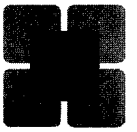

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Tailoring antihypertensive therapy in 1991

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■ Tailored care will increasingly become the hallmark of treatment for patients with hypertension in the 1990s. In mildly hypertensive patients, treatment should begin with nonpharmacologic approaches to lower blood pressure and reduce the patient's cardiovascular risk profile. The ever–increasing array of antihypertensive drugs and drug classes will enable clinicians to select agents based on the advantages and disadvantages for a particular patient, while continuing to move away from the rigid guidelines of stepped care. Physicians more often will base their choice of antihypertensive therapy not on safety and efficacy alone, but rather on the safety and efficacy of the drug in long-term care and the impact of therapy on quality of life.

□ INDEX TERMS: HYPERTENSION, THERAPY □ CLEVE CLIN J MED 1990; 58:277–284

FEW CLINICIANS today would disagree that treatment of patients with moderate or severe hypertension is important, based on the significant and well–documented decline in annual morbidity and mortality from cardiac disease and stroke in treated individuals.

Physicians are not as united in their thinking about the importance of aggressive treatment in patients with mild hypertension, those whose diastolic pressures are between 90 and 105 mm Hg. The resulting annual decline in morbidity and mortality from cardiac disease is relatively small for mildly hypertensive patients and the majority do not have target organ damage. However, since 85% of the 60 million Americans with hypertension have mild hypertension, even a 0.1% reduction in morbidity and mortality from cardiac disease and stroke would mean that 40,000 to 60,000 persons with mild hypertension stand to benefit from aggressive treatment.[1]

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MANAGEMENT OF MILD HYPERTENSION

Treatment of the patient for any degree of systolic and/or diastolic hypertension should include nonpharmacologic means that address the multiple risk factors for cardiac disease. In addition to lowering blood pressure, patients should be encouraged to reduce their total cholesterol intake to 200 mg/day or less, to discontinue cigarette smoking, and to reduce their weight to at least within 15 to 20% of the ideal body weight. Diabetic patients should be advised to control hyperglycemia strictly because of evidence suggesting that this can delay the progression of vascular complications.

A regular program of aerobic exercise can induce a modest reduction in systolic and diastolic blood pressure. Relaxation techniques may also have a beneficial effect. Relaxation techniques have not been studied in rigidly controlled clinical trials; however, non-controlled studies suggest that stress management may be important in the overall management of hypertension.[2]

TABLE 1
THE OPTIMAL ANTIHYPERTENSIVE AGENT

Once-a-day dosage
Few side effects (quality of life)
Subjective
Biochemical
Compatibility with other antihypertensives and other drugs
Treat concomitant diseases
Freedom from serious side effects
Long-term blood pressure-lowering effect regardless of age or race
Improve the hemodynamic abnormality

For mildly hypertensive patients, particularly those with diastolic blood pressures between 90 and 94 mm Hg who have no complications and few other risks for cardiovascular disease, the total cardiovascular risk should be assessed, and blood pressure should be monitored every 3 to 4 months. Initially these patients should be given the choice of using either drug therapy or nondrug intervention. But if their blood pressure continues to rise, or if any target organ damage is suspected, drug therapy should be started. Most clinicians in the United States follow this approach for patients with mild hypertension.

The recommendations of the World Health Organization and the International Society of Hypertension are somewhat more conservative for patients with diastolic blood pressures between 90 and 100 mm Hg who have a low cardiovascular risk profile.[3] According to their recommendations, these patients may be managed without drugs for 6 months. If blood pressure is not controlled at this point, they recommend pharmacologic therapy be initiated. For mildly hypertensive patients with a high cardiovascular risk profile, they recommend that nonpharmacologic means of treating hypertension should be tried for at least 3 to 6 months before drug therapy is initiated.

SELECTING DRUG THERAPY: CRITERIA

As recently as 10 to 15 years ago, when only a few drugs were available for the treatment of hypertension, the emphasis in selecting a drug was its ability to control hypertension safely and effectively. The concept of stepped care was promoted to provide guidelines for a systemic approach to hypertension management at a time when drug therapies were limited.

The development of newer classes of antihypertensive drugs and multiple drugs within those classes with a demonstrated ability to safely control hypertension has broadened the choice of treatment, particularly for patients with mild to moderate hypertension. Today the emphasis in choosing a drug has switched from safety and efficacy to issues centering on long-term compliance and quality of life. The reason is that adverse effects are the single most common reason why patients stop taking antihypertensive drugs, and why they are often lost to continued supervision and management of their hypertension.

The fourth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC IV), published in 1988,[4] recommended that better use be made of nonpharmacologic approaches to management of hypertension. If nonpharmacologic approaches were ineffective, then an initial therapy was recommended from one of four classes of antihypertensive agents: diuretics, beta blockers, calcium-channel blockers, or angiotensin-converting enzyme (ACE) inhibitors.

Although it was published only 3 years ago, this approach is already considered by many to be too restrictive. Today, in addition to the four drug classes mentioned in JNC IV, any of the currently available antihypertensive agents will control blood pressure in selected cases, and these agents should be considered as initial therapies. Among these are the combined beta- and alpha-blocking drugs or blocker-dilators such as labetalol, and the newer celiprolol, now in clinical trials; the central agonists such as clonidine and guanfacine; the alpha-1 blockers including prazosin, terazosin, and doxazosin; and any other available antihypertensive agent.

The response to the initial choice of therapy is usually evaluated over a 1- to 3-month interval. If the response is inadequate, the physician then has the option of increasing the dose of the drug if it is below the maximum recommended, adding an agent from another class, or discontinuing the initial choice and substituting a drug from another class. Combining antihypertensive drugs with different modes of action will often allow control to be achieved with small doses of drugs, thereby minimizing the potential for dose-dependent side effects. When additional drugs are added and the combination controls blood pressure, later attempts can be made to reduce the dose and, if possible, to eliminate the initial drug.

Desirable characteristics

Although the optimal antihypertensive drug has not yet been developed, many of the available drugs meet an impressive number of the desired criteria (*Table 1*). In selecting an initial antihypertensive agent, a drug that approaches the optimum should be selected.

The optimal drug should be long-acting so dosage can be once a day, with few subjective and/or biochemical side effects that interfere with the patient's quality of life. It should be compatible with other antihypertensive agents used in combination therapy, and with any other drugs that the patient is taking. On an average, 55- to 65-year-old patients with hypertension are taking five or six medications for a variety of medical and/or surgical problems.

The optimal antihypertensive drug should have some beneficial effects on concomitant diseases. It should not produce serious adverse effects (and most currently available agents do not). Finally, the ideal agent should lower blood pressure adequately over the long-term, regardless of the patient's race or age. Some currently available drugs act differently based on age or race, and this can be a consideration in tailoring therapy.

The ideal antihypertensive agent should reduce afterload and lower peripheral vascular resistance, which is the primary hemodynamic abnormality in most hypertensive patients.

In approximately 50% of patients with mild to moderate hypertension the initial drug prescribed will control blood pressure. Any two agents used in combination (provided they are not in the same drug class) will control blood pressure in 85 to 90% of all patients with mild to moderate hypertension.

TABLE 2
FACTORS TO CONSIDER IN TAILORED CARE

1. Prior experience and efficacy of therapy
2. Concomitant diseases: potential benefit *vs* contraindications
3. Concomitant drugs: potential for drug-drug interactions
4. Other risk factors: carbohydrate intolerance, elevated lipids, gout
5. Age: young *vs* elderly
6. Sex: few gender differences
7. Race: response of blacks *vs* whites
8. Level of recreational or physical activity

ANTIHYPERTENSIVE DRUGS: THE MAJOR CLASSES

Each of the drug classes of antihypertensive agents recommended by JNC IV will continue to be useful, and each of the classes has certain attributes that should be considered in tailoring therapy to the individual patient. The movement today is to select initial and subsequent antihypertensive therapy according to the patient's age, race, other risk factors, and concomitant illnesses, as well as other pharmacologic agents the patient is taking (*Table 2*).

Diuretics

Diuretics will continue to be useful in the management of arterial hypertension. According to data from multiple clinical trials,[5–7] diuretics are particularly effective in blacks and in the elderly, although they are also effective in younger whites. Diuretics are the only class of antihypertensive agents that are natriuretic. They are indicated for any hypertensive patient with a tendency to retain fluid, including those with parenchymal renal disease and retention of sodium and water with or without edema, and those with hypertension complicated by poor cardiac function and congestive heart failure. Control of hypertension would be difficult in these patients without the aid of diuretics. Women with premenstrual edema will also benefit from small doses of diuretics.

Patients who take diuretics run the risk of hypokalemia, and diuretics should be used with caution in the hypertensive patient with coronary artery disease or cardiac ectopy because of this risk and because of concerns that diuretic use increases the patient's risk for coronary ischemia and/or ectopy and sudden cardiac death.

Most data suggesting that diuretics increase the risk of hypokalemia and cardiac ectopy are from clinical trials in which much higher doses of diuretics were used than are used today.[8] The movement toward use of lower doses of diuretics has reduced the risk of hypokalemia and probably also the risk of cardiac ectopy and arrhythmias associated with these drugs.

Warnings concerning the effects of diuretics on glucose intolerance and on hyperlipidemia will persist until these issues are resolved by large-scale clinical trials. A further caution on the use of diuretics is that they should not be used as initial therapy in any patient with a personal or family history of gout.

Beta blockers

Beta blockers are the only class of antihypertensive drug that protects patients from a recurrence of myocardial ischemia[9,10] and/or sudden death. In addition to being used to treat hypertension, beta blockers are also antianginal and antiarrhythmic, so their use may be beneficial for the hypertensive patient with angina or ectopy.

Beta blockers also control symptoms of concomitant illnesses such as migraine, anxiety, glaucoma, and central nervous system tremor. Hypertensive patients who have any of these illnesses may benefit from the use of beta blockers. Beta blockers suppress renin and

TABLE 3
EFFECTS OF SELECTED CALCIUM-CHANNEL BLOCKERS ON CARDIOVASCULAR PARAMETERS

	N	V	D	I
Vasodilation	↑↑↑	↑	↑↑	↑↑↑↑
Heart rate	↑ (acute) 0 (chronic)	↓	↓↓	0
AV conduction	0	↓↓↓	↓↓	0
Contractility	0	↓↓	↓↓	0

N = nifedipine; V = verapamil; D = diltiazem; I = isradipine

have been useful in the management of patients with renovascular hypertension, particularly those with unilateral kidney disease, although they may also be effective in bilateral disease. They may also be effective in hypertrophic cardiomyopathy.

On the negative side, beta blockers would not be a good choice for treatment of patients with hypertension and congestive heart failure or poor left ventricular function because their use decreases cardiac output. All beta blockers may induce bronchospasm and decrease forced expiratory flow in 1 second (FEV_1). Therefore, they should not be used as the initial antihypertensive drug in patients with chronic obstructive pulmonary disease (COPD) or asthma, even if it is controlled by medication. Beta blockers can affect glucose tolerance and so are not a good choice for the hypertensive patient with diabetes. They are also associated with increases in lipid levels. Use of beta blockers in patients with hypertension and concomitant variant angina or coronary spasm, Reynaud's phenomenon, or peripheral vascular disease and claudication may worsen these coexisting illnesses.[11,12] Short-term use of beta blockers may lead to increased peripheral resistance. When beta blockers are used for long periods, they do not cause significant long-term afterload reduction or peripheral vasodilation.

In some hypertensive patients, use of beta blockers (particularly the lipophilic agents) may induce depression, insomnia, and nightmares.

Angiotensin-converting enzyme inhibitors

ACE inhibitors have become very widely used for the treatment of hypertension, as well as for treatment of congestive heart failure. Certainly any patient with hypertension and congestive heart failure is an excellent candidate for ACE inhibitors as initial or subsequent therapy.

Early trials of ACE inhibitors showed that they were particularly effective in younger patients with hypertension,[6,13] and more effective in whites than in blacks. However, more recent trials have shown that many older hypertensive patients respond well to ACE inhibitors.[5,14,15]

ACE inhibitors have proved effective for management of all degrees of hypertension, including as monotherapy in selected patients with mild to moderate arterial hypertension.

ACE inhibitors have a demonstrated ability to reduce afterload. They suppress renin-stimulated production of angiotensin II, a potent vasoconstrictor. Thus, they are useful in the treatment of renovascular hypertension, particular in patients with unilateral disease in whom renal function is essentially normal. Intrarenal hemodynamic changes induced by ACE inhibitors may reduce the glomerular filtration rate, particularly glomerular permeability to proteins. The actions of these agents may slow the progression of renal disease in the diabetic patient with nephropathy,[16–19] and possibly in various other renal parenchymal diseases associated with a progressive loss of renal function, particularly diseases that lead to heavy proteinuria.

ACE inhibitors should be used with caution in patients with bilateral renal artery stenosis or severe unilateral renal artery stenosis. Numerous reports[20,21] tell of sudden, rapidly progressive renal failure in patients with these conditions who were given ACE inhibitors. This acute renal failure is reversible. Nevertheless, it might be wise to screen older patients with generalized atherosclerosis and evidence of occlusive disease in other arteries to determine if they have renal artery disease before considering ACE inhibitor therapy.

In any patient whose glomerular filtration rate is down in the range of 10 to 30 mL/min, use of ACE inhibitors may lead to further deterioration in renal function. In diabetic patients, especially those with renal insufficiency, use of ACE inhibitors may increase the likelihood of hyperkalemia because of the effects of ACE inhibition on plasma potassium levels.

Calcium-channel blockers

Calcium-channel blockers were available for a decade for use as both antianginal and antiarrhythmic agents before they gained approval in this country for the treatment of hypertension. Calcium-channel blockers are vasodilators. They are a good choice as initial therapy for the hypertensive patient with coronary artery disease and angina, or for the hyperten-

sive patient with variant angina and evidence of cardiac arrhythmias (*Table 3*). Cardiovascular effects differ among the subtypes of calcium blockers. They may be beneficial for the patient with claudication or for patients with both hypertension and Raynaud's phenomenon.

In considering the use of calcium-channel blockers with an eye to treatment of concomitant diseases in the hypertensive patient, many patients will benefit from their action on migraine symptoms. These agents are also used extensively in patients with esophageal spasms and/or irritable bowel syndrome because of evidence that they decrease smooth muscle motility. At least one calcium-channel blocker, diltiazem, may exert a cardioprotective effect. While it may not offer primary protection against myocardial infarction, it may offer secondary protection to survivors of a myocardial infarction who do not have pulmonary congestion or congestive heart failure when therapy with diltiazem is initiated.[22] However, not all studies have reported such an effect.[23] And unlike beta-blockers, which can induce or worsen bronchospastic disease, calcium-channel blockers have been used successfully in patients with co-existing obstructive pulmonary disease and hypertension.

Some precautions are warranted in the use of calcium-channel blockers. Because of the negative inotropic effect exerted by calcium-channel blockers such as verapamil or diltiazem, they should be used with caution in patients with hypertension and marginal left ventricular function or mild congestive heart failure, since their use may exacerbate these concomitant conditions. Calcium-channel blockers undergo extensive hepatic metabolism, and for this reason they must be used cautiously in any patient with liver disease.

Because they undergo extensive hepatic metabolism, no adjustments in dosage of the currently available calcium-channel blockers are necessary for patients with impaired renal function. Furthermore, because they undergo extensive first-pass metabolism, oral doses of these agents must be much larger than parenteral doses. Patients who take these drugs show a wide range of plasma concentrations, so that oral doses must be titrated individually to achieve the best possible benefit from treatment.

Slow-release formulations of calcium-channel blockers are now available that can be taken once or twice daily, and these have extended their usefulness particularly as monotherapy in the treatment of hypertension. One of the benefits of monotherapy with calcium-channel blockers is the lack of postural effects. Blood pressure is lowered in the supine, sitting, and standing positions.

Calcium-channel blockers appear to be equally effective in black and white hypertensive patients. They can be useful in elderly patients with adequate cardiac reserve. These drugs have a potential advantage over diuretics, because they do not adversely affect lipid metabolism. They work well in several groups of hypertensive patients who are at least partially resistant to beta-blockers: blacks and the elderly, patients with cardio-pulmonary disease, and those with low-renin hypertension.

Combined alpha/beta blockers

Of those agents that exert pharmacologic activity on both alpha and beta receptors, labetalol, the prototype agent, has been used effectively to treat patients with all degrees of hypertension. It reduces peripheral vascular resistance without causing a substantial change in cardiac output, and with no change or a slight decrease in heart rate. Second-generation blocker-dilators celiprolol and medroxalol are currently undergoing clinical trials.

Labetalol is used as a single agent and in combination therapy. It is available in oral and intravenous forms and is useful in managing hypertensive emergencies. Labetalol is contraindicated in patients with bronchial asthma, overt congestive heart failure, heart block greater than first-degree, cardiogenic shock, and severe bradycardia.

Post-synaptic alpha-1 blockers

Post-synaptic alpha-1 blocking agents exert selective antagonism on post-synaptic alpha-1 receptors. Prazosin, terazosin, and doxazosin belong to this drug class. All three drugs have demonstrated efficacy in hypertension and congestive heart failure. Terazosin has a more gradual onset of action and a less variable duration of action than prazosin. Terazosin and doxazosin may be suitable for once-daily dosing, whereas prazosin requires twice-daily administration. Early clinical trials suggest terazosin may be effective intravenously in managing hypertensive emergencies.

INDIVIDUALIZED THERAPY: SPECIAL CONSIDERATIONS

The increasing experience with antihypertensive agents, based on clinical experience and research with the array of current and newly developed drugs, will allow us to tailor therapy to the individual patient by

TABLE 4
ANTIHYPERTENSIVE THERAPY IN ELDERLY PATIENTS: SPECIAL CONSIDERATIONS

Initial treatment with smaller doses
Increase dosages in smaller steps and at longer intervals
Use caution with drugs that may cause orthostatic hypotension
alpha blockers
combined alpha/beta blockers
guanethidine
diuretics
ACE inhibitors (in volume-depleted patients)

TABLE 5
RECOMMENDED ANTIHYPERTENSIVE THERAPY IN BLACK PATIENTS

Diuretics
Diuretics plus beta blockers
Diuretics plus ACE inhibitors
Combined alpha/beta blockers
Calcium antagonists
Centrally acting alpha-adrenergic agonists
Peripheral alpha blockers

taking into consideration such factors as age; race; concomitant diseases; potential benefits *v* contraindications; potential for drug interactions; and the effects of therapy on such things as carbohydrate intolerance and lipid metabolism.

Left ventricular hypertrophy

In the management of patients with hypertension, clinicians have grown interested in the use of afterload-reducing agents that have demonstrated an ability to induce a regression of left ventricular hypertrophy (LVH). This came about because of observational studies such as Framingham and others, which show a direct relationship between increasing LVH and an increased incidence of myocardial infarction and mortality from myocardial disease.

Some of the older antihypertensive agents are very effective in reducing blood pressure, and their use is associated with decreasing stroke rates, decreasing incidence of renal failure and congestive heart failure. But they do not induce regression of LVH because they induce reflex cardiac stimulation.

The beta blockers, calcium-channel blockers, ACE inhibitors, and central agonists such as clonidine and methyldopa promote regression of LVH in association with controlled blood pressure. This observation makes these agents more interesting in the treatment of hypertension. The data on diuretics are not as clear. Some data from clinical trials suggest that diuretics do not promote regression of LVH. Other studies suggest that chronic diuretic therapy is associated with a modest decrease in LVH.

Age and race

Experience has taught that hypertensive drugs must be used cautiously in black and elderly patients because of the heightened risk of unexpected adverse effects (*Tables 4 and 5*). Because of the sensitivity of elderly patients to antihypertensive therapy, it should be initiated at low doses and increased slowly. Diuretics and calcium-channel blockers work particularly well in elderly patients. In the elderly, any agent that may induce orthostatic or postural hypertension should be used cautiously. This includes agents that can induce volume depletion such as diuretics, the combined alpha/beta blocking agents such as labetalol, peripheral inhibitors such as guanethidine, and alpha blockers. Similarly, ACE inhibitors may induce hypotension if administered to a volume depleted patient.

In the black hypertensive patient, diuretics are particularly efficacious. Other effective agents include labetalol; the calcium channel-blockers; the centrally acting agents, clonidine and guanabenz; and the postsynaptic alpha-1 blockers, terazosin, prazosin, and doxazosin.

Studies[24,25] showed that beta blockers and ACE inhibitors were not as effective in lowering hypertension in blacks as they were in white subsets of hypertensive patients, but further experience demonstrated that combining a small dose of a diuretic with an ACE inhibitor or beta blocker provides a very effective treatment for hypertension in blacks.[6,26] The combination therapy eliminates any differences in therapeutic response attributable to race or age.

Concomitant disease

The potential effects of antihypertensive agents on concomitant diseases are diverse. COPD and asthma are common among hypertensive patients. Experience has demonstrated that use of any beta blocker in patients with COPD or asthma nay induce bronchoconstriction. Similarly, ACE inhibitors should be used cautiously in patients with COPD or asthma, because they may induce cough.

The antihypertensive agents that can be used safely in patients with COPD or asthma include diuretics, central agonists, alpha-1 blockers, and calcium-channel blockers. Certainly ACE inhibitors may be used in these patients if their use does not produce cough.

Drug interactions

Numerous potential drug-drug interactions must be considered when prescribing antihypertensive therapy. Use of diuretics will increase plasma levels of lithium, probably by inducing or increasing proximal tubular resorption.

The nonsteroidal anti-inflammatory agents inhibit prostaglandin and may therefore reduce the efficacy of diuretics and also hamper the efficacy of captopril and, possibly, other ACE inhibitors.

Concomitant use of tricyclic antidepressants decreases the antihypertensive action of agents such as clonidine, guanabenz, guanethidine and guanadrel, and possibly of methyldopa.

Concomitant use of cimetidine, an H_2 inhibitor, may affect the bioavailability of the lipophilic beta blockers that undergo hepatic metabolism. Concomitant use of cimetidine may also increase plasma concentrations of nifedipine, a calcium-channel blocker that undergoes hepatic metabolism.

Plasma levels of lidocaine, chlorpromazine, and warfarin will be increased by concomitant use of a lipophilic beta blocker since all these agents undergo hepatic metabolism and, during concomitant use, will compete for the same metabolic mechanisms in the liver.

The combined inotropic effects of quinidine and verapamil may induce pronounced bradycardia in selected hypertensive patients. Plasma levels of digoxin may be increased by concomitant use of certain calcium-channel blockers. Concomitant use of diuretics and digoxin may also lead to digoxin toxicity.

Lipid effects

The adverse effects of thiazides and beta blockers on lipid profiles will continue to influence clinicians in their decisions to select drugs from these classes as initial therapy.

Many drugs in other classes do not adversely affect lipid profiles. These so-called lipid neutral drugs include the blocker-dilator labetalol, the alpha-1 blockers, the alpha-2 central agonists (eg, clonidine, guanabenz), ACE inhibitors, and calcium-channel blockers (*Table* 6).

TABLE 6
EFFECTS OF ANTIHYPERTENSIVE DRUGS ON SERUM LIPIDS

	TC	TG	HDL	LDL
Thiazides	↑	↑	—	↑
Beta blockers				
without ISA	—	↑	↓	—
with ISA	—	—	—	—
Blocker-dilators	—	—	—	—
Alpha-1 blockers	↓	—	–or↑	–or↑
Alpha-2 agonists	↓	—	–or↑	–or↑
ACE inhibitors	—	—	—	—
Calcium blockers	—	—	—	—

TC= total cholesterol; TG= triglycerides; HDL=high-density lipoproteins; LDL= low-density lipoproteins; ISA= intrinsic sympathomimetic activity

FUTURE GOALS

Without a doubt, the 1990s will see an increasing use of ACE inhibitors and calcium-channel blockers, as well as more tailoring of antihypertensive therapy. As clinical experience with newly developed drugs grows, clinicians will be more effective in individualizing therapy. The goal of tailoring treatment, obviously, will be to control hypertension while reducing side effect profiles and optimizing quality of life.

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Corrections

In the article by Avashia JH, Walsh TD, Thomas AJ, Kaye M, and Licata A (*Cleve Clin J Med* 1990; **57**:636-638), reference 2 contained misspellings and should have read as follows:

2. Olsson AM, Jönsson G. Advanced cancer of the prostate combined with hypercalcaemia. Scand J Urol Nephrol 1977; **11**:293–296.

In addition, references 3–6 were cited in the text of the article but omitted from the list. The complete entries are provided as follows:

3. George AL Jr, Remler RB, Heim CR, Warner JJ. Hypercalcemia in carcinoma of the prostate: case report and review of the literature. J Urol 1987; **137(2)**:309–311.
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