Clinical Evaluation and Differential Diagnosis of the Individual Hypertensive Patient
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The increasing emphasis on differential diagnosis in hypertensive diseases is a most heartening development, reflecting the growing recognition that high blood pressure is a sign that is common to a number of widely disparate physiologic dysfunctions, which are separately and differently treatable. What is particularly encouraging about this development is that it has, at last, penetrated the largest and least understood branch of the hypertensive population—that category known, in a virtual confession of ignorance, as "essential hypertension."

The case for heterogeneity in essential hypertension has long been made (or should have been made) by common clinical experience. Virtually every physician in office practice knows that the blood pressure reading is an unreliable indicator of the type, the severity, or the prognosis of hypertension. The universal medical experience is that many patients with spectacularly elevated blood pressure readings live a normal life span without serious health problems, whereas some with relatively mild hypertension succumb early to heart attack, stroke, or other cardiovascular incident. Only in broad statistical reference can it be stated that the higher the blood pressure, the greater the organ damage, the more severe the illness, and the shorter the survival (1–3).

The pharmacologic evidence for heterogeneity in hypertension, considering the varying response of patients to antihypertensive drugs with radically different mechanisms of action, is equally compelling. The variation in response is seen in patients with equal degrees of hypertension. Any one type of drug is at best fully effective only in 30–50%, of patients (4). Significantly, patient response is highly individual: some respond only to beta blockers, others only to diuretics. Only a minority of patients respond to dietary sodium deprivation, and in some, as in laboratory animals, it may actually raise blood pressure (5). It is also sometimes forgotten that a low-salt diet is not always free of risk: with significant renal involvement, as in malignant or renovascular hypertension, it can be overtly harmful.

Epidemiologic studies (2) and insurance statistics (3) suggest that about 10–15% of hypertensive persons, but only 1–2% of normotensive persons, are prone to coronary disease or stroke. However, this also means that 85% or more of hypertensive patients—particularly those with mild elevations—are at no more risk than anyone else. It may very well be that no more than 1% of patients with mild hypertension are at added risk and that, for the remaining 99%, uncritically applied long-term drug therapy may introduce more risk than that imposed by the untreated "disease." Indeed, in such mild hypertension, blood pressure often returns spontaneously to normal. In fact, 15% of patients with severe disease remained normotensive for 18 months after stopping all drugs (6).

Unquestionably, patients with severe disease, i.e., those with diastolic pressure >110 mmHg or with target organ damage, need drug therapy. Treatment can protect significant numbers of those patients from cardiovascular trauma (7). At the same time, it must be said that the large majority even of this group is not at greater than normal risk; in fact, most patients in the untreated portion of the original Veterans Administration trial suffered no additional morbidity during the five years of observation (7).

Recent years have produced abundant evidence that hypertensive patients are also heterogeneous with regard to their endocrinologic profile. Patients with essential hypertension show an abnormally wide range of plasma renin activity (8, 9). A significant development, to be discussed in this paper, is the analysis of these endocrinologic differences as important features for differential diagnosis and for determining specific treatment.

The practice of automatic, uncritical, undifferentiated drug therapy of hypertensive patients exposes large numbers of them to risks, likely unpleasant side effects, and the costs of a lifetime of therapy from which they can derive no real benefit. Differentiation, the hallmark of good medical practice, is the better course, seeking to identify patients who are truly at risk and, thus, to reduce or even withhold therapy from those in the more benign ranges of the risk-benefit equation. For those who need therapy, this differentiation serves the primary goal of specific treatment.

The Workup of The Hypertensive Patient

The evaluation of a new patient with high blood pressure embraces all the principles of good medical practice. It relies on a complete history and physical examination and the routine application of appropriately chosen laboratory tests. A thorough initial evaluation can avoid needless or inappropriate drugs for the lifetime commitment that hypertension may often require; furthermore, at the start, it can reveal surgically curable hypertension or other important and definable medical diseases.

For most hypertensive patients the pretreatment evaluation is most efficiently accomplished in the office setting. Multiple visits have the advantage of defining
the persistence or lability of the hypertensive process. Generally, the milder or more labile the hypertension, the longer the evaluation period before any commitment to therapy (10). Except when the hypertension is severe, or complications are impending or present, treatment should be withheld throughout the evaluation. For patients already on ineffective therapy it is worthwhile to consider withdrawing the drugs cautiously during the initial evaluation in order to determine whether or not the hypertension is persistent, or even drug-induced, and in the case of multiple drug therapy whether all or any of the agents are in fact necessary. In this general approach, hospitalization is reserved for those patients with severe hypertensive disease, those with impending complications, and those for whom the outpatient data suggest the need for specialized diagnostic procedures.

For some patients already on relatively simple and well-tolerated therapy, the physician may decide that the program already in force is adequate and need not be disturbed. But he or she should not hesitate to stop medications in those in whom the regimen appears even slightly unsatisfactory or unpalatable. A repeated observation at The Hypertension Center at the New York Hospital–Cornell Medical Center is that when hypertension persists in patients receiving multiple drug therapy (sometimes involving as many as four or five different agents) stopping medications gradually and serially usually does not lead to any further rise in blood pressure. Surprisingly, the blood pressure may often actually improve as the medical regimen is simplified. In the Veterans Administration study of severe hypertension (diastolic >110 mmHg), 15% of those in whom all drugs were stopped remained normotensive for the ensuing 18 months of observation (6). This figure may be much higher in milder forms. Serial withdrawal of drugs in patients who are poorly controlled on multiple drug therapy can put the physician in the best position for reevaluating the disease process and setting up new therapeutic strategies.

In our Center the initial evaluation of the patient is guided by five goals:

1. To establish whether or not the hypertension is sustained and would benefit from treatment.

Normal blood pressure is a variable with a rather wide range, but a definition of hypertension requires that a point be set somewhere, and experience advises that such a point should vary with age. Hypertension can be said to be present at 130/85 mmHg at age 10, at 140/90 in adults under age 40, and at 160/95 in patients over 40.

At least three blood pressure measurements on three separate visits should be made. Only in this way can it be ascertained that the hypertension is consistent. It would be wise to even further extend the evaluation period in patients with mild, borderline, or labile hypertension before concluding that the hypertension is sustained and of a degree warranting further investigation. The use of 24-h monitoring instruments can be helpful here (11).

2. To define the presence of coexisting disease.

The patient's total health must be taken into consideration. The hypertension may be secondary to other diseases or to their drug treatment, and these problems may have greater bearing on the patient's survival and management than does the hypertension. Diabetes or gout will contraindicate the use of thiazide diuretics when considering treatment for hypertension, and a history of bronchial asthma, congestive heart failure, or peripheral vascular disease may contraindicate the use of beta blockers. Antihypertensive drugs that depress mood and mentation are especially contraindicated in depressed patients. Adverse drug reactions related to the clinical setting must be fully considered.

3. To identify target organ damage.

The brain, heart, optic fundi, kidneys, and peripheral vasculature require special appraisal. Target organ damage in these areas affects the patient's outlook and carries important weight in the risk–benefit equations relating to management and in the decision-making process on whether or not to treat a mild or borderline hypertensive patient.

4. To identify other risk factors.

Some other factors that influence blood pressure are (a) obesity; (b) the use of estrogens, corticosteroids, nonsteroidal anti-inflammatory agents, nasal decongestants, antidepressants, tobacco, or alcohol; and (c) a family history of coronary or hypertensive vascular disease, with or without known hyperlipidemia, or of diabetes or gout.

5. To rule in or out curable causes for the hypertension.

All possible secondary causes for the hypertension should be explored (see Table 1). With more widely available and more definitive screening tests, we are learning that secondary causes of hypertension are far more common than once believed; this information is of encouraging relevance because of a vastly improved ability to treat the primary disorder successfully. Identifying a curable cause can spare the patient a lifetime of unnecessary, intrusive, and costly drug therapies.

The Office Evaluation

The History

It is important to evaluate the severity and pace of the hypertensive disorder in order to plan the pace of the medical workup and treatment. Normally, the workup is accomplished in an unhurried manner during several visits spaced at weekly or biweekly intervals. However, the initial examination should bring out enough information so that the workup can be accelerated for the more critically ill patients.

Accordingly, after learning of any current symptoms, the physician should record the duration of the hypertension, the circumstances of its onset, and the highest known readings. Was the blood pressure elevation merely discovered on routine examination? Has there been loss of well-being, decline in general vigor, or weight loss? What drugs has the patient tried, and with
what effect? Has the patient taken oral contraceptives known to cause hypertension (12, 13)? Are there drug allergies? Special attention should be paid for potential drug interactions. For example, aspirin or cyclo-oxygenase, both in common use, might worsen the blood pressure of a patient treated with a variety of other agents (14).

There then follows a review of systems focusing on the primary target organ areas—brain, cardiovascular system, and kidneys.

Headache may be a neurologic symptom of hyperten-

sion, but it is moot as to whether or not headaches occur more frequently in hypertensive than in normotensive people. Classically, headaches in hypertensive patients are said to be occipital and pulsatile, most prominent on awakening and wearing off during the day (15). In some patients, however, the headaches may be constricting and nonpulsatile, with either a tight cap or temporal distribution; these are the so-called “tension” headaches. Possibly, this symptom is no more common in hypertensive patients than in normotensive people (16). Moreover, studies indicate that when headaches do occur in hypertensive patients they are not well correlated with the degree of elevation in blood pressure.

Symptoms of autonomic nervous system instability, however, are definitely more common in hypertensive patients. These manifestations include a tendency for flushing and the characteristic red facies (16). Some hypertensive patients manifest either abnormal or subnormal sweating. Blurred vision (possibly reflecting vascular changes in the fundi), unsteady gait, depression, insomnia, sluggishness, or depressed libido may also be reported. In advanced, severe cases, more-defined focal sensory or motor neurologic changes may be experienced, either in acute association with transient ischemic attacks or as sustained symptoms presaging hypertensive encephalopathy or stroke. Some of these phenomena may be related to fairly common findings of slightly elevated catecholamines in hypertensive patients (17, 18). A variety of other neurologic symptoms may be present that may be more common in hypertensive than in normotensive people. There may be symptoms of cerebrovascular insufficiency, which can be transient (TIA) or sustained and related to ischemic episodes with infarction, to vasospasm or hemorrhage. A range of motor sensory or cognitive symptoms is possible.

Early or uncomplicated hypertension is usually free of cardiovascular symptoms. However, palpitations, increased fatigability, and shortness of breath are some early signs. Patients with labile or largely systolic hypertension may show tachycardia and signs of an unstable or hyperdynamic circulation, although this may also occur in normotensive persons (19). Sometimes, these patients are young, with moderately elevated plasma renin values (20). A history of angina, even documented myocardial infarction, is not unusual in hypertensive patients.

A renal history should be elicited. Evidence of glomerulonephritis, proteinuria, hematuria, nocturia, polyuria, recurrent urinary tract infection, renal colic, or renal trauma may suggest a renal basis for the hypertension. An abrupt onset of hypertension with rapid progression, particularly at an inappropriately young or old age, or associated with trauma, should clue the possibility of renovascular hypertension. This possibility is reinforced by concomitant retinopathy or cardiac or renal involvement. Polyuria or nocturia may reflect renal hypertension, hypokalemia, or hypercalcemia. Polydipsia, polyuria, and nocturia are common in pri-
ary aldosteronism, malignant hypertension, glomerulonephritis, polycystic disease, pyelonephritis, or diabetic nephropathy reflecting impaired tubular function. Muscular weakness may accompany hypokalemia or hypercalcemia.

The possibility of other types of secondary hypertension should be fully explored. The diagnosis of essential hypertension is made only by exclusion, when all other causes for the arbitrarily defined elevation in diastolic blood pressure have been excluded. The known forms of hypertension for which causes have been identified are referred to as secondary hypertension (see Table 1). Up to about 90% of all hypertensive patients have primary or essential hypertension, that is, hypertension with no identifiable cause. However, identification of secondary hypertension is important because this group comprises >1% of the adult population in the U.S., many of whom can be cured by specific medical or surgical approaches. The secondary forms of hypertension (Table 1) include a range of kidney and adrenal diseases, less common endocrine and neurogenic disorders, and the iatrogenically induced hypertensions.

The most important form of secondary hypertension—is renovascular hypertension, resulting either from fibromuscular hyperplasia (usually younger patients) or atherosclerosis (older patients). In recent years this disorder has become highly curable with balloon angioplasty or surgery. Also, its diagnosis has been greatly improved with the use of a modern ambulatory plasma renin assay followed (when indicated) by the "captopril test" as a basic screening procedure. When indicated by the captopril test, definitive angiography with a renal vein study should be performed (see below). It is also important to identify other kidney diseases that may cause hypertension (see Table 1) as well as the curable adenocortical (primary aldosteronism) and medullary tissue (pheochromocytoma) disorders.

Women patients should be queried about their use of estrogen preparations or oral contraceptives, particularly in conjunction with the onset of hypertension (12, 13). This is an underappreciated and rather common cause of hypertension that at times can be severe and that is usually reversible on cessation of therapy. The possibility of pheochromocytoma (see the paper by KRAKOFF AND GARBOWIT, pp. 1849–53 in these Proceedings) should be entertained when there is a history of a (a) excessive perspiration, (b) palpitations, (c) hypermetabolism with weight loss, (d) tremor, (e) tachycardia, and (f) vasomotor changes in the skin of the face. However, these classic symptoms may be lacking in some patients with pheochromocytoma whose clinical picture more closely resembles essential hypertension. Primary aldosteronism should be suspected in patients with polydipsia, polyuria, and muscular weakness, all reflecting potassium wastage; when these symptoms combine with truncal obesity and a diabetic tendency, Cushing disease may be suspected.

Many other variant hypertensive patterns can be recognized. Thus, hypertension can be purely systolic (21, 22) and accompanied by a normal or even a lowered diastolic pressure or even a lowered value. This usually occurs in the elderly and is a manifestation of another disease process, often atherosclerosis. The increased systolic pressure results from decreased elasticity of the larger arteries.

Labile hypertension is the descriptive term for intermittent hypertension, in which some blood pressures are elevated and some are within the normal range in an untreated patient. Although some of these patients exhibit pressures that are above average for the general population, it is not certain that such patients go on to develop sustained hypertension with the consequent secondary cardiovascular damage (23).

Borderline hypertension (24) is the term used to define blood pressure readings that are close to the upper limits of the normal range but perhaps slightly elevated. Diastolic hypertension is usually accompanied by systolic hypertension. If persistent, and especially if severe, it results in the development of so-called hypertensive vascular disease, a condition that involves the arterioles, most frequently in the kidneys, but also in the eyes and brain, and that also produces cardiac enlargement and left ventricular failure. Sustained hypertension induces thickening of the walls and occlusion of the lumina of the small arteries and arterioles and may favor the development of atherosclerotic changes in the large arteries.

Malignant hypertension (25, 26) is a syndrome characterized clinically by severe accelerated hypertension, with neuroretinopathy or papilledema of the optic nerves and by evidence of renal damage. Pathologically, it is characterized by fibrinoid and necrotizing arteriolitis (27). Accelerated hypertension is a term often used synonymously with malignant hypertension but sometimes used just to imply a significant increase in pace and severity of the hypertensive process as evidenced by higher pressures or increasing damage to the retinal arterioles or the kidneys.

A family history may suggest a familial basis for the patient's high blood pressure, e.g.: (a) inherited renal disorders such as polycystic kidney disease (28) and fibromuscular disease of the renal arteries (see Table 1), (b) café-au-lait skin discolorations or neurofibromatosis associated with pheochromocytoma, (c) pheochromocytoma in association with medullary carcinoma of the thyroid and a tendency to parathyroid hyperfunction from hyperplasia or multiple adenomas (Sipple syndrome) (29, 30). Hypertension is common in unusual endocrine disorders such as hyperparathyroidism with recurrent renal stones and peptic ulcer (31) or in congenital adrenal or gonadal defects producing an abnormal mineralocorticoid profile and associated with hypokalemia with or without abnormal virilization, amenorrhea, and lack of maturation at puberty (see Table 1).

Questions about the patient's lifestyle and environ-
ment may uncover hypertensive risk factors susceptible to some control. Obesity, particularly when body weight is greater than 20% above normal, is an important factor (32). Centrally located or upper-body fat predominance is also positively related to blood pressure (33) and also suggests Cushing syndrome. Correction of a drinking problem can sometimes correct high blood pressure (34). Smoking, with its known vasoconstrictor effects, is contraindicated, and the lack of regular physical exercise may be a contributing factor in sustaining hypertension (35).

Emotional and psychological factors should be given attention in view of the persistent scientific opinion that they may cause or intensify high blood pressure despite the lack (so far) of a convincing demonstration that specific emotional patterns or central nervous system disorders can sustain hypertension. The use of tranquilizers or sedatives in highly stressed patients may have some broad benefits, although their value in improving blood pressure is more a matter of clinical and patients' impressions than hard demonstration.

The Physical Examination

General appearance. A florid facies suggests vasomotor instability, possibly due to an underlying metabolic dysfunction, although chronic alcoholism may also produce such signs. A ruddy complexion with a bluish tinge characterizes some patients with essential hypertension and associated polyctemia (e.g., Cushing syndrome, Gaisböck syndrome). High-renin patients may have a dusky appearance and even acrocyanosis (e.g., malignant scleroderma) (36) associated with vasoconstriction and a higher hematocrit. Cushing syndrome is suggested by the occurrence of the following symptoms: (a) truncal obesity with moon facies, (b) frontal baldness, (c) atrophic extremities with abdominal striae, (d) skin atrophy, and (e) spontaneous ecchymoses (37). Hypothyroidism and acromegaly are easily recognized causes of hypertension. As noted here earlier, multiple neurofibromas or café-au-lait skin discolorations suggest a familial basis for a possibly associated pheochromocytoma. Mucosal neuromas may be associated with other components of the syndrome of multiple endocrine adenomatosis with hypertension. Renal failure may be expressed by a pale mucosa and skin, periorbital and peripheral edema, and a uremic breath. But most likely the hypertensive patient will not show any of these signs and will be indistinguishable from any healthy person with normal blood pressure.

Measuring blood pressure. It is good practice to measure blood pressure in both arms (38). Normally, there should be no difference, but the second reading may reflect a more relaxed adjustment to the surroundings. A disparity of 10 mmHg or more between the two arms should be confirmed by repeated measurements; a consistent difference may signal an occlusive atherosclerotic plaque in the subclavian artery, usually on the left. On the first visit, blood pressure should be measured in three positions: seated, after being supine for at least 5 min, and after standing for at least 2 min. Postural changes in blood pressure are especially prominent in elderly patients with deficient autonomic function.

A longer and wider cuff, the so-called thigh cuff (19 cm wide), will help minimize falsely high readings in patients with obese arms. Blood pressure measurements in the thigh, even with the large cuff, are difficult to make because of the large muscle mass, and they are usually overestimated. In view of the technical difficulties it is not necessary to perform this procedure routinely if the femoral or popliteal pulses are readily palpable and there is no other reason for suspecting an aortic occlusion. A reading equal to or less than that recorded in the arm is abnormal and may be due to obstructive disease in the proximal aortic tree, perhaps a coarctation.

In addition to the blood pressure measured by the physician, we also recommend that the blood pressure be measured by a nurse or a trained assistant. Newer studies indicate that (a) some patients show significantly higher blood pressure readings when they are taken by the physician, and (b) the difference between pressures taken by a nurse and by a physician may be a marker of a hyperadrenergic state and could be predictive for cardiac morbidity and mortality (39, 40). Some borderline hypertensive patients show consistently higher or elevated readings when the pressure is taken by the physician. In such cases it is also helpful to train the patient to measure the blood pressure by him- or herself and to record the reading outside the doctor's office. Furthermore, as mentioned above, 24-h blood pressure recordings are very useful in borderline hypertensive patients to decide whether or not to treat them.

The fundoscopic examination. The fundoscopic examination provides direct assessment of (a) target organ damage, (b) the severity and duration of the hypertension, and (c) the urgency of treatment. The Keith–Wagener–Barker classification system of grading retinal changes is a useful reference standard. In this system, grade 0 is normal; the others follow:

Grade 1. Minimal disease characterized by spasm or so-called copper or silver wire appearance of the arterioles with some tortuosity and perhaps some segmental constriction. Such spasm can be visualized as a ratio of subnormal lumen to wall. When this occurs with little or no sclerosis, it may be interpreted as purely angi spas tic disease, reflecting the recent onset of hypertension.

Grade 2. In addition to grade 1 vaso spastic changes there is evidence of arteriolar sclerosis—heightened light reflex, arterio venous nicking, and other phenomena suggesting impingement on the retinal venous system by a sclerotic arteriolar vessel. Such changes generally indicate that the disease has been present for at least several months and probably several years.

Grade 3. In addition to the above, overt hemorrhages or exudates are seen. The hemorrhages can be diffuse and asymmetric or flame-shaped, radiating from the optic disk along the vascular tree. To some extent, their appearance may reflect the age of the process. "Soft" exudates are seen as "cotton-wool" spots, indicating
fibrinoid changes. "Hard" exudates are shinier and more circumscribed, usually reflecting deposition of lipids from older extravasations. Generally, the hard exudates indicate an older, healing process. Soft exudates and hemorrhages suggest ongoing severe or accelerated hypertension requiring urgent treatment.

Grade 4. Here papilledema of edema of the optic disk margins can be seen, especially on the temporal side, since blurring of the nasal margin may occasionally occur without disease. Elevation of the optic nerve is generally considered characteristic of malignant hypertension. It is usually accompanied by the hemorrhages and exudates of grade 3 changes, which are especially prominent when the hypertension is associated with the overt vasocstriction of renin or norepinephrine excess.

When the hypertension is of very recent onset, papilledema may occur without grade 3 changes or any discernible vascular change. This is more common in the various low-renin states, in which volume excess is pathogenically more important. The more acute low-renin forms of hypertension include those of acute nephritis, acute renal failure, lower tract obstruction, and toxemia of pregnancy. Papilledema without attendant vascular changes may also suggest pseudotumor cerebri or central nervous system disease with increased intracranial pressure, as may occur postictally or in water intoxication. Attendant neurologic symptoms, seizures particularly, may help establish the diagnosis. Whenever there are neurologic symptoms, the physician should look for microemboli in the retinal arteries and increased extracranial pressure, since these manifestations could point to an ulcerated plaque in the internal carotid artery on the ipsilateral side.

Examination of the heart. In hypertensive disease the heart is frequently more affected than either the brain or kidneys. Hypertension in adults is a leading cause of cardiac hypertrophy and dilatation as well as congestive heart failure. The mechanical effects on the heart of sustained increase of pressure work may be reflected in the physical findings.

A forceful apical thrust may be found even in early hypertensive disease and may be especially exaggerated in the variant hyperdynamic state. A sustained, heaving left ventricular thrust indicates substantial hypertrophy. The fourth heart sound, the "atrial gallop," may be the earliest sign of hypertension, although it may be heard occasionally in normotensive individuals. Believed to be caused by reduced ventricular compliance leading to a more forceful atrial contraction, it is usually heard before hypertrophy can be detected. The sound may correlate with the finding of P-wave abnormalities on the electrocardiogram. A third heart sound, the venricular gallop, may occur in young patients with rapid ventricular filling, but in older patients it can be a late manifestation of hypertension, reflecting the reduced diastolic compliance of a failing left ventricle (41).

In severe hypertension an accentuated aortic second sound may be accompanied by an aortic insufficiency murmur heard in the second right interspace and along the left sternal border. Suggesting dilation of the aortic ring, the soft murmur indicates the need for more urgent therapy. However, it should not be confused with the diastolic murmur of calcific aortic disease more commonly found in hypertensive patients over age 60. When associated with primary aortic regurgitation, hypertension in elderly patients is usually systolic, with a wider pulse pressure. This is best treated with agents that reduce peripheral resistance—vasodilators, alpha-adrenergic blockers, and anti-angiotensin drugs. Diuretics and beta blockers are relatively contraindicated in this syndrome. Aortic stenosis in the elderly, usually from calcific valvular disease, is reflected instead by a systolic murmur, a narrow pulse pressure, and a slow carotid upstroke. In cases with severe aortic stenosis, diastolic hypertension is rare or mild.

The hyperkinetic or hyperdynamic circulation syndrome may be encountered in adolescents and young adults with or without hypertension (19, 20). If hypertension is present, it is labile, largely systolic, and accompanied by (a) tachycardia at rest, (b) a forceful apical thrust, and (c) occasional prominent pulsation in the carotid arteries. In such cases, the clinician should consider the possibility of other metabolic or psychiatric factors.

A harsh systolic murmur over the precordium or midscapular area of the back in a younger patient may be due to coarctation of the aorta. With this finding the clinician should compare blood pressures in the arms and legs and obtain an echocardiographic examination of the aortic valve, since bicuspid aortic valves commonly occur with coarctation of the aorta.

Examination of the vascular system. Hypertension patients are prone to occlusive disease, which should be searched for throughout the arterial tree. The auscultation should cover not only the peripheral arteries but also the carotid arteries, the abdominal aorta, the renal arteries, and the femoral arteries. Generally, a diastolic component to a bruit or palpable thrill over a peripheral artery suggests a higher stenosis. Systolic bruits without diastolic components tend to have less significance and are not important at all when in the abdomen. This is not an easy distinction. When an abdominal bruit disappears in the lateral position, it is probably not a fixed lesion. However, a systolic bruit over the carotid artery can be quite significant.

Bruits can be unilateral or bilateral, and can be audible throughout the cardiac cycle or only during systole. Although they are likely to occur in normotensive or hypertensive persons, they have grave significance in the latter. Although bruits are premonitory of subsequent cardiovascular disease, they do not predict the location of the lesion. Our experience has been that patients with carotid bruits are more apt to have heart attacks than cerebrovascular accidents.

A systolic bruit over the femoral artery suggests atherosclerotic disease but does not necessarily imply that it is occlusive. When pulses in the lower extremities are absent or dampened in a young person, coar-
tation of the aorta should be suspected; in an older patient occlusive aortic femoral disease is possible.

Examination of the abdomen. The aorta should be carefully palpated in all patients, since aortic dilation or aneurysm is a highly treatable condition often identifiable on the physical examination. A systolic and diastolic bruit in the upper epigastrum or in one or both upper quadrants of the abdomen suggests renal artery stenosis, a diagnosis that should be pursued if other criteria are compatible. A palpable enlargement of one or more kidneys can suggest polycystic renal disease, hydronephrosis, or a renal tumor. Very rarely is a pheochromocytoma large enough to be palpable.

Neurologic examination. Gross deficits in sensory or motor function, mentation, or mood are not likely to be missed, but more subtle deficits indicating transient cerebral ischemia or autonomic dysfunction should be sought for clinically, especially if the history is suggestive.

Laboratory and Instrumented Evaluation

Together with the history and the physical examination, the purpose of the laboratory and instrumented evaluation is to

- Identify specifically all curable causes of hypertension (Table 1).
- Stratify pathophysiologically the remaining heterogeneous group with essential hypertension.
- Assess and characterize the risk profile of the individual patient by identifying target organ damage, and the presence of coexisting disease and of attendant biochemical risk factors.

The initial laboratory workup should include a complete blood count and hematocrit, a complete urinalysis, a lipid profile, and measurement of blood urea nitrogen, serum creatinine, serum uric acid, fasting blood sugar, and serum electrolytes. If the serum potassium concentration is borderline or low (i.e., <3.6 mmol/L) it should be repeated on two or three separate occasions. A low potassium concentration often provides the first laboratory clue to the presence of aldosterone excess.

Because plasma renin is part of a cybernetic control system that responds to changes in sodium balance, an evaluation of the renin system in hypertensive patients (carried out under standardized conditions) should be part of the initial laboratory workup. This enables the clinician to rule out or go on to diagnose curable disorders (e.g., renovascular disease and primary aldosteronism). Also, it stratifies all patients pathophysiologically according to the degree of their renin and sodium involvement.

The renin–sodium profile, plasma potassium, serum urea, and creatinine and 4-h urinary microalbumin excretion rate, together with the 24-h urinary sodium and potassium values, make up an especially valuable primary biochemical package to screen for and then identify secondary causes of hypertension and characterize all patients pathophysiologically. Plasma renin concentrations in curable renovascular disease or coarctation are often increased and are never low, whereas they are markedly suppressed in primary aldosteronism. The assay is no more expensive or complicated than the cholesterol assays so common nowadays, and it is potentially far more relevant, not only because it can enable the absolute diagnosis of curable forms but also because it can be used for evaluating the pathophysiology of essential hypertension and for planning its treatment. The test involves the collection of a 24-h urine sample for measurement of sodium excretion and a venous blood sample for renin measurement, the latter collected while the patient is seated quietly in the office. The plasma renin activity value is plotted against the 24-h urinary sodium concentration, thereby correcting for the fact that renin, a regulatory hormone, rises normally in response to a low-salt diet and declines in response to a high-salt diet. Where the test is done while the patient is on his or her own diet, it provides basic information about salt appetite. If the kidneys are healthy and there is no edema, it can be presumed that the daily sodium output reliably reflects the sodium intake.

Because all antihypertensive medications can affect plasma renin values, accurate interpretation of a renin–sodium profile requires that the test be carried out after the patient has been off drugs for at least three weeks in the case of diuretics, six weeks for spironolactone, and two weeks for all other antihypertensive treatments. The renin–sodium profile as a diagnostic test, like most other laboratory tests, is most powerful when the deviations are extreme. Patients exhibiting very high or very low plasma renin concentrations can be immediately selected for special workups.

The simultaneous measurement of the 24-h urinary potassium helps evaluate the normalcy of aldosterone secretion. If urinary potassium excretion exceeds 40 mmol per day when plasma concentrations are <3.6 mmol/L, the pattern suggests oversecretion of aldosterone (perhaps due to an adenoma) and thus suggests the need for more diagnostic testing.

Furthermore, the determination of albumin in the 24-h urine helps to identify renal hypertension or microalbuminuria, reflecting a degree of renal damage in essential hypertension or in diabetic nephropathy (42–44). In our own laboratory, normal values are <10 mg/day (42–44). This test is a valuable guide to determine occult renal damage in hypertensive patients and can be used to follow effects of drug therapy (44).

With the current widespread use of automated laboratory testing, a variety of other relevant tests may be added at little or no extra cost. Serum calcium and circulating thyroid hormone concentrations may point to parathyroid or thyroid disease, which can sometimes exist without clear-cut clinical evidence.

Tests of lipid, cholesterol, and triglyceride metabolism are usually offered as part of these automated testing profiles. However, even the advocates of this group of tests (45) agree that in people over the age of 60 and perhaps over the age of 50, blood lipids have less prognostic value except when markedly abnormal.
cent national guidelines, while probably overly enthusiastic (45), provide one basis for anti-lipid therapy. A more cautious viewpoint has recently been offered (46, 47).

When pheochromocytoma is suspected, measurements of plasma and (or) urinary catecholamines or of their urinary metabolites can be extremely beneficial (48, 49). Also, measurement of urinary free cortisol or urinary 17-hydroxycorticosteroids can be suggestive, but sometimes the dexamethasone suppression test may be necessary to define the nature of the Cushing syndrome (37).

Determination of urinary aldosterone concentrations is most valuable for revealing the rate of adrenal aldosterone secretion. This test is essential for establishing the diagnosis of primary or pseudopri mary aldosteronism and is very helpful in evaluating other hypertensive situations associated with high renin concentrations and (or) potassium wasting, but it is not necessary to perform it routinely. However, it is very useful to store a urine sample for later determination of urinary aldosterone if plasma renin is low.

A roentgenogram of the chest is highly desirable as part of every initial workup, particularly in patients over age 40. It can reveal coarctation of the aorta and can be useful in assessing cardiac hypertrophy.

A routine electrocardiogram should be part of the evaluation of every new patient with established high blood pressure. Manifestations of hypertensive heart disease include T-wave abnormalities, expressed either by notching or a biphasic form, particularly in the precordial leads. As left ventricular hypertrophy progresses, there is increased voltage of the R-waves and then a characteristic strain pattern involving ST segment depressions and T-wave inversion (50).

Studies show that patients with electrophysiographic or radiographic abnormalities have twofold or greater increases in premature mortality rates (61–63). Yet, electrocardiography and chest radiography detect left ventricular hypertrophy in only about 5% or fewer of unselected hypertensive patients (52, 54). Significantly greater sensitivity has been demonstrated by echocardiography (54–56). In recent years it has become apparent that a routine M-mode echocardiogram can provide more sensitive information than the electrocardiogram or a chest roentgenogram on the presence and degree of left ventricular hypertrophy and enlargement of chamber size. Moreover, recent studies from two groups (55, 56) indicate that the finding of increased left ventricular mass by echocardiographic studies has prognostic reference and may be even more prognostic than the blood pressure level itself for anticipating subsequent morbidity (i.e., stroke, heart attack, sudden death). Nevertheless, it should be remembered that left ventricular hypertrophy may occasionally be identified by electrocardiographic criteria when echocardiographic results are normal. This may occur when cardiac enlargement is still minimal but in the presence of myocardial ischemia sufficient to produce the inverted T-waves of the so-called strain pattern (57).

The intravenous pyelogram (IVP) should not be routinely used to screen for surgically curable renovascular disease. It has now been shown to be inefficient for that purpose. False-negative results occur in 10–30% of patients subsequently treated surgically (58, 59). False-positive results of a similar degree also occur (58, 60). At best, a positive IVP merely indicates the need for more specific testing, and a negative IVP should not deter the physician from more specific tests when renovascular disease is strongly suspected.

In patients diagnosed as having renal disease, the IVP remains useful for defining renal architecture, size, and capacity for concentrating dye. However, as a screening procedure, it is relatively expensive, invasive, and carries some hazard. Simpler, more practical, and more specific screening tests are now available.

Identifying Curable Forms of Hypertension

The importance of identifying curable hypertension has been magnified nowadays by recent technologic advances—in particular, the advent of balloon angioplasty as a treatment for renovascular disease. With the development of the simple and inexpensive captopril test (61–64), discussed below, increasing numbers of candidates for balloon angioplasty are being found. In the last three years at The New York Hospital–Cornell Medical Center, >400 successful balloon dilatations have been carried out. Similar experiences are being reported from other large centers. It is safe to say that if not for the availability of the new diagnostic technology, a very large proportion, perhaps the majority, of these patients might have been assigned erroneously to the category of "essential hypertension" and kept on a regimen of antihypertensive drugs for the rest of their lives.

In view of this experience, it is not particularly unreasonable for the physician to apply long-term drug therapy before using this technology to identify curable forms of hypertension. Rather, after a significant and sustained hypertension has been demonstrated, the first step is the establishment of normokalemia or hypokalemia and the determination of a normal renal function by assaying serum urea and creatinine and 24-h urinary albumin. These are simple but highly relevant primary screening procedures, because they make it unnecessary to pursue identification of mineralocorticoid causes in the normokalemic group.

The renin–sodium profile is also included in the initial evaluation (9). As indicated in the flow diagram (Figure 1), low-renin patients who have hypokalemia are evaluated for curable adrenocortical disease. Curable primary aldosteronism is characterized typically by the diagnostic triad of (a) serum potassium <3.5 mmol/L; (b) markedly suppressed plasma renin activity (plasma renin concentrations are typically <0.5 μg/L per hour but occasionally may be as high as 1.3); and (c) hyperaldosteronism, revealed by urine or plasma aldosterone measurements. These aldosterone values may not be very high, but they should be assessed in relation to the degree of hypokalemia, which markedly suppresses
untreated patients (patients receiving only a beta-blocker may also be considered), is based on the remarkable specificity of captopril to eliminate the angiotensin II effect and hence to induce a sharp reactive increase in renin secretion from the ischemic kidney. Patients who are salt-depleted either because of a low-salt diet or diuretic are ineligible for the test because they start with high renin concentrations and may show a falsely positive reactive increase (61).

A single dose of 25 mg of oral captopril is given to a quietly seated patient. The agent is rapidly absorbed, blocking the renin system within 1 h. Patients with renovascular hypertension react to the blockade with an unusually vigorous rise in renin secretion from the ischemic kidney, whereas hypertensive patients without renal artery obstruction show little or no plasma renin response (see Figure 2). With the angiotensin II effect wiped out by the captopril, the kidney with renovascular disease abruptly loses its intense efferent constriction, and its filtration and perfusion are threatened. In reaction, renin secretion from the stenotic kidney soars in the attempt to restore the situation.

The protocol for performing the captopril test in the office setting is displayed below, as are the criteria for interpreting the test.

**Instructions for performing a captopril test**

Maintain the patient on normal salt intake and give no diuretic agents.

If possible, withdraw all antihypertensive medications three weeks before the test.

Allow for patient to sit quietly for at least 30 min.

Measure blood pressure after 20, 25, and 30 min of sitting (average the three readings to obtain baseline).

Draw a venous blood sample for measurement of baseline renin activity.

Administer 25 mg of captopril orally.

Measure blood pressure at 15, 30, 40, 45, 50, 55, and 60 min after captopril administration.

At 60 min, draw a second venous blood sample for measurement of stimulated plasma renin activity.

**Captopril test criteria for identifying patients with renovascular hypertension**

Stimulated plasma renin activity of ≥12 μg/L per hour

Absolute increase in plasma renin activity of ≥10 μg/L per hour

Increase in plasma renin activity of ≥150% (or ≥400% if baseline plasma renin activity is <3 μg/L per hour)

The 60-min plasma response (not the blood pressure response) to this test is the indicator of renovascular hypertension. Although a substantial blood pressure fall may accompany the sharp plasma renin change, this cannot be depended on to reflect renin-dependent renovascular hypertension, because other, more transient defenses of blood pressure may have been invoked by the procedure.

A positive test result meeting the criteria listed above strongly implicates renovascular disease. In a series comparing 56 patients with proven renovascular disease against 112 with essential hypertension, the test was found to be 95% sensitive and 95% specific for renin-dependent hypertension related to renal artery stenosis (61). However, although false-positive results may occur
for this and other reasons (i.e., malignant hypertension, scleroderma, and other types of renal diseases), such false-positive results can help uncover an unsuspected secondary hypertension besides that caused by obstruction of the renal artery (Figure 1). The test is a very powerful screening test with few false-negatives.

However, a positive captopril test does not discriminate between unilateral or bilateral kidney disease nor between a parenchymal or arteriolar lesion. Such questions can be answered only by digital subtraction angiography or arteriography of the renal vessels and by a renal vein renin study. In typical renovascular disease, renin is secreted from only one kidney; a simple mathematical analysis of the concentration of renin in each renal vein can be used to identify the renin-secreting kidney and assess its degree of ischemia. At the same time, the peripheral blood concentration reflects the secretion rate of renin from that kidney (64, 65). In addition, the captopril test may also be useful for distinguishing between adrenal hyperplasia and adenoma because, in the former, blockade of the renin system can cause some fall in plasma aldosterone concentrations.

Chronic bilateral renal disease or bilateral renal artery stenosis is possible when the creatinine value is >12 mg/L. In the former hypertensive state, plasma potassium values tend to be high and renin is often suppressed because of impaired sodium excretion and volume expansion. Proteinuria may also be present. In bilateral renovascular disease, however, parenchymal function is less impaired, proteinuria is absent or mild, and sodium-volume expansion will dampen activation of the renin system.

Of course, to complete the initial pretreatment evaluation, special tests for other uncommon but curable forms such as pheochromocytoma, Cushing syndrome, and thyroid disease should also be performed whenever the clinical picture is suggestive.

**Summary**

This paper attempts to define the theory and practice of a modern approach to the initial workup of the patient with hypertension. The process includes a complete general medical evaluation along with special measures to enable the fullest characterization and clinical differentiation of the disease.

The initial workup aims to (a) establish that the hypertension is sustained and should be treated; (b) identify all definable and curable causes for the hypertension; (c) identify the presence and degree of attendant risk factors such as smoking, alcohol use, obesity, diabetes, and abnormal lipid metabolism; (d) characterize the hypertension in terms of its pathophysiology; and (e) assess the presence and degree of target organ damage to the heart, brain, and kidneys.

Because all diastolic hypertension is due to arteriolar vasoconstriction, a fundamental strategy of this process is to distinguish between renin-mediated and sodium-related vasoconstrictive forces and to evaluate which is preponderant. The chief instruments of this strategy are the renin–sodium profile and the response of plasma renin activity and blood pressure to specific antirenin system drugs. The captopril test, an important protocol in making this distinction, is primarily a powerful screening tool for confirming the possible presence or absence of curable renovascular disease or curable primary aldosteronism.

That renin profiling cannot accurately discriminate between the contributions of either the renin or sodium-volume factors in that large fraction of medium-renin patients is not a viable reason for not performing the test. The test has its greatest strength for identifying sizable numbers of otherwise unrecognizable patients with very high or very low renin concentrations who might have curable disorders and who likely reflect different pathophysiologic vasoconstrictive mechanisms for which entirely different drug therapies are appropriate. However, the baseline renin test is also useful for assessing prognosis and the likelihood of a heart attack (9, 39) and it is valuable for deciding whether to use an anti-renin system drug (for medium and high renin concentrations) as opposed to natriuretic agents (low-renin patients) such as a diuretic or calcium antagonists as the primary step.

In our present state of knowledge, the basic diagnostic biochemical workup includes the renin–sodium profile and the 24-h urinary sodium, potassium, and microalbumin excretion rates. This package is further enriched by baseline electrocardiography and echocardiography and the evaluation of glucose and lipid patterns. Together, these procedures enable the physician, supported by data from the general medical evaluation, to make full assessment of pathophysiologic mechanisms involved and to weigh severity, pace, and prognosis at the outset and as he or she follows and treats the patient. In this mode the clinician is in the best possible position to select, apply, and evaluate long-term nonpharmacologic and drug therapy programs.
References

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