasis) stage, grade, tumor size, performance status, and platelet count were significant predictors for survival following multivariate analysis. The 5-year survival rate for platelet counts < 450,000 was 70% compared with 38% for platelet counts  $\geq$  450,000.

Several studies also focused on the pathologic subtype as a determinant of location of primary tumors and metastatic lesions. Schacter and colleagues<sup>53</sup> from the Memorial Sloan-Kettering Cancer Center studied 485 consecutive renal cortical tumors in 469 patients to determine whether lesion location within the kidney is associated with the histologic subtype of RCC. The authors reported that 69.7% of all central tumors were clear cell as opposed to 53.7% of exophytic lesions. Conversely, only 30.3% of all central tumors were non-clear cell in contrast to 42.3% of exophytic lesions. The authors concluded that exophytic lesions are significantly more likely than central lesions to be non-clear cell whereas clear cell tumors are significantly more likely to be central in location. The authors further extrapolated their conclusions, arguing that because clear cell tumors have historically been demonstrated to portend a worse prognosis, exophytic versus central location is a predictor of better prognosis in patients with RCC. Gillett and associates<sup>54</sup> from the Mayo Clinic, in contrast, evaluated the role of histologic subtype in predicting the site

of distant metastases. The authors evaluated 870 tumors treated with radical nephrectomy, 94% of which were clear cell, 4% were papillary, and 2% were chromophobe. The authors reported that clear cell tumors (53.9%) were more likely to metastasize to the lungs as compared with papillary (31.4%) and chromophobe (33.3%) RCC. In contrast, chromophobe (33.3%) and papillary (17.1%) tumors were most likely to metastasize to the liver. Patard and associates<sup>55</sup> reported an international multi-institutional analysis on the prognostic value of histologic subtypes in RCC. In univariate analysis, clear cell carcinoma had a worse survival rate compared with other histologic subtypes, whereas chromophobe RCC exhibited a better survival rate. However, when adjusted for tumor stage and grade, chromophobe carcinoma had survival rates comparable to other tumors. In addition, following multivariate analysis, TNM stage, Fuhrman grade, and performance status were retained as independent prognostic variables, whereas histologic subtype was not.

#### *Molecular Markers for Kidney Cancer*

Methods based on gene arrays, which screen for differential expression of thousands of genes, have identified large numbers of new, potentially important prognostic markers for patients with RCC. The evaluation of protein expression in a high-throughput tissue array is a natural extension to the efforts for molecular staging. Several abstracts were presented on this topic. Bui and colleagues<sup>56</sup> from the University of California-Los Angeles reported on the prognostic value of carbonic anhydrase isozyme IX (CA IX) and Ki67 as independent predictors of survival. Moreover, when Ki67 and CA IX were combined into a single parameter, RCC tumors could be stratified into low-, intermediate-, and

high-risk groups with median survival of >101, 31, and 9 months, respectively ( $P < .0001$ ). The combined parameter consisting of Ki67 and CA IX was a significant predictor of survival ( $P < .0001$ ) and was able to displace histologic grade following multivariate analysis. Taking this concept another step further, Kim and associates<sup>57</sup> from the University of California-Los Angeles proposed a novel molecular staging system for clear cell RCC based on RCC molecular markers. Immunohistochemical analysis of Ki67, p53, gelsolin, CA IX, CA XII, PTEN, epithelial cell adhesion molecule (EpCAM), and vimentin was performed on a custom tissue array using clear cell RCC from 318 patients, representing all stages of localized and metastatic RCC. Increased staining for Ki67, p53, vimentin and gelsolin correlated with worse survival, whereas the inverse was true for CA IX, PTEN, CA XII, and EpCAM. A prognostic model based primarily on molecular markers including metastasis status, p53, CA IX, vimentin, and gelsolin as predictors had a statistically validated C-index of 0.75. A prognostic marker based on a combination of clinical and molecular predictors included metastasis status, tumor stage, Eastern Cooperative Oncology Group (ECOG) performance status, p53, CA IX, and vimentin as predictors and had a statistically validated C-index of 0.79. The predictive ability of the various models was quantified by calculating the C-index, and this demonstrated that prognostic systems based on protein expression profiles for clear cell RCC perform better than standard clinical predictors such as TNM stage, histologic grade, and performance status. Both nomograms were calibrated, using bootstrap bias-corrected estimates, to be accurate to within 10% of the actual 2- and 4-year survival rates. Petros and colleagues<sup>58</sup> from Emory University

described a new approach to identifying and quantifying novel gene expression markers in renal tumors using a quantitative reverse transcriptase polymerase chain reaction (RT-PCR) technique to distinguish among various histologic subtypes. The genes analyzed consisted of novel expressed sequence tag (EST), reproduction 8, fms-related tyrosine kinase 1 (FLT1; vascular endothelial growth factor [VEGF] receptor), adipophilin, four-and-a-half LIM domain protein 1 (FHL1), chloride channel Kb, and cytochrome c heme lyase. Consistent with previous microarray findings, chloride channel Kb and cytochrome C heme lyase were most highly expressed in chromophobe RCC and oncocytoma, FLT1 was expressed in clear cell RCC, and FHL1 was expressed in papillary RCC. Novel EST, reproduction 8, and FHL1 were also more highly expressed in chromophobe RCC than in oncocytoma, whereas chloride channel Kb tended to be overexpressed in oncocytoma relative to chromophobe RCC. Bensalah and colleagues<sup>59</sup> reported on the prognostic value of vascular endothelial growth factor in a series of pT3 renal tumors in 112 patients. A 30% VEGF cutoff was determined according to receiver-operator curves. Grade, fat invasion, renal vein invasion, distant metastasis, and VEGF expression were significantly associated with survival following multivariate analysis.

[John S. Lam, MD, Oleg Shvarts, MD, and Arie S. Belldegrun, MD, FACS]

### Symptoms of Overactive Bladder Affect Sexual Activity of Women

Women who experience overactive bladder are less likely to enjoy sexual activity. Overactive bladder, a condition in which the muscle surrounding the bladder contracts spastically, causing frequent urination and incontinence, affects more than 20 million women worldwide. Female sexual dys-

function is a condition that is underdiagnosed, with uncertain treatment. We all have had female patients who present with one condition while also complaining of the other, and yet, a correlation between overactive bladder and female sexual dysfunction has not been established. The results from a study of this issue were presented at the AUA meeting.

Dr. Ankur Patel and colleagues<sup>60</sup> from the University of Pittsburgh

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*The researchers found that women who expressed a higher degree of bother as a result of urge urinary incontinence were less likely to enjoy sexual activity and were less sexually active.*

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studied 78 women with diagnosed overactive bladder who completed 2 questionnaires: 1 that evaluated the presence and degree of bother caused by their symptoms and 1 that evaluated their sexual function. By comparing each patient's answers on both questionnaires, the researchers found that women who expressed a higher degree of bother as a result of urge urinary incontinence were less likely to enjoy sexual activity and were less sexually active. Those who experienced a significant amount of genital or abdominal pain were less likely to enjoy sexual activity but were more likely to experience sexual thoughts or fantasies.

"Overactive bladder is so prevalent, and, as shown by this study, its effects reach beyond the commonly thought of symptoms like incontinence to the inability to enjoy sexual activity," said Dr. Patel. "There is still a stigma about talking to a doctor about overactive bladder. Women need to know that they don't have to accept the symptoms of overactive bladder and that there are treatments that can ease their symptoms. Perhaps if we can lessen the burden of overactive bladder, we may also improve the

sexual enjoyment of these women."

More than 17 million Americans, half of whom are women, suffer from overactive bladder, a condition that significantly affects the patient's quality of life. An estimated 80% of these patients do not seek help or treatment for this condition. It is only recently that an association between overactive bladder and female sexual dysfunction has emerged. It remains to be established whether correcting the

overactive bladder actually improves female sexual function as it has improved other aspects of the patient's global quality of life.

[Michael B. Chancellor, MD]

### Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Attendees of the 2004 AUA meeting continued the tradition of presenting the most up-to-date clinical trials in chronic prostatitis therapy. This year's important reports evaluated antibiotics,  $\alpha$ -blockers, phytotherapy, corticosteroids, and transurethral needle ablation (TUNA) for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and also assessed a standard monotherapy treatment strategy for this condition.

#### *Antibiotics and $\alpha$ -Blockers*

The National Institutes of Health (NIH) Chronic Prostatitis Collaborative Research Network randomized 196 men with category III CP/CPPS in a 2-by-2 factorial-designed study to 6 weeks of treatment with either ciprofloxacin, tamsulosin, both drugs, or placebo.<sup>61</sup> The NIH-Chronic Prostatitis Symptom Index (CPSI)

declined modestly in all treatment groups, but there was no statistically significant difference in the primary end point for ciprofloxacin versus no ciprofloxacin or tamsulosin versus no tamsulosin. There were no significant differences between treatments for any of the secondary outcomes at either 6 weeks or 12 weeks (6 weeks post therapy). The group concluded that ciprofloxacin and tamsulosin were not effective in reducing substantially the symptoms of CP/CPPS over a 6-week treatment period among patients who were heavily pretreated and refractory to many prior therapies.

**Comment.** These data certainly do not support use of these agents as empiric therapy for men with a long history of CP/CPPS who have been heavily pretreated with these agents in the past. However, this does not negate the possibility that antibiotic therapy and  $\alpha$ -blocker therapy may be effective in treatment-naïve patients, and further trials must address patients with an early diagnosis of CP/CPPS who are naïve to the treatment drugs.

#### *Phytotherapy*

In a study by Reissigl and colleagues,<sup>62</sup> 142 patients with category III CPPS were randomized to saw palmetto (*Serenoa repens*/Permixon [Pierre Fabre Medicament, Castres Cedex, France]) or placebo. The response to therapy was evaluated at 6 and 12 weeks, 6 months, 12 months, and 18 months. At 12 and 18 months, 76.4% and 71.8% of the *Serenoa repens* group had at least mild improvement (35% improvement in subjective global assessment and NIH-CPSI vs 24.3% and 18.5%, respectively, in the control group). Overall, a 30% reduction of the NIH-CPSI score was observed in the active group versus 6.3% in the control group. The investigators noted that the PSA decreased by 18% in the active group whereas PSA did

not differ from baseline in the control group. The researchers suggested that Permixon may provide clinical benefit in patients with category III CPPS.

**Comment.** A perceptible improvement in subjective global assessment in NIH-CPSI was observed in more than 60% of patients treated over the year with *Serenoa repens*. This appears to be a clinically significant response rate compared with placebo

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*A perceptible improvement in subjective global assessment in NIH-CPSI was observed in more than 60% of patients treated over the year with Serenoa repens.*

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and suggests that phytotherapy with *Serenoa repens* may benefit some patients with CPPS. Further therapeutic trials with phytotherapy are certainly indicated, but at the present time, long-term phytotherapy with either quercetin (another phytotherapy that has shown efficacy in a placebo-controlled trial) or *Serenoa repens* appears to be justified.

#### *Corticosteroids*

In a study by Dimitrakov and associates,<sup>63</sup> 133 men with category III CP/CPPS were randomly assigned to 1 of 4 treatment regimes: 0.5 mg, 1 mg, or 5 mg of methylprednisolone per kilogram of body weight, or placebo. The methylprednisolone was tapered, but the ultimate dose and duration were not obvious. A dose-dependent improvement in symptom score was noted in patients on corticosteroids compared with the placebo group, but significant side effects were noted at the higher doses. The authors concluded that steroids might be a valuable addition to the urologic treatment regime of CP/CPPS patients, although the potential benefit must be weighed against the frequency and severity of the side effects.

**Comment.** Steroids were success-

fully used for many inflammatory syndromes, including chronic prostatitis, decades ago. The use of high-dose steroids was abandoned because of the significant and serious side-effect profile. It is unlikely, even based on the results of this trial, that steroids will make a comeback as an important treatment modality. The importance of this study is that anti-inflammatory/immune suppressive therapy does

result in amelioration of symptoms. What is needed, therefore, is a viable alternative to steroid therapy: an anti-inflammatory, immune suppressant that can be safely given for a long duration and that has an acceptable safety profile. Clinical trials with these types of agents should be strongly considered.

#### *Transurethral Needle Ablation*

TUNA of the prostate was evaluated by Guiannakopoulos and coworkers<sup>64</sup> for the treatment of chronic nonbacterial prostatitis, but the follow-up was short. The investigators reported their long-term data of TUNA for the treatment of this condition. The researchers treated 39 consecutive patients who had failed conventional therapies for category III CP/CPPS. The results of therapy were assessed up to 36 months. Of the 34 patients available for follow-up, the authors noted that 31 patients had an improvement in prostatitis symptom score of more than 50%. Patients noted a significant improvement in quality of life, and there was even a decrease in the white blood cell count in the expressed prostatic secretion. Interestingly, the investigators noticed no change in morphology or motility

of the sperm when comparing pre- and post-TUNA data. They suggested that this 3-year follow-up study supports the place of TUNA as an effective treatment option in patients with chronic nonbacterial prostatitis who have failed conventional therapies.

**Comment.** This type of trial, assessing minimally invasive therapies for CP/CPPS, is important because it provides solid preliminary data. The data suggest that these therapies may be effective, but before they can be recommended, minimally invasive therapies such as TUNA and transurethral microwave thermotherapy must be evaluated in randomized, sham-controlled studies.

#### *Monotherapy*

In a study by Nickel and colleagues,<sup>65</sup> 100 consecutive CP/CPPS patients who were referred to a specialized prostatitis clinic after failure of prescribed therapy were treated with a “best” evidence-based monotherapeutic strate-

remain relatively poor. It is apparent that either novel therapies or multimodal therapeutic strategies employing our standard therapies need to be assessed for this condition.

[J. Curtis Nickel, MD, FRCSC]

#### **Advances in Basic Science, Prostate Cancer, and Laparoscopic Oncology**

This review highlights three important subjects covered at the AUA Annual Meeting. First, a few noteworthy basic science research projects that have an impact on our clinical practice are discussed. Next, advances in the most common malignancy in men, prostate cancer, are presented. Finally, results from the field of laparoscopic urooncology are reviewed.

#### *Basic Science*

In the treatment of androgen-independent prostate cancer, Gardner and colleagues<sup>66</sup> developed a novel adenoviral vector, Ad-PSES-TRAIL (tumor

SVV-specific siRNA constructs to inhibit the growth of p53-mutated human Bca (bladder cancer) cell lines. A significant reduction up to 47% of viability was observed in siRNA SVV284-treated EJ28 and 5637 cells up to 72 hours after the start of transfection but not after siRNA SVV094 treatment. The authors concluded that SVV expression and cell growth were inhibited more effectively by siRNA SVV284 than by siRNA SVV094 in the tested Bca cell lines. The inhibition of cell growth was associated with an induction of apoptosis and a failure of cytokines.

SVV expression is also associated with characteristics of benign prostatic hyperplasia (BPH). Shariat and associates<sup>68</sup> compared the expression patterns of SVV in normal prostate and BPH to determine whether the expression of SVV is associated with clinical characteristics of BPH. Immunohistochemical staining for SVV was performed on radical prostatectomy specimens that were further differentiated into normal tissue and BPH tissue. SVV expression was found to be distributed mainly in the stromal compartment as compared with the distribution in the luminal cells of the prostatic glandular epithelium in normal prostate tissues. Furthermore, the staining score for SVV was higher in BPH than that in normal prostate tissue and was correlated with International Prostate Symptom Score, quality-of-life score, postvoid residual, maximum flow rate, and transforming growth factor (TGF)- $\beta$ 1 expression. In conclusion, the expression of SVV was higher in hyperplastic nodules than in normal prostatic cells, and SVV expression was further associated with established objective and subjective clinical features of BPH. SVV may also play a crucial role in spermatogenesis, and dysregulation may be associated with infertility.

Weikert and colleagues<sup>69</sup> investi-

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*Clinical trials of anti-inflammatory, immune suppressants should be strongly considered as these types of agents may be viable alternatives to steroid therapy.*

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gy. At 1 year, there was a statistically significant decrease in total NIH-CPSI, pain, and quality-of-life scores, but a perceptible 25% decrease in the NIH-CPSI was noted in only 37% of patients. The authors concluded that approximately one-third of treatment-refractory CP/CPPS patients undergoing extensive evaluation and therapy based on a sequential monotherapy treatment strategy in a specialized prostatitis clinic had at least modest improvement in symptoms over 1 year.

**Comment.** This study confirms that the results of the traditional treatment strategy based on sequential application of monotherapies for patients with a long history of severe CP/CPPS

necrosis factor-related apoptosis-inducing ligand), to androgen-independent prostate cancer cells for arresting the development of recurrent tumors. This prostate-specific chimeric-enhancer PSES sequence was developed by a selective combination of transcriptional regulatory and enhancer elements derived from PSA and prostate-specific membrane antigen (PSMA).

Antiapoptotic protein survivin (SVV), a bifunctional molecule that counteracts cell death and controls mitotic expression, is an interesting research topic in the different fields of urology. Ning and coworkers<sup>67</sup> compared the therapeutic efficacy of 2

gated the qualitative expression of the apoptosis inhibitor SVV in testicular tissue of infertile men. Testicular biopsies were obtained in 43 men presenting with azoospermia of various causes. Median SVV mRNA expression was highest in normal spermatogenesis and was significantly reduced in specimens with postmeiotic spermatogenic arrest and in those without haploid germ cells. A lack of SVV expression was also seen in specimens with Sertoli-cell-only syndrome. The authors suggested that SVV is a potential molecular marker of spermatogenesis whose expression is altered in specific spermatogenic disorders.

The role of Rho-kinase inhibitors was investigated in both BPH and erectile dysfunction. Ress and coworkers<sup>70</sup> examined the effects of a selective Rho-kinase inhibitor (Y-27632) on both the calcium-sensitizing contractile mechanism within the smooth muscle cells and smooth muscle cell proliferation in other tissues within the prostate. The smooth muscle cell culture displayed a gradual increase in cell number, but this increase was significantly reduced in the presence of Y-27632. In addition, Y-27632 inhibited noradrenergic contractions elicited within the electrical field stimulation and phenylephrine-induced tone in a concentration-dependent manner. The authors concluded that Rho-inhibitors could represent a single "dual action" potent agent for the future treatment of BPH.

On the other hand, Bivalacqua and colleagues<sup>71</sup> aimed to investigate whether the reduction in the penile endothelial nitric oxide synthase (eNOS) and erectile dysfunction in the streptozotocin (STZ) diabetic rat was related to RhoA/Rho-kinase activation in the diabetic penile vascular bed. The rats were divided into 3 groups: 1) age-matched controls, 2) STZ-induced diabetic rats transfected with

AAVCMV $\beta$ gal, and 3) STZ rats with an inhibitor of RhoA; all received intracavernous injections of the Rho-kinase inhibitor Y-27632. There was an increase in erectile response to Y-27632 in STZ rats that was greater than responses in the control rats. STZ rats transfected with  $\beta$ gal had significantly decreased erectile function as determined by cavernosal nerve stimulation. The peak and total intracavernosal pressures in response to cavernosal nerve stimulation were significantly enhanced in STZ rats transfected with RhoA inhibitors to a value similar to control rats. The study implied that the inhibition of RhoA/Rho-kinase improved eNOS protein and activity, thus restoring endothelial and erectile function in diabetic rats. The same group of authors examined the feasibility of ex vivo expanded mesenchymal stem cells (MSCs) alone or modified with eNOS on improving the erectile function in aged rats.<sup>72</sup> With the use of cavernosal nerve stimulation, the investigators were able to demonstrate that MSCs alone or genetically modified with eNOS could improve diminished erectile responses in aged rats. Furthermore, the results indicated that MSCs give rise to smooth muscle cell and endothelial cells in the corpus cavernosum, thereby aiding in the improvement of corpus cavernosum function and thus erectile function.

On the issue of tissue engineering, Kwon and colleagues<sup>73</sup> compared the effects of injections of muscle derived cells (MDCs) and fibroblastic cells on the leak point pressure (LPP) in a rat model of stress incontinence. Results showed that both MDCs and fibroblasts increased the LLP in the denervated rat, and there was no adverse effect observed except urinary retention in the high-dose fibroblast cell injection group. The authors concluded that MDCs might be more functional

than fibroblasts as a bulking agent for stress urinary incontinence. Similarly, Yiou and coworkers<sup>74</sup> explored the possibility of using autologous muscle precursor cells (MPCs) for the functional restoration of irreversibly damaged sphincters in a rat model. Urodynamic studies of the MPC-treated sphincters resulted in the restoration of sphincter function (41%) by 1 month after injection. The study demonstrated that the precursor cells with myogenic properties, obtained from muscle fibers, were able to form new myotubules within irreversibly damaged sphincters, and illustrated the possibility of using MPCs for the functional improvement of irreversible urinary sphincter muscle insufficiency.

It is reported that statins may exert renoprotective effects on diabetic rat glomeruli and cultured rat mesangial cells through the pleiotropic effects. Mizuguchi and associates<sup>75</sup> conducted a study to determine whether atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, could diminish renal TGF- $\beta$  levels in unilateral ureteral obstruction (UUO) and concomitantly affect renal tissue damage in UUO. Atorvastatin was administered to rats 1 day prior to unilateral ureteral ligation and every day thereafter. Atorvastatin was found to significantly decrease tissue TGF- $\beta$  of the obstructed kidney, renal tubule apoptosis, and the amount of leukocyte infiltration in the tissues. The study suggested that atorvastatin is a promising agent to prevent renal tubular damage in unilateral ureteral obstruction by decreasing tissue TGF- $\beta$  and interstitial fibrosis.

#### *Prostate Cancer*

Screening for prostate cancer has been a matter of debate, especially in Europe. Roobol and associates<sup>76</sup> presented the final results of the initial and second (after 4 years) prostate cancer screening round of the European

randomized study of screening for prostate cancer. Table 3 shows that although lower than at initial screening, the cancer detection rate at the second round was substantial and cancers detected at the second round were mostly in men with no previous biopsy, PSA levels between 3.0 and 4.0 ng/mL, and disease more localized to the prostate. It was also noticed that screening tests used in the initial round were no longer predictive 4 years later, and it may be more efficient to biopsy on the indication of a combination of predictors at a subsequent screening round instead of a fixed PSA threshold.

Quantitative GSTP1 methylation assay, a recently developed methylation-specific PCR-based technique, has been shown to allow accurate discrimination of benign prostate tissue and prostate cancer. Zhou and colleagues<sup>77</sup> investigated whether GSTP1 methylation levels correlated with Gleason grade and tumor volume in prostate biopsies. The sensitivity and specificity of GSTP1 methylation assay for predicting prostate cancer was 86.5% and 100%, respectively. Quantitative GSTP1 levels correlated with Gleason grade and cancer volume, demonstrating higher levels in higher tumor grades and cancer percentage per biopsy. The authors suggested that quantitative GSTP1 methylation levels might be a useful prognostic tool for prostate cancer.

In the search for a better tool for detecting early prostate cancer, Tinzl and Marberger<sup>78</sup> evaluated a newly developed urinary assay (uPM3 assay; Diagnostec, Inc., Quebec, Canada) in patients referred for prostate cancer. In a study population with a cancer detection rate of 38%, overall sensitivity, specificity, positive predictive value and negative predictive value of uPM3 assay was 82%, 76%, 69%, and 90%, respectively. uPM3 appears to be an attractive clinical tool for

**Table 3**  
**Results of Initial and Second Prostate Cancer Screening Round in Europe**

Parameter	Initial screening	Second screening
Men with PSA $\geq$ 3.0 (%)	21.1	19.5
Men with PSA $\geq$ 10.0 (%)	2.5	1.4
PPV (n cancers/n biopsied)	29.2	17.6
Detection rate (n cancers/n screened)	5.3	4.4
Mean PSA (ng/mL)	6.8	4.4
Mean prostate volume (mL)	49.7	47.9
% previous biopsied	NA	30.4
Significant predictors for the presence of CaP	PSA, Vol, DRE, TRUS, Age, PFH	Vol, PNB
<b>Tumor characteristics</b>		
Cancers (n)	541	241
Mean PSA (ng/mL)	9.9	4.3
Mean prostate volume (mL)	43.1	40.2
% previous biopsied	NA	17.4
% T3, T4	15.5	3.7
% Gleason $\geq$ 3 + 4	541	18.5

CaP, prostate cancer; DRE, digital rectal examination; NA, not applicable; PFH, positive family history; PNB, prostate needle biopsy; PPV, positive predictive value; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; Vol, volume.

early prostate cancer diagnosis, with minimal invasiveness.

Androgens influence prostate carcinogenesis. Parsons and coworkers<sup>79</sup> analyzed the association between serum androgen levels and risk in a cohort of healthy, aging males in the Baltimore Longitudinal Study on Aging. Serum testosterone, sex hor-

association until data from long-term prospective trials become available. On the other hand, high-grade prostate cancer is associated with low serum testosterone. Schatzl and associates<sup>80</sup> investigated the impact of PSA gene polymorphism on serum testosterone levels and Gleason grade in patients with untreated prostate cancer. PSA

*The study suggested that atorvastatin is a promising agent to prevent renal tubular damage in unilateral ureteral obstruction by decreasing tissue TGF- $\beta$  and interstitial fibrosis.*

monone-binding globulin, and dehydroepiandrosterone levels were measured and correlated with prostate cancer risk. It was found that higher serum free testosterone was associated with a significantly increased risk of prostate cancer in older men. Older men receiving testosterone replacement should be counseled as to this

polymorphism was determined by PCR-based methods using DNA from peripheral blood in 134 men. The investigators found that the PSA G/G genotype is associated with lower serum testosterone levels and higher Gleason score, suggesting a genetic risk factor for poor outcome of prostate cancer.

Radical prostatectomy remains the treatment of choice for localized prostate cancer. Bianco and colleagues<sup>81</sup> studied the 15-year cancer-specific and PSA progression-free rates after radical prostatectomy. Of 1700 patients, 261 experienced disease progression and were then followed a mean of 6.3 years (1–15 years). At 5, 10, and 15 years, cancer-specific survival was 99%, 96%, and 93%, respectively, and overall survival was 96%, 85%, and 63%. At 15 years, 79% of patients with PSA > 10 ng/mL, 68% with Gleason 3 + 4, 51% with Gleason 4 + 3, 73% with focal extracapsular extension, and 42% with established extracapsular extension remained free of recurrence. The authors concluded that with a cancer-specific mortality of 7% at 15 years, cancer control with radical prostatectomy was remarkably good, even for patients with adverse prognostic factors. In comparison, Rassweiler and coworkers<sup>82</sup> presented the functional (continence and potency) and oncologic (positive margins, PSA recurrence, survival) outcome of the first 500 cases of laparoscopic radical prostatectomy. Twelve months after surgery, 83.6% of the patients were continent, whereas after 24 months, 97.4% of the patients did not require any pad. Thirty-eight percent of the patients with unilateral and 67% with bilateral neurovascular bundle preservation reported sufficient erection, with or without phosphodiesterase inhibitors, 12 months after surgery. Positive margin rate was reported in 19% of cases: 7.4% of pT2, 31.8% of pT3, and 100% of pT4. After a median follow-up of 30 months, 7.4% of the patients showed PSA recurrence, whereas only 2% suffered from clinical progression. The authors suggested that the functional results and midterm oncologic outcomes of laparoscopic radical prostatectomy are comparable to those reported after open retropubic radical

prostatectomy.

In the choice of laparoscopic approach, Cathelineau and colleagues<sup>83</sup> compared the transperitoneal with the extraperitoneal approach for laparoscopic radical prostatectomy in 200 patients. The two procedures were equivalent in terms of operative, postoperative, and pathologic results, suggesting no gold standard approach for laparoscopic radical prostatectomy.

Biochemical recurrence after radical prostatectomy is a challenging issue for urologists. Djavan and associates<sup>84</sup> evaluated the use of a new power Doppler-enhanced transrectal ultrasound (TRUS) protocol for accurate prediction of early local recurrent cancer in a biopsy-controlled study. Color Doppler-enhanced TRUS had a sensitivity and specificity of 81.3% and 90.6%, respectively, in predicting local recurrence. In a comparison of area under the curve (AUC), power Doppler was superior to time to recurrence and PSADT. The authors suggested that power color Doppler TRUS has the potential to replace anastomotic biopsies for detection of local recurrence. On the other hand, Partin and colleagues<sup>85</sup> evaluated the use of PSADT as a predictor of cause-specific survival after radical prostatectomy. Of 4115 men, 825 (19%) demonstrated PSA recurrence in an average of 8.4 years, 4% demonstrated metastatic progression, and 2.4% died from prostate cancer. Receiver operating characteristics–AUC for PSADT predicting prostate cancer death was 0.77, and actuarial cause-specific survival at 5 and 10 years for > 10 month PSADT and < 10 month PSADT was 98% and 47%, respectively. The authors concluded that PSADT can be used as a surrogate for cause-specific survival and may allow the implementation of clinical trials for advanced prostate cancer.

In the treatment of advanced prostate cancer, Tunn and coworkers<sup>86</sup>

compared intermittent and continuous androgen deprivation in patients with PSA relapse after radical prostatectomy. In this multinational prospective trial, the intermittent androgen-deprivation arm (IAD) was given a pause in treatment after 6 months and reintroduced by clinical or/and PSA progression, whereas the continuous androgen-deprivation arm (CAD) continued. With a mean follow-up of 28 months, IAD showed the same efficacy as CAD concerning progression-free survival in this interim analysis. Patients in the IAD group were off treatment for up to 58.3% of cycle length and reached up to 90.9% normal testosterone levels. The authors suggested that IAD offers efficacy similar to CAD, with the additional benefit of off-treatment time.

PSMA is an attractive molecular target for cancer immunotherapy. Slovin and associates<sup>87</sup> conducted a phase I trial of an adjuvant recombinant soluble PSMA vaccine. Similarly, Bcl-2 and Bcl-xL antiapoptotic genes have been linked to treatment resistance and tumor progression in prostate cancer. Yamanaka and coworkers<sup>88</sup> examined whether antisense (AS) Bcl-2 and Bcl-xL bispecific oligonucleotide could induce apoptosis and enhance the chemosensitivity of paclitaxel in human independent prostate cancer cells. Cell growth inhibition, activation of caspase-3, PARP cleavage, and an increase in the apoptotic sub-G1-G0 fraction were observed in the prostate cancer cells treated with the bispecific oligonucleotides. The authors suggested that combined treatment with AS Bcl-2/Bcl-xL bispecific oligonucleotides plus paclitaxel could be an attractive strategy for inhibiting progression of androgen-independent prostate cancer through effective induction of apoptosis. Another antisense CK2 gene therapy was investigated by Slaton and coworkers<sup>89</sup> for induction of apopto-

sis in prostate cancer. The investigators found that growth and CK2 expression and activity in the PC3-LN4 cells were down-regulated by the antisense CK2- $\alpha$  but not by the control vector. Tumors treated with 200  $\mu\text{g/mL}$  of the antisense vector were completely obliterated. Substantial apoptosis was noted in the *in vitro* and *in vivo* PC3-LN4 cells treated with antisense CK2- $\alpha$  but not in the prostate epithelial cell line (PrEC) or normal murine prostate. These results suggested the potential for antisense CK2- $\alpha$  as a novel therapeutic strategy for prostate cancer.

#### *Laparoscopic Oncology*

With the advent of laparoscopic surgery, laparoscopic radical nephrectomy has fast become the standard treatment for RCC. Peschel and colleagues<sup>90</sup> reviewed the long-term outcome of laparoscopic radical nephrectomy in 425 patients. The disease-free rate for pT1 tumors was 95% after 3 years and 94% after 5 years. Overall patient survival rate was 98% after 3 years and 96% after 5 years. No local recurrence or port site metastasis occurred. To investigate the incidence of peritoneal dissemination and port site metastasis, Micali and colleagues<sup>91</sup> conducted an international survey regarding tumor seeding following urologic laparoscopy. A total of 20 centers participated, with 18,100 laparoscopic procedures performed. A total of 13 cases (0.1%) of tumor seeding were reported: port seeding occurred in 10 cases and peritoneal spread in 3. These results suggested that incidence of tumor seeding after laparoscopic oncologic surgery is rare and does not appear greater than what has been historically reported for open surgery.

Laparoscopic partial nephrectomy has emerged as an attractive treatment option for certain renal tumors. In an effort to assess morbidity, Ramani and coworkers<sup>92</sup> assessed the complications

of laparoscopic partial nephrectomy in 200 patients in a single center. Open conversion was necessary in 2 patients. Complications occurred intraoperatively in 13 patients (6.5%) and postoperatively in 45 (22.5%), including hemorrhage (21 [10.5%]), pulmonary (10 [5%]), urine leak (9 [4.5%]), cardiovascular (6 [3%]), acute renal insufficiency (4 [2%]), port site hernia (3 [1.5%]), gastrointestinal (2 [1%]) and ureteral transection (1 [0.5%]). The authors concluded from this largest series of laparoscopic partial nephrectomy that this operation is an advanced procedure with potential for complications.

In an attempt to improve hemostasis, Murat and colleagues<sup>93</sup> evaluated the use of microporous polysaccharide hemispheres (MPHs) as a novel hemostatic agent in partial nephrectomy in the porcine model. As compared with conventional technique, MPH significantly decreased hemostatic time and trended toward less blood loss, using weighed-sponge analysis. Further experimental and clinical evaluation is warranted to define the hemostatic role of MPH during partial nephrectomy in humans.

It has been commonly accepted that the safe limit for warm ischemia time during open partial nephrectomy is 30 minutes. Maynes and colleagues<sup>94</sup> conducted a study to determine the maximum safe laparoscopic warm ischemia time in the porcine solitary kidney model. It was found that laparoscopic warm ischemic times up to 90 minutes were well tolerated in the solitary porcine kidney, but warm ischemia times longer than 90 minutes could result in permanent damage to the kidney. Theories to explain this increased tolerance to warm ischemia in this model include the potential protective effect of relative ischemic preconditioning provided by the pneumoperitoneum and the protective effect of a solitary kidney.

Regarding long-term results of laparoscopic partial nephrectomy, Allaf and coworkers<sup>95</sup> evaluated the long-term oncologic outcome in a cohort of 48 patients with a mean follow-up time of 37.7 months. Only 1 patient with VHL was found to have a recurrence 18 months after the initial operation. However, these promising oncologic results need to be further validated by larger, multicenter studies.

This review concludes with a novel laparoscopic technique. Corvin and associates<sup>96</sup> evaluated the suitability of laparoscopic sentinel lymph node (SLN) dissection in the staging of prostate cancer. For visualization of individual SLN distribution, an image fusion system consisting of a gamma camera with integrated x-ray tube was used. <sup>99m</sup>Tc-Nanocoll was injected into the prostate transrectally 1 day preoperatively and SLNs were identified using a laparoscopic gamma probe intraoperatively. Sixty-one percent of SLNs were found in the region of the internal and common iliac artery and the internal inguinal ring, as well as in the presacral area outside the standard lymphadenectomy area. In 4 patients, lymph node metastases were found lying outside the standard lymphadenectomy area. The authors suggested that laparoscopic SLN dissection is a technically feasible tool for the staging of intermediate- and high-risk prostate cancer.

[Yan Kit Fong, MD, Theodore Anagnostou, MD, Bob Djavan, MD, PhD]

#### **Increasing Awareness of the Obesity Epidemic**

This year, there was a dramatic increase, relative to last year, in the number of presented abstracts that related obesity to prostate cancer. This increase is likely the result of two factors: the continuing obesity epidemic, which now affects more than 30% of the US adult population, and an increasing awareness of the rela-

relationship between obesity and prostate cancer. Below, we outline highlights from 5 abstracts that provide some insight into the association between obesity and prostate cancer development and/or aggressiveness.

Two abstracts presented interesting data regarding the relationship between obesity and findings at the time of prostate needle biopsy or among newly diagnosed men.<sup>97,98</sup> Presti and colleagues<sup>97</sup> presented data from 787 consecutive men undergoing prostate biopsy at the Palo Alto Veterans Administration Hospital. They found that in general, men with a normal body weight (body mass index [BMI] < 25 kg/m<sup>2</sup>) had the highest incidence of cancer detection and the greatest percentage of biopsy tissue with cancer. This was particularly true among younger men. The authors concluded that the lower testosterone levels seen among obese men may be protective against developing prostate cancer, though more research is needed. Kane and associates<sup>98</sup> presented data on 3684 men with newly diagnosed prostate cancer using the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database. The authors found that overweight but not obese men were more likely to be younger and have low-risk disease at the time of diagnosis, relative to normal-weight men. The overweight men also had lower PSA values and earlier-stage disease. However, among men with an elevated BMI (> 25 kg/m<sup>2</sup>), as BMI increased, the risk of high-risk disease also increased. The authors felt that the most likely explanation of their data was that overweight men, because of their greater comorbidities, had a greater interaction with their health care providers, and thus more opportunities to be screened. However, the fact that high-risk disease increased as BMI increased suggests that obese men who are

diagnosed with prostate cancer had higher-risk disease.

Three different groups examined the relationship between obesity and biochemical progression following radical prostatectomy.<sup>99-101</sup> Two of the groups found that increased BMI was associated with higher risk of biochemical progression: Freedland and coworkers<sup>99</sup> using data from 1106 patients from the SEARCH database and Nelson and colleagues<sup>100</sup> using data from 431 patients treated at Vanderbilt University. Although each of these 2 studies found that, on the whole, higher BMI values were associ-

the differences in the patient populations. Alternatively, different cut points used to define the highest BMI group may have affected the results. For example, the group from Memorial Sloan-Kettering used BMI > 40 kg/m<sup>2</sup> to define their highest BMI group. Although this group did appear to have worse outcomes, the limited number of patients in this group prevented the observations from reaching statistical significance. Thus, if the data were reanalyzed using a > 35 kg/m<sup>2</sup> cut point, would the results be more in line with the other 2 studies?

In conclusion, the 5 abstracts pre-

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*The authors concluded that the lower testosterone levels seen among obese men may be protective against developing prostate cancer, although more research is needed.*

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ated with worse outcomes, the exact BMI cut points used to define the highest BMI group differed: > 25 kg/m<sup>2</sup> by the Nelson group and ≥ 35 kg/m<sup>2</sup> by the Freedland group. Both groups concluded that among men with prostate cancer, those who are obese may have a more aggressive form of the disease. Interestingly, the larger multicenter study from the SEARCH database found that black race was associated with a higher incidence of obesity, analogous to findings in the general US adult population. The authors concluded that the higher incidence of obesity in black men may in part explain the disproportionate burden of prostate cancer among black men. Conflicting results were presented by Di Blasio and associates<sup>101</sup> using data from Memorial Sloan-Kettering Cancer Center. In this latter study, no statistically significant relationship between BMI and biochemical progression following radical prostatectomy was noted. Differences in results between this study and the other two may lie in

presented at this year's AUA meeting relating obesity to prostate cancer development and/or aggressiveness appear to conflict with one another: one found obese men had lower risk disease, one found overweight but not obese men had lower risk disease, two found worse outcomes after surgery among obese men, and one found no relationship between obesity and outcomes after surgery. As Dr. Judd Moul, who moderated the press briefing discussing all 5 of these abstracts, noted, "There is a real dichotomy in the data." However, it must be kept in mind that these data are not mutually exclusive. For example, it may well be that obesity is protective for developing prostate cancer because of lower testosterone, but among men who develop the disease, it is more aggressive. If nothing else, it is hoped that these apparently conflicting results will stimulate more people to examine their own data as they relate to obesity. If that happens, at next year's meeting, we hope to have more than 5

abstracts to discuss.

[Stephen J. Freedland, MD, Alan W. Partin, MD, PhD]

### Male Fertility Treatment Update

The AUA Annual Meeting provided a forum for a number of important presentations in the area of male reproductive medicine.

In the area of erectile dysfunction, Levine and associates<sup>102</sup> presented a poster entitled “Longitudinal Randomized Placebo-Controlled Study of the Return of Nocturnal Erections After Nerve-Sparing Radical Prostatectomy in Men Treated with Nightly Sildenafil Citrate.” In this study, 76 men who underwent bilateral nerve-sparing radical retropubic prostatectomy were randomized to either sildenafil citrate 50 mg, sildenafil citrate 100 mg, or placebo, all of which were given nightly. Nocturnal penile tumescence was then evaluated 4, 12, 24, 36, and 48 weeks post surgery. Additionally, subjects were assessed using standard questionnaires for the evaluation of erectile function.

From this study, the authors concluded that the nightly administration of sildenafil citrate following radical prostatectomy enhanced the return of erectile function as well as the return of nocturnal penile tumescence. This study provides additional information supporting the concept that long-term administration of sildenafil may enhance the return of sexual function following nerve-sparing radical prostatectomy.

In the area of penile prosthesis implantation, Carson<sup>103</sup> presented data suggesting that the use of antibiotic-coated penile prostheses may be associated with a lower infection rate than comparable prosthetics that are not treated with antimicrobials. In this study, data from 5310 prosthesis revisions using non-InhibiZone-treated prosthetics were compared with 3444 revisions in which InhibiZone-treated

prosthetics (American Medical Systems, Inc., Minnetonka, MN) were used. The results indicated that there was a 43.56% reduction in infection rate when using InhibiZone-treated prostheses versus non-InhibiZone-treated prosthetics.

In the area of male fertility, a number of important presentations were also made. In one report, Ezeh and Turek<sup>104</sup> reviewed standard versus invagination techniques for the performance of microscopic epididymovasostomy for the management of idiopathic epididymal obstruction. A

frozen sperm in IVF yielded equivalent outcomes when compared with fresh specimens in terms of mean fertilization rate, embryo quality, and the chance of having at least 1 live birth from a single oocyte retrieval. The authors concluded that these results support the continued use of frozen sperm for IVF procedures performed for male factor infertility and that these results were valid regardless of the method of sperm collection.

One of the challenges of clinical medicine is to provide optimal care while minimizing the cost associated

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*It is hoped that these apparently conflicting results will stimulate more people to examine their own data as they relate to obesity. If that happens, at next year's meeting, we hope to have more than 5 abstracts to discuss.*

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total of 35 men underwent exploration and epididymovasostomy using either invagination or standard technique. The patients treated with the invagination technique demonstrated a trend toward higher patency rates and a significantly shorter time to patency compared with those treated with the standard technique. The invagination technique for epididymovasostomy continues to gain popularity in the reproductive medicine community. This report offers additional support for its use.

The use of frozen sperm in in vitro fertilization (IVF) has found frequent application in the management of male infertility. The use of frozen sperm tends to offer additional convenience for the reproductive medicine team and may decrease the potential for IVF cancellation due to inadequate sperm the day of oocyte retrieval. Russell and associates<sup>105</sup> reported their results using frozen sperm during 2039 consecutive IVF cycles performed between 1993 and 2003 at the Mayo Clinic. The researchers found that the use of

with treatment. A routine component of the assessment of the infertile male is an endocrinologic assessment. If such assessments could be reserved for patients likely to demonstrate endocrinopathy, the cost of assessing the infertile male would be reduced. Desai and colleagues<sup>106</sup> demonstrated that computational tools including neural network and logistic regression models accurately predict the presence of endocrinopathy based on testis volume, sperm density, and motility. By accessing these computational tools via the Internet, clinicians involved in the management of male infertility can utilize this methodology in the assessment of their patients. Ultimately, the application of computational methods such as this should prove quite useful in refining the assessment of men suffering from a variety of medical conditions.

[Randall B. Meacham, MD]

### Erectile Dysfunction

Essentially, there was one major theme at the AUA meeting this year with respect to erectile dysfunction.

This involved the relationship between erectile dysfunction and other disorders, such as diabetes and atherosclerosis. Another theme involved the etiology and possible therapies for the post-radical prostatectomy impotent patient. In addition, there were some outstanding studies done in a variety of experimental settings that collectively provide the scientific and clinical urologic community with insight into how we may be treating erectile dysfunction in the future.

With respect to the relationship between erectile dysfunction and diabetes, Greco and Balbi<sup>107</sup> from Rome, Italy, showed that the addition of glu-

these animals, suggesting that the vitamin E had a beneficial effect on the apoptotic diabetic corpora. In other words, this combination prevented the deterioration of the corporal tissue that is known to occur in diabetes.

The Boston University group showed that when iliac arterial insufficiency to the penis was experimentally produced in rabbits by making the vessels atherosclerotic, the corporal tissue underwent apoptosis in tandem with up-regulation of the expression of inducible nitric oxide synthase (iNOS) in the corporal tissue.<sup>109</sup> iNOS obviously makes nitric oxide (NO), and because NO can be either cytotoxic

nerve neurotomy in a canine model, the primary histologic observation was apoptosis of the corporal smooth muscle resulting in a relative fibrosis of the cavernosal tissue. Most interestingly, some of the markers of apoptosis that the Zaramo group<sup>111</sup> measured marked their appearance within 24 hours of the injury to the cavernous nerve, suggesting that if prevention of post-prostatectomy is to be attempted, treatment must be initiated prior to or at the time of the injury to the nerves. The Northwestern University group<sup>112</sup> continued to provide experimental evidence that the protein sonic hedgehog may play a major role in the apoptosis of the cavernosal tissue following transection of the cavernous nerve. When Podlasek and associates<sup>112</sup> treated their animals with this protein at the time the cavernosal nerves were transected, apoptosis of the cavernosal tissue was minimized, suggesting that this protein protected the cells from undergoing apoptosis.

Seizing upon the idea that transected nerves begin to sprout fibers at the site of the transection, Hisasue and coworkers<sup>113</sup> placed a biodegradable conduit at the site of the nerve injury to help the regenerating nerve direct itself toward the distal axon. They found that erectile function as measured by electrical stimulation of the cavernosal nerve was ameliorated by this mechanical interposition. This experimental design resembles what has been reported clinically when neural interposition has been used in patients who have undergone radical prostatectomy.

Sticking with the theme that the injured cavernous nerve can be protected or repaired so that erectile function may be maintained and/or preserved in radical prostatectomy patients, the group from Pittsburgh<sup>114</sup> presented data to show that pluripotent cells derived from skeletal muscle,

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*The researchers found that the use of frozen sperm in IVF yielded equivalent outcomes when compared with fresh specimens in terms of mean fertilization rate, embryo quality, and the chance of having at least 1 live birth from a single oocyte retrieval.*

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tathione (GTT), a free radical scavenger, augmented the response of oral sildenafil in diabetic patients. The only catch here was that the GTT was given intracavernously twice a week. Because diabetes induces free radicals within the cavernous tissue, such a combination, ie, phosphodiesterase 5 (PDE5) inhibitor and an antioxidant, merits further investigation not only as a form of treatment but possibly as a method to prevent further deterioration of the cavernosal tissue, which would, in theory, allow patients to remain responsive to oral therapy for longer time periods than without such treatment. Scientific rationale for such a combination comes from the observation of DeYoung and colleagues<sup>108</sup> from London, Ontario. This group showed that antioxidant therapy with vitamin E in rats that were made diabetic with streptozotocin resulted in increased neuronal nitric oxide synthase (nNOS) and smooth muscle cell staining in the corpora of

or cytoprotective, it was speculated that this iNOS response to "ischemia" was involved with either promoting the fibrosis of the corporal tissue or acting as a defense mechanism by the tissue to combat the fibrosis, given that NO has been shown to be an antifibrotic compound.

Regarding the postprostatectomy impotent patient, there were a number of studies that attempted to shed light on this issue. Rabbani and associates<sup>110</sup> showed in a review of 200 patients who underwent nerve-sparing radical prostatectomy that it may take up to 4 years to fully regain potency with or without PDE5 inhibitors; therefore, patients should be aware that after this type of surgery, there may be continuing improvement over time. To unravel what goes wrong within the cavernosa when the cavernous nerves are injured during radical prostatectomy, the Cleveland Clinic group<sup>111</sup> demonstrated that with bilateral cavernous

when injected into the area where the cavernous nerves were transected, seemed to help the nerves to regenerate somewhat. Intracorporeal pressure (ICP), a measurement of rigidity of an erection following stimulation of the nerves themselves resulted in a 50% increase in the ICP when

procedures, such as laparoscopic prostatectomy, cystectomy, and partial nephrectomy were presented. Reconstructive procedures involving the urinary tract were also discussed. Twelve submissions covered laparoscopic pyeloplasty, and there was also work detailing ureteral reimplanta-

endopelvic fascia dissection and then suture ligation of the dorsal venous complex (DVC). The Eichel group found that this ligation resulted in a large bundle of anterior tissue, which made precise dissection of the apex difficult in their first 60 robotic cases. After adapting the new technique, which also includes stapling of the DVC, for their last 28 cases, positive margin rates at the apex dropped substantially in their comparison of pT2 patients in each group (25% vs 0%,  $P = .004$ ).

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*Rabbani and associates showed in a review of 200 patients who underwent nerve-sparing radical prostatectomy that it may take up to 4 years to fully regain potency with or without PDE5 inhibitors, and that there may be continuing improvement over time.*

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pluripotent cells were injected into the area of the injury compared with the animals whose nerves were not exposed to these cells. Although this 50% improvement appears significant, the ICP was still 25% less than in the normal control animals, suggesting that perhaps the 2-week time frame following the injury was not long enough for complete regeneration of the nerves to occur with these cells.

It could be said that the data emanating from the AUA this year suggests that the time for us to either prevent and/or reverse erectile dysfunction regardless of etiology gets closer and closer as scientific discoveries lead the march toward this goal.

[Jacob Rajfer, MD]

### Robotic Surgery

The widening interest in robotic surgery was apparent at the AUA Annual Meeting this year. Nearly all the robotic surgery performed today is with the daVinci surgical robot (Intuitive Surgical, Inc, Sunnyvale, CA). A search of abstracts accepted this year with terms including robotic, robot, and daVinci revealed 34 submissions. Of these, 14 were video presentations and 20 were discussed posters. This year was notable for an increasing breadth of urologic applications involving robotics. Oncologic

tion and sacrocolpopexy. Infertility procedures using the robot, such as vasovasostomy and vasoepididymostomy, were presented for the first time at this year's conference. Finally, as with any other new technology, work investigating financial costs, clinical outcomes, and models for training physicians interested in robotics was also discussed.

### Oncology

Numerous institutions presented work in the field of oncology and robotics. In the area of prostate cancer, presented studies compared robotic radical prostatectomy results with the high standards already established by open radical retropubic prostatectomy.

Adaptation of new techniques was apparent as well in the presentation by Chien and associates.<sup>116</sup> Although the reported series of patients was small ( $n = 16$ , mean age: 59), the investigators found that antegrade nerve preservation resulted in 15 of 16 patients reporting varying degrees of potency at a mean follow-up of only 1 month. Only 1 patient reported no erection. The robotic procedure allowed them to dissect the neurovascular bundles along with the vascular pedicles starting from the posterior midline of the prostate and moving anteriorly and antegrade after the seminal vesicles were exposed.

In 120 patients undergoing laparoscopic surgery with bilateral nerve sparing, 80% were potent postoperatively. Functional outcomes were

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Eichel and colleagues<sup>115</sup> demonstrated efforts to reduce positive margins at the prostatic apex using the daVinci robot. Meticulous steps were demonstrated that allowed a clean, anatomic dissection at the apex of the prostate. These steps diverged from the traditional routine in open surgery of

obtained at 6 and 12 months using validated questionnaires. The authors suggest these results are applicable to robotic-assisted as well as conventional laparoscopic cases.

Although care in improving the morbidity of radical prostatectomy is important, oncologic surgeons must

be sure that positive margin rates are better than or equal to the already low rates seen by experienced surgeons performing open surgery. Our institution presented a video demonstrating our approach to robotic laparoscopic radical prostatectomy, which maintains a positive margin rate insignificantly different from our much larger experience in open surgery (6% overall for both open and robotic procedures).<sup>118</sup> Along similar lines, Wood and Wolf<sup>119</sup> also reported that oncologic experience, not laparoscopic experience, was important in performing robotic-assisted radical prostatectomy.

Although researchers continue to examine the oncologic and functional outcome of patients undergoing robotic-assisted radical prostatectomy, studies investigating costs are also important. An interesting report from Guru and associates<sup>120</sup> showed costs to be nearly equal at a center performing a high-volume (300 cases/year) of surgery. However, inclusion of depreciation and maintenance costs for the robotic system added \$1000 per robotic case performed.

Menon and coworkers,<sup>121</sup> who have led much of the development in robotic surgery, demonstrated their successful initial experience with robotic-assisted laparoscopic radical cystectomy in women. Cases described included urethral- and uterine-sparing procedures.

Although robotics may have a meaningful role in surgery for prostate and bladder cancer, its role in partial nephrectomy has yet to be defined. Taneja and colleagues<sup>122</sup> explored the utility of robotics in this operation in 10 patients with exophytic masses (mean size, 2 cm). The robot was introduced at the initiation of warm ischemia. No advantages of decreased ischemia time were noted, and 2 intraoperative complications related to bleeding required aborting the robotic approach to the case.

### Reconstruction

More than 10 abstracts covered various aspects related to robotic-assisted pyeloplasty. Although no reports indicated better functional outcome with the robotic approach, many hinted that the anastomosis was more precise, which may lead to differing outcomes with robotics as time and volume of experience progresses. Studies by Siddiq and associates<sup>123</sup> and Hamilton<sup>124</sup> compared internal experiences with robotic (RPL) and conventional laparoscopic pyeloplasty (LP) and reached somewhat conflicting conclusions. The Siddiq group<sup>123</sup> retrospectively analyzed a single surgeon's experience with 47 consecutive LPs followed by 17 RPLs. Overall, robotic times were shorter (362 vs 253 minutes,  $P < .0001$ ), but repeating this comparison after experience had been gained with LP showed no difference between RPL and the last 24 LP cases. No other significant differences in outcome were noted at this early stage of study. In contrast, Hamilton<sup>124</sup> reported that fellowship-trained surgeons (presumably experienced) performing LP and RPL could expect clearly shorter operative times performing RPL. Also, outcomes were slightly better and hospital stay was shorter for RPL patients, although exact numbers were unavailable and the number of patients in each group was only 18 and 6 for LP and RPL, respectively.

Other groups showed promising results with RPL as well. For example, Gettman and colleagues<sup>125</sup> reported that their initial series of 45 patients undergoing RPL showed encouraging results. No conversions were performed due to the robot, although the authors stressed that clinical experience with the anatomy of the ureteropelvic junction (UPJ) obstruction is needed to execute effective port placement for the robot.

Interestingly, at this time, there

appear to be two ways of using the robot to perform pyeloplasties. Many surgeons will use standard laparoscopy to identify the UPJ before docking the robot to perform further dissection, division, and reanastomosis of the UPJ. Hubert and colleagues<sup>126</sup> and Shoma and associates<sup>127</sup> demonstrated feasible performance of the entire pyeloplasty with the robot docked for the entire case. No conclusions were drawn as to which approach was better.

Finally, Ball and coworkers<sup>128</sup> investigated operative costs and found, not surprisingly, that robotic surgery was more expensive than LP (\$14,097 vs \$6,947). The authors theorized that optimizing robotic instrument selection and reducing operative time could reduce this difference in operative costs.

Robotic assistance has found a role in other types of urologic reconstruction. Patel and Burrus<sup>129</sup> not only demonstrated good outcomes with 21 pyeloplasties, they also showed good functional outcomes in 4 patients requiring a distal ureteral reimplantation with a psoas hitch. Their experience suggested advantages of recovery inherent with minimally invasive surgery, but they did not comment on whether there were better functional outcomes compared with conventional laparoscopy.

Another aspect of reconstruction involves work in the field of infertility. Two groups presented work with robotic-assisted vasectomy reversals. Schiff and associates<sup>130</sup> reported results from a randomized prospective study undertaken in rats undergoing vasectomy and then vasoepididymostomy by microsurgery or by robotics. Surgical time and patency rates were not found to be significantly different. Kuang and coworkers<sup>131</sup> presented a pilot study of 10 vasovasostomies performed on fresh human vas specimens using microsurgery or the robot. Both

groups had 100% patency, but the robotic group had a longer operating time (84 vs 38 minutes,  $P = .01$ ) and significantly more "adverse" events (eg, broken needles, loose knots).

As work continues with robotics in infertility, it would be interesting

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to study the impact on the learning curve when performing microsurgical reversals using the robotic system. Comparisons between experienced and inexperienced microsurgeons could be performed. Similar investigations performed with radical prostatectomy and pyeloplasty have demonstrated varying results.

#### *Training*

Research, in fact, suggests that the robotic system is capable of diminishing the learning curve in performance of laparoscopic surgery. Anderson and colleagues<sup>132</sup> showed that robot assistance allowed laparoscopic tasks to be performed faster, even by beginners. Anderson's group concluded that even older surgeons unaccustomed to laparoscopy would be able to derive much improvement with robotic assistance.

#### *Summary*

Robotic-assisted surgery clearly will become an integral part of urology as complex laparoscopic procedures attain an increasingly prominent role in our field. Abstracts have suggested that robotics not only diminishes the learning curve in many of these procedures, but it could actually better results currently obtained with conventional procedures. Further work and time will help make any conclu-

sions. Reconstructive fields outside of laparoscopy, such as microsurgery, may also benefit from robotic assistance. At this point, robotics may not be clearly helpful for procedures such as partial nephrectomy, but most of the abstracts presented at this year's

AUA suggest that robotics can help well-trained surgeons interested in minimally invasive surgery.

[Naveen Kella, MD, Kevin M. Slawin, MD]

#### **Lower Urinary Tract Symptoms and BPH**

Out of several hundred submissions, approximately 120 abstracts were selected for oral or poster presentation at this year's AUA meeting. The abstracts were divided in a podium session presenting the most significant findings in the area of medical and hormonal therapy, and poster sessions focusing on basic research, epidemi-

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*Anderson and colleagues showed that robot assistance allowed laparoscopic tasks to be performed faster, even by beginners. Anderson's group concluded that even older surgeons unaccustomed to laparoscopy would be able to derive much improvement with robotic assistance.*

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ology, and natural history, as well as minimally invasive surgical treatments (MISTs), and advances in surgical techniques.

It is quite clear that the efficacy of medical therapy for lower urinary tract symptoms (LUTS) and BPH has reached a glass ceiling. Recent years have seen the approval of the new  $\alpha$ -receptor blocker alfuzosin (Uroxatral; Sanofi-Synthelabo, New York, NY) and a new dual inhibitor of both types

I and II 5 $\alpha$ -reductase isoenzymes, dutasteride (Avodart; GlaxoSmithKline, Philadelphia, PA). However, although sufficiently efficacious and safe, it is also clear that these new drugs do not appear to have efficacy above and beyond what other  $\alpha$ -blockers and 5 $\alpha$ -reductase inhibitors have offered in the past. One of the highest priorities is a renewed focus on basic research attempts to better understand the etiology and pathophysiology of BPH in hopes of identifying new therapeutic targets.

#### *Basic Research*

One such search into the etiology of LUTS and BPH was conducted by the group from Innsbruck, Austria.<sup>133,134</sup> They conducted two sets of experiments using transrectal color Doppler ultrasound and color pixel density to measure perfusion changes of the lower urinary tract during filling of the bladder. In healthy young men, perfusion of the lower urinary tract increased substantially during the filling of the bladder with 0.2 mL potassium chloride (KCl), which can be compared with concentrated urine. However, all patients with LUTS

showed a reduced maximum bladder capacity during filling, and perfusion of the lower urinary tract was decreased in patients with LUTS. After 5 weeks of therapy with an  $\alpha$ -receptor blocker, perfusion of the lower urinary tract in the presence of intravesical KCl solution was significantly improved. The authors suggest that LUTS is associated with chronic ischemia of the prostate and the urinary bladder, a mechanism that

apparently is exploited by  $\alpha$ -receptor blockade increasing blood flow in the urinary tract and also maximum bladder capacity. In a second abstract, the same group studied 15 patients suffering from diabetes mellitus type II for several years. As a control group, patients with BPH were utilized and divided into those with prostate volumes above and below 30 mL. Resistive indices were measured and found to be significantly higher in diabetic patients compared with the 2 control groups, indicating damage to prostatic vessels caused by arteriosclerosis. Taken together, these abstracts suggest a significant role of ischemia and arteriosclerosis in the etiology and pathogenesis of LUTS as well as BPH.

A group of Polish researchers<sup>135</sup> examined the impact of the  $\alpha$ -receptor blocker doxazosin on the expression of VEGF in BPH by means of comparing patients who underwent surgery for BPH with or without receiving prior doxazosin therapy. The patients exposed to doxazosin showed increased VEGF expression, and the patients with the most severe symptomatology demonstrated decreased expression of VEGF. Although semiquantitative in nature, these data corroborate the suggestion made by the group from Innsbruck, namely, that  $\alpha$ -blockers somehow increase the vascularity and perfusion in the lower urinary tract, a mechanism of action to this date not attributed to this particular class of drugs.

Few drug developments in urology have been as revolutionary as the exploitation of the NOS-NO-cyclic guanosine monophosphate (cGMP) pathway, which induces relaxation of the smooth muscle of the corpus cavernosum of the penis and, thus, leads to penile erection. The understanding of this pathway has led to the development of a class of drugs known as PDE inhibitors for the treatment of

erectile dysfunction. PDEs are responsible for the breakdown of cGMP to GMP, a phenomenon that can be reversed or at least slowed down by the administration of PDE inhibitors, 3 of which are currently used for the treatment of erectile dysfunction. Laboratory and clinical observations suggest a potential role of the NOS-NO-cGMP pathway in the prostate, with the potential of a new therapeutic target. Richter and colleagues<sup>136</sup> studied the occurrence of eNOS and nNOS in the transition zone of the prostate and found nNOS to be present in axon and small nerve fibers, whereas eNOS was present in endothelial cells of the small vessels supplying glands but not in epithelial cells. The researchers speculate that nNOS may be involved in the regulation of stromal and glandular tissue function, with eNOS being involved in the control of perfusion. The group from Northwestern<sup>137</sup> investigated NOS isoform distribution in the BB/Wor diabetic rat prostate. For the first time, they demonstrated that NOS-I and NOS-III protein is decreased in the dorsal prostate of the diabetic rat model. In addition, the morphology of the ducts of the diabetic ventral prostate appeared abnormal on visual observation. The authors speculate that altered NOS signaling may contribute to increased severity of LUTS in individuals with diabetes and BPH. From Germany, an experienced group of researchers<sup>138</sup> reported abundant expression of PDE-11A in glandular structures of the transition zone, suggesting a significance of this particular isoenzyme in the control of glandular function (secretory function and epithelial proliferation), as well as the rationale for the use of PDE inhibitors in the treatment of BPH. In this context, it should be noted that 2 small studies have been reported demonstrating therapeutic benefit in patients with erectile dysfunction and LUTS with the use of the PDE

inhibitor sildenafil citrate (Viagra; Pfizer Inc., New York, NY). In one trial, patients with an International Prostate Symptom Score (IPSS) > 10 were enrolled and queried before and 3 months after the commencement of on-demand therapy with the PDE inhibitor sildenafil citrate.<sup>139</sup> Erectile function normalized in 75% of patients, and 62% of those patients improved their IPSS score. Thirty-seven percent of the patients had a 5-point improvement. A similar study was reported by Sairam and associates.<sup>140</sup> These investigators examined patients in an erectile dysfunction clinic and gave sildenafil citrate to 112 men. One-third of the patients had an initial symptom score of > 7 points. Eighty-one percent reported improved erections, and IPSS and other LUTS-specific quality-of-life scores also improved at the 3-month follow-up. All patients initially presenting with severe LUTS improved to a moderate disease stage, and 60% of those with moderate LUTS converted to mild symptomatology. All in all, these findings suggest a possible role for the NOS-NO-cGMP pathway and the use of PDE inhibitors in the treatment of LUTS and BPH.

The role of estrogens in the prostate has been debated in the past with equivocal outcomes. Two groups studied several aspects of the presence and role of estrogens in the prostate. Shapiro and coworkers<sup>141</sup> used immunohistochemistry to stain for estrogen receptor ER $\alpha$  and ER $\beta$  in human fetal prostate specimens. They demonstrated stromal and epithelial ER $\alpha$  expression mediating specific effects of estrogen on prostatic epithelium, such as the induction of squamous metaplasia, whereas they speculated that ER $\beta$  may play a role in normal glandular growth and proliferation. In summary, the investigators suggest that important estrogen-signaling pathways are involved in

both epithelial-epithelial and epithelial-stromal interactions. Lee and colleagues<sup>142</sup> studied the expression in the prostate of cytochrome P-450 aromatase enzyme, which converts testosterone to estrogen in an irreversible step. They found cytochrome P-450 aromatase localized in the stromal compartment, and it was also detected in cultured stromal cells by Western blot. These authors suggest that the data provide supportive evidence for the role of estrogens in the development of BPH, such as the differentiation of fibroblasts into smooth muscle. In this context, it is of interest to review an abstract presented by Lieber and associates,<sup>143</sup> who studied the association of prostate size with estradiol levels from the Olmsted County study. In a subset of patients, testosterone levels—bioavailable testosterone as well as serum estradiol levels—were available. In patients in whom the bioavailable testosterone level was above the median, the authors showed the odds ratio for having a prostate volume of > 30 mL increased with increasing estradiol levels. In the first estradiol tertile, the odds ratio was set to 1, and it increased to 1.7 and 3.5 in the second and third estradiol tertiles. Parallel to this, the probability of having a PSA level > 1.4 ng/mL increased to 1.1 and 1.9, respectively. Although the interpretation is not entirely straightforward, these results suggest that in patients with higher-than-median bioavailable serum testosterone levels, serum estradiol levels are involved in particularly large prostates with higher than normal serum PSA levels. The use of aromatase inhibitors (atamestane) was explored in clinical trials of LUTS and BPH.<sup>144</sup> This compound prevents the conversion of testosterone to estradiol and thus increases serum testosterone. It was found to be ineffective in terms of symptomatic improvement. An interesting study

would be the combination of such an aromatase inhibitor with a 5 $\alpha$ -reductase inhibitor. Such a combination would increase serum testosterone significantly. However, it would not, as with 5 $\alpha$ -reductase inhibitor monotherapy, be available for aromatization. Thus, the less harmful or beneficial testosterone level would increase and the effects of dihydrotestosterone (DHT) and estradiol on the prostate would be eliminated.

Another interesting therapeutic target might be the Rho-kinase pathway. It is known that spontaneously hypertensive rats (SHRs) have increased

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*Reported findings suggest a possible role for the NOS-NO-cGMP pathway and the use of PDE inhibitors in the treatment of LUTS and BPH.*

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sympathetic nervous activity; their prostates show increased contractile responses to stimulation, and the  $\alpha$ -adrenergic-mediated contractions involve the Rho-kinase pathway. Lindberg and coworkers<sup>145</sup> demonstrated that the prostatic smooth muscle of control animals had only 53% of immunoreactivity for RhoA compared with SHRs. Rees and colleagues<sup>146</sup> developed primary cultures from human and rat smooth muscle cells and demonstrated the effect of a Rho-kinase inhibitor (Y-27632) on the proliferation rate and adrenergic contractions. Surprisingly, the researchers demonstrated that the Rho-kinase inhibitor reduced both proliferation rate and adrenergic contractions, therefore suggesting that Rho-kinase inhibitors are a therapeutic agent with dual action against both the proliferative aspect of BPH and the increased muscle tone.

*Epidemiology, Natural History, and Evaluation*

Lieber and colleagues<sup>143</sup> performed an interesting analysis using the Olmsted

County study in comparing long-term outcomes such as acute urinary retention, symptom progression, and surgery rates with the Medical Therapy of Prostatic Symptoms (MTOPS) study placebo arm. To this end, they identified a select group of the Olmsted County study participants who fulfilled the MTOPS criteria by being older than 50 years and having a baseline symptom score > 7 and a peak urinary flow rate of < 15 mL/s. When the rate per 1000 person-years of observation was evaluated, the “selected Olmsted County cohort” had higher rates of acute urinary retention

(19.2 vs 6), symptomatic progression (89.2 vs 36), and surgery or minimally invasive treatments (17.7 vs 13) compared with the MTOPS placebo group. The incidence rate for any of these outcomes was 113.4 versus 45, respectively. These findings are somewhat surprising, but they highlight the observation that although useful in studying the natural history of a disease, placebo-control groups do not entirely replace carefully done longitudinal follow-up studies of community-dwelling men, even if these patients are matched to mimic as best as possible the placebo-control group.

The role of PSA and its subforms as a potential marker for BPH and prostate volume was analyzed by several groups. BPSA has been demonstrated to be a useful clinical predictor of LUTS and BPH.<sup>147</sup> BPSA is preferentially expressed in the transition zone of BPH nodules and has been shown to correlate with clinical parameters of BPH, such as the AUA Symptom Index, total prostate volume, and transition zone volume. Further clinical studies will test the hypothesis

that BPSA, in addition, predicts prostate growth and, most importantly, BPH progression. The relationship between total serum PSA and prostate volume was reanalyzed by Bosch and associates.<sup>148</sup> They used 3 methods for prostate volume measurement based on TRUS and set these methods as the "gold standard." The AUC for serum PSA to estimate prostate volume was 0.79, significantly better than that for DRE at 0.69 but inferior to that of the ultrasound method. Although it is accepted that there is a relationship between serum PSA and prostate volume in white men, which is clinically useful, these data have not been available in Asian men. Gupta and colleagues<sup>149</sup> studied the relationship between the PSA level and prostate volume in 535 Japanese men and found lower prostate volumes per unit of PSA, ie, a higher PSA density in the absence of an age relationship. It will be of interest to compare the relationship between serum PSA and prostate volume directly in Asian, white, African American, and Hispanic patients to determine whether racial differences indeed exist.

The concept of bladder wall thickness as an indirect and noninvasive parameter for bladder outlet obstruction has been published in the literature. Gerber and associates<sup>150</sup> found an average bladder wall thickness of 1.9 mm in patients who did not have obstruction according to Abrams-Griffith nomogram criteria, whereas bladder wall thickness was 2.7 mm in those who had obstruction, based on the sample size of 50 patients. Of interest, if the bladder wall thickness was > 3 mm, 83% of the patients had obstruction. Another noninvasively measured parameter, namely, intravesical prostatic protrusion (IPP), was reported by Nose and Foo.<sup>151</sup> This parameter had been reported by Foo and associates before and was found to correlate well with bladder outlet

obstruction as measured by invasive urodynamics and Abrams-Griffith number. In this effort, the authors investigated 168 men and determined the intravesical prostatic protrusion that is measured in centimeters and correlated it with the bladder outlet obstruction by the Abrams-Griffith number. The correlation coefficient was  $r = 0.62$ , and the IPP parameter was 0.2 cm in patients without obstruction versus 1.1 cm in those with obstruction. The patients falling into the equivocal zone had an IPP parameter of 0.8 cm. Clearly, the efforts of developing noninvasive parameters to predict bladder outlet

episodes of -1.8, nocturia episodes of -1.3, and voiding episodes with urgency -1.5, all over a 24-hour period. This is an encouraging study, and it reminds all of us not only to prescribe tablets, but also to interact with our patients and explore their lifestyle, eating, and fluid intake habits, which offer a significant opportunity for symptomatic improvement. A new analysis from the MTOPS study was presented.<sup>153</sup> In this analysis, attention was focused on the per-protocol population in which the question was whether or not changes from baseline in terms of maximum flow rate, IPSS score, BPH Impact

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*Although useful in studying the natural history of a disease, placebo-control groups do not entirely replace carefully done longitudinal follow-up studies of community-dwelling men.*

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obstruction by invasive urodynamics should be applauded, as most of our patients do not like to have invasive urodynamics performed. Most of these parameters, nonetheless, require further validation in multicenter trials to exclude the possibility of intraindividual examiner variability.

#### *Medical Therapy*

In the area of medical therapy, an interesting study was presented from the United Kingdom.<sup>152</sup> Based on the observation that many men can be helped in terms of the severity of their LUTS by fluid management, a program was developed and applied to 25 men who attended a self-management program. The analysis was based on frequency volume charts filled out at baseline and at 3 months. As it turned out, with a program based on fluid management, abstinence from caffeine, and bladder retraining, the fluid intake over 24 hours was reduced by 227 mL/24 h with a concomitant decrease in the number of voiding

Index, and quality-of-life index might be influenced by baseline characteristics such as total and transition zone volume and serum PSA. It was demonstrated that in the placebo group, the patients in the highest tertile of prostate volume, the highest tertile of transition zone volume, and the highest tertile of serum PSA had the least improvement in all 4 parameters. This would suggest that patients with larger glands and higher PSA values have a more aggressive natural history and that the placebo effect is most pronounced in those with the least aggressive natural history, ie, patients with small total and transition zone volumes and low PSA values. Another important observation was that in the patients with a prostate volume < 20 mL, a transition zone volume < 10 mL, and a serum PSA < 1.4 ng/mL, doxazosin was equivalent in terms of all 4 outcome parameters compared with combination therapy and superior to finasteride and placebo. Quite the converse took

place in the “high-risk” patients, namely, those patients with a prostate volume > 40 mL, a transition zone volume > 20 mL, and a serum PSA > 4.0 ng/mL. In these patients, the placebo effect was quite blunted and doxazosin was slightly inferior or equivocal to finasteride. However, combination therapy was superior to both single arm therapies and clearly to placebo. The interpretation of this analysis would suggest that medical therapy should be tailored to the risk status of the patient. Those with small prostate volumes and low PSA levels are best served with an  $\alpha$ -blocker as monotherapy, whereas those with prostate volume > 40 mL and a PSA level > 4.0 ng/mL most certainly benefit the greatest from combination medical therapy. Although these findings are new, an analysis from the MTOPS study presented in 2003 already had suggested that combination therapy is most effective in “high-risk patients” in terms of outcome prevention.

In addition to the already-existing nontitratable  $\alpha$ -receptor blockers, doxazosin, a well-known and familiar drug to all urologists, has now been released in a slow-release formulation called doxazosin GITS (gastrointestinal therapeutic system) (Cardura XL; Pfizer, New York, NY). A placebo-controlled, randomized study was presented in which doxazosin GITS was found to be superior to placebo in terms of symptoms, flow rate, and a variety of other parameters.<sup>154</sup> In fact, the onset of action in terms of symptom improvement was as early as day 3 of treatment and in terms of flow rate, as early as day 1 of treatment. Although Cardura XL is currently not available in the United States, it is already used in several European countries.

It is well established that  $\alpha$ -blockers increase the chances of a patient to resume successful voiding after an

episode of acute urinary retention. Several such studies have been reported, including a study with alfuzosin versus placebo. An extension of such a study was presented focusing on the long-term outcome of these patients when maintained on alfuzosin or switched to placebo after resumption of normal voiding.<sup>155-157</sup> The authors found that ongoing therapy with alfuzosin results in a smaller number of patients requiring surgery in the 6th month after the retention episode and that the therapeutic benefit of alfuzosin versus placebo in terms of resumption of normal voiding is greatest in older men. As it turns out, age is a very significant predictor of the probability of resuming normal voiding. Although younger men with or without an  $\alpha$ -blocker resume normal voiding in 70%–80% of cases, in men 80 years and older, the probability of resuming normal voiding drops to only 20% or less. It is in this group of men that the  $\alpha$ -blocker is particularly effective in allowing the patients to resume normal and spontaneous voiding.

The new  $5\alpha$ -reductase inhibitor, dutasteride (Avodart) has been available in the United States since last year. It is a dual inhibitor of both  $5\alpha$ -reductase types I and II. The results of a 4-year open-label extension study of the 2-year randomized placebo-controlled trial were presented in a series of abstracts.<sup>158-166</sup> Fundamentally, dutasteride proved to induce sustained, ongoing improvement in the AUA Symptom Score as well as in peak urinary flow rate from baseline to 48 months. In fact, the additional improvement from month 24 to month 48 in the dutasteride-treated patients was significant for both symptoms and flow rates. It was also shown that while at baseline, 42.4% of the patients were severely symptomatic and at month 48, this number dropped to 8%, with

38.7% of the patients converting to a mild symptom status, ie, a symptom score of < 8. Dutasteride has also been shown to significantly reduce the probability of acute urinary retention and surgery compared with placebo, and after the placebo-treated patients were switched to open-label dutasteride, they were found to assume the baseline risk of dutasteride-treated patients. A peculiarity of dutasteride is its long half-life of 37 days. An interesting study was presented demonstrating that after withdrawal of dutasteride, return of DHT levels to baseline takes up to 4 months and longer. The implication of this finding, quite in contrast to the quick return to DHT baseline after finasteride withdrawal, suggests that dutasteride is of benefit in poorly compliant patients; for example, a patient who forgets to take dutasteride over a weekend is unlikely to lose its therapeutic benefit. Lastly, it should be noted that in the 24-month placebo-controlled part of the trial, dutasteride was found to reduce the incidence of prostate cancer diagnosis by 57%. This observation has led to the design and initiation of a prostate cancer chemoprevention trial using dutasteride (REDUCE).

#### *MISTs and Surgical Techniques*

A multitude of abstracts were presented in the areas of minimally invasive surgical treatment interventions for BPH. Several authors focused on the injection of absolute ethanol either in liquid or gel form. A histologic study was conducted demonstrating hemorrhagic necrosis with a wide diffusion into the prostatic tissue that, however, did not extend to the capsule and spared the urethra.<sup>167</sup> Results from several trials involving 279 patients in 37 institutions were reported by Eisenberg and Badlani.<sup>168</sup> Symptom score improved by 52% and peak flow rate by 45%. In general,

the safety profile was acceptable; however, in the early European experience, 2 patients experienced a near-total necrosis of the bladder as a result of inappropriate diffusion of ethanol into the bladder and required a urinary diversion. It appears that such a severe complication is not acceptable for a MIST intervention, and even if it occurs in only a very small number of patients, it would not be acceptable as a risk to patients when confronted with these odds. To avoid these problems, an ethanol gel injection (EGI) has been proposed, and at this year's AUA meeting, it was presented by Matheus and colleagues.<sup>169</sup> Unfortunately, only 52 patients were treated and further divided into a transrectal, transurethral, and transperineal approach. For all 3 treatments, the outcomes were not necessarily equally good; for example, flow rate improvement for the transurethral route was only 7.9 to 9.8 mL/s, whereas for some of the other routes, it was superior. Similarly, the improvement in the symptom score was not the same for all treatments. Most disturbingly, however, a significant number of failures occurred, namely, 10% in the transrectal, 37% in the transurethral, and 60% in the transperineal route. The authors' conclusion that EGI is "easy to perform, showing good preliminary results" appears to be overly optimistic. Multicenter trials and a larger number of patients might be needed to verify these observations. The Targis machine (Urologix, Minneapolis, MN) with its newest catheter, the Cooled ThermoCath (CTC), has been tested in a US multicenter trial involving 70 patients.<sup>170</sup> Forty-three of these patients are now available for 12 months of follow-up and, in general, good improvement in symptom score—from 20.7 to 8.4 points—and in maximum flow rate—from 8.3 to 12.7 mL/s—was observed,

with an acceptable safety profile.

Two interventions dominated the posters presented on surgical therapies, namely, the photoselective vaporization of the prostate (PVP) with potassium titanyl phosphate (KTP), or the "green light" laser, and the holmium laser resection enucleation as well as the plasma kinetic (Gyrus; Gyrus Medical, Osseo, MN) enucleation. Malloy and colleagues<sup>171</sup> presented a multicenter trial on 139 men with a mean prostate volume of 54 mL who underwent KTP green light laser photoselective vaporization. At 24 months, the symptom score had decreased from 24 to 2.0 points and the maximum flow rate had improved from

with a mean preoperative volume of 63 g. In an average operating room time of 85 minutes, the procedure was performed with no mortality and limited morbidity, and the symptom score dropped from 20.6 to 5.4. Montorsi and coworkers<sup>175</sup> reported on a randomized trial comparing HoLEP with transurethral resection of the prostate (TURP) in 100 patients. There were no differences in efficacy or safety, but the catheterization time and hospital stay were shorter in the HoLEP group. The original inventor of this technology, the Gilling group from New Zealand, reported on 2 randomized trials.<sup>176,177</sup> In the first trial, 40 patients were randomized to under-

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7.8 to 22.4 mL/s, certainly outstanding results in this multicenter trial. Sixty-four patients with a prostate volume > 60 mL and an average size of 101 mL underwent PVP treatment, also achieving outstanding improvement in symptoms and flow rate, with the only drawback being the long operating room time of 120 minutes.<sup>172</sup> A New York consortium randomized 88 patients to either PVP or transurethral vaporization (TVP) of the prostate and found that both procedures improved the symptom score to a similar degree (18.6 to 8.3 for PVP, and 21.3 to 9.3 for TVP).<sup>173</sup>

Holmium laser resection and enucleation of the prostate (HoLEP) is now a well-established method gaining more and more widespread acceptance around the world. This was highlighted by several abstracts at this year's AUA meeting. Kuntz and associates<sup>174</sup> reported on a very large numerical experience of 950 patients who underwent HoLEP for prostates

go HoLEP versus plasmakinetic enucleation using the Gyrus technology. The latter technology allows resection in a saline environment, reducing the risk for the TURP syndrome. Safety and efficacy parameters, as well as catheter time and hospital stay, were identical, although these authors were able to perform the HoLEP procedure in 44 minutes versus 58 minutes for the Gyrus procedure. In the second randomized trial, Gilling and colleagues<sup>177</sup> compared the HoLEP procedure with a bladder neck incision for patients with a prostate volume < 40 mL. Five patients in the bladder neck incision group, all of whom had a prostate volume between 30 mL and 40 mL before therapy, remained obstructed. The authors recommend limiting the bladder neck incision either by electrocautery or by holmium laser to glands < 30 mL at baseline.

#### Summary

When attempting to summarize this

year's abstracts on LUTS and BPH, it is quite clear that currently existing medical therapies have reached a glass ceiling in terms of efficacy. Furthermore, it is also clear that the perfect MIST intervention has yet to be identified, namely, an intervention that is safe to be performed in the office setting with proven efficacy and reliability. Concerning surgical interventions, it has been shown that KTP photoselective vaporization and the plasma kinetic Gyrus vaporization, as well as holmium laser resection or enucleation, are as effective as a standard TURP and in many ways safer compared with the "gold standard."

Of greatest interest are the basic research efforts into the etiology and pathophysiology of LUTS and BPH that are likely to provide new therapeutic targets in the future. These areas of interest with future therapeutic targets are ischemia and arteriosclerosis, the NOS-NO-cGMP pathway, and the use of PDE inhibitors; the Rho-kinase pathway and its inhibitors; inflammatory changes and the use of anti-inflammatory agents (abstracts not discussed); the role of the sympathetic nervous system and catecholamines (abstract not discussed), and, lastly, newly identified genes that are known to be either up- or down-regulated in BPH and ultimately may lead to new therapeutic targets as well.

[Claus G. Roehrborn, MD, FACS]

### Treatment of Kidney Stones

There were a number of interesting nephrolithiasis papers presented at the 2004 AUA meeting. Three are highlighted because of their practicality and applicability to current practice.

Zhou and associates<sup>178</sup> from Durham, North Carolina, investigated the impact of gradually increasing or decreasing shock wave lithotripsy power settings using an in vitro artificial stone model. Stones were

fragmented using an unmodified Dornier HM-3 device (Dornier GmbH, Friedrichshafen, Germany). All stones were treated with 1500 shock waves delivered at 1 Hz. There were 3 different treatment strategies: 1) 1500 shocks at 20 kV; 2) 500 shocks at 18 kV, 500 shocks at 20 kV, and 500 shocks at 22 kV; and 3) 500 shocks at 22 kV, 500 shocks at 20 kV, and 500 shocks at 18 kV. The best fragmentation occurred in the group in which there was a progressive increase in output voltage. Clinicians now have 2 methods of improving fragmentation: slowing the shock wave delivery rate, which was presented at last year's meeting, and ramping up of power settings during therapy.

Two studies demonstrated that treatment with  $\alpha$ -blockers facilitated spontaneous stone passage in patients with distal ureteral stones. Dellabella and colleagues<sup>179</sup> from Ancona, Italy, performed a study in which 210 patients with distal ureteral stones were randomized to 1 of 3 daily regimens: 1) florglucine-trimetossibenzene (a spasmolytic agent) and deflazacort (a steroid agent), 2) tamsulosin and deflazacort, or 3) nifedipine and deflazacort. The tamsulosin group had the highest spontaneous passage rate, the fastest time to expulsion, reduced need for pain medications, and the lowest rate of endoscopic intervention. These results are similar to those of a smaller study, which this group reported in 2003.<sup>180</sup> Tekin and associates<sup>181</sup> from Istanbul, Turkey, reported on a study in which 75 patients with distal ureteral stones were randomized to either 5 mg of terazosin daily or nothing. The mean stone size was similar for both groups: 7.3 mm for tamsulosin and 6.8 mm for no treatment. The spontaneous rate of passage was significantly higher in the tamsulosin group (77% versus 46% at 4 weeks). The latter study indicates

that concomitant administration of steroids is probably unnecessary to facilitate stone passage when  $\alpha$ -blocker therapy is utilized. This should decrease drug-related morbidity.

[Dean G. Assimos, MD]

### Pediatric Urology

Dhanani and colleagues<sup>182</sup> from the University of Texas Health Science Center at Houston presented their experience with the staged Fowler-Stephens orchidopexy (FSO) for intra-abdominal testes. Prior analyses have shown that the 1-stage FSO has a 68.5% success rate whereas a 2-stage FSO has a 76.8% success rate. One hundred twenty-eight nonpalpable testes (NPT) were identified in 119 patients. An inguinal incision was performed in most cases, opening the peritoneum and placing traction on the testis toward the groin. A primary orchidopexy was performed if any portion of the testis or epididymis reached the pubis. An FSO was performed if the testis was high with short vessels. The testicular artery and vein were ligated 1–2 cm superior to the testis using nonabsorbable suture. A second-stage Fowler-Stephens procedure was performed through a Pfannenstiel incision at about 4 months. Primary orchidopexy resulted in 100% success, whereas a 2-stage FSO was 98% successful, with 1 atrophic testis noted on late follow-up. All patients with bilateral undescended testes had 2 viable gonads. Minimum follow-up has been 1 year. Primary orchidopexy is feasible in about 25% of intra-abdominal NPT. Mobility of the testis to the pubis is a good predictor of the ability to perform primary orchidopexy.

Schwentner and colleagues<sup>183</sup> from Medical University in Innsbruck performed a prospective randomized trial in 43 boys. Group 1 underwent a gonadotropin-releasing hormone (GnRH) nasal spray administration

for 4 weeks prior to orchidopexy and biopsy. Group 2 underwent biopsy alone. The fertility index was determined histopathologically and was the number of adult spermatogonia per tubule. The group's results showed that a mean fertility index after GnRH treatment prior to surgery was

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*Concomitant administration of steroids is probably unnecessary to facilitate stone passage when  $\alpha$ -blocker therapy is utilized. This should decrease drug-related morbidity.*

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1.05 (standard deviation  $\pm$  0.71). The mean fertility index after surgery alone was 0.52 (standard deviation  $\pm$  0.39), which is statistically significant ( $P = .007$ ). The best fertility index was 1.27, which was found in the GnRH group  $<$  2 years. In this study, neoadjuvant GnRH therapy led to significantly higher fertility indices than did surgery alone.

Franc-Guimond and associates<sup>184</sup> reported their success with catheterizable channels implanted into intestinal segments. Continent catheterizable channels (CCCs) were created with the appendix or transversed tubularized bowel and were implanted into either the intestinal segment of an augmentation or the intestinal continent reservoir when it permitted umbilical placement of the stoma. Implantation into the intestinal segment was accomplished by creating a submucosal tunnel or a mucosal trough (LeDuc method), or by using an extravesical technique. Thirty-two patients were studied for a mean follow-up period of 2.2 years. Three patients required a revision to achieve continence, and in those patients, the CCCs were constructed using the Monti technique, which had been implanted into the ileum, sigmoid, and a seromuscular colocoloplasty in 1 patient each. Two other patients developed stomal stenosis requiring

revision. All the patients were continent through the catheterizable stoma at 2.2 years follow-up. CCCs constructed with either appendix or transverse tubularized bowel and implanted into intestinal segments have a very high success rate. The length of the tunnel and the short-

ness of the extravesical conduit, not the site of implantation or the location of the stoma, were important for success. The bowel segment used for implantation did not adversely affect the outcomes.

Perez-Brayfield and coworkers<sup>185</sup> reported the use of dextranomer-hyaluronic acid (Deflux; Q-Med AB, Uppsala, Sweden) for catheterizable stoma incontinence. Nine patients (ages 9–49 years) underwent submucosal injection of Deflux for significant catheterizable stoma incontinence. The type of bowel used for the stoma included 7 appendices and 2 small bowel. The Deflux volume injected ranged from 2 to 6 mL (mean 3.7 mL).

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*Macroplastique is ineffective for bladder outlet incontinence because most patients have had prior bladder neck reconstruction and/or multifactorial incontinence.*

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Six patients were continent after 1 injection, 1 patient was continent after 2 injections, and 2 patients had refractory incontinence. The overall success rate was 78%. Endoscopic Deflux injection should be considered for the initial management of stomal incontinence.

Halachmi and associates<sup>186</sup> from The Hospital for Sick Children in Toronto reported their experience in

using Macroplastique (Uroplasty, Geleen, The Netherlands) at the bladder outlet for incontinence in children. They examined 33 children, 25 boys and 8 girls, who had incontinence either through a diverting stoma or through their urethra. The investigators defined cure as no involuntary leakage and improvement as a twofold decrease in the use of absorbing pads or a twofold increase in the dry interval between intermittent catheterization. The patients with leakage through the urethra had spina bifida, exstrophy, hypospadias, and urethral duplication. In patients with incontinent stomas, 3 of 5 (60%) were cured, 1 of 5 (20%) improved, and 1 of 2 (20%) had no change. Of the 28 patients with bladder outlet incontinence, there were no cures, but 42% were improved whereas 58% showed no change. Macroplastique is ineffective for bladder outlet incontinence because most patients have had prior bladder neck reconstruction and/or have multifactorial incontinence involving abnormal pelvic anatomy, abnormal pelvic musculature, deficient sphincter elements, and abnormal bladder and sphincter innervation.

Xiao and colleagues<sup>187</sup> from Tongji Medical College (Huazhong University,

China) performed a new surgical treatment for neurogenic bladder incontinence. Twenty spina bifida children were studied. Preoperative urodynamics revealed 2 types of bladder dysfunction: areflexic with incontinence ( $n = 16$ , 80%) and hyperreflexic bladder with external sphincter dyssynergia (DESD) manifested as overflow incontinence ( $n = 4$ , 20%). A limited laminectomy and a lumbar

ventral route (VR, usually L5) to S3 VR microanastomosis were performed. The L5 dorsal route (DR) was left intact as a trigger of micturition after axonal regeneration. The mean follow-up period was 2 years. Sixteen of 20 patients gained satisfactory bladder control and continence within 8 to 12 months. Thirteen of 16 patients with areflexic bladder gained control. The average bladder capacity increased from 72 to 210 mL, and the detrusor became contractile with mean pressures > 33 cm H<sub>2</sub>O. Three of 4 patients with detrusor hyperreflexia with DESD gained control and developed near-normal storage and synergistic voiding after the surgery. The average residual urine decreased from 282 to 38 mL. Four patients failed to exhibit any improvement. The artificial-somatic-central nervous system-autonomic reflex arch procedure is an effective and safe treatment for spina bifida patients to gain bladder control and continence.

Shukla and colleagues<sup>188</sup> from The Children's Hospital of Philadelphia presented their long-term follow-up of antenatally detected primary obstructed megaureter (POM). Their study group included 40 patients diagnosed with POM between 1986 and 1989. Four patients with poor renal function and severe hydronephrosis underwent surgery. Hydronephrosis resolved in 21 of 40 patients (52%), whereas 19 of 40 patients (48%) had unresolved POM, which was improved or stable with a mean follow-up of 100 months. One patient developed unexpected severe worsening of hydronephrosis at 13.6 years of follow-up. This patient had completely resolved hydronephrosis of his upper tract with only minimal dilation of his ureter 9 years ago. The study shows that although there is a high incidence of resolution or improvement in hydroureteronephro-

sis due to POM, periodic ultrasonography should be performed until complete resolution is documented.

Hoffman and Fung<sup>189</sup> from the University of Minnesota reported on their prospective trial evaluating surgical outcome of patients with hypospadias and significant corporal disproportion (curvature > 35 degrees) after aggressive release of skin,

scar tissue, and urethral tethering. Patch grafts were performed initially in 12 patients using bovine pericardium (BPC), whereas AlloDerm (LifeCell Corp., Woodlands, TX) was subsequently used in 27 patients. Satisfactory penile straightening was accomplished in all patients, with no recurrent chordee at a mean follow-up of 42 months. The majority of patients (6/7) with BPC had residual induration at the graft site, which was considered severe in 50%. In those with AlloDerm, none had noticeable induration at the graft location. All postpubertal children had spontaneous erections with normal sensation. In contrast to BPC, AlloDerm caused no significant induration and postoperative results were satisfactory at 5 years of follow-up. AlloDerm is an excellent off-the-shelf patch material for the repair of corporal disproportion in pediatric penile chordee.

Nelson and colleagues<sup>190</sup> reported on a 10-year experience using buccal mucosal graft urethroplasty at the University of Michigan. Sixty-six patients underwent 69 urethroplasties using buccal mucosal grafts. Mean follow-up was 25 months. Prior urethral repair had been performed in 52% of the patients, whereas 38%

had prior first-stage repairs (chordee release). Only 5 patients (7%) had no prior penile or urethral surgery. Mean graft length was 4.2 cm. A tube graft was used in 19% of the patients and an onlay graft was used in 81%. Buccal graft urethroplasty was successful on 48% of the patients. Complications included fistula (16%), meatal stenosis (14%), stricture (12%),

meatal stenosis and stricture (7%), and other combinations (3%). There were no urethral diverticula. Oral complications were uncommon, including slight asymmetry and mild numbness. There were no complications in patients without a history of prior surgery. The data suggested buccal mucosal grafts are useful for difficult primary repairs as well as complex revisions. ■

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