

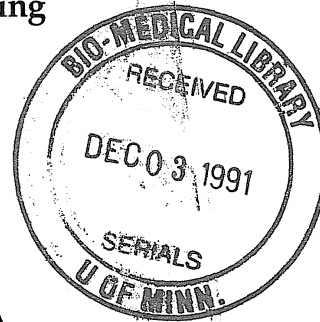
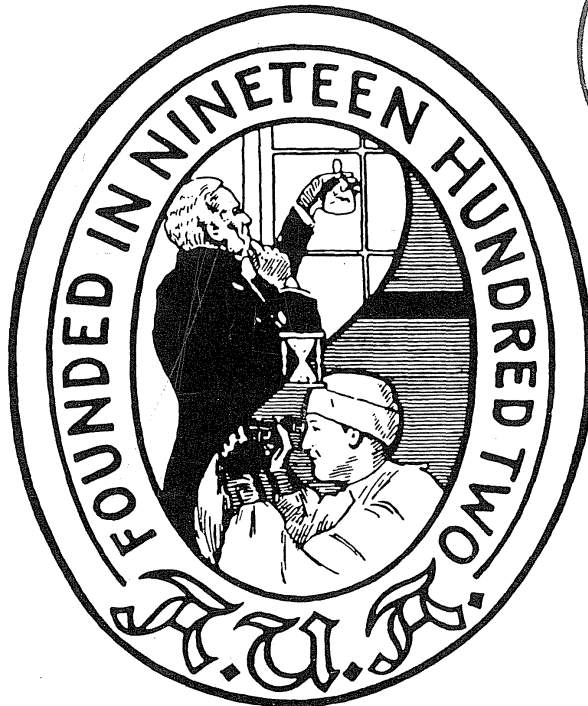
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mate interchange might possibly be misinterpreted and misused. I, therefore, asked Dr. H. Logan Holtgrewe, whose opinions I value highly as a urologist and as a leader in the interactions on the social scene, about his reaction to publication of the Letter. I received the following Letter in reply and believe that it warranted sharing with all of you.

Note by Dr. H. Logan Holtgrewe. The thrust of the paper by Katz et al was to extol the virtue of transurethral incision over transurethral resection of small prostate glands. They dealt lightly, if at all, with the indications for the operation. As Doctor Rohlfs notes, the only specific reference was "patients were candidates for incision if they had a clinically benign prostate, peak urinary flow rate of less than 15 ml. per second and an estimate 15 gm. or less of resectable prostatic tissue." Katz et al may well have insisted upon other criteria before operating but if they did so, their paper fails to state these additional criteria, leaving the reader with the assumption that a slow stream was the sole indication for the operation.

Doctor Rohlfs is right on! A flow rate of less than 15 cc per second is certainly not of itself an indication for a prostate operation. Doctor Rohlfs also is correct that variation in practice styles of urologists accounts for the variation in the incidence of prostatic surgery in age-adjusted populations in different geographic areas of our country—the variation is as great as 3-fold. He is equally correct that this variation in the incidence of prostate surgery has brought this operation to the attention of the Government and its health care agencies, including the Health Care Financing Administration. It also may account for the fact that benign prostatic hyperplasia was among the first 3 diseases for which the Federal Government decreed there would be guidelines of treatment. Fortunately, due to the fact that the American Urological Association was already well along in a scholarly construction of guidelines for the treatment of benign prostatic hyperplasia, the governmental agency that the Congress created to oversee guideline development literally hired the existing American Urological Association committee chaired by Dr. John McConnell to complete these guidelines, which were in the hands of the Federal Government by December 1, 1990.

Reply by Authors. Our patients were not selected for transurethral incision of the bladder neck and prostate based on a single parameter. We agree with Doctor Rohlfs that a transurethral operation should not be performed solely for a slow urinary stream. We evaluated men 50 years and older who presented with symptoms of prostatism. As noted in the Methods Section, our patient assessment included a symptoms questionnaire, physical examination, urine culture, uroflowmetry and cystoscopy. The symptoms evaluated included force of stream, hesitancy, intermittency, daytime and nighttime urinary frequency and urgency/incontinence. The symptom scoring system is given in table 1 in the article. Treatment recommendations were based on this evaluation and not on a single factor. After evaluation those patients who decided to proceed with surgical intervention underwent examination while they were under anesthesia. The decision was then made to proceed with either transurethral prostatectomy or, for patients with a small prostate, incision.

Except for a total outflow obstruction, the indications for a bladder outlet operation are not absolute. We excluded symptomatic patients with peak urinary flow rates of greater than 15 ml. per second because they are less likely to have bladder outlet obstruction and have significantly lower success rate after a prostatic operation than those with lower preoperative flow rates.¹ Doctor Rohlfs discusses other criteria for bladder outlet obstruction, including residual urine without stating what volume he considers to be significant. However, residual urine may occur in the absence of bladder outflow obstruction and markedly obstructed bladders may empty completely.^{2,3}

We believe that our selection criteria were appropriate in identifying symptomatic patients with bladder outlet obstruction. With a mean followup of more than 2 years, the incisional procedure resulted in a statistically and clinically significant decrease in total symptom scores (table 3 in article) and an increase in peak flow urinary flow (table 2 in article).

1. Jensen, K. M.-E., Jørgenson, J. B. and Mogensen, P.: Urodynamics

3. Bruskewitz, R. C., Iversen, P. and Madsen, P. O.: Value of postvoid residual urine determination in evaluation of prostatism. *Urology*, **20**: 602, 1982.

RE: PROSTATE SPECIFIC ANTIGEN FOR ASSESSING RESPONSE TO KETOCONAZOLE AND PREDNISONE IN PATIENTS WITH HORMONE REFRACTORY METASTATIC PROSTATE CANCER

G. S. Gerber and G. W. Chodak

J. Urol., **144**: 1177-1179, 1990

To the Editor. Since so much of the literature pertaining to prostate cancer is directed toward treating potentially curable or endocrine responsive tumors, it was gratifying to read an article directed toward endocrine unresponsive carcinoma of the prostate. This is an area that requires much more basic and clinical research. In 1973 the Veterans Administration Cooperative Urological Research Group suggested that when a patient with advanced prostate cancer became refractory to 1 form of androgen deprivation and had relapse it was unlikely he would respond significantly to any other form of endocrine therapy.¹ In 1976 Prout et al suggested that prostate cancer consists of a heterogeneous population of cancer cells, some of which are androgen sensitive and others that are not.² The further proliferation and spread of the latter group of cells eventually causes endocrine refractory prostate cancer.

The authors reported on 15 patients with endocrine refractory metastatic carcinoma of the prostate who were treated with ketoconazole and prednisone. All patients had been treated previously with bilateral orchiectomy alone or with luteinizing hormone-releasing hormone agonist alone. Of the 15 patients 10 had also received radiotherapy. None of these 15 patients showed a significant improvement in terms of increased survival, or an objective or subjective response except for a decrease in prostate specific antigen (PSA) and bone pain. Since ketoconazole presumably acts by inhibiting gonadal and adrenocortical steroid synthesis, the authors have again substituted 1 form of endocrine therapy for another. Therefore, one would not expect a significant improvement unless the new therapy had an effect beyond androgen deprivation, for example a direct cytotoxic effect. Eichenberger et al recently suggested a direct cytotoxic effect for ketoconazole.³ Perhaps a reason why estramustine phosphate has not been too successful in the treatment of endocrine refractory prostate cancer patients is that the principal activity of this drug has been largely through its estradiol moiety.⁴

It is likely that the effects of ketoconazole and prednisone in decreasing PSA levels have little or nothing to do with clinical improvement. All of us who treat prostate cancer patients have noted an increasing PSA value when a patient has a relapse after radical prostatectomy or radiation therapy. After androgen ablation the PSA level often decreased or returned to normal even though the prostate cancer was progressing clinically. Kaplan et al suggested that this phenomenon might occur partly because "testosterone is required to drive the synthesis of PSA by prostatic tissue."⁵ Therefore, a decrease in the PSA level after endocrine intervention is not necessarily synchronous with clinical improvement.

Reduction in bone pain is largely subjective and difficult to evaluate. The reduction in bone pain reported by the authors could have been related partly to bed rest, simultaneously administered analgesics and/or the prednisone. Almost all of us can treat organ-confined disease or prostatic carcinoma still responsive to androgen deprivation but what can we do for the patient with endocrine unresponsive carcinoma of the prostate? We definitely need more research in this area.

Respectfully,
Clyde E. Blackard
Park Nicollet Medical Center
Minneapolis, Minnesota 55416

- Hurst, K. S. and Byar, D. P.: An analysis of the effects of changes from the assigned treatment in a clinical trial of treatment for prostatic cancer. *J. Chron. Dis.*, **26**: 311, 1973.
- Prout, G. R., Jr., Kliman, B., Daly, J. J., MacLaughlin, R. A., Griffin, P. P. and Young, H. H., II: Endocrine changes after diethylstilbestrol therapy; effects on prostatic neoplasm and

mustine phosphate on pituitary, gonadal, and adrenal function in the green monkey (*Cercopithecus aethiops sabaeus*). *Invest. Urol.*, **15**: 151, 1977.

5. Kaplan, I., Prestidge, B. R., Cox, R. S. and Bagshaw, M. A.: Prostate specific antigen after irradiation for prostatic carcinoma. *J. Urol.*, **144**: 1172, 1990.

Reply by Authors. Doctor Blackard raises important questions about the significance of our observations regarding the effect of ketoconazole in patients with hormone refractory prostate cancer. Secondary hormonal therapy in various forms has been used for many years with a small but real response rate of approximately 20%. As cited in our paper, other studies observed an objective response in approximately 20% of the patients treated with ketoconazole using other objective tests. The focus of our report was to show that perhaps this subset can be identified more easily by following serum PSA levels, thereby obviating the need for the other studies and identifying nonresponders more rapidly. Doctor Blackard suggests that a decrease in PSA may have no clinical significance and he states that the PSA level often decreases or returns to normal when the patient has clinical progression. This latter comment is an uncommon event, however, since less

than 10% of the patients demonstrate progressive disease without first having an increasing PSA level. Furthermore, we have not said that survival was unaffected but, rather, we have insufficient data to determine the impact on survival. We acknowledge that the improvement in bone pain is subjective and may be due to the simultaneous administration of prednisone. However, the clear reduction in analgesics by many of these patients would argue that the benefit is real, even if short-lived. Furthermore, a recent report by Trachtenberg provides evidence that ketoconazole is effective in the absence of steroids.¹ Finally, although radiation had been previously administered to some of these patients, the timing of the ketoconazole and the demonstration of an increase in PSA after radiation but before the medication argue for attributing this response to the drug. We certainly agree that more research is needed but the observations by others as well as our own findings suggest that more investigation with ketoconazole or its analogue appears to be warranted, since the drug does appear to have some clinical benefit in these patients in addition to its effect on serum PSA.

1. Trachtenberg, J.: Ketoconazole therapy in advanced prostatic cancer. *J. Urol.*, **137**: 959, 1987.