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## You Can Lower the Blood Pressure 10 mm Hg with Diet Alone!

ABSTRACT & COMMENTARY

**Synopsis:** *The DASH diet combined with low sodium intake can lower systolic blood pressure more than 10 mm Hg after only 30 days.*

**Source:** Sacks FM, et al. *N Engl J Med* 2001;344:3-10.

The dietary approaches to stop hypertension (dash) trial demonstrated that a diet that emphasizes fruits, vegetables, and low-fat dairy products, that includes whole grains, poultry, fish and nuts, that contains small amounts of red meat, sweets, and sugar-containing beverages, and that contains decreased amounts of total and saturated fat and cholesterol, lowers blood pressure substantially both in people with hypertension and those without hypertension.<sup>1</sup>

The effect of large amounts of sodium in the diet has been controversial, however. This study was designed to evaluate the effects of varying amounts of sodium in the diet. A total of 412 participants were randomly assigned to eat either a control diet typical of the intake in the United States or the DASH diet. Within the assigned diet, participants ate foods with high, intermediate, and low levels of sodium for 30 consecutive days each, in random order. The primary outcome was systolic blood pressure at the end of each 30-day period of dietary intervention. The secondary outcome was diastolic blood pressure.

Reducing the sodium intake from high to the intermediate level reduced the systolic blood pressure by 2.1 mm Hg ( $P < 0.001$ ) in the control diet (the so called average American diet) and 1.3 mm Hg in the DASH diet. Reducing the sodium intake from the intermediate level to the low level caused additional reductions of 4.6 mm Hg in the control diet ( $P < 0.001$ ) and 1.7 mm Hg in the DASH diet ( $P < 0.01$ ). The effects of sodium were observed in participants with and in those without hypertension, blacks, and those of other races, and both women and men. The DASH diet was associated with significantly lower systolic blood pressures than the control diet at each sodium level. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a systolic blood pressure that was 7.1 mm lower in participants without hypertension,

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and 11.5 mm Hg lower in participants with hypertension.

## ■ COMMENT BY RALPH R. HALL MD, FACP

The first report of the DASH diet<sup>1</sup> made significant additions to the prevention and treatment of hypertension. The findings were rapidly incorporated into the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure<sup>2</sup> and have more recently influenced the guidelines released by the American Heart Association.<sup>3</sup>

The first DASH trial maintained the sodium intake at 3 g per day and still resulted in significant drops in both systolic and diastolic blood pressure. This latest study varied the sodium intake from 3.5 g, 2.3 g, and 1.3 g per day in both the DASH and control diets. There was a reduction of 8.9 mm Hg in systolic blood pressure and 4.5 mm Hg in diastolic blood pressure between the high and low sodium intake. Greenland notes in the accom-

panying editorial<sup>4</sup> that the blood pressure reductions in this study are similar to the ones achieved with blood pressure lowering medications.

These findings have great importance when one considers the findings of Cook that a reduction in diastolic pressure of 2 mm Hg results in a decrease of 6% in coronary heart disease and a 15% decrease in stroke.<sup>5</sup>

In the past, most nutrition studies have emphasized the specific effects of one nutrient factor. Jacques and Tucker use the example of diets high in fiber which “tend to be high in vitamin C, folate, various carotenoids, magnesium, potassium. So when we see the association between fiber and disease risks, can we be certain the relation is not a consequence of folate or carotenoid intake.”<sup>6</sup> As they point out, the DASH diet along with other recent successful studies, are examinations of dietary patterns. They provide strong evidence that dietary patterns can be significantly related to measures of health and an important approach to nutrition research.

If we examine these diets we note that many of us have been on the wrong track. We have used low-fat mayonnaise and shunned nuts and, thus, in reducing our total fat intake, have reduced gamma vitamin E, the “good fats,” and potentially beneficial flavonoids from our diet.

Now, how do we put these nutrients back into our diet without gaining weight? The widespread use of these diets will call for both physician and patient education! ♦

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# Remission Rates of Urinary Incontinence

ABSTRACT & COMMENTARY

**Synopsis:** In a population-based cohort of women younger than 65 with urinary incontinence, on average, 6% will experience spontaneous remission each year.

**Source:** Samuelsson EC, et al. *Am J Obstet Gynecol* 2000; 183:568-574.

Urinary incontinence is an extremely common condition in the adult female population. Symptoms

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vary greatly from minor disturbances to complete incontinence. The prevalence of the condition increases with age. The purpose of this study was to determine both the incidence and the spontaneous remission rates of urinary incontinence in a population of women 20-59 years of age.

This study was carried out in Sweden where all women are eligible for routine gynecologic examinations on a regular basis. Those women scheduled for an examination during 1993 in the population district chosen to serve as the basis for this study were potential participants. Pregnant and lactating women, and those with mental retardation, were excluded. In addition, a small number of women with severe incontinence who required immediate treatment were also excluded.

Incontinence was broadly defined and all women who reported any degree of incontinence were included as being affected. Samuelsson and colleagues then subdivided this group into those who experienced symptoms monthly, weekly, or daily. Four hundred ninety-one women answered the questionnaire, and 487 were examined and represented the starting point of this study. Five years later a similar questionnaire was administered and 382 women responded (88% participation rate).

The average age of the study group was 42.5 years at follow-up. Sixty-two percent had given birth at least once. Of those women 45 years old or older, 30% were receiving estrogens.

Of the 383 women who participated throughout the study, 23.6% were incontinent at baseline, and 27.5% were incontinent at the time of the follow-up questionnaire. However, considerable crossover had occurred. Specifically, 40 of the women who were originally continent became incontinent at follow-up, while 25 of the 90 women who were originally incontinent became continent at follow-up. Thus, the remission rate was approximately 6% and the incidence rate was approximately 3%.

In an effort to determine which variable might be responsible for the occurrence of incontinence, a multivariate logistic regression analysis was performed. Only estrogen treatment was found to be significant. However, the effect of the estrogen treatment was interesting. Those women who were receiving estrogen were more likely to be incontinent than those who were not. Samuelsson et al were unable to determine whether women with more severe symptoms had been given estrogen, or whether estrogen therapy itself might be a predictor of incontinence. The duration of incontinence prior to the study did not predict whether the disease would remit during the follow-up period.

■ **COMMENT BY KENNETH L. NOLLER, MD**

Urinary incontinence is an almost unbelievably com-

plex condition. The more it is studied, the more obvious it is that some of our long-held beliefs have been in error. For example, when I was in training it was common to suggest to women who were experiencing incontinence of a mild-to-moderate degree that they should have surgical correction while they were still "young" as the condition only worsened with age. A number of previously published articles using elderly populations as study participants have shown that incontinence is not always irreversible or progressive. This article from Sweden now demonstrates that the same facts are true for younger women. Specifically, women 20-65 years of age who have incontinence, and who are followed for five years, have approximately a one-in-four chance of the incontinence disappearing.

The observations concerning exogenous estrogen therapy in this study are certainly worthy of some thought. For many years it has been suggested that estrogen therapy can decrease the frequency of urinary incontinence among women who have no or low levels of endogenous estrogen. While the studies supporting this "fact" have not always been well conceived or executed, I think most of us have believed that estrogen could help reduce incontinence. This article found exactly the opposite effect; and namely, that women on exogenous estrogen had more incontinence than those not on estrogen. Because the reason for estrogen therapy was not known in this study it is likely that Samuelsson et al's observation was due to the "fact" that the women with more significant incontinence were placed on estrogen, whereas those with minor difficulties were not. However, it must be recognized that it is at least possible that estrogen therapy does not help and may even hinder the remission of incontinence. The subject certainly deserves further study. (Dr. Noller is Professor and Chairman, Department of OB/GYN, Tufts University School of Medicine, Boston, Mass.) ❖

## Dramamine Superior to Lorazepam for Treatment of Acute Vertigo

ABSTRACT & COMMENTARY

**Synopsis:** *Dramamine was more effective and had less side effects in the treatment of vertigo.*

**Source:** Marill KA, et al. *Ann Emerg Med* 2000;36:310-319.

Vertigo is one of the most commonly encountered and difficult to treat complaints in neurologic

as well as general practice. A multitude of treatment options may be used, but none are clearly preferred as the agent with an ideal ratio of benefits to side effects. Anticholinergics, benzodiazepines, antihistamines, neuroleptics, and other agents have been used with variable success.

Marill and associates performed a study of 74 patients presenting to the emergency room (ER) with acute vertigo. Patients were prospectively randomized in a double-blind fashion to either intravenous lorazepam (2 mg) or dimenhydrinate (50 mg). The latter agent is available in oral form under the brand name Dramamine. It is a salt of the antihistamine diphenhydramine and 8-chlorotheophylline.

Vertigo was assessed by a 10-point patient rating scale. In a pilot study, vertigo during ambulation was found to be more sensitive than vertigo while lying in bed, sitting, or with head turn. This was, therefore, the primary outcome variable. The severity of vertigo during ambulation was also of practical significance as patients must be able to walk to be discharged from the ER. Secondary end points included symptoms such as nausea, treatment-related sedation, and overall "readiness to go home."

The mean magnitude of vertigo decreased from 6.4 to 2.6 (decrease = 3.8) in the dimenhydrinate group compared with 7.4 to 4.8 (decrease = 2.6) in the lorazepam group—a statistically significant difference. As Marill et al note, patients in the lorazepam group had higher pre-treatment vertigo severity. In the overall cohort, however, patients with more severe vertigo benefited more from treatment. This would have biased in favor of lorazepam rather than against it.

Patients treated with lorazepam experienced significantly more sedation. Nausea decreased similarly in both treatment groups. Overall, 32 (86%) patients in the dimenhydrinate groups were "ready to go home" two hours after treatment compared with 25 (69%) in the lorazepam group. This assessment was made variably by the treating physician or the patients, with comparable results by either method.

#### ■ COMMENT BY ALAN Z. SEGAL, MD

As assessed by ER physicians, the discharge diagnosis assigned to the majority of patients was "acute vertigo," presumably of peripheral origin, rather than a more specific neurological disorder. It is not completely clear how many of the patients had true vertigo as opposed to more nonspecific dizziness. Patients were evaluated for nystagmus (present in > 60%) but not for other neurological signs. As Marill et al acknowledge, central vertigo (e.g., related to brainstem or cerebellar ischemia)

probably comprised a negligible fraction of this population of patients (mean age = 45). Indeed, among the minority of patients in whom neuro-imaging was performed (n = 12, primarily CT), only one was positive (a cerebellar infarct). It is possible that patients with central-type vertigo were considered "too sick" for study enrollment or were considered ineligible due to concerns of stroke or TIA. Marill et al do not have specific data regarding these possible exclusions.

Despite these diagnostic considerations and the lack of any placebo-control group (considered unethical by Marill et al), this study is useful and important. An informal poll of neurologists in Marill et al's practice showed that most did not consider Dramamine to be efficacious in their patients with vertigo. Rather, they commonly prescribe benzodiazepines for this purpose. The data from Marill et al suggest that Dramamine, an easily obtained over-the-counter preparation, may be equally or more effective than lorazepam, a schedule II drug that is restricted and has significant abuse potential. (Dr. Segal is Assistant Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, New York Presbyterian Hospital, New York, NY.) ❖

## Prognosis of Cancers Associated with Venous Thromboembolism

ABSTRACT & COMMENTARY

**Synopsis:** *There was a higher mortality in patients diagnosed with cancer at the time of or within one year of the thromboembolic event. There was a higher association of distant metastasis at the time of diagnosis in this group as well.*

**Source:** Sorensen HT, et al. *N Engl J Med* 2000;343:1846-1850.

It has long been known that malignancy increases the risk of a venous thromboembolism (VTE). In fact, the incidence of cancer after such an event is higher than in the general population. Little is known, however, of the prognosis if the malignancy is discovered at the time of or after the event. This study tries to answer this question and evaluates the association between a history of thromboembolism and the extent of disease at the time of diagnosis.

Henrik and colleagues conducted a retrospective

case-control study using data retrieved for the Danish National Registry of Patients from Jan. 1, 1977, to Dec. 31, 1992. Exclusion criteria included previous diagnosis of cancer, surgery within six months of the event, secondary diagnosis of venous thromboembolism, pregnancy, or childbirth within nine months. The remaining patients had demographic and clinical data collected including extent of disease at the time of diagnosis. Patients were divided into those diagnosed at the time of the initial event, within the first year of the initial event, or 1-17 years after the event. The 3135 patients were matched with approximately 10 times the number of controls.

Patients diagnosed with cancer at the time of the thromboembolism had a higher risk of distant metastasis (44%) when compared to controls (35%). For those diagnosed within one year, the risk was 39.6% compared to 32%. For those diagnosed after one year, the risk of distant metastasis was not significantly higher. A comparison of mortality showed similar results. In the first group, the one-year mortality was 78% in cases compared to 64% of controls. The mortality ratio was 2.46 in the first year and 2.2 over the entire period. For patients in the second group, the one-year mortality was 62% in cases compared to 53% of controls. The mortality ratio was 1.35 over the first year and 1.3 over the entire period. The mortality rates for the third group were 47% in cases compared to 45% of controls. The mortality ratio was 1.08 for the first year and 1.1 thereafter. All differences up to one year were statistically significant at the *P* less than 0.05 level.

Sorensen and colleagues conclude that patients diagnosed with cancer at the time of a thromboembolic event have a poorer prognosis and are more likely to have advanced disease. These risks are evident if cancer is diagnosed within one year of the event as well. These risks are not significant in those diagnosed after one year of the event. These findings may indicate that venous thromboembolism in a patient diagnosed with cancer suggests the presence of advanced and aggressive disease. Sorensen et al suggest that because there is evidence that the pathways of coagulation and tumor growth intersect, prolonged anticoagulation therapy may be of benefit in this population.

■ **COMMENT BY DAVID OST, MD,  
& DHEERAJ KHANNA, MD**

The increased risk of VTE in cancer patients is well known. There is growing evidence to support that patients with VTE are at higher risk for malignancy, especially within the first six months to two years.<sup>1-3</sup> This risk is present whether the initial event is a primary

deep vein thrombosis or pulmonary embolism.<sup>3</sup> Whether VTE will be the first manifestation of malignancy depends on the type of cancer. In a study by Monreal et al, VTE on presentation was found more often in prostate and pancreatic cancer, while it was more often a terminal event in malignancies of the lung, breast, uterus, and brain.<sup>4</sup>

The present study suggests that venous thromboembolism in patients with cancer is associated with more aggressive disease and a poorer prognosis. Aggressive cancer screening of patients who have idiopathic VTE has not been shown to be cost effective. However, prolonged anticoagulation may be of benefit.<sup>2</sup> ❖

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## Clinical, Biological, and Histologic Parameters as Predictors of Relapse in Ulcerative Colitis

ABSTRACT & COMMENTARY

**Synopsis:** Relapses of ulcerative colitis are common and may be predictable. Risk factors include youth, frequency of prior relapses, and increased plasma cells in rectal biopsies.

**Source:** Bitton A, et al. *Gastroenterology* 2001;120:13-20.

Ulcerative colitis is a disorder that commonly relapses, but exacerbations have not been predictable clinically. Bitton and colleagues find that younger age, multiple prior relapses (for women), and basal plasmacytosis on biopsies of the colon seem to predict early relapse. This could help optimize medical management of ulcerative colitis patients.

Seventy-four patients were closely monitored for up to a year (less if earlier relapse occurred). A variety of clinical and laboratory measures were collected.

Twenty-seven patients relapsed (19/42 women and 8/32 men). Risk factors for early relapse appeared to

include younger age, more prior relapses (significant only in the women), and basal plasmacytosis on rectal biopsy.

■ **COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG**

Ulcerative colitis is difficult to manage, and it is clear that some patients will require particularly aggressive intervention to achieve and maintain remission. Knowledge of the most important factors that might signal a particularly high risk of relapse could guide more “advanced” therapy to those patients most likely to benefit. ❖

## Pharmacology Update

### Nateglinide Tablets— Starlix (Novartis)

By William T. Elliott, MD, FACP,  
and James Chan, PharmD, PhD

**N**ateglinide is the newest oral agent for the management of type 2 diabetes. Nateglinide is a D-phenylalanine derivative, nonsulfonylurea that has a short duration of action similar to repaglinide (Prandin). These agents are taken at mealtime to stimulate the release of insulin—thus reducing mealtime blood glucose excursions. Nateglinide is marketed as Starlix by Novartis.

#### Indications

Nateglinide is indicated as monotherapy in patients with type 2 diabetes who have not achieved adequate glycemic control by diet and physical exercise and who have not been chronically treated with other antidiabetic agents. It is also indicated for use in combination with metformin. Nateglinide should not be initiated in patients who have been inadequately controlled on other agents that act by stimulating insulin secretion.<sup>1</sup>

#### Dosage

The recommended starting dose for monotherapy or in combination is 120 mg three times a day, 1-30 minutes before meals. A lower 60 mg dose may be used in patients who are near HbA1c goal when therapy is initiated.<sup>1</sup>

No dosage adjustment is required in patients with mild to severe renal impairment or mild hepatic impairment.<sup>1</sup> The drug is available in 60, 120, and 180 mg tablets.

#### Potential Advantages

Compared to repaglinide, the other marketed short-acting insulin secretagogue, nateglinide appears to have a lower incidence of hypoglycemia. In placebo-controlled trials, the frequency of hypoglycemia was 2.4% for nateglinide vs. 0.4% for placebo and 31% vs. 7% for repaglinide vs. placebo.<sup>1,2</sup> Short-acting secretagogues permit mealtime flexibility and reduce between meal and nocturnal hypoglycemia. The patient can skip a tablet if a meal is missed thus avoiding hypoglycemia, which could be problematic with a long-acting secretagogue such as glyburide. Insulin profiles after repaglinide or nateglinide reflect more closely those of nondiabetic patients.<sup>3,4</sup>

Nateglinide appears to be tissue specific. At concentrations that stimulate insulin secretion, nateglinide is least likely to inhibit cardiovascular potassium-dependent adenosine triphosphate (K [ATP]) channels in animal models compared to glyburide or repaglinide.<sup>5</sup>

#### Potential Disadvantages

Nateglinide appears to be less potent than repaglinide and glyburide for inhibition of K (ATP) channels.<sup>6</sup> Results from clinical trials reported by the manufacturer indicated a 1% point reduction in HbA1c compared to placebo in treatment-naive patients (mean baseline 8.1%) and 0.6% reduction nonnaive patients (baseline 8.5%).<sup>1</sup> There are no published comparative trials between nateglinide and repaglinide.

In general, sulfonylureas or repaglinide as monotherapy generally decrease HbA1c by 1.5-2%.<sup>7</sup> Nateglinide is only recommended for use in sulfonylurea-naive patients while repaglinide is not restricted to use in treatment-naive patients.<sup>1,2</sup> Nateglinide is a potential inhibitor of cytochrome P450 2C9 and may inhibit drugs metabolized by this isoenzyme. Nateglinide requires three times a day dosing, with each meal.

#### Comments

Nateglinide is a rapid and short-acting phenylalanine derivative that releases insulin from pancreatic beta cells by inhibiting the K (ATP) channels. It is a less potent inhibitor and the inhibition may be of shorter duration.<sup>6</sup> It restores early insulin secretion phase and post-prandial glucose excursion in type 2 diabetics.<sup>3,8</sup> As monotherapy, nateglinide is more effective in treatment-naive patients compared to previously treated patients.<sup>1</sup> The addition of metformin to nateglinide improves glycemic control compared to monotherapy in treatment-naive patients and is more effective than metformin alone in patients previously treated with glyburide.<sup>1,9,10</sup> Glycosylated hemoglobin reductions compared to placebo of up to 2 percentage

points have been reported with the combination.<sup>1,8</sup>

### Clinical Implication

Nateglinide offers an alternative to repaglinide as a rapid short-acting insulin secretagogue. Its lower potency may limit its use to treatment-naive mild diabetics or in combination with other drugs with a different mechanism of action such as metformin. Its primary advantage is a low incidence of hypoglycemia. The wholesale cost for nateglinide is about \$2.50 per day (120 mg 3 times a day) and is more expensive than repaglinide, about \$2 (1 mg 3 times a day). ❖

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## CME Questions

#### 14. Which one of the following statements is true?

- a. Patients have much greater drops in blood pressure when one drug is used than with the DASH diet.
- b. A 2 mm Hg drop in diastolic blood pressure results in a 15% decrease in the incidence of stroke.
- c. The dietary guidelines of the American Heart Association did not use the DASH diet results.

#### 15. Patients with idiopathic thromboembolism and cancer should:

- a. receive aggressive anticoagulation.
- b. have an increased risk of death.
- c. have an increased risk of distant metastasis at the time of diagnosis.
- d. All of the above

#### 16. In the study by Samuelsson et al, which one of the following statements concerning urinary incontinence is true?

- a. Once established, urinary incontinence persists and progresses.
- b. Urinary incontinence is a dynamic condition with spontaneous remissions.
- c. During a five-year study period, approximately one woman in four developed urinary incontinence.
- d. Treatment with exogenous estrogens decreases the incidence of urinary incontinence.

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By Louis Kuritzky, MD

## Effects of Intercessory Prayer on Patients with Rheumatoid Arthritis

Numerous observational data sets acknowledge that religious involvement is associated with favorable health outcomes. However, the few studies that have examined religion as an intervention, (e.g., prayer) have had mixed results. The current study prospectively investigated the effect of intercessory prayer (IP), both direct-contact (in-person) and/or distant (no personal contact between subject and person(s) praying) upon 40 rheumatoid arthritis patients in a private rheumatology practice. Individual prayer sessions in which Christian ministers prayed aloud and touched affected body parts (2 h/d × 3) were enhanced in one group with distant prayer, in which ministers prayed at least 10 minutes daily for the patient, with whom they did not have additional contact.

IP was associated with significant increases in mean grip strength, reduction in number of tender and swollen joints, and improvements in patient pain, fatigue, and level of functional impairment. Supplemental distant IP had no additional statistically significant effect.

The study was not randomized or placebo controlled. IP was associated in this study with improvements in RA. Distant IP added no further benefit. The authors comment that the degree of improvement seen compares favorably with recipients of DMARD therapy. ❖

Matthews DA, et al. *South Med J* 2000;93(12):1177-1186.

## Nasal Carriage as a Source of *Staphylococcus aureus*

Both community acquired and nosocomial infections with *Staphylococcus aureus* (SA) are important causes of morbidity and mortality. Concern about progressively more difficult levels of antibiotic resistance has prompted investigation for opportunities to interrupt the cycle of infection. It has already been determined that SA colonization is the primary source of SA infections in hospitals, and as many as 40% of hospitalized persons harbor SA as nasal carriers. Though interventional trials have shown that elimination of SA from nasal carriers reduces the frequency of SA hospital infection, such studies did not use modern molecular methods to define the correlation between nasal carrier and clinical infection strains.

In the first part of this two-segment study, nasal swab cultures were immediately obtained from all patients in 32 hospitals who had blood cultures positive for SA, and genotyping was performed if SA positive. The second segment of the study consisted of prospectively obtained nasal cultures from hospital patients; in those who subsequently developed bacteremia, analysis was done to confirm if the same strain was involved.

In both segments of the study, more than 82% of isolates from blood were identical to those obtained in nasal cultures. von Eiff and associates conclude that elimination of nasal SA carriage may prevent subsequent SA infections. ❖

von Eiff CV, et al. *N Engl J Med* 2001; 344:11-16.

## Transurethral Resection of the Prostate: Failure Patterns and Surgical Outcomes

Alpha-antagonists (e.g., doxazosin, tamsulosin, terazosin) have become the mainstay of therapy for most symptomatic men with lower urinary tract symptoms due to benign prostatic hyperplasia (BPH). Unfortunately, not all men respond to alpha-antagonist (AA) treatment, and must often be treated surgically. This report details results of a retrospective chart review of three years of data on men at the Department of Urology, Ochsner Clinic, in New Orleans, La. Study subjects were divided into two groups: group 1 had undergone transurethral resection of the prostate (TURP) after failure of AA therapy; group 2 had undergone TURP for symptomatic BPH but had not undergone AA therapy.

Outcomes in Group 2 were better than Group 1: persistent irritative voiding symptoms, new stress incontinence, and chronic urinary retention appeared more often as persistent problems in Group 1. Complete resolution of symptoms occurred more frequently in group 2 (92% vs 71%). Contrary to popular wisdom, prostate size did not contribute to relative success or failure of therapy. Blanchard and associates counsel that men who fail AA treatment should be informed that surgical results for them might not be as good as for other candidates. ❖

Blanchard K, et al. *South Med J* 2000; 93(12):1192-1196.