Best of the 2000 AUA Annual Meeting

Highlights from the 95th American Urological Association Annual Meeting
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The 2000 American Urological Association (AUA) Annual Meeting in Atlanta provided thought-provoking and practical information to attendees. Here, Contributing Editors of *Reviews in Urology* and associates describe the outstanding presentations in their fields of expertise.

Key Words
Benign prostatic hyperplasia • Bladder dysfunction • Cancer, renal • Erectile dysfunction • Gene therapy • Lower urinary tract symptoms • Prostate cancer, markers • Prostate cancer, treatment • Prostatitis • Surgery, laparoscopic

Main Points

- Mortality from prostate cancer may be decreasing in areas where there is high early-screening penetration.
- The level of prostate-specific antigen (PSA) achieved after androgen suppression may have significant prognostic importance.
- For patients with metastatic renal cell carcinoma with the primary tumor in place, nephrectomy preceding immunotherapy appears superior to immunotherapy alone.
- Baseline serum PSA levels are clinically useful predictors of future prostate growth.
- Phase I and II trials of gene therapy for prostate cancer are under way.
- The NIH Chronic Prostatitis Symptom Index can be useful for evaluating and following patients with chronic prostatitis.

Serum Prostate Cancer Markers

Screening. A major theme of the meeting was our increased ability to detect cancers that are curable, a fact that may be contributing to the decrease in prostate cancer mortality increasingly seen in the United States and elsewhere. Mäkinen and associates[1] from Finland evaluated patients randomized to screening for prostate cancer or to a control group. Of the 10,308 men who participated in the screening, 266 had carcinoma detected because of either an abnormality on digital rectal examination (DRE), performed on those with a prostate-specific antigen (PSA) between 3 and 3.9 ng/mL, or a PSA of 4 ng/mL or higher. Eighty-six percent of the tumors were clinically organ-confined. A comparison of the control group through the Finnish cancer registry demonstrated that only 67% of contemporaneously diagnosed cancers were organ-confined. Of great interest was the absence of a difference in the grade distribution between the screened population and the control group.

Another important study was reported by Bartsch and colleagues[2] from Innsbruck, Austria. In an impressive effort at screening the men of the Tyrol within 4 years, they were able to perform a PSA test for 66% of all men aged 45 to 75. There was a significant migration to lower stage and an increase in the amount of organ-confined disease, compared with historical controls. The researchers noted that the mortality from prostate cancer among the men in the Tyrol, which had been constant from 1970 to 1993, had begun to decline. Whether early detection is leading to this decrease in mortality or other factors are involved remains to be determined from prospective, randomized trials. These data seem to confirm similar findings in the United States and suggest that prostate cancer mortality may be decreasing in areas with high early-screening penetration.

The optimum criterion for the cutoff level of normal PSA remains ill-defined. Babaian and coworkers[3] from Houston evaluated 156 men with a

PSA level between 2.5 and 4 ng/mL. Of these, 111 agreed to participate in this trial and had an 11-core, ultrasound-guided prostate biopsy performed. Carcinoma was demonstrated in 26.3%. The median Gleason score was 7 (3 ± 4), and the median number of positive cores was 2. The findings suggest that these cancers were significant.

The report by Babaian would seemingly indicate that we should use a lower cutoff than the standard 4 ng/mL to identify men who are to undergo biopsy. Thomas Stamey, MD,[4] presenting the John K. Lattimer lecture, raised some concern in this regard. In an extensive review of the experience with radical prostatectomy at Stanford University, Dr Stamey was unable to show a correlated outcome based on preoperative total PSA (tPSA) levels between 2 and 9 ng/mL. That is to say, until the PSA level exceeded 9 ng/mL, there was no correlation with surgical failure. Outcome was based on biochemical disease-free survival. The intriguing data suggest that lowering PSA cutoff levels may not impact cancer control.

In contrast, Shekarriz and associates[5] from Detroit examined the effect of different levels of PSA between 0.1 and 10 ng/mL in 585 men who underwent radical prostatectomy for clinically localized prostate cancer. Overall disease-free survival was 87.1%, with a median follow-up of 33.1 months. A trend toward higher rates of disease-free survival was seen with sequential increase in PSA level between 4.1 and 10 ng/mL ($P = .06$). Disease-free survival rates were significantly higher for patients with PSA levels up to 4 ng/mL, compared with those with PSA levels higher than 4 ng/mL ($P = .005$). The data suggest that disease outcome progressively worsens with increasing levels of PSA, even at relatively low levels. Because these reports leave the clinician confused, further studies are required to resolve this issue.

The optimum PSA level has also generated a controversy with respect to racial differences. Fowler and colleagues[6] from Jackson, Miss, evaluated 306 African Americans and 315 whites with a normal DRE and a PSA level greater than 4 ng/mL. All underwent ultrasound-guided prostate needle biopsy. Age and prostate volume were similar between the 2 groups. PSA levels were significantly higher in the African Americans (mean, 8.2 vs 6.3 ng/mL). Cancer was detected in 41% of the African Americans and 21% of the whites ($P = .001$). While 40% of the African Americans had a Gleason score of 7 to 10, this high-grade disease was only found in 21% of the whites. When adjusting for PSA level, the risk for high-grade malignancy was 1.9 times greater in African Americans. These findings suggest that identification of curable malignancy in African Americans will be compromised by an increased threshold of the PSA level for biopsy.

The appropriate age at which to initiate prostate cancer screening was the subject of an evaluation by Moul and coworkers[7] from the Department of Defense. They evaluated 602 active duty military officers aged 40 to 49. Only 1.7% had a PSA level higher than 2.5 ng/mL (the threshold for biopsy), and only 0.5% had a PSA level higher than 4 ng/mL. Only 1 of the 602 men was diagnosed with carcinoma (PSA level, 15.5 ng/mL). It was concluded that it is unlikely that there will be significant detection of carcinoma in this age group.

Rayford and colleagues[8] (New Orleans and Tarrytown, NY) evaluated tPSA levels, levels of PSA complexed with α_1-antichymotrypsin (cPSA), and %cPSA (cPSA/tPSA) in 748 African Americans and 240 whites between the ages of 40 and 69. While PSA and cPSA levels increased significantly as a function of age, there was no difference in %cPSA. No racial differences were observed at any age group.

Monitoring. PSA's utility in monitoring established disease is irrefutable. Klotz and associates[9] from Toronto studied the change in PSA over time (minimum 12-month follow-up) in 113 patients who underwent initial watchful waiting for clinically localized carcinoma of the prostate. The authors calculated the PSA doubling times (TDPSA) from linear regression of the initial PSA (Table 1). Median TDPSA was 5.27 years and was longer than 10 years in 35% of the subjects. These data suggest that the TDPSA in patients with untreated, low- to intermediate-grade prostate cancer is highly variable.

The importance of TDPSA is suggested in the report by Roberts and colleagues[10] of Rochester, Minn. They evaluated 2809 patients who underwent radical prostatectomy. With a biochemical failure defined as a PSA higher than 0.4 ng/mL, 879 men (31%) failed. The average time to biochemical recurrence was 2.9 years. Metastasis-free survival from the time of biochemical recurrence was 90% and 83% at 5 and 10 years, respectively. Using a multivariate Cox model, the investigators demonstrated that only TDPSA remained a significant risk factor for the development of metastasis. Five-year metastasis-free survival was 99%, 95%, 92%, and 67% for patients who had a TDPSA greater than 10 years, 1.0 to 9.9 years, 0.5 to 0.9 years, and less than 0.5 years, respectively.

The effect of androgen suppression on serum PSA level is dramatic. Unfortunately, there may be an uncoupling of the effect of the actual cancer and the PSA, because this marker is also under androgen regulation. Pace and coworkers[11] from Dallas examined the nadir PSA level following androgen suppression in men with advanced prostate cancer. The median follow-up of 180 men was 66 months. A rising PSA level was seen in 4% of the patients. The median duration of response to antiandrogen deprivation was 21 months, and the median time to nadir PSA level was 10.1 months.

An undetectable nadir PSA level was achieved by 45% of patients. The authors observed a significant correlation between nadir PSA level and time to androgen independence. More than half of the men who had achieved nadir levels lower than 2 ng/mL were alive without serologic evidence of androgen independence. In contrast, all those who failed to obtain a PSA level lower than 2 ng/mL had a rising PSA level at 24 months ($P < .001$). These findings suggest that the level of PSA achieved after androgen suppression is of significant prognostic importance.

New Markers. A number of new markers are under investigation. In an effort to enhance the discriminatory power of PSA for cancer and benign changes, Wang and associates[12] (from 4 institutions) have developed an immunoassay for benign PSA (BPSA), a specific form of PSA found only in men with benign prostatic hyperplasia (BPH). Applying this marker in a sandwich immunoassay, they demonstrated mean PSA levels for normal women, normal men, men with BPH, and men with prostate cancer of 0.5, 10.7, 38.9, and 13.3 pg/mL. This analyte may help in discriminating men with cancer from those with BPH.

Human kallikrein type 2 (hK2) remains the focus of much research activity. Haese and colleagues[13] from Germany and Sweden demonstrated a correlation between hK2 levels and pathologic stage. They demonstrated that among 38 men with pT2a/b organ-confined cancers, the mean hK2 concentration was 0.09 ng/mL, as compared with 0.30 ng/mL in 30 men with pT3a or greater malignancy. hK2 improved the preoperative evaluation of organ confinement in patients.

cPSA is also the subject of increased investigation. Lynn and coworkers[14] from the United Kingdom studied this assay in comparison with tPSA and also examined the densities of the products of these analytes. Of 162 men undergoing ultrasound-guided biopsy, 31% had malignancy. These researchers noted that of 74 men who had PSA levels between 4 and 10 ng/mL, 19% had cancer. By utilizing cPSA with a cutoff of 4.35 ng/mL, 31% of the negative biopsies could have been avoided, missing only 7% of those with cancer. Using PSA density with a cutoff of 0.09 ng/mL/cc could reduce negative biopsies by 30%, but 7% of cancers would be missed. By utilizing cPSA density with the same cutoff, negative biopsies could be reduced by 40%, again at 93% sensitivity. These investigators concluded that cPSA would perform the same specificity enhancement (to help prevent unnecessary biopsies) without the requirement of transrectal ultrasound.

Table 1
PSA Doubling Times in 113 Men With Untreated, Low- to Intermediate-Grade Prostate Cancer

Number of men	Doubling time (years)
20	< 2
12	2 - 3
14	3 - 4
9	4 - 5
19	5 - 10
9	10 - 20
5	20 - 50
25	> 50

PSA, prostate-specific antigen.

Sokoll and associates[15] from Baltimore studied non-α_1-antichymotrypsin (non-ACT) cPSA using an investigational assay. They evaluated 123 men with tPSA levels between 4 and 10 ng/mL and negative DREs. Of these patients, 69% had cancer. The specificity at the 95% sensitivity level for tPSA, free PSA, and cPSA was 5, 10, and 15%, respectively. In their investigation, the ratios of free, complexed, and non-ACT cPSA provided greater specificity, ranging from 26% to 32%.

Brawer and colleagues[16] from Seattle investigated the utility of ACT cPSA in men undergoing repeat ultrasound-guided prostate needle biopsy. The investigators evaluated 93 men, of whom 26 were shown to have carcinoma on repeat biopsy. PSA and cPSA were not discriminatory. The percentage was significantly higher in men with cancer ($P = .011$). At the 100% sensitivity level (at which all cancers would be found), tPSA provided a specificity of 30% at a cutoff of 2.1 ng/mL. With the same cutoff point, cPSA specificity was 28%. The %cPSA afforded significant enhancement of specificity—to 39%—utilizing a cutoff of 69%. These data suggested that cPSA may avoid 30% more negative repeat biopsies than PSA without missing more men with cancer. Thus, cPSA should provide an important addition to the evaluation of men who have had a negative ultrasound-guided prostate needle biopsy but in whom the clinician suspects that carcinoma may have been missed. [Dr Brawer]

Metastatic Renal Cancer

Before the era of immunotherapy, the natural history of metastatic renal cell carcinoma (RCC) was not improved by debulking nephrectomy.[17] Despite its failure to improve survival or delay progression of disease, nephrectomy did play an unquestioned role in palliation of symptoms and was often recommended for patients with bleeding, pain, or hypercalcemia to improve

quality of life. At the University of California, Los Angeles,[18] and elsewhere, aggressive combination therapy using surgery with biologic response modifiers has resulted in durable clinical responses. The relative efficacy of initial cytokine treatment versus initial adjuvant nephrectomy, however, remained controversial and was widely debated.

Proponents of surgery have cited the increasing evidence to suggest that debulking of RCC may remove tumor growth–associated factors (such as transforming growth factor-ß), which have potent immunosuppressive effects and which, when removed, may make the host more capable of responding to immunotherapy.[19] The question surrounding the sequence of treatment involves the surgical recovery time and whether this time may allow for progression of disease by hindering the timely delivery of immunotherapeutic agents. Proponents of immunotherapy have argued that surgery may delay or even prevent patients from receiving systemic treatment and that, because of surgery's potential morbidity and mortality, it should be reserved for those who demonstrate the ability to respond to immunotherapy.

The results of 2 randomized, phase III trials (1 American and 1 European) that address this question have been long awaited. Flanigan and coworkers[20] presented the results of the Southwest Oncology Group (SWOG) trial 8949, which began 9 years ago. This trial randomized 246 patients with metastatic RCC and an operable primary tumor to 2 arms: radical nephrectomy followed by interferon-alpha (INF-α) (arm I) versus INF-α alone (arm II). End points examined were survival and clinical response. In arm I, 79% of patients had no surgical complications, there were no surgical deaths, and only 1 patient did not proceed to immunotherapy (for medical reasons). Grade 4 toxicity secondary to INF-α was equivalent in both arms. Despite having similar response rates, median survival was 8 months in arm II, compared with 12 months in arm I. This difference reached statistical significance (P = .02). Furthermore, the trend for increased survival was maintained across all stratification factors, including measurable disease, performance status, and site of metastasis.

In the European, randomized phase III European Organisation for Research and Treatment of Cancer Genitourinary Group (EORTC-GU) trial 30947, Mickisch and colleagues[21] used the same protocol as was used in the SWOG study. Over a 3-year period, 83 patients were randomized to treatment with cytoreductive nephrectomy plus INF-α (arm I) and to INF-α alone (arm II). Distribution of patients between arms I and II was equivalent in regard to age, sex, performance status, tumor type, tumor grade, presence or absence of venous invasion, sites of metastasis, and other comorbidities. There were few surgical complications, and only 1 patient in arm I did not go on to receive immunotherapy. Interferon-related toxicity was the same in both arms of the study. There were 5 of 41 complete responses in arm I and only 1 of 42 complete responses in arm II. Both time to progression and survival were significantly improved in arm I. Median survival was only 7 months in arm II, improving to 17 months in arm I.

These 2 trials are the first prospective studies of the benefit of nephrectomy in the modern immunotherapy era. Furthermore, the results of these 2 landmark trials provide compelling evidence to suggest that for patients with metastatic RCC with the primary tumor in place, combination therapy with nephrectomy preceding immunotherapy is superior to immunotherapy alone in terms of both progression and survival. As a result, these data should form the basis for how we manage metastatic RCC in the future. Future studies are necessary to define whether the combination of surgery with other cytokines, such as interleukin-2, that have been thought to result in more frequent and durable responses than does interferon can further improve the current survival advantage. [Dr Pantuck, Dr Zisman, Dr Belldegrun]

Erectile Dysfunction

One of the more interesting and imaginative presentations came from Montorsi and associates[22] from Milan, Italy, in which the authors attempted to see whether sildenafil taken at bedtime affected nocturnal erections. They studied 30 men (age range, 28 to 68 years) who complained of erectile dysfunction and who underwent testing in a sleep laboratory using penile tumescence monitoring equipment. Excluded from the study were patients who had sleep disturbances or neurogenic erectile dysfunction or who were receiving nitrate therapy.

Evaluation was done over a 3-night period; there was 1 night of adaptation followed by 2 nights of recording. During the 2 nights of recording, 100 mg of sildenafil was given randomly on 1 night. Rigidity and tumescence activity were recorded.

The authors found that sildenafil significantly increased both rigidity and length of erections, although (as expected) there was no increase in the quantity of erections. This suggests that the phosphodiesterase effect on the cavernosal smooth muscle is only dependent on cavernosal nerve stimulation. Although there were no age-matched controls, such a study begs the question of whether the erections of normal men (as measured by nocturnal penile tumescence monitoring) will show any increases in tumescence if there is circulating phosphodiesterase activity. [Dr Rajfer]

Laparoscopic Surgery

Ono and colleagues[23] from Nagoya, Japan, analyzed a series of 125 patients with localized RCC who were

treated with laparoscopic radical nephrectomy. The majority of patients underwent transperitoneal nephrectomy, with a small subset (18 patients) undergoing retroperitoneal endoscopy. In 123 of the 125 patients, there was no local recurrence or port site seeding. Of those patients with tumors smaller than 5 cm, metastasis developed in only 3. This is with up to 7 years of follow-up.

The authors conclude that laparoscopic radical nephrectomy is comparable to open techniques for patients with localized, small-volume RCC.

Gill and associates[24] from the Cleveland Clinic reviewed their experience with laparoscopic radical nephroureterectomy, comparing their patients with a historical group treated with open surgical technique. Interestingly, the operative time for laparoscopic nephroureterectomy was significantly less than that in the open surgical group ($P < .001$). In addition, blood loss, hospital stay, and complications rate were also much lower than those for the open surgical group. It was the belief of these authors that laparoscopic radical nephroureterectomy, with its reduced postoperative recuperation and hospitalization times, not only is a viable option for patients with this disease but may also become the standard of care in the future. [Dr Grasso]

Natural History of LUTS and BPH

The *Clinical Practice Guidelines for the Diagnosis and Treatment for Benign Prostatic Hyperplasia,* published in 1994 by the Agency for Health Care Policy and Research (AHCPR), identified several areas of future research needs in the natural history and epidemiology of this highly prevalent condition:

- Define the prevalence of BPH symptoms in the aging male population and investigate possible ethnic and regional differences.
- Define the natural history of untreated BPH (progression) in terms of the probabilities and rates of further prostatic enlargement; changes in symptom severity, uroflow, and measures of urodynamic obstruction; urinary retention; infection; bladder dysfunction; and renal insufficiency.
- Determine whether disease progression (worsening of symptoms or development of complications) can be predicted by baseline assessment of symptoms, prostate size, uroflow, residual urine, or degree of obstruction.
- Determine the prevalence of silent but clinically significant BPH.

This call for research into the natural history of lower urinary tract symptoms (LUTS) and BPH was resoundedly answered by the Olmsted County Study of Urinary Symptoms and Health Status Among Men. This study, conducted in Rochester, Minn (located in Olmsted County), has yielded more information and publications enhancing our understanding of the natural history of the disease than have any other efforts in the past and present combined.

Background. Between 1989 and 1990, 2015 men between the ages of 40 and 79 were recruited from a random sample of male residents of Olmsted County (a 55% response rate). All patients completed a self-administered questionnaire assessing LUTS severity with questions similar to those of the American Urological Association's Symptom Index (AUA-SI), and a similar questionnaire was completed biannually thereafter through 1998. Men who died or refused subsequent participation in the study were replaced with other men of the same age, randomly selected from the community. Overall, 2078 completed 3 or more questionnaires during follow-up. Of these patients, a 25% subsample was selected for detailed clinical assessment, including peak urinary flow rate measurements, PSA determination, and prostate volume measurements by transrectal ultrasonography. These evaluations were conducted at the Mayo Clinic every 18 to 24 months during the follow-up.

Two presentations in Atlanta looked at the long-term (92 months) natural history of changes in LUTS[25] and at longitudinal prostate volume changes with a 7-year follow-up in the clinic cohort.[26]

In epidemiologic studies, there is a fundamentally important difference between cross-sectional and longitudinal studies. It is relatively easy to perform a cross-sectional study enrolling either community-dwelling participants or patients stratified by age for a one-time clinical assessment. Such data yield information regarding the incidence rates of certain conditions and/or information regarding the severity of a condition in the population tested across various baseline parameters. In epidemiologic studies, the participants are often stratified by age. Thus, there are good data available on cross-sectional distribution of symptom severity, serum PSA, and prostate volume from various cohorts in North America and from some European and Asian countries. It is far more difficult to establish a cohort of participants stratified by age and follow these participants longitudinally. The logistics and efforts involved in such a project far exceed those involved in a cross-sectional assessment. If one wishes to understand the natural history of disease and disease progression, it is important to perform such longitudinal studies, the result of which might be different from those anticipated and predicted by cross-sectional studies.

LUTS Changes. Jacobsen and associates[25] assessed longitudinal changes in LUTS severity using a questionnaire similar to the AUA-SI (International Prostate Symptom Score [IPSS]). Based on 2078 men completing at least 3 questionnaires during the 14,875 person-years of follow-up, Jacobsen reported that symptom severity at baseline (measured by IPSS) increased cross-sectionally about 0.08

Table 2
Distribution of Measures of Longitudinal Change in LUTS Severity by Age

	Ages 40 – 79	
	Mean	SD
AUA Symptom Index	0.34	1.16
Daytime frequency	0.04	0.34
Nocturia	0.02	0.42
Weak stream	0.08	0.43
Straining	0.03	0.28
Stop	0.06	0.30
Urgency	0.06	0.29
Incomplete emptying	0.04	0.24
Dribbling	0.04	0.32
Wet clothes	0.05	0.30
Frequency	0.03	0.20
Dysuria	0.01	0.18
Hesitancy	0.02	0.26

LUTS, lower urinary tract symptoms; AUA, American Urological Association; SD, standard deviation.

units/year. That is to say, the increase in symptom severity from decade to decade was just shy of 1 unit point (0.8 points/decade). In the longitudinal cohort followed for 92 months with a median follow-up of 7.7 years, the annual change observed was 0.34 ± 1.16 standard deviations (SD) per year for all participants. Approximately 31% of men reported at least a 3-point increase in the symptom severity index. This number is relevant, as it has been shown by Barry and coworkers[27] that a 3-point difference in the symptom score is subjectively noticeable to patients. The average annual change depended on the baseline age of the participants. In men in their 40s, the annual change was only 0.19 ± 0.91 SD, while it was 0.60 ± 1.47 for men in their 60s; change then declined to 0.48 ± 1.68 for men in their 70s. Of all symptoms included in the questionnaire, a self-reported weak stream demonstrated the strongest age-related increase in severity. For this question, the average annual increase in severity was 0.06 ± 0.32 for men in their 40s, 0.09 ± 0.37 for men in their 50s, and 0.14 ± 0.53 for men in their 60s; severity decreased to 0.03 ± 0.73 for men in their 70s. The annualized increase in severity for other symptoms was less than that for weak stream (Table 2). Especially, the symptom of dysuria showed almost no increase in severity for men in their 40s, 50s, and 70s, while the increase for men in their 60s was 0.04 ± 0.2 SD.

The authors conclude that the longitudinal progression of LUTS in community-dwelling men during 92 months of follow-up suggests that previous estimates of symptom progression based on cross-sectional data may have markedly underestimated the natural history of disease progression. This becomes clear when one compares the *cross-sectionally* measured increase in baseline symptom severity of 0.08 per year with the *longitudinally* measured increase of 0.34 per year. This would suggest that the longitudinally observed worsening is approximately 4 times that of the *cross-sectionally* observed increase in severity.

Prostate Volume Changes. Rhodes reported on longitudinal prostate volume changes as measured by transrectal ultrasonography. Prostate volume was measured—at baseline and at 18, 42, 66, and 84 months of follow-up—with a multiplane transducer, applying the volume formula for an ellipsoid. At baseline, the median prostate volume showed an increase from 21.4 mL for men in their 40s to 33.9 mL for men in their 50s, with an overall median of 28.7 mL (Table 3). A peak urinary flow rate showed a decrease from 19.7 to 11.6 mL/s, with a median of 16.9 mL/s. The median PSA level was 0.9 ng/mL in this cohort of community-dwelling men, with a range from 0.7 ng/mL for men in their 40s to 2.1 ng/mL for men in their 70s.

Statistical analysis used mixed-effects linear models, which allow for an estimation of group average longitudinal changes and the inclusion of subjects who may not have measurements at all time points. Overall, the median prostate growth rate was 1.9% per year (25% to 75% confidence interval: 1.5% to 2.2% per year). Of greatest interest are the correlations between baseline parameters and the median annual prostate growth rates (Table 4). While the median percent increases are essentially flat for men in their 40s, 50s, and 60s, there is a decrease in the median percent increase for men in their 70s (1.6%). Similarly, baseline peak urinary flow rate (above or below 12 mL/s) did not differentiate between men with more or less prostate growth over time, and the same was true when men were stratified by symptom severity.

Both prostate volume and serum PSA at baseline did predict future prostate growth. For example, men with prostate volumes lower than 30 mL had a median percent increase of 1.7% per year, while men with a prostate volume at baseline higher than 30 mL had a median percent increase of 2.2% per year. When men were divided into tertiles of serum PSA levels (0 to 0.6, 0.7 to 1.3, and greater than 1.3 ng/mL), the median percent increase in prostate volume

Table 3
Median Baseline Characteristics by Age

	All men 40 - 79 (N = 635)	40 - 49 (n = 269)	50 - 59 (n = 161)	60 - 69 (n = 119)	70 -79 (n = 86)
Prostate volume (mL)	28.7	21.4	27.2	31.8	33.9
AUA Symptom Score	3	2	3	6	6
Peak flow rate (mL/s)	16.9	19.7	17.9	13.6	11.6
Voided volume (mL)	299	344	294	252	224
PSA (ng/mL)	0.9	0.7	0.9	1.4	2.1

AUA, American Urological Association; PSA, prostate-specific antigen.

changed from 1.6% to 1.9% and 2.1% per year, respectively.

In this longest follow-up of prostatic growth in untreated community men not diagnosed with BPH or LUTS, a median increase of 1.9% per year in prostate volume is greater than previously reported, based on 5-year data from the same cohort. Of note: larger prostate volumes at baseline and higher levels of serum PSA are predictive of greater prostate growth rates in these untreated community-dwelling men.

These data are of great interest and significance in that they represent the best characterized cohort of men observed longitudinally. Men diagnosed with moderate to severe LUTS and (by DRE) with enlarged prostates were followed for 4 years on placebo treatment in the Proscar Long-term Efficacy and Safety Study (PLESS).[28] Serum PSA was a strong predictor of future prostate growth in this group of men as well. This cohort of 164 patients had a mean age of 63 years, an average prostate volume at baseline of 54.6 mL (by MRI), and a baseline serum PSA level of 2.7 ng/mL. Table 5 shows the increase in prostate volume from baseline to months 12, 24, 36, and 48, respectively, for the population stratified by tertiles of serum PSA level at baseline.

Table 4
Categorical % Volume Increases by Age, Peak Flow Rate, AUA-SI, Prostate Volume, and PSA

	Number	Median % Increase	25% - 75% CI
Age			
40 - 49	269	1.9	1.6 - 2.1
50 - 59	161	1.9	1.5 - 2.2
60 - 69	119	1.8	1.4 - 2.3
70 - 79	89	1.6	1.2 - 2.2
Peak flow rate			
< 12 mL/s	171	1.8	1.6 - 2.1
> 12 mL/s	464	1.8	1.4 - 2.2
AUA-SI			
None to mild	486	1.8	1.6 - 2.2
Moderate to severe	149	1.9	1.4 - 2.2
Prostate volume			
< 30	419	1.7	1.4 - 1.9
> 30	209	2.2	1.9 - 2.6
Serum PSA			
0 - 0.6	199	1.6	1.4 - 1.9
0.7 - 1.3	234	1.9	1.6 - 2.1
> 1.3	202	2.1	1.6 - 2.5

AUA-SI, American Urological Association Symptom Index; PSA, prostate-specific antigen; CI, confidence interval.

Table 5
Changes in Prostate Volume in 164 patients in PLESS Sorted by Baseline PSA Tertiles

PSA tertile/ N per tertile (Mean ± SD)	12 Months	24 Months	36 Months	48 Months
0.2 to 1.3/52 (39.7 ± 12.6 mL)	1.1 ± 5.3 (−21.5 to 9.3)	2.5 ± 3.7 (−4.9 to 11.1)	1.6 ± 4.9 (−8.5 to 15.3)	2.8 ± 5.3 (−8.6 to 14.7)
1.4 to 3.2/65 55.8 ± 22.6 mL	2.5 ± 6.4 (−11.4 to 24.4)	5.5 ± 7.9 (−4.6 to 47.1)	8.7 ± 9.2 (−4.2 to 47.1)	8.3 ± 9.5 (−15.6 to 26.7)
> 3.2/47 69.3 ± 32.0 mL	3.9 ±6.4 (−8.8 to 18.0)	7.0 ± 7.5 (−7.7 to 20.9)	10.6 ± 8.3 (−4.4 to 28.9)	13.3 ± 8.7 (+1.1 to 29.9)

PLESS, Proscar Long-Term Efficacy and Safety Study; PSA, prostate-specific antigen; SD, standard deviation.
Adapted from Roehrborn CG et al. *J Urol.* 2000.[28]

It is evident that serum PSA at baseline was also a strong predictor of future prostatic growth, since the patients in the lowest tertile of PSA had an overall increase of only 2.8 mL over 4 years (0.7 mL per year), while the patients in the highest tertile had an overall increase of 13.3 mL over 4 years (3.3 mL per year).

Longitudinal data from both community-dwelling men (Olmsted County Study) and men with LUTS and BPH confirm that baseline serum PSA level is a clinically useful predictor of the future behavior of the prostate in terms of its growth tendencies. Further data are expected from the Olmsted County Study to verify whether other aspects of the natural history of LUTS and BPH (symptom worsening, flow rate deterioration, retention, etc) are also predictable, based on the PSA level at study entry or for the clinician at the time of first contact with the patient. In this sense, serum PSA level would be a clinically useful tool for the assessment of both the risk of prostate cancer and the risk of progression of LUTS and BPH. [Dr Roehrborn]

Emerging Concepts in Prostatitis

An increased awareness of the importance and impact of prostatitis, more peer-reviewed funding, and an awakening interest by industry has resulted in an explosion of new studies in the field. For the first time in decades, prostatitis was highlighted at the plenary "State of the Art" section of the meeting. Mark Litwin, MD,[29] reviewed new emerging epidemiologic data on chronic prostatitis and exciting research in the associated basic sciences (see below). The new definition of chronic pelvic pain syndrome (chronic genitourinary pain in the absence of accepted uropathogenic bacteria detected with standard microbiologic techniques) and the new and now reasonably well-accepted NIH classification system of the prostatitis syndromes (which stratifies patients into 4 categories) have radically changed the way we look at patients in both research and clinical practice. Dr Litwin described the groundbreaking work of the NIH-funded Chronic Prostatitis Collaborative Research Network and the International Prostatitis Collaborative Network, including the development, validation, and publication of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). The NIH-CPSI, described below, has proved useful not only in research studies but also during evaluation and follow-up of patients with chronic prostatitis in clinical practice. He also outlined the important controlled clinical treatment trials for chronic prostatitis (for example, phytotherapy, finasteride, anti-inflammatory agents, α-blockers, pentosan polysulfate, etc) that have been or will soon be initiated in 2000.

Epidemiology. Prostatitis is the most common urologic diagnosis in men younger than age 50, making up 8% of office visits to urologists (more than 2 million office visits per year). The NIH-CPSI evaluates the domains of the prostatitis experience (location, frequency, and severity of pain; irritative and obstructive voiding symptoms; and impact/quality of life) in 9 simple questions and has become the standard assessment tool in research studies and clinical practice. Downey and coworkers[30] from Canada reported 1 of the first population-based studies to determine the prevalence of prostatitis-like symptoms among men at risk. Employing the NIH-CPSI, these investigators identified 9.7% of men in the community as having chronic prostatitis-like symptoms (6.5% had moderate to severe symptoms).

Clinicians have always known that patients with prostatitis suffered consequences other than pain. McNaughton-Collins and colleagues[31] from the NIH Chronic Prostatitis Collaborative Research Network evaluated quality of life parameters in patients enrolled in the Chronic Prostati-

tis Cohort Study using the Medical Outcomes Short-Form 12 (SF-12) and the NIH-CPSI. They noted that quality of life (mental health impact) is profoundly impaired in men with chronic prostatitis. Optimal care of these patients requires particular attention to quality of life issues.

Etiology. We do not know what causes the findings and symptoms in the 95% of men with chronic prostatitis syndrome but no cultured uropathogenic bacteria (category III, chronic pelvic pain syndrome [CPPS], previously known as chronic nonbacterial prostatitis). Shoskes and Shahed[32] from California analyzed expressed prostatic secretions (EPS) and voided bladder 1 (VB1) urine from 47 men with CPPS by reverse transcriptase polymerase chain reaction assay for bacterial signal using 16S rRNA. They noted that the presence of positive bacterial signal (10 times stronger signal in EPS, compared with VB1) can help predict response to antimicrobial therapy. The same investigators[33] examined markers of tissue injury and injury response in EPS specimens from 100 patients with CPPS. They concluded that gram-positive bacteria may be pathogens, based on the injury response measured in the EPS. They also suggested that oxidative stress may be a key pathway in CPPS that can be successfully targeted with antioxidant therapy in patients with negative cultures. MacLennan and associates[34] from Cleveland investigated the relationship between prostatitis, BPH, and prostate cancer by examining immunostained prostatectomy specimens. The data suggested that chronic prostatitis is associated with both BPH and prostate cancer but has a greater tendency to be associated with BPH, without zonal predilection. The role of prostatic inflammation in these 2 prostate diseases remains to be elucidated.

Diagnosis. The classic key to diagnosis has been the standard Meares-Stamey 4-glass test, which differentiates symptomatic patients by the results of microscopy and culture of specific lower urinary tract specimens. Lee and colleagues[35] from Seattle evaluated 84 men with CPPS and 49 control patients with standard 4-glass urine tests and transperineal digitally guided prostate biopsies. They noted no significant difference between men with CPPS and controls in the distribution and density of white blood cells (WBC) in the EPS. Bacteria were found in prostate biopsy cultures of 46% of CPPS patients and 29% of control patients. There did not appear to be significant correlation between bacteria grown in postprostatic massage urine specimens and the prostatic biopsy cultures. Patients in category IIIA (prostatic inflammation, no infection) with WBC in the EPS were more likely to have bacteria in prostate biopsy cultures than were those in category IIIB (no prostatic inflammation, no infection). This and other studies question the relevance of WBC and bacteria in the prostate gland and prostate-specific specimens of patients with chronic prostatitis/CPPS. Hochreiter and coworkers[36] from Chicago measured periodic cytokine levels in 18 men with CPPS and asymptomatic inflammatory prostatitis (category IV). These authors concluded that serial monitoring of cytokine levels in EPS seems to be a reliable diagnostic tool that might be useful in the evaluation of patients with CPPS. It was interesting to note that in 93% of the cases in which antibiotic treatment was given, cytokine levels decreased regardless of changes in symptoms or inflammatory status.

Treatment. The most popular treatment employed by urologists for patients with chronic prostatitis, regardless of culture results, has been with antibiotics. Other therapeutic modalities that have been suggested or are presently undergoing investigation include α-blockers, phytotherapy, immune modulation, 5α-reductase inhibitors, cyclooxygenase-2 inhibitors, pentosan polysulfate, microwave heat therapy, and various physical therapies. Nickel and the Canadian Prostatitis Research Group[37] stratified 102 patients with chronic prostatitis/CPPS into category II (chronic bacterial prostatitis), category IIIA, and category IIIB, based on leukocyte, culture, and immunologic status. All patients were treated with ofloxacin for 12 weeks and were evaluated at baseline, 4 weeks, 12 weeks (end of therapy), and 24 weeks. More than 50% of patients had a moderate to marked improvement, as measured by validated prostatitis symptom indices; however, culture, leukocyte, or immune status of prostate-specific specimens did not predict response to antibiotics. The perceived beneficial effects of antibiotics in all categories need to be evaluated in a randomized, placebo-controlled trial.

Clemens and associates[38] from Chicago evaluated the results of a 12-week program of biofeedback directed to pelvic floor reeducation and bladder training in 19 patients with CPPS. This preliminary study suggested that a formalized program of neuromuscular reeducation of the pelvic floor muscles, together with interval bladder training, can provide significant and durable improvement in pain, urgency, and frequency in patients with CPPS.

The field of prostatitis is changing. The research presented this year signaled a major shift from the standard approach of previous decades of just evaluating various antibiotics for chronic bacterial prostatitis. It appears that the major thrust of research in this decade will be directed toward an understanding of the condition in the many men without positive cultures (CPPS) and toward a serious commitment to develop an evidence-based approach to therapy. [Dr Nickel]

Prostate Cancer Treatment

With increasing options for treatment of patients with localized prostate

cancer, the decision for an individual patient and his physician as to the optimal modality has become an important issue in outcomes research. Lacking randomized clinical trials comparing the various therapies for prostate cancer (radical surgery, external beam radiation therapy, brachytherapy, etc), it is difficult to compare the efficacy of individual treatment options to assist men in making this decision. In an attempt to better understand this important issue, Menon and colleagues[39] from the Henry Ford Health System in Detroit reported on a large series of nonrandomized patients who, between 1980 and 1997, underwent therapy at the Henry Ford Hospital for presumed localized prostate cancer. This group of 3553 men (all under age 76)—treated with conservative (no curative) therapy, irradiation, or radical prostatectomy—had an average follow-up of 69.5 months (range, 31 to 234 months).

Comorbid disease was measured and corrected for, using the Charlson score. A Cox proportional hazards model (which accounted for various factors known to influence survival) was used to compare these groups of nonrandomized patients in a long-term survival analysis. For this cohort of patients, the overall survival rates at 15 years were 30% for patients who had conservative treatment, 25% for those who received irradiation, and 50% for those who underwent radical prostatectomy. Corresponding 15-year prostate cancer–specific survival rates were 70% for conservative therapy, 65% for radiation, and 92% for radical prostatectomy. Overall, 1215 patients died during follow-up. After adjustments for comorbidity, age, stage, grade of tumor, socioeconomic status, and year of diagnosis, the patients undergoing radical retropubic prostatectomy continued to demonstrate a lower relative risk for both overall mortality and prostate cancer–specific mortality.

This study demonstrated that radical prostatectomy had the lowest mortality rate, compared with conservative treatment or radiation therapy. This mortality decrease was seen also in patients with coexisting illnesses and was greatest in those men with moderately to poorly differentiated tumors. While the study suffers from the limitations of most nonrandomized clinical trials, it clearly shows a survival benefit to patients undergoing radical retropubic prostatectomy for clinically localized prostate cancer and supports the hypothesis that radical retropubic prostatectomy provides optimum cancer control for these patients. [Dr Partin]

Neurogenic Bladder Dysfunction

Apomorphine is a dopamine receptor agonist that acts on the central nervous system. Once absorbed and transported to the brain, apomorphine initiates a chain of reactions that result in increased blood flow to the male genital organs and an erection. In clinical studies, patients who received apomorphine had an approximate 60% effect, compared with a 30% effect in those who received placebo. The most common reported side effect is nausea.

Steers and associates[40] at the University of Virginia looked at apomorphine for a different indication—neurogenic bladder dysfunction. It is for this brave pilot study and exciting preliminary results that this investigation deserves the "best in show" award.

The investigators studied 9 men (mean age, 37.3 years) with complete spinal cord injury (SCI). The patients underwent urodynamic evaluation 20 minutes after receiving a sublingual tablet of either placebo or apomorphine (2, 4, or 5 mg). Each patient served as his own control. Urodynamic parameters, including detrusor contraction, rectal vault contraction, presence of urinary leakage, and erection, were evaluated. Apomorphine consistently had a stimulatory effect on the bladder, with an increase in the number, maximum amplitude, and maximum duration of detrusor contractions. Although detrusor sphincter dyssynergia persisted, the urethral opening pressure was decreased, which may be clinically significant.

This first report demonstrated that apomorphine can induce bladder activity through presumed spinal receptors. Because time from apomorphine administration to detrusor contraction was consistent, this agent may be effective for patients with SCI and neurogenic bladders. Patients may be able to manage their bladders with reflex voiding and reduction in residual urine. [Dr Chancellor]

Gene Therapy for Prostate Cancer

Preclinical studies in the field of gene therapy for urologic cancers (primarily, prostate cancer) fall into 2 main categories: studies evaluating new therapeutic transgenes and those exploring the more technical aspects of delivering therapeutic transgenes to the desired location (vectors, doses, methods, numbers of injections, etc). These preclinical studies have laid the theoretical and practical groundwork for a small number of clinical trials in patients.

The transfer of this technology to the clinic remains difficult. Only 6 abstracts presented clinical data from gene therapy trials for prostate cancer; the information presented was limited primarily to the safety of therapy in standard dose-escalation trials, reflecting the predominance of early phase I studies in this field.

To date, the largest experience treating patients with gene therapy for prostate cancer remains the group of trials using adenovirus containing the herpes simplex virus thymidine kinase gene (Ad.HSV-*tk*) plus ganciclovir (GCV), first performed by a group at Baylor College of Medicine in Houston. These trials were done in a variety of clinical settings, including use in patients with radiorecurrent prostate cancer as well as in those with

locally advanced prostate cancer treated with neoadjuvant gene therapy before radical prostatectomy. Shalev and colleagues[41] reported on the toxicity of Ad.HSV-*tk* + GCV therapy, shown in 3 clinical trials in which 36 patients received 46 separate injections into the prostate under transrectal ultrasound guidance. This important report demonstrated that Ad.HSV-*tk* + GCV treatment is safe even after repeated injections. After 46 injections, 17 toxic events were recorded; they were mostly mild and resolved spontaneously. Four patients experienced grade 1 fever, and 3 patients had grade 2 fever, immediately after viral injection. Five patients had abnormal liver function tests that returned to normal after treatments ended. Researchers from Mt Sinai School of Medicine[42] (New York) presented preliminary data on their similar experience with neoadjuvant Ad.HSV-*tk* + GCV gene therapy in patients before radical prostatectomy.

To further improve the overall safety of gene therapeutic strategies, including HSV-*tk* + GCV suicide gene therapy for use in the clinic, researchers are working on ways to restrict the expression of these agents to the targeted tissue, hoping to spare the deleterious effects on normal tissues that can result from significant treatment toxicity. For prostate cancer, these strategies have included methods of directly injecting gene therapeutic agents into the prostate or into metastatic prostate cancer deposits. Additional approaches have focused on the development of tissue-specific promoters that allow expression of the therapeutic transgenes only in cells of the targeted tissue.

Gardner and associates,[43] at the Universities of Virginia and Indiana, reported their results from a phase I clinical trial of intralesional injection of Ad.OC-TK (adenovirus containing HSV-*tk* with an osteocalcin promoter) followed by oral valacyclovir, a derivative of ganciclovir, in men with metastatic and recurrent prostate cancer. In this vector, the thymidine kinase therapeutic transgene is driven by the osteocalcin promoter, limiting expression to both the epithelial and stromal cellular components of prostate cancer metastases in which this promoter is active. The Gardner group treated 11 men (5 with osseous metastases, 4 with lymph node metastases, and 2 with recurrent disease) with escalating doses of this vector, followed by 21 days of treatment with oral valacyclovir. Systemic distribution of viable vector was demonstrated by a biologic assay performed on the urine of men with recurrent disease and on the serum of men who received injections into lymph node or bony metastases. Six of 11 men experienced mild, flu-like symptoms. Five of 11 men demonstrated grade 1 elevation of partial thromboplastin time, which was found not to be clinically significant. The treatment appeared to lead to a biologic response, including alteration in the TDPSA and changes in the growth of treated lesions, as evaluated by imaging studies. A phase II trial began at both institutions in June 2000 to further evaluate this strategy.

In addition to these approaches, several small phase I clinical trials evaluating other strategies were reported, including vaccination with vaccinia virus expressing MUC-1/IL-2 for patients with advanced and metastatic prostate cancer[44]; direct injection with CN706, a PSA-specific oncolytic adenoviral vector, for patients with locally recurrent prostate cancer following radiation therapy[45]; and direct injection of Ad.CAIL-2 in men with locally advanced prostate cancer before radical prostatectomy.[46]

These pioneering studies should be viewed as the earliest tentative approaches evaluating the use of gene therapy for the treatment of patients with prostate cancer. Until significant therapeutic responses are demonstrated by any of these approaches, the interest of the general urologist will remain limited. [Dr Slawin] ■

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COMING IN REVIEWS IN UROLOGY

TRANSCATHETER THERAPEUTIC EMBOLIZATION OF GENITOURINARY PATHOLOGY

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