Editorials

Pharmacologic Management of Benign Prostatic Hyperplasia—Changing Times

THIS PERIOD OF MEDICAL HISTORY has been officially designated as the "Decade of the Brain," but from the perspective of a urologist, it feels much more like the "Decade of the Prostate." Elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, Drs Narayan and Indudhara comprehensively review a fascinating aspect of this history—the evolution of medical therapy for benign prostatic hyperplasia (BPH).[1] Benign prostatic hyperplasia makes up one arm of the triad of prostate cancer, prostatitis, and BPH that affects the prostates of aging men. This disease serves as a link between man and man's best friend, the dog, as the only two mammals in whom the malady is knowsn to develop.[2] Until recently, it was a disease whose treatment was relegated almost exclusively to the use of surgical therapy and, in particular, transurethral resection of the prostate (TURP). After cataract surgery, this operation remains the second most common and most costly surgical procedure under Medicare. In 1986 it constituted 36% of urologists' surgical load.[3,4] The incidence rate for surgical therapy for BPH in the United States for 1990 of 13 per 1,000 men is one of the highest in the world.[5] More recent Medicare data show, however, that the use of TURP is on the decline, down nationally almost 18% in 1992 from a peak of 253,000 operations in 1987.[4] Our own experience at the University of New Mexico School of Medicine would suggest that this figure may be closer to 50% based on TURP numbers for 1993. Much of the decline in surgical therapy is attributable to the use of medical therapy for the disease, and as this article makes clear, times are changing.

Ten years ago, urologists argued about the most appropriate way to manage prostate cancer, but there was a general consensus about the treatment strategy for BPH. Ten years later, urologists still argue about prostate cancer, but now we have BPH to worry about as well. In the early 1980s, a patient seen at our institution with symptoms of prostatism underwent a standard workup consisting of a careful history and physical examination, urinary flow rate, postvoiding residual determination by catheterization, cystoscopy, intravenous pyelogram to rule out upper tract disease, measurement of the serum urea nitrogen and creatinine levels, and urinalysis. Once the diagnosis of BPH had been established, there were only three options for treatment. These included "watchful waiting," a Foley catheter, or prostatectomy, usually by transurethral resection. Patients opting for prostatectomy seemed satisfied with the results, and the morbidity and mortality seemed to be low. In the later part of the 1980s, however, a number of studies were published which suggested that the long-term mortality of TURP was higher than that of open prostatectomy because of an excess of cardiovascular deaths.[6] Further, the reoperative rate of 2% per year[6] and the overall complication rate of 18% were higher than expected.[7] The long-term mortality risk was ultimately debunked by a study which showed that when existing comorbidities were accounted for at the time of the operation, there were no differences in long-term mortality risk ratios.[8] Data such as these, however, coupled with the medicoeconomic effects of the procedure, fueled efforts to introduce alternatives to TURP including the use of pharmacotherapy.

On February 8, 1994, the Agency for Health Care Policy and Research under the US Department of Health and Human Services issued practice guidelines for the diagnosis and treatment of BPH.[9] For patients presenting with symptoms of prostatism in the 1990s, in addition to a detailed medical history and physical examination, the cornerstone of the diagnostic evaluation is a quantitative symptom assessment using the thoroughly validated American Urological Association Symptom Score, which is identical to the International Prostate Symptom Score (IPSS) discussed by Narayan and Indudhara.[1] This symptom index allows symptoms to be stratified as mild (score = 0 to 7), moderate (score = 8 to 19), or severe (score = 20 to 35). Patients with mild symptoms are not recommended to have treatment other than watchful waiting. Patients with moderate symptoms compose the largest subgroup and more frequently select pharmacologic therapy. Although patients with severe symptoms more often select surgical therapy, there is still considerable overlap with medical therapy as an initial choice for these patients. Finally, in this era of alternative therapies, it is important not to ignore the traditional absolute indications for surgical therapy, including recurrent bouts of gross hematuria, refractory urinary retention, recurrent urinary tract infection, and azotemia proved to be caused by bladder outlet obstruction.

Because reimbursement for the treatment of the disease will ultimately be tied to the use of this symptom index, it is necessary for treating physicians to familiarize themselves with the index and to incorporate it into their day-to-day evaluation of patients with BPH. Uroflowmetry and postvoiding residual determination, which is now performed largely by ultrasonography, are considered optional tests in the 1990s. Like Narayan and Indudhara, we also obtain a prostate-specific antigen measurement on most of the patients whom we see for a BPH workup, and the guidelines allow this as an optional test.[1] Intravenous pyelography or renal ultrasonography for upper tract evaluation is not recommended unless hematuria or other findings are present to justify these tests. Cystoscopy is allowed only for surgical planning if invasive therapy has been selected.

In addition to the treatment options of the 1980s, treating physicians are now confronted with a panorama of new therapies to consider, including balloon dilation, urethral stints, microwave hyperthermia, laser prostatectomy, cryotherapy, and pharmacotherapy. Pharmacotherapy in-

ABBREVIATIONS USED IN TEXT

BPH = benign prostatic hyperplasia
FDA = US Food and Drug Administration
TURP = transurethral resection of the prostate

cludes the use of α-adrenergic blockers or antiandrogens, particularly 5α-reductase inhibition with finasteride. Physicians need to have some familiarity with all of these alternatives because most patients have either seen or read about these treatments in the media, often before peer-reviewed literature is available. Of the therapies evaluated by the panel that developed the federal practice guidelines, sufficient data were available to draw conclusions only for "watchful waiting," prostatectomy, balloon dilation, α-blockade, and finasteride therapy. An exhaustive meta-analysis of treatment outcomes showed that the 90% confidence interval for the chances of improvement with TURP (94% to 99%) were better than that for nonsurgical options including α-blockade (59% to 86%) or finasteride administration (54% to 78%).[9] Further, the degree of symptomatic improvement was greatest for TURP (85%) versus other therapies including α-blockade (51%) or finasteride therapy (31%).[9] The need for controlled randomized trials to evaluate the efficacy of any new therapy for BPH was highlighted in the guidelines by the fact that the median probability for symptomatic improvement was as high as 45% in patients treated with placebo, similar to the 42% figure for "watchful waiting."[9] The downside of surgical therapy is obviously the possible increased morbidity of TURP, the loss of work time due to recovery, and the need for admission to a hospital.[9] The use of laser for prostatic ablation or incision promises to improve on these factors in the future.

The old idea of dealing with the static or anatomic component of obstruction by "shrinking the prostate" is a tenet of antiandrogen therapy for BPH and addresses predominantly the epithelial component. The agent of choice because of its low incidence of side effects is the 5α-reductase inhibitor finasteride. The development of finasteride began as a study of a kindred in the Dominican Republic who had ambiguous genitalia and underdeveloped prostates.[10] They became virilized at puberty, and BPH never developed. Ultimately this disorder was linked to a deficiency of the enzyme 5α-reductase, which converts testosterone to dihydrotestosterone, the predominant androgen in the prostate.[11] A search for inhibitors of this enzyme led to the discovery and development of finasteride, which has US Food and Drug Administration (FDA) approval for the treatment of BPH. Because this drug preserved serum levels of testosterone, impotence occurred in a small percentage (3%) of patients. True to form, the drug in 5-mg daily doses "shrinks" the epithelial component of the prostate, and prostatic size decreases substantially in most patients, but this has translated to symptomatic improvement in only about a third of patients.[12] These results are similar to those for other antiandrogen therapies for BPH, including the classic study by White in 1895 documenting a 25% response rate in patients undergoing bilateral orchiectomy for BPH treatment.[13] Other problems with the drug include its slow onset of symptomatic improvement, which may take as long as six months, and a predictable decrease in serum prostate-specific antigen levels.[12]

A new idea pioneered by Marco Caine, MD, in early work on the use of α-adrenergic blockade for the treatment of BPH, was that smooth muscle in the stroma of the prostate produced a dynamic component of obstruction.[14] This concept has been validated, and several selective α_1-blockers are available for use, with differences attributed to dosing intervals, cost, and initial side effects rather than any real differences in effect. Terazosin has been the most widely studied of these drugs and has FDA approval for the treatment of BPH. These drugs must be titrated slowly to 5 or 10 mg to avoid side effects of dizziness and postural hypotension. The medication is taken at bedtime, and the symptomatic improvement is noted within days. As Narayan and Indudhara mention, studies with the combination of α-blockade and finasteride are currently in progress.[1]

A number of issues remain unresolved for the role of TURP and pharmacotherapy in the management of BPH. First, the assumption that the cost of treatment will be less may not hold if medical therapy ultimately only prolongs the interval to TURP. Figuring total average charges for prostatectomy in the United States at $11,670 in 1990 and the cost of terazosin hydrochloride ($1.00 per day) and finasteride ($1.75 per day), break-even values are obtained at 31 and 18 years, respectively. This simplistic analysis, however, ignores added physician visits, urinary flow tests, and other charges that might make these numbers less attractive.[5] Will long-term compliance or as-yet-unrecognized long-term side effects limit the usefulness of pharmacotherapy? Although the use of chip cameras has shortened the learning curve for endoscopic procedures, will urologists trained in the next decade do an adequate number of TURP procedures during their training, or will the procedure be supplanted entirely by laser or other technologies? Will medical therapies fade, leaving the next decade of BPH management to look more like the last? If the next decade changes as much as the last, perhaps we will once again have a consensus about the management of this disease.

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REFERENCES

1. Narayan P, Indudhara R: Pharmacotherapy for benign prostatic hyperplasia. West J Med 1994; 161:495-506

2. Walsh P: Benign prostatic hyperplasia, chap 25, *In* Walsh PC, Retic AB, Stamey TA, Vaughn ED (Eds): Campbell's Urology—Vol 1, 6th edition. Philadelphia, Pa, WB Saunders, 1992, pp 1009-1027

3. Holtgrewe HL, Mebust WK, Dowd JB, Cockett ATK, Peters PC, Proctor C: Transurethral prostatectomy: Practice aspects of the dominant operation in American urology. J Urol 1989; 141:248-253

4. Holtgrewe HL: Lecture to New Mexico Urologic Society, 32nd Annual New Mexico Urologic Seminar, Albuquerque, April 7, 1994

5. Holtgrewe HL: The economics of BPH, *In* Cockett ATK, Aso Y, Chatelain C, et al (Eds): Proceedings of the Second International Consultation on Benign Prostatic Hyperplasia, World Health Organization, Paris, France, June 1993. Jersey, Channel Islands, Scientific Communication, 1993

6. Roos NP, Wennberg JE, Malenka DJ, et al: Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. N Engl J Med 1989; 320:1120-1124

7. Mebust WK, Holtgrewe HL, Cockett ATK, Peters PC: Transurethral prostatectomy: Immediate and postoperative complications—A cooperative study of 13 participating institutions evaluating 3,885 patients. J Urol 1989; 141:243-247

8. Concato J, Horwitz RI, Feinstein AR, Elmore JG, Schiff SF: Problems of comorbidity in mortality after prostatectomy. JAMA 1992; 267:1077-1082

9. Agency for Health Care Policy and Research: Clinical Practice Guideline Number 8—Benign Prostatic Hyperplasia: Diagnosis and Treatment. Rockville, Md, US Dept of Health and Human Services publication No. 940582, 1994

10. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE: Steroid 5α-reductase deficiency in man: An inherited form of male pseudohermaphroditism. Science 1974; 186:1213-1215

11. Walsh PC, Madden JD, Harrod MJ, Goldstein JL, MacDonald PC, Wilson JD: Familial incomplete male pseudohermaphroditism, type 2—Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. N Engl J Med 1974; 291:944-949

12. Gormley GJ, Stoner E, Bruskewitz RC, et al: The effect of finasteride in men with benign prostatic hyperplasia—The Finasteride Study Group. N Engl J Med 1992; 327:1185-1191

13. White JW: The results of double castration in hypertrophy of the prostate. Ann Surg 1895; 22:1-80

14. Caine M: The present role of alpha adrenergic blockers in benign prostatic obstruction. Br J Urol 1976; 48:255-263

How to Capture a Revolution

WHAT IS IT LIKE to try to capture the flavor and meaning of a revolution while you are in the middle of it? That is what Neil W. Toribara, MD, PhD, has tried to do in the medical staff conference, "Colorectal Cancer—A New Look at an Old Problem," elsewhere in this issue.[1] The understanding of colorectal carcinogenesis is rapidly being transformed by a multifaceted revolution in genetics and cellular biochemistry. The title of Toribara's review could just as easily have been "Colorectal Cancer—The New Look of an Old Problem" because this scientific revolution has converted the concept of colonic carcinogenesis from a relatively simple, multistep, histologic progression (the adenoma-carcinoma sequence) to a multidimensional process with histologic, biologic, genetic, and biochemical components.

The conceptual advances in the genetics and cellular biochemistry of colonic carcinogenesis have important clinical meaning for the prevention, early detection, and treatment of human colorectal cancer. Revolutions pose new challenges for all involved, and this one is no exception. The challenge for basic science and clinical investigators is to define the clinically useful components of the genetic and biochemical understanding of colonic carcinogenesis. The challenge for clinicians is to incorporate the useful concepts into the care of patients with or at risk for colorectal cancer.

As reviewed (and referenced) by Toribara,[1] several specific acquired genetic events—activation of the K-*ras* oncogene, inactivation of the putative tumor suppressor genes, *APC* ("adenomatous polyposis coli"), *DCC* ("deleted in colorectal cancer"), *P53*, and *hMSH2*—have become accepted as relevant to the process of colonic carcinogenesis. Exciting as these genetic discoveries are, they are only the beginning of the story. The depth of understanding of the cellular and biochemical consequences of these genetic alterations and the speed at which this field is advancing may not be as widely recognized.

Activation of the K-*ras* oncogene is a good example of the first point (depth of understanding). The normal K-*ras* gene codes for a 21-kd guanosine triphosphate (GTP)-binding protein called p21 that is critically positioned on the inner surface of the plasma membrane to function in transducing signals from the cell surface to intracellular targets. This protein is anchored to the plasma membrane by a lipid (farnesyl) intermediate that is added after translation. The biochemical details of at least one K-*ras*-dependent pathway have been recently described.[2] A simplistic description of the pathway is that epidermal growth factor binding to the transmembrane epidermal growth factor receptor results in tyrosine autophosphorylation of the cytosolic tail of the receptor. This tyrosine phosphorylation results in an interaction between two cytosolic proteins, GRB2 and SOS. The complex facilitates the release of guanosine diphosphate (GDP) from p21 (the K-*ras* gene product) and allows GTP to bind to p21. This GTP binding activates P21, and the activation initiates an intracellular kinase cascade (raf1, methylamino-purine [MAP] kinase kinase, MAP kinase) that ultimately results in transcriptional regulation. The normal p21 also has a guanosine triphosphatase (GTPase) activity that hydrolyzes bound GTP to GDP and inactivates p21, thus turning off the signal transduction pathway. Thus, the normal p21 plays a central role as an on-off switch (activation by GTP, inactivation by GTP hydrolysis) in regulating signal transduction. Mutations in K-*ras* occur in about 50% of colonic adenomas and carcinomas. The mutations are almost always point mutations in codons 12, 13, or 61 of the gene. These mutations result in a loss of the GTPase activity of p21, thus preventing inactivation of the signal transduction pathway. Cells with mutated K-*ras* can be viewed as having a constitutively activated signal transduction system. It is easy to imagine how constitutive activation of some signal transduction systems (growth factor systems) could result in a clone of cells with a growth advantage.

The detailed understanding of the biochemical consequences of K-*ras* mutations provides the basis for interventions to block the abnormality. At least two inhibitors of the farnesyl transferase that is required to properly anchor p21 to the plasma membrane have been developed and are being tested as chemopreventive or treatment agents in cell culture and animal systems.[3]

Although not all of the oncogene and tumor suppressor gene products are as precisely characterized as p21, a great deal is known about many of them, and the field is moving rapidly. The known functions of the genes frequently mutated in colon cancer are listed in Table 1. The common pattern of progress in this field is that the finding of genetic abnormalities in colonic cancers and adenomas led to the identification of the specific gene(s) involved, which allowed the identification and characterization of the relevant gene product. In some cases the precise function(s) of the gene products has been determined. It seems