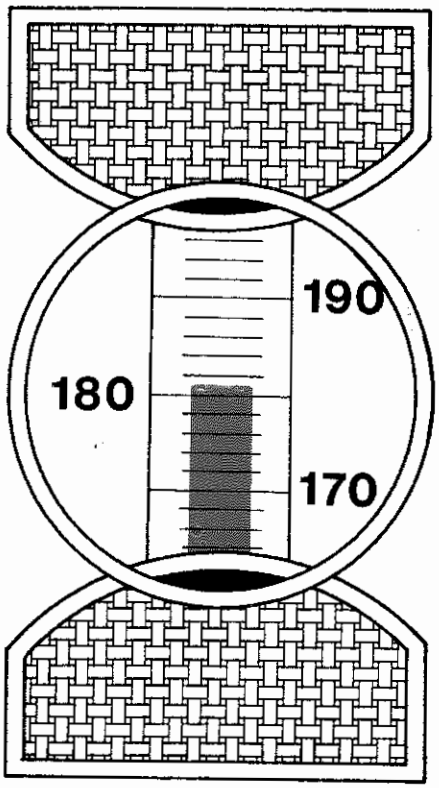
Management of the Patient with Uncomplicated Hypertension: An Update



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In this first of a series of three articles dealing with hypertension, a comprehensive but simple approach is advocated for the management of hypertension in patients without major complicating factors. Drugs discussed are in groups: the diuretics, the adrenergic inhibiting agents, and the vasodilators. The next article in this series will deal with common complications found in our hypertensive population, and how their treatment programs can be modified appropriately.

Who has not been caught up in the recent national surveys designed to identify persons with unknown hypertension? The American Heart Association, the National Institutes of Health, the Public Health Departments, and many lay groups cooperated to make May 1975 a hypertension screening month. An enormous effort and considerable enthusiasm (especially on the part of our lay colleagues) went into this, and the results at this early time appear very encouraging. In conjunction with the surveys, there has also been a real effort at public and physician education on the need for blood pressure control. This was not a one shot effort, since there will be a continuation of screening with the intent that all physicians' and dentists' offices will become centers for detection. Perhaps our state of Nebraska was typical. We estimated that there are 140,000 to 224,000 persons (10 to 16 percent) with hypertension in the state whose population is 1,400,000. The survey effort was enthusiastic, but only approximately 30,000 persons came for screening, which nevertheless was considered a satisfactory turnout. The number of persons with hypertension was on the order of 5,000, while a conservative estimate of the prevalence of hypertension in this state would be 30 times that amount.

The success of such surveys will eventually center on efforts of primary care physicians and their teams to make a strong treatment follow-up. Frankly, in the past follow-up has often been haphazard and there are skeptics who believe mass screening surveys may be premature and ill-advised.[1] Screening is only the first step; the real task is in the follow-up. The comprehensive approach suggested here will say little about detection, but will emphasize an appropriate "patient-oriented" work-up and a balanced, sustained treatment.

Three General Concepts for the Family Physician

First, it is generally agreed that hypertension is a serious, lifelong

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problem and one wonders why it is difficult *to find* persons with hypertension and *to treat* them. Fortunately, both diagnosis and treatment are generally simple but the major problem is that hypertension is mostly a chronic, asymptomatic disease in which patient adherence as well as physician adherence are apt to be poor, and in which therapy may make the patient feel worse, not better.

Secondly, it seems obvious that in the past too much emphasis has been placed on extensive work-up of hypertension and too little on its therapy.[2] Hypertension is chiefly a disease of middle age, although it is being recognized more and more frequently in adolescence.[3] Once the patient with hypertension becomes a senior citizen, surgical management becomes less and less frequent, but the proper drug management can become even more important and must be more carefully adjusted. The concept has been well accepted that if the typical middle-aged patient responds readily to drug management, there is no pressing need for detailed laboratory search for underlying disease causes of the hypertension. On the other hand, if the patient does not respond to simple drug programs, then further study for secondary causes of the hypertension is warranted.

Thirdly, it is being recognized that we as doctors are in partnership with our patients and their families, and if they lack follow-through on medication, it is as much our responsibility as theirs. The need for reminders to patients to return for their scheduled appointments and for frequent blood pressure checks must become as routine as reminders sent out for dental checks and Pap smears. Too often primary care physicians do not follow up if a patient with hypertension misses an appointment. Fortunately, in 1975 there has been renewed emphasis given to the *flow sheet* with a means whereby a physician and patient can tell at a glance what the blood pressure responses have been, how effective the medication is, and what problems have occurred (Figure 1).

What to do When a Patient with Newly Discovered Hypertension Comes to Your Office

The first task, of course, is to decide if there is persistent hypertension and to make at least an educated guess as to whether there is underlying kidney, heart, brain, or endocrine disease by means of a careful history and physical examination and simple screening laboratory tests. A complete blood count, urinalysis, blood sugar, creatinine, uric acid, chest x-ray, and electrocardiogram suffice for baseline studies for most patients. Is the hypertension of an established or labile nature? How well is the patient educated as to the nature of the disease? Should the patient or his nearest friend or relative record his blood pressure at home? These are simple questions for which the answers are usually easy if addressed by the physician. It need only be stated here that if the blood pressure is elevated on several visits, then the treatment need not be delayed further. All hypertension, even labile hypertension, should be treated, particularly in the younger patient, or if it is not treated, then careful follow-up should be made at appropriate intervals of three to six months, or even more frequently.

In 1975 What are our Major Antihypertensive Drugs?

Here the physician should think in threes. Antihypertensive drugs may be classified as: (1) diuretics, (2) adrenergic inhibiting agents, and (3) vasodilators. Hypertension is treated with one or more of these three classes of drugs, but in general no more than one drug is used in each classification. The diuretics form the base of almost all drug regimens, despite the tendency of the blood renin level to rise after diuretics are administered. A number of studies now have shown that despite such rise, no adverse effects can be seen from that rise and that whether the renin is initially high or low, the blood pressure response appears to be very similar. In a subsequent report, the implications of high versus low plasma renin activity and the possible management of the former with drugs of the propranolol-hydralazine group will be considered.

Diuretics

Diuretic drugs are the foundation upon which most all antihypertensive regimens are based. In patients with mildly elevated blood pressure, no other therapy may be required. The effectiveness of diuretics seems to depend on a reduction of the plasma volume and the creation of a slightly negative sodium balance, despite the fact that there are a number of mechanisms working in a homeostatic manner to restore sodium and water balance to pre-treatment state. Volume depletion activates the renin-aldosterone system, and the enhanced aldosterone secretion then tends to inhibit sodium excretion.

The patient may have a high salt intake and thereby exhibit resistance to diuretics. A "no added salt to the cooked food" diet is recommended for almost all patients with essential hypertension. If the clinician suspects that excessive salt ingestion is occurring, such as a seeming resistance to diuretics, the matter can be settled by history or by measuring a 24-hour urinary sodium excretion. Diuretics need not be stopped for this test if the patient's weight is stable, since salt and water balance is almost certainly present in the absence of weight fluctuations. Urinary sodium levels in excess of 100 mEq/day indicate a salt intake of greater than 5 gm daily, and suggest that salt restriction is indicated rather than increasing the dosage of the drugs or adding other antihypertensive agents. We use collection of 24-hour samples of urine in almost all our patients. We have found that the discipline of its collection is helpful in encouraging the patient to adhere to our program. It has the added dividend of allowing us to measure the creatinine clearance, and the 24-hour protein excretion, an easy way to estimate the kidney status regarding possible nephrosclerosis.

A very large number of diuretic agents are available, but they can be classified into three subgroups: (1) the thiazides, (2) the potassium-sparing diuretics, and (3) the loop diuretics. Combinations of diuretics using members of these various subgroups may be desirable on occasion, but little is to be gained from the use of more than one member of a single subgroup.

The *thiazides*, along with chlorthalidone (Hygroton), have a rather flat dose-response curve. That is to say, the difference between the minimum effective and the maximum effective dose may be in a range of only four-fold to six-fold. In the case of

hydrochlorothiazide, this would be from 25 to 200 mgm/day, beyond which no useful hypotensive or saluretic effect is seen, though side-effects may increase. It may be useful to start with smaller doses, gradually increasing the dose over a month's time, thus avoiding abrupt fatigue and dehydration which are apt to occur when large doses are given initially. All drugs of the thiazide-chlorthalidone family share the same three faults: they produce unwanted potassium losses in the urine, elevation of the blood sugar, and elevation of the blood uric acid. Their cost is approximately the same. The choice among them might be based on their duration of action, which varies from 6 to 12 hours (hydrochlorothiazide) to over 24 hours (chlorthalidone, methylclothiazide, polythiazide, etc). None of this group of diuretics works effectively in patients who have moderate or advanced renal failure with low glomerular filtration rates. A serum creatinine in excess of 2 to 3 mgm/dl (approximately equivalent to a BUN of about 30 to 50 mgm/dl) is an indication to choose a more potent (loop) diuretic such as furosemide (Lasix) or ethacrynic acid (Edecrin).

There is controversy over whether or not to treat the hypokalemia produced by diuretics. Actually, the serum potassium seldom falls below 3 mEq/l in patients with uncomplicated hypertension on full doses of thiazides, and serum potassium levels lower than this should suggest excessive aldosterone secretion, due either to an adrenal cortical tumor or hyperreninemia. However, it is well known that seemingly small decreases in serum potassium may reflect appreciable losses of total body potassium. While there are many exceptions, in general a serum potassium of 3 mEq/l represents about 100 mEq of total body potassium depletion, while a serum potassium of 2.5 mEq/l may reflect total body losses of 200 to 300 mEq. Clinical symptoms of fatigue, muscle weakness, and cardiac arrhythmias are usually absent until the serum potassium is below 3 mEq/l. If digitalis is being administered, mild hypokalemia becomes much more significant, and serious arrhythmias can be seen with serum potassium levels of 3.5 mgm/l or less. Almost routinely the physician should give supple-

Figure 1. University of Nebraska Hospital, Hypertensive Patient Flow Sheet

	Date						
Blood Pressure	Supine						
	Standing						
	Pulse						
	Weight						
Therapy							
Laboratory values	Creatinine						
	BUN						
	Na/K						
	Chol/TG						
	Uric Acid						
	Glucose						
	Chest x-ray						
	EKG						
	UA						
	IVP						
	Renin						
Clinical findings	Dizziness						
	Somnolence						
	Depr/Nasal Sx						
	Impotence						
	Heart Sds						
	Fundi						
	Next visit						

mentary potassium to patients receiving both diuretics and digitalis, unless renal failure is also present. The effects of chronic body potassium depletion are not known in humans, but animal studies have shown that severe hypokalemia may produce renal tubular lesions as well as skeletal and myocardial muscle degeneration.[4] Therefore, some clinicians believe that chronic hypokalemia of any degree is to be avoided. However, most physicians do not try to correct the hypokalemia unless serum levels fall to 3 mEq/l without digitalis therapy or fall to 3.5 mEq/l with digitalis therapy.

Correction of hypokalemia can be accomplished either by minimizing urinary potassium losses or by replacing them. One can reduce urinary losses either by (1) using diuretics which block tubular potassium secretion, such as triamterine (separately or incorporated into the capsule Dyazide), and spironolactone (Aldactone), or (2) decreasing the urinary sodium load, since tubular reabsorption of sodium involves exchange for either potassium or hydrogen ion. Of course, the urinary sodium load can be reduced appreciably by adherence to a "no added salt to the cooked food" diet, and this approach is adequate in many, if not most patients. Replacement of potassium lost in the urine is more difficult, since potassium chloride, and not the more palatable gluconate salts of potassium should be used. Hypokalemia produces metabolic alkalosis and unless potassium is administered as the chloride salt, metabolic correction will not occur. Recently KCl in a wax base has become available (Slow K or KAON-Cl). It is relatively inexpensive, seems to be well absorbed, and is relatively safe as compared to earlier potassium chloride tablets relating to ulceration of the small intestine.

There is controversy over whether the hyperuricemia induced by diuretics merits treatment. Hyperuricemia certainly should be treated in anyone with a past history of gout, uric acid stones, or who develops acute gout while on therapy. The anti-metabolite allopurinol (Zyloprim) (300 to 800 mgm/day in divided doses) is simple and effective in lowering uric acid levels in the blood and body. Some authorities suggest use of allopurinol whenever the serum uric acid level exceeds 9 to 10 mgm/dl, even in the absence of symptoms, while other authorities would ignore asymptomatic hyperuricemia which is diuretic-induced. Probenecid (Benemid) acts differently but is approximately as effective in reducing serum uric acid.

The mild hyperglycemic effect of thiazides may require an increase in hypoglycemic agents in diabetic patients, but thiazides seldom produce severe hyperglycemia. The hyperglycemic effect seems to be related to hypokalemia, with impairment of endogenous insulin release. Correction of hypokalemia is thus another way of attacking the hyperglycemia problem.

The *potassium-sparing diuretics,* spironolactone and triamterine, also have a rather restricted dose-response curve, with a range of about four to six-fold. These agents are seldom used as the sole diuretics, but are commonly used in combination with thiazides or loop diuretics, especially where hypokalemia is a problem. These agents by themselves do not produce elevations in blood glucose or uric acid. Spironolactone may be useful in place of thiazides in those few situations where hyperglycemia or hyperuricemia cannot be readily managed. In renal failure, not only are these agents ineffective but they may be dangerous, since severe hyperkalemia can occur. In such patients, concomitant use of these diuretics and potassium supplements may be hazardous because of the danger of hyperkalemia, hence frequent monitoring of the serum potassium, BUN or creatinine, and urinary volume is mandatory.

The *loop diuretics,* furosemide (Lasix) and ethacrynic acid (Edecrin) are characterized by steep dose-response curves, with a clinically useful range of about ten-fold. They are somewhat more expensive than the thiazides, and have a shorter duration of action which requires more frequent administration, and hence have not replaced thiazides for these hypertensive patients with good renal function. They also produce hypokalemia, hyperglycemia and hyperuricemia, sharing these disadvantages with the thiazides. Because of their greater potency, excessive contraction of the plasma volume may occur with rapidity, producing hypotension and acute deterioration of renal function. The major advantage of the loop diuretics over the others is that they are effective in patients with moderate renal impairment when given in larger doses, after the thiazides have ceased to be effective at any dose. However, with the very severe reduction of glomerular filtration rates which occurs in advanced renal failure, even the loop diuretics may be ineffective.

Adrenergic Inhibiting Agents

This next broad category of drugs useful in the treatment of chronic hypertension acts by depleting the body stores of norepinephrine and generally interferes with the action of norepinephrine. These agents reduce the blood pressure by impairment of the sympathetic nervous system function, centrally or peripherally. Their exact mechanisms of action are not always established, and need not be of great concern, since the clinical application of these agents is quite thoroughly understood. Most of these agents share the same side-effects but in varying proportions: diarrhea, bradycardia, orthostatic hypotension, lethargy, impaired sexual function in males (decreased libido, occasionally impotence, or retrograde ejaculation) and depression.

The oldest drug of this category is reserpine. It remains a very effective agent for some patients. It is inexpensive and long-acting, requiring only one daily dose. Its therapeutic range is 10 to 20-fold when given parenterally, but chronic oral administration should be restricted to 0.1 mgm/day since larger doses are more likely to produce psychotic depressions which can be life-threatening. Onset of depression may be delayed over a year after starting reserpine. Less serious side-effects troublesome to some patients are nasal stuffiness, bradycardia, and enhanced appetite; the latter being disadvantageous in the average obese patient with hypertension. The chief use of reserpine today is to continue its administration to patients whose blood pressure has been controlled satisfactorily with it in the past, and in those who need low-cost, once daily regimens. Recently three retrospective studies[5,6] have rather unexpectedly linked the administration of reserpine to the development of cancer of the breast in females. Another retrospective study similarly conducted failed to show such correlation.[7] In susceptible experimental animals, accelera-

tion of cancer growth can be demonstrated in reserpine treated animals, but this acceleration has been found also with phenothiazines. In any case, at present there is no reason to discontinue the use of reserpine because of a "cancer scare."

Methyldopa (Aldomet) is a very useful member of this group of adrenergic inhibiting drugs. It has a complex mode of action which may be related in part to the generation of false neurotransmittors centrally and peripherally within the adrenergic nervous system. It has a relatively short half-life, so administration two to three times a day seems desirable, and perhaps four times a day for maximum effect. The principle side-effects include drowsiness (especially initially), lethargy, and orthostatic hypotension. Hepatitis, drug fevers, and a positive Coombs test also may occur, but are infrequently encountered. The dose-response curve is about ten-fold, with starting doses of 250 mgm/day to over 2 gm/day in four doses at the maximum. This agent is expensive at high dose levels and side-effects are more frequent. If resistance seems to be developing to methyldopa, effectiveness can often be restored by adding or increasing the dosage of the diuretic agents.

Propranolol (Inderal) is a drug which is coming into great popularity in the treatment of hypertension, despite the absence of FDA approval for its use as an antihypertensive drug. Its mechanism of action in reducing blood pressure is still somewhat uncertain. It is clearly indicated in the hypertensive patient with angina pectoris. A combination of propranolol and hydralazine (a vasodilator) has become very popular because propranolol offsets the palpitation and tachycardia of hydralazine while both synergistically reduce the blood pressure. Propranolol is well tolerated by most patients but probably should be given in at least three daily doses, if not four, because of the rather short duration of its effect (four to six hours). Asthma is a recognized contraindication to its use, as is congestive heart failure. The dose-response curve of propranolol covers a range of 10 to 20-fold; it is commonly started at 10 mgm t.i.d. or q.i.d. and raised incrementally to 40 mgm t.i.d. or q.i.d. or more as needed.

Guanethidine (Ismelin) is the most potent sympatholytic agent now available, with the additional advantage of having a very long duration of action, permitting administration once a day. Its major disadvantage is that it can produce marked orthostatic hypotension, chiefly due to dilation of the veins. A side-effect seen in male patients is retrograde ejaculation of semen into the bladder, an effect which cannot be considered all bad if carefully explained to the patient! The dose-response curve of this drug is very broad, with starting doses of 5 to 10 mgm/day, increasing gradually to 150 mgm/day or even higher. The hypotensive effect must be gauged by measuring standing blood pressures (as well as supine), and the dose should not be increased at intervals shorter than one week, since the maximum effect of the previous dose-level takes time to occur. Gradual increases in dosage will also minimize the side-effects and make therapy more acceptable. The effect of guanethidine will be blocked by concomitant administration of tricyclic antidepressant medications (eg, Thorazine) by virtue of a peculiar pharmacologic interaction.

A number of new agents are being introduced which may be helpful. Clonidine hydrochloride (Catapres) seems to act centrally, has a broad dose-response curve, and produces some sedation along with other sympatholytic side-effects. One problem with this drug is that sudden withdrawal of the agent (as when a patient fails to renew his prescription) may precipitate a dangerous hypertensive crisis.

Vasodilators

The third group of drugs includes the vasodilators. Only one agent of this group is now available for oral use, namely hydralazine. (Diazoxide and sodium nitroprusside are very useful vasodilators parenterally, but not orally). Hydralazine has been in clinical use for many years, but it has produced tachycardia, aggravated angina pectoris, and could produce a lupus erythematosus-like syndrome when given in large doses, reversible on withdrawal of the agent. Tachycardia, palpitations, headache, and angina pectoris are side-effects related to enhanced reflex sympathetic tone, and those can be blocked effectively by the concomitant use of reserpine or propranolol. Lupus erythematosus-like manifestations usually can be avoided by not using over 225 mgm/day, since it is a dose-related side-effect. Hydralazine has a short half-life, and must be given at least three, and preferably four times daily. Despite these limitations, the drug is very useful in the patient with moderate and severe hypertension.

A Plan

The agents in these three groups, diuretics, adrenergic inhibiting drugs, and vasodilators, constitute our present "weapons" in the "war" against hypertension. The following guidelines are suggested for their deployment.

The patient with mild or borderline hypertension should be started on salt restriction and on modest doses of a diuretic, with serial observations of the blood pressure continued over several weeks. If hypertension persists, larger doses of diuretics may be given or methyldopa may be added. The patient with moderate hypertension will certainly require larger doses of diuretics and an adrenergic inhibiting agent, in addition to salt restriction, and these could be started on the first visit (after drawing the serum potassium specimen). Choose methyldopa in the patient who can afford it and if he is likely to accept multiple daily doses, with reserpine or guanethidine as alternatives especially in cases of limited finances, or in one who would be inconvenienced by multiple daily doses. The severely hypertensive patient with complications should be hospitalized, and more elaborate target organ assessment carried out. Obviously, the treatment program must be sustained, probably for the patient's lifetime, and this requires systematic follow-up of all the patients who fail to keep their appointments.

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