Hypertension may be difficult to treat for multiple reasons. First, some patients have pseudoresistance, displaying high pressure readings only in the physician’s office from the “white coat” effect. Second, volume expansion, usually from inadequate diuretic therapy, is the most common reason for true resistance. A number of other mechanisms may be involved, which can usually be ascertained and overcome.

Introduction

Most hypertension will respond satisfactorily to the nondrug and drug therapies described in the previous two Executive Summaries. But most hypertensive patients are not under adequate control, as witnessed by the data from the most recent survey of a representative sample of the U.S. population (Table I). In the second phase of the third National Health and Nutrition Examination Survey (NHANES III) taken from 1991-1994, only 27.4% of those identified as having hypertension by either an elevated blood pressure or the current use of antihypertensive medication had their hypertension under control (defined as the average of 2 sets of 3 blood pressures below 140/90 mmHg) (1). As seen in Table I, this figure is far better than that found in 1976-1980 but represents some slippage in control from that noted 3 years previously. The lower overall prevalence of hypertension in 1991-1994 almost certainly reflects the greater
care taken in determining the blood pressure of these subjects with a possible contribution from an actual lowering of some people’s blood pressure by more widespread adoption of the lifestyle modifications described in the first Executive Summary.

The percentage of hypertensives receiving any treatment is close to half and again only about half of those on treatment are being well controlled.

Reasons for the Shortfall
Even in the very expensive and fairly sophisticated U.S. health care system, some third of hypertensives remain unaware of their diagnosis. Most of these patients are likely among the 40 million Americans who are uninsured, many in poverty and without access to any type of consistent health care. The failure of about 15% of hypertensives who are aware of their diagnosis to be receiving any treatment may also reflect the socioeconomic burdens of many Americans. But even in places such as England where a nationalized health system supposedly covers the entire population, a significant number of hypertensives remain on no or inadequate treatment.

Nature of Hypertension
The fundamental problem of patients receiving little or no treatment, even in societies where health care is supposedly universally available, likely reflects the basic nature of hypertension: a lifelong, chronic and incurable condition that remains asymptomatic for 15-20 years and whose treatment offers no immediate benefit but may induce bothersome side effects. I have often thought that the treatment of hypertension would be far more successful if uncontrolled high blood pressure caused some discomfort, reminding the patient of the need to remain on therapy.

Multiple Mechanisms for Resistance to Therapy
Beyond the very nature of the condition, there are a large number of reasons for failure to respond to therapy (2) (Table II). The term “resistance” is usually applied to the failure of the blood pressure to remain below 140/90 (or in those over age 65 to below 160/90) despite the prescription of 2 or more medications in usually effective doses. Some would insist that a diuretic be included among the drugs being used. As we shall see, inadequate diuretic therapy is among the most common causes of true resistance.

Pseudoresistance
The blood pressure may appear to be poorly responsive if the readings are exclusively taken in the physician’s office, a reflection of the “white coat” effect described in the first Executive Summary. Therefore, before additional therapy is given, the possibility of pseudoresistance should be considered, particularly in patients with high office readings but little or no target organ damage as would be expected with truly resistant hypertension. In such patients, home readings and, if available, confirmatory ambulatory recordings should be obtained (3) (Fig. 1). If they are also elevated, true resistance is present and should be more aggressively treated. However, in some series, as many as half of such patients turn out to have well controlled hypertension by readings outside the office (4), so more therapy for them could lead to symptomatic hypotension.

Nonadherence to therapy
Patients may not take their medications for many reasons, some the fault of the medications, others the fault of the providers, still others the fault of the patients (Table II). Providers must share a large part of the blame, i.e., prescribing multiple daily doses of medications that cause significant side effects. Fortunately, it is possible to use one or more medications on once-daily basis that will provide smooth and persistent control of the blood pressure, without invoking bothersome side effects. As noted in the second Executive Summary, this may involve the combination of long-acting ACEIs and CCBs along with at least a small dose of a diuretic.
Table II: Causes for inadequate response to therapy.

**Pseudoresistance**
- White coat or office elevations
- Pseudohypertension in elderly

**Nonadherence to therapy**
- Side effects or costs of medication
- Lack of consistent and continuous primary care
- Inconvenient and chaotic dosing schedules
- Instructions not understood or inadequate patient education

**Drug-related causes**
- Doses too low
- Inappropriate combinations (e.g., two centrally acting adrenergic inhibitors)
- Rapid inactivation (e.g., hydralazine)
- Drug interactions
- Nonsteroidal antiinflammatory drugs
- Sympathomimetics
- Nasal decongestants
- Appetite suppressants
- Cocaine
- Caffeine
- Antidepressants (MAO inhibitors, tricyclics)
- Oral contraceptives
- Adrenal steroids
- Liquoric (e.g., chewing tobacco)
- Cyclosporine or tacrolimus
- Erythropoietin
- Cholestyramine
- Excessive volume contraction with stimulation of renin-aldosterone
- Hypokalemia (usually diuretic-induced)
- Rebound after clonidine withdrawal

**Associated conditions**
- Smoking
- Increasing obesity
- Sleep apnea
- Insulin resistance/hyperinsulinemia
- Ethanol intake more than 1 ounce (>3 portions) a day
- Anxiety-induced hyperventilation or panic attacks
- Chronic pain
- Intense vasoconstriction (Raynaud’s, arteritis)

**Secondary hypertension from any cause**
- (including renal insufficiency)
- Volume overload
- Excess sodium intake
- Progressive renal damage (nephrosclerosis)
- Fluid retention from reduction of blood pressure
- Inadequate diuretic therapy

**Drug-related causes**
The most common of these is likely interference with the efficacy of the antihypertensive drugs by their interactions with other agents taken simultaneously for other conditions. Nonsteroidal antiinflammatory drugs (NSAIDs) are the most common culprits, interfering with the efficacy of most antihypertensive agents (with the probable exception of CCBs) (5). A number of other agents may also be responsible, including sympathomimetics used to reduce appetite, relieve nasal congestion or provide euphoria.

A particularly difficult interaction is often seen in transplant recipients who take cyclosporine or tacrolimus for immunosuppression. Fortunately CCBs are usually effective, while at the same time reducing the doses of cyclosporine required.

**Associated conditions**
Virtually no antihypertensive regimen can bring the blood pressure down in a patient who is obese and continuing to gain weight, thereby certainly affected by hyperinsulinemia from insulin resis-

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**Fig. 1. Evaluation of resistant hypertension.** (With permission from Pickering, T.G. Blood pressure monitoring outside the office for the evaluation of patients with resistant hypertension. Hypertension 1988, 11 (Suppl. II): II96-100. Copyright American Heart Assoc.)
tance and possibly affected by obstructive sleep apnea as well. If smoking and excessive alcohol intake are added to the obesity, the situation may truly be untreatable.

When difficulty in treating hypertension is noted, particularly in patients who are most concerned about their condition, a great deal of anxiety may arise. As a consequence, anxiety-induced hyperventilation is frequently experienced, the symptoms further adding to the underlying anxiety and the vasoconstriction adding to the hypertension (6) (Fig. 2). If this syndrome is recognized by a period of voluntary overbreathing, the condition explained, and the use of rebreathing into a paper sack demonstrated as a way to relieve the symptoms, a great benefit may be provided.

Secondary hypertension
Most of these known causes of hypertension can be easily identified by readily available diagnostic procedures (Table III). If the initial screening studies are abnormal, additional confirmatory tests should be obtained. Depending upon the physician’s expertise and experience, referral to a hypertension specialist may be appropriate for these additional studies.

Of those listed in Table III, renovascular hypertension is the most common in truly resistant patients and not as easily recognized as the others by simple routine physical examination or routine laboratory workup. Therefore, a screening test, usually a captoprilenhanced isotopic renogram, should always be obtained in patients whose resistance is not easily explained. In those with severe, life-threatening hypertension, a renal arteriogram is usually indicated since screening studies are falsely negative in up to 15% of patients with renovascular hypertension (7).

Volume overload
In serious resistant hypertension, the most common cause is volume overload, usually from inadequate diuretic therapy superimposed on the other factors that may lead to volume excess in treated hypertensives, as shown in Table II (8). Therefore, if an adequate dose of a long-acting diuretic agent is not being used, one should be provided. For those with good renal function (serum creatinine <1.5 mg/dl), a thiazide should be adequate. For those with renal insufficiency, a long-acting loop diuretic such as torasemide taken once daily is usually better than the 2 or 3 daily doses of furosemide needed to maintain slight volume contraction. Metolazone is an excellent alternative which will work in a once-daily dose, even in the presence of significant renal insufficiency.

Conclusions
Most causes for resistance to hypertensive therapy can be identified and overcome. The best course is to avoid resistance by applying the vari-
ous guidelines for the evaluation and therapy of hypertension described in these Executive Summaries (Table IV).

References