Essential (Primary) Hypertension

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Epidemiology

High blood pressure (hypertension) is the most important risk factor for cardiovascular disease, heart failure, stroke, and the progression of chronic renal disease. Cardiovascular disease is the most common cause of death in the world and is a major cause of morbidity and mortality worldwide [1]. The importance of treating hypertension to prevent cardiovascular disorders was long neglected by physicians; however, this picture is changing, and the number of hypertensive patients who are undetected, or detected but not treated, is now declining. Nevertheless, considerable numbers of patients treated for hypertension have inadequately controlled blood pressure values. Numerous studies have examined the epidemiology of hypertension and its negative impact worldwide. While blood pressure increases with age in both sexes, women appear relatively protected from this increase until menopause, after which their blood pressures increase at an accelerated rate. The age-related blood pressure increase is accelerated in certain groups. For instance, in black persons living in the United States, blood pressure values are higher than those of whites at every age. The risk for developing a stroke or a myocardial infarction is linearly related to the blood pressure level. A recent meta-analysis of the major studies is shown in Figure 1, panels A and B [2]. For both stroke and myocardial infarction, the relationship is linear and begins at blood pressure ranges considered to be normal. This finding has important therapeutic implications. The risk of stroke has been reduced considerably by antihypertensive treatment, so that almost the entire increased stroke risk attributable to hypertension can be eliminated by treatment. This degree of risk reduction has not yet been shown for myocardial infarction; however, the positive influence of treatment on reduced cardiovascular risk is no longer disputed.

Hypertension (except in its extreme malignant phase) is asymptomatic and should therefore be considered a risk factor, rather than a disease. Convincing a patient to take medication with possible side effects for the rest of his life in the hope of prolonging life is not easy. Thus, hypertension must be considered in relationship to other cardiovascular risk factors. The Framingham data clearly illustrate the interrelationships between hypertension, cholesterol, glucose intolerance, cigarette smoking and left ventricular hypertrophy. These five primary risk factors are the most important determinants of cardiovascular risk and appear to operate independently of one another. Other contributing risk factors, such as family history, obesity, hypertriglyceridemia and hyperuricemia exert their influence for the most part through one of the five major risk determinants. Still others, such as lipoprotein (a) concentrations, low HDL/cholesterol, and hyperhomocysteinemia, are currently being identified and evaluated. The threshold at which a patient should be treated is lowered for patients at high risk for cardiovascular disease. High car-

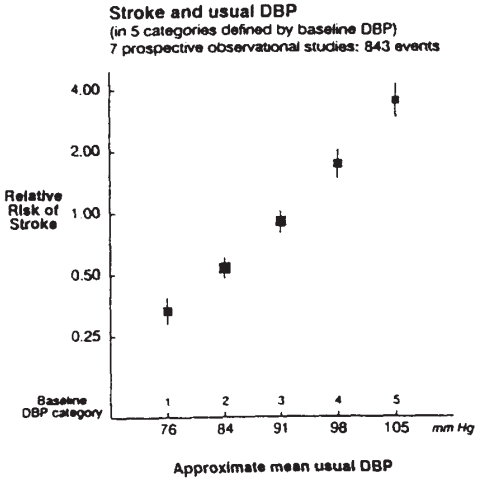

Figure 1a.

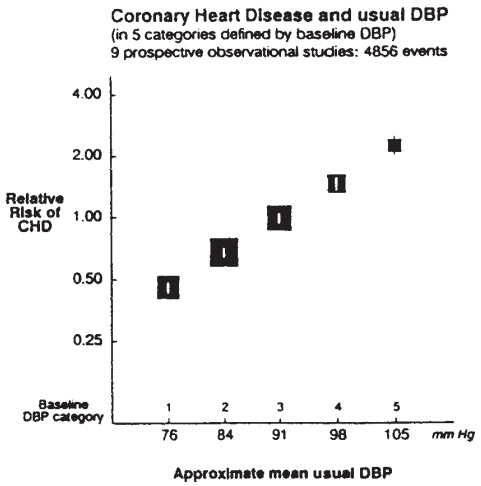

Figure 1. The upper panel shows the relationship between approximate mean diastolic blood pressure and the relative risk of stroke.The lower panel shows the same for relative risk of coronary heart disease. The relationships are linear and are apparent even at the lower end of the blood pressure scale. [MacMahon et al. Lancet 1990; 335: 765-774] with permission.

diovascular risk also calls for a more aggressive approach to treatment.

Epidemiological investigations have also been conducted to examine factors that might promote the development of hypertension in populations. The Intersalt study was performed to examine the influence of body mass index (obesity), salt intake, alcohol ingestion, potassium intake, and protein intake on blood pressure across the world's populations with age. The data were recently reanalyzed [3]. Over 10,000 persons were examined in 50 centers, and 24-hour urine specimens were collected to assess salt, potassium, and protein intake. The study design allowed examination of the effect of these variables on blood pressure increases with advancing age. Obesity has the most pronounced effect on blood pressure. The body mass index is highest in the United States, where currently > 30% of the population can be classified as obese (body mass index > 27.5). Salt intake may influence the age-related blood pressure increase, possibly reflecting a threshold effect of the renin-angiotensin system to altered salt intake. Alcohol and Potassium intake are inversely related to blood pressure. Higher potassium intake increases baroreceptor sensitivity, which decreases short-term blood pressure variability. Blood pressure variability is a cardiovascular risk factor, independent of blood pressure levels. Other studies have shown a convincing influence of potassium intake on stroke incidence, which may be independent of blood pressure. Still other studies suggest that dietary calcium intake is inversely related to blood pressure. This influence may be especially important in pregnancy.

Considerable excitement has been generated by the recent observation that children with low birth weight are likely to be at risk for the development of hypertension and cardiovascular disease as adults. These observations originally stemmed from Great Britain, where excellent birth weight and body length measurements were available from several large hospitals [4]. Several studies from Scandinavia and elsewhere have since confirmed

this observation. These epidemiological studies have strong implications in terms of socioeconomic issues, prenatal health care and nutritional issues, as well as allowing the formulation of additional long-term preventative strategies.

Diagnosis and Clinical Findings

Blood Pressure Measurement

There is no critical blood pressure level that delineates excess risk, since the risk relationships are linear across the range of blood pressure levels (Figure 1). Those blood pressure levels associated with a > 50% increase in mortality are arbitrarily defined as hypertensive. These values are: > 130/90 mm Hg for men younger than 45 years, > 140/95 for men 45 years or older, and > 160/95 mm Hg or greater for all women. Systolic hypertension is present when the systolic blood pressure > 140 mm Hg with diastolic pressure < 90 mm Hg. Borderline hypertension is intermittent elevation of systolic or diastolic pressure exceeding the accepted normal value for the person's age and sex. Criteria for children and adolescents have been established by the National Heart, Lung and Blood Institute of the United States. The following levels are associated with significant risk: > 116/76 mm Hg (3 – 5 years of age), > 122/78 mm Hg (6 – 9 years of age), > 126/82 mm Hg (10 – 12 years of age), and > 142/92 mm Hg (16 – 18 years of age).

Casual blood pressure measurements i.e. standard sphygmo-manometry with an arm cuff using proper technique, is reliable in determining blood pressure, and was used in the above epidemiological studies. Blood pressure should be measured in both arms with the patient comfortably seated. In children and young adults, blood pressure should also be determined in a lower extremity. The arm should be straight with the hand supine. The cuff should be at the level of the heart. If the arm is allowed to hang dependently, or if the cuff is too small, inappropriately high values may be obtained. The cuff width should be greater than two-thirds of the arm's diameter, and the length of the inflatable portion should be greater than two-thirds of the arm's circumference. Systolic pressure is determined at the point at which the sound becomes audible (Korotkoff 1). The diastolic pressure is determined by the point at which sound disappears (Korotkoff 5). Two measurements should be obtained and their values averaged. The patient who on three separate occasions demonstrates a pressure equal to or greater than the above guidelines should be classified as hypertensive. A diastolic pressure of ≥ 90 mm Hg should be confirmed within 3 months. A diastolic pressure of ≥ 105 mm Hg should be confirmed within 2 – 3 weeks.

In older patients with widened pulse pressures, or in patients with severe calcified peripheral vessels (e.g. dialysis patients), the physician must consider the possibility of "pseudohypertension." Pseudohypertension is a falsely elevated blood pressure reading caused by inability of the inflated sphygmomanometer cuff to properly collapse the calcified brachial artery. Palpating the radial artery in the face of an inflated cuff (Osler's sign) is an unreliable physical finding in such patients. Only direct, intra-arterial measurement is adequate to determine the blood pressure of such patients; however, the procedure is tedious and not without morbidity, such as pain and bleeding.

24-hour Ambulatory Blood Pressure Measurement

Technical advances now also permit the measurement of 24-hour ambulatory blood pressure [5]. Such measurements give insight into the expected nocturnal decrease in blood pressure (termed "dipping") and also permit the calculation of the daytime and night-time blood pressure load (values greater than normal during the given period). Blood pressure load is estimated at upper limits 140/90 mm Hg during the daytime and upper limits 120/80 mm Hg at night. The percentage of blood pressure measurements above these values is calculated, and pressure loads > 20% are considered abnormal. Such measurements may be helpful when the diagnosis of hypertension is in doubt, particularly if pharmacological intervention is being considered. Ambulatory 24-hour measurements are also useful to avoid overtreatment. Furthermore, the presence of dipping is quite reliable in excluding secondary causes of hypertension, while the absence of dipping is of little value in suggesting secondary hypertension [6].

White Coat Hypertension

Some persons seem to react to the act of blood pressure measurement in the physician's office with an exaggerated rise in blood pressure [7]. This exaggerated response is termed "white coat" hypertension. Currently, there are no set guidelines for white coat hypertension. However, studies suggest that white coat hypertension is not a harmless phenomenon. Indeed, cardiac changes (decreased ventricular compliance and increased ventricular mass index) have been observed in persons with white coat hypertension, even though the resting blood pressures were not elevated.

History

The history of patients with hypertension should include the identification of other risk factors, namely smoking, hyperlipidemia, diabetes mellitus, family history, and age of hypertension onset. The presence of asthma and chronic lung disease should be noted. The dietary history is important and should cover calorie and electrolyte intake, as well as unusual foods such as licorice. Medications are important, particularly oral contraceptives, steroids, thyroid hormones, anorectics and amphetamine-containing decongestants. Over-the-counter drugs, such as phenylethanolamines, nonsteroidal anti-inflammatory drugs, or materials that contain compounds inhibiting β-OH-steroid dehydrogenase (licorice and certain chewing tobaccos) should be recorded. Symptoms of secondary hypertension should be elicited, such as episodes of headache, perspiration, palpitation, and tachycardia (pheochromocytoma), muscle cramps, weakness, polyuria (primary aldosteronism), peripheral vascular disease, intermittent claudication, previous episodes of pulmonary edema (renovascular hypertension), history of heart murmur and leg claudication (coarctation), family history of renal disease (autosomal dominant polycystic kidney disease) or flank trauma ("Page" kidney). Postural symptoms should be sought, which may indicate baroreceptor reflex failure (autonomic dysfunction or hypokalemia, for example) or hypertension with hypovolemia (pheochromocytoma).

Physical Examination

The physical examination should record height and weight so that the body mass index (weight in kg/[height in m]^2) can be calcu-

lated. Physicians should carefully assess the presence of obesity, and the waist-hip ratio should be measured. They should also evaluate obese hypertensive patients for sleep apnea syndrome, an often overlooked contributor to hypertension. The optic fundi should be evaluated. The thyroid gland deserves attention. In contrast to prevailing opinion, hypothyroidism rather than hyperthyroidism shows a greater association with hypertension. The cardiac examination, including the central and peripheral arteries, should be particularly thorough. Blood pressure should be measured in both arms. Younger patients particularly should have blood pressure measured in the lower extremities, and an infrascapular murmur should be sought. The size of the heart should be estimated and the presence of gallop rhythms recorded. The presence of Cushing's syndrome should be considered. The abdomen must be palpated for polycystic kidneys, and auscultated for systolic and diastolic bruits above the aortic bifurcation. Cutaneous stigmata of Cushing's syndrome and neurofibromatosis should be noted.

Most patients with long-standing hypertension show arteriolar narrowing and increased light reflex (grade I) on funduscopic examination. The veins may be constricted at the site of arteriolar crossing (grade II). Flame-shaped hemorrhages or exudates (ill-defined pale areas) may be present in patients with severe hypertension and are an important finding (grade III). If the optic nerve cannot be distinguished from the surrounding retina or if the optic nerve head is raised (choked), papilledema is likely to be present (grade IV). Such patients should have their mental status (orientation, short-term memory, serial sevens backwards, etc.) carefully evaluated for signs of hypertensive encephalopathy.

Laboratory Evaluation

A complete blood count, urinalysis, electrolytes, serum creatinine, fasting blood sugar, plasma lipids (HDL cholesterol, LDL cholesterol, triglycerides), serum uric acid, and a resting electrocardiogram (ECG) are adequate, provided that the history and physical examination have not revealed other pertinent findings. Patients < 35 years, patients with hypertension of abrupt onset, those with a negative family history, or patients whose hypertension is severe despite treatment warrant further laboratory evaluation. Additional screening procedures for such patients include urine collections for metanephrines (or equivalent), a renal scan before and after captopril (or equivalent such as computed tomography (CT) angiography of the kidney), a chest roentgenogram or other evaluation of to cardiac size, and a stimulated (upright posture) plasma renin activity (PRA) value. Table 1 shows a summary of routine tests for patients with uncomplicated primary (essential) hypertension and patients with suspected secondary hypertension.

An additional consideration in high-risk patients is echocardiography. Patients with moderate to severe hypertension should have a careful assessment of left ventricular hypertrophy, particularly if signs of heart disease are present on physical examination or routine electrocardiogram. Finally, high-risk patients may benefit from the determination of microalbuminuria, which is the first sign of nephropathy in patients with diabetes mellittus and an independent risk factor for heart disease, stroke, and peripheral vascular disease in nondiabetic hypertensive patients [8].

Table 1. Screening Tests for Primary and Secondary Hypertension

Primary hypertension	*Tests*
	Complete blood count Electrolytes Serum creatinine and/or urea concentration Urinalysis, consider microalbuminuria
Special	Optional tests Electrocardiogram 24 h ambulatory blood pressure Echocardiogram
Secondary hypertension	*Tests*
Coarctation	Chest roentgenogram
Cushing's syndrome	Plasma cortisol after dexamethasone suppression
Pheochromocytoma	Urinary vanillylmandelic acid, metanephrines clonidine suppression test
Primary aldosteronism	Serum electrolytes, PRA and Aldosterone with upright posture, PRA/Aldosterone ratio
Renovascular hypertension	Renal scan before and after captopril Renal artery duplex Doppler studies Renal angiography

Pathogenesis of Hypertension

Genetics of Hypertension

Essential (Primary) Hypertension

The familial predisposition to hypertension and its sequelae was observed early in sibling pair, family and monozygotic and dizygotic twin studies. Early investigators concluded that hypertension was inherited as a simple, autosomal dominant trait, suggesting a monogenic defect. In the 1950s, Pickering and coinvestigators convincingly showed that primary hypertension was not inherited in an autosomal dominant, but rather was a complex genetic condition in which 5 – 20 or more genes might be involved. However, unusual forms of inherited hypertension exist in which the hypertension is indeed inherited as a simple monogenic trait. Modern molecular techniques have allowed identification of the gene loci and the cloning of several such hypertension genes. General physicians should be aware of such syndromes; they may be more

common than appreciated and have contributed much to our understanding of blood pressure regulation.

The genetics of primary hypertension has generated great interest. Association and linkage studies have identified susceptibility gene loci. Examples include mutations in the angiotensinogen gene (substitution for methionine by threonine, M235T) and mutations in the catecholamine beta receptor gene. An insertion/deletion mutation in the angiotensin converting enzyme (ACE) gene, which has a substantial effect on ACE plasma levels, has been associated not with hypertension, but rather with the propensity to develop cardiac hypertrophy. Recently, the locus for adducin, a cytoskeletal protein, was linked to hypertension in salt-sensitive individuals.

Rare Genetic Causes of Hypertension

Glucocorticoid remediable aldosteronism (GRA) resembles primary aldosteronism. The mode of inheritance is autosomal dominant, which means that about half the family members are affected, men and women are both involved, and father-to-son transmission occurs. Patients commonly have hypokalemia. The stimulated PRA (upright posture) is low, while the aldosterone values in plasma and urine are elevated. There is no lateralization (adrenal vein aldosterone concentrations are not different), and no tumor is seen on CT or magnetic resonance imaging (MRI). In affected persons, 5 mg prednisone daily relieves the hypertension, suggesting a pathogenic role for adrenocorticotropic hormone (ACTH). The hypertension responds to both thiazide diuretics and to spironolactone, suggesting volume expansion and involvement of the mineralocorticoid receptor. Suspected individuals can have their urine tested for the abnormal steroid products 18 oxo-cortisol and 18 OH-cortisol. Patients have an abnormal chimeric gene located between the genes for 18 β-hydroxylase and aldosterone synthase, containing the promoter region for 18 β-hydroxylase and the structural portion of aldosterone synthase. The gene is expressed in the zona fasciculata, where its product metabolizes cortisol further to aldosterone and the abnormal steroid products. Prednisone 5 mg/day suppresses ACTH, thereby shutting off the chimeric gene. The disease may be diagnosed on the basis of clinical features and with a molecular genetic test. Since the availability of testing, hundreds of families have been found with this disease [9].

Liddle's syndrome is a similar autosomal dominant form of hypertension. These patients also may have hypokalemia; they exhibit a decrease in blood pressure with thiazide, amiloride or triamterene but not spironolactone treatment. Stimulated (upright posture) PRA is low in these patients, however the aldosterone values are also low and abnormal steroids are not found in the urine. Prednisone 5 mg/day makes the disease worse rather than better. Molecular techniques have identified a mutation in genes responsible for the β and γ subunits of the amiloride-sensitive epithelial sodium channel, which is responsible for sodium reabsorption in the distal portion of the distal tubule and collecting duct. Thus, the channel is abnormally active (open state) and sodium (with chloride) is inappropriately reabsorbed, resulting in volume expansion and low-renin hypertension. This defect is probably rare, nevertheless Liddle's disease could account for a portion of patients currently classified as having "low-renin" primary hypertension [9].

Apparent mineralocorticoid excess (AME) is a rare autosomal recessive disease. Affected persons have low stimulated PRA and low

aldosterone concentrations and superficially resemble patients with Liddle's syndrome. However, their blood pressure decreases with both thiazide diuretics and spironolactone, implicating the mineralocorticoid receptor. These characteristics are similar to those observed with licorice gluttony, a rare form of diet-induced secondary hypertension. Licorice contains a substance (glycyrrhizic acid) that interferes with the enzyme 11 β-OH steroid dehydrogenase, responsible for converting cortisol to cortisone in the renal distal tubule. Cortisol has the same affinity for the mineralocorticoid receptor as aldosterone. If the enzyme 11 β-OH steroid dehydrogenase does not function properly, the mineralocorticoid receptor can be inappropriately occupied by cortisol, resulting in a low renin, salt retention form of hypertension. In AME, mutations in the gene responsible for the production of 11 β-OH steroid dehydrogenase have been identified, resulting in a defective gene product. Identification of this disease and elucidation of the syndrome induced by licorice gluttony have drawn attention to this important regulatory system. Numerous plant products contain substances that may inhibit this enzyme, thereby promoting the development of low renin hypertension.

Autosomal dominant hypertension with brachydactyly is an autosomal dominant, monogenic form of hypertension that closely resembles essential hypertension, in that the hypertension is not salt sensitive and the renin-angiotensin axis is normal. A large affected family was found in northeastern Turkey and several affected families in the United States have subsequently been found. Affected family members also have brachydactyly. The responsible gene is not yet cloned, so the mechanisms causing the hypertension have not been elucidated. However, a linkage analysis isolated the gene locus to the short arm of chromosome 12. It is possible that the responsible gene could be relevant to patients with primary hypertension [10].

Autosomal dominant forms of pheochromocytoma exist. Patients with pheochromocytoma should be considered as possibly having one of these diseases. Neurofibromatosis may exhibit bilateral pheochromocytomas. Not all patients with neurofibromatosis have prominent cutaneous neurofibromas, a positive family history, or mental retardation. The skin should be examined carefully for tags, cafe au lait spots and axillary freckling. Von Hippel-Lindau disease (vHL) patients generally have ophthalmologic findings and signs of cerebellar disease. MRI is the diagnostic procedure of choice. Multiple endocrine adenomatosis type II (MEN II) patients have medullary thyroid carcinoma with elevated calcitonin levels, islet cell tumors, parathyroid hyperplasia and a propensity for pheochromocytoma. The pentagastrin test is helpful in making the diagnosis.

Genetic renal diseases may present with hypertension. Patients with autosomal dominant polycystic kidney disease (ADPKD) are invariably hypertensive. Patients with Alport's disease also frequently have hypertension. Family history, physical examination (auditory and ophthalmologic in the case of Alport's disease), simple renal function tests (urinalysis, protein excretion and creatinine clearance), and renal ultrasound are generally sufficient for the diagnosis. Thin membrane disease appears to be familial. This condition features premature glomerular obsolescence and hypertension.

Pathogenic Mechanisms

Blood pressure is determined by the blood flow (cardiac output) and the peripheral vascular resistance. The pathogenesis of primary

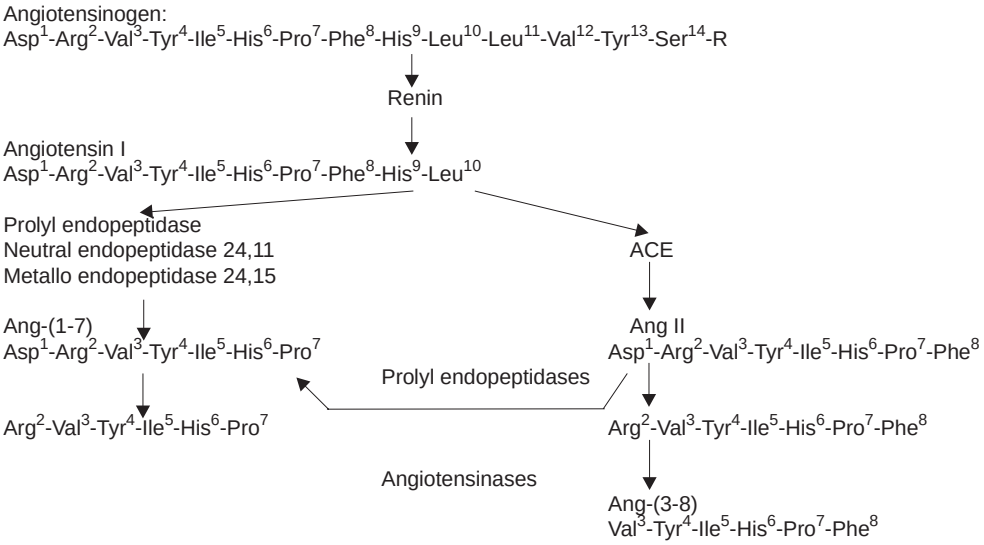

Figure 2. An abbreviated view of the renin-angiotensinogen system.

hypertension involves a series of feedback loops and regulatory systems. These regulatory systems are all interrelated in a cybernetic framework. Disturbances in any system or minor perturbations of several systems can increase blood pressure. Concomitant genetic modifications of several systems probably combine to produce primary hypertension in most cases.

Short-term Blood Pressure Regulation

Changes in blood pressure are sensed by baroreceptors located primarily in the great vessels, especially the aortic arch and the carotid sinus. These receptors relay information to the central nervous system via the vagus and glossopharyngeal nerves. When the blood pressure is low, sympathetic output produces vasoconstriction and a reflex increase in heart rate, as well as secretion of various agents to restore homeostasis. When the blood pressure is high, sympathetic tone is reduced and the heart rate reflexively decreased through parasympathetically-mediated mechanisms. In patients with primary or secondary hypertension, the baroreceptor mechanisms are altered, or "reset," and their sensitivity to a given pressure level decreased.

The Renin-angiotensin System

The renin-angiotensin system a fundamental system of blood pressure and blood volume regulation, is illustrated in Figure 2. Renin is a proteolytic enzyme produced by modified afferent arteriolar smooth muscle cells in the juxtaglomerular apparatus of the kidney. Its release can be stimulated by a local baroreflex mechanism within the kidney involving stretch receptors, by increased renal sympathetic tone, and by altered salt delivery at the macula densa of the distal tubule. Once

released into the circulation, renin acts on the α-globulin angiotensinogen produced by the liver. Renin cleaves off the decapeptide angiotensin (Ang) I. This decapeptide, which has no physiological effects, is cleaved by the ACE primarily in the pulmonary circulation to Ang II, a powerful vasoconstrictor, salt-retaining compound and potential growth factor, which in turn also stimulates aldosterone release from the zona glomerulosa of the adrenal cortex. This biochemical cascade is termed the renin-angiotensin system. Ang II is subsequently degraded to other fragments, Ang (2 – 8), Ang (1 – 7) and Ang (3 – 8). These fragments also have biological activity, especially Ang (1 – 7), which has influences opposite to those of Ang II. Ang (1 – 7) can also be produced directly from Ang I. The renin-angioensin system is extremely complex. Its components are present within the brain, where they regulate salt appetite, drinking behavior, and regulation of autonomic tone. Ang II is generated within the vascular wall of peripheral arterioles and within the heart. Angiotensinogen may be cleaved by enzymes other than renin, and Ang II may be generated by enzymes other than ACE. The importance of these alternative pathways in blood pressure regulation and primary hypertension is imperfectly defined. The renin-angiotensin system is undoubtedly important in primary hypertension, as the recently identified M235T substitution in the angiotensinogen gene suggests.

Primary hypertension can be classified in terms of plasma renin responses to dietary salt intake. Hypertensive patients can be categorized as having low renin, normal renin, and high renin hypertension. This classification has some prognostic implications. For instance, patients with high renin hypertension appear at greater risk to develop myocardial infarction and may benefit less from a salt-restricted diet than patients with normal renin or low renin hypertension. However, many specialized centers have elected not to routinely classify patients with primary hypertension in terms of renin levels, because the therapeutic implications of such classifications are not sufficiently clear. Patient renin levels may be determined in 3 ways: a low salt diet for approximately a week followed by a 24-hour urine sodium excretion compared to the PRA (in the seated position); a volume expansion-contraction protocol (2 L intravenous saline over 4 h on one day, followed by a 10 mmol sodium diet and 40 mg furosemide given 3 time on the second day); or measuring PRA before and after captopril 25 mg. This test is termed the “captopril test” and has been advocated by some groups to identify high renin patients and patients more likely to have renovascular hypertension. Renin and aldosterone responses in various clinical states are given in Table 2. Rarely, renal tumors and cysts can produce renin. The responses in Bartter’s syndrome and diuretic abuse are shown for comparison.

Other Humoral Systems

The kallikrein-kinin system is important to blood pressure regulation. Kallikrein is a renal enzyme that acts on kininogen, a plasma substrate, to release bradykinin. Bradykinin is a vasodilator peptide with important endothelial effects. Bradykinin is degraded to inactive products by ACE. The inhibition of ACE not only blocks Ang II formation, but also raises bradykinin-related effects on blood pressure, renal salt and water excretion, prostaglandin release, and nitric oxide release.

Arginine vasopressin (AVP) is primarily involved in osmoregulation, however the hormone may play a role in volume and blood pressure regulation under special conditions which are not normally associated with hyper-

Table 2. Renin (PRA) and Aldosterone (aldo) Levels in Various Hypertension Syndromes and Bartter's Syndrome

Diagnosis	PRA	ALDO
Renovascular	high	normal to high
Primary ALDO	low	high
Renal tumors and cysts	high	high
Primary hypertension	normal	normal
Low renin hypertension	low	normal
*GRA	low	high
*Liddle's	low	low
*AME	low	low
Hypertension with brachydactyly	normal	normal
*Bartter's	high	high
Diuretic abuse	high	high
High salt intake	low	low

*GRA is glucocorticoid remediable aldosteronism. Liddle's syndrome and hypertension with brachydactyly are other autosomal dominant genetic forms of hypertension. AME is apparent mineralocorticoid excess, an autosomal recessive form of hypertension. Bartter's syndrome (hypotension) is caused by mutations in the Na, 2Cl, K transporter in the ascending limb of Henle's loop.

tension, such as shock, hemorrhage, severe heart failure, and liver disease. Nevertheless, AVP, a powerful vasoconstrictor, is important in certain volume-related forms of hypertension, especially in accelerated or "malignant" hypertension. In these forms, competitive AVP antagonists lower blood pressure acutely. AVP is found at various places in the central nervous system, where it may have important regulatory effects.

In the last decade, a series of endogenous natriuretic factors have been identified. Atrial natriuretic peptide (ANP) is produced in special cells within the atria, and released in response to atrial stretch. The peptide inhibits renin and aldosterone release, and vasomotor tone; modulates glomerular filtration rate (GFR); and promotes diuresis and natriuresis. In addition, ANP increases capillary permeability.

The Vascular Endothelium

The identification of potent vascular endothelial-derived vasoactive substances in the past decade has underscored this organ's major role in blood pressure regulation. The most important vasodilator may be the endothelial-derived relaxing factor nitric oxide (NO). Other vasodilators from the endothelium are the vasodilator prostaglandins, such as prostacylcine, and the endothelial-derived hyperpolarizing factor. The endothelium also produces potent vasoconstrictors such as the prostanoid thromboxane and endothelin. Endothelin is the most potent constrictor known and may contribute to increased peripheral vascular resistance in advanced hypertension, where impaired endothelial function is evident. The endothelium, in response to shear stress and a host of circulating factors, modulates underlying vascular smooth muscle cell tone, as well as growth, differentiation, and angiogenesis.

The Kidney in Hypertension

Short-term regulators (e.g. the baroreceptor reflex mechanism), intermediate-term regulators (e.g. the renin-angiotensin system and cardiac atrial natriuretic factors), and local regulators (e.g. the endothelial cell mechanisms) directly and indirectly influence the kidneys in terms of pressure-natriuresis relationships [11]. A summary is given in Figure 3. The kidneys are responsible for controlling the volume in the body and thereby control the flow relationships determining arterial pressure. The kidneys excrete all salt and water,

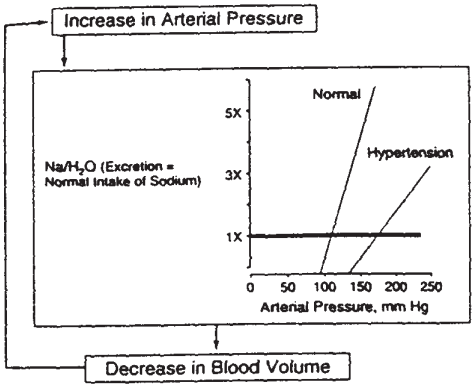

Figure 3. Schematic representation of the pressure-natriuresis relationship for the long-term control of arterial pressure. In normal individuals, any elevation in arterial pressure would be expected to increase sodium and water excretion by pressure natriuresis. Because sodium and water excretion is determined by intake and remains relatively fixed, the increase in sodium and water excretion slowly lowers blood volume sufficiently until arterial pressure returns exactly to control values. If sodium and water are lost from the body, the kidneys retain sodium and water to restore blood pressure to normal. The pressure-natriuresis relationship in hypertension either exhibits a slope reduction or is shifted in a parallel manner toward a higher set point. With reduced slope, the change in blood pressure for any given change in sodium and water intake is greater than normal (sodium sensitivity). With a parallel shift, the relationship between sodium and water intake and blood pressure is changed, however the blood pressure is higher for any given sodium and water intake. [Cowley & Roman. JAMA 1996; 275: 1581 – 1588] with permission.

except that lost through insensible mechanisms. Thus, a relationship between urinary salt and water excretion and the arterial pressure can be defined for every level of arterial pressure or salt and water intake. This relationship, the renal function curve, defines the long-term pressure-regulatory system of the body. In hypertension, the pressure-natriuresis relationship is necessarily shifted to the right. The steepness of the curve defines the relationship between arterial pressure and dietary salt intake and excretion. A relatively flat curve is observed in salt-sensitive hypertension. A steep curve is observed in salt-resistant hypertension. Rarely, e.g. in extreme high-renin hypertension, an inverse relationship may be observed, whereby blood pressure actually decreases with increased salt intake. In physiological experiments, the pressure-natriuresis curve is shifted to the right by the renin-angiotensin-aldosterone system, by catecholamines or sensitivity to catecholamines, AVP, and endothelin. The curve is shifted leftward by ANP, NO, and other vasodilators. Alterations in any and all of these variables, genetic or acquired, can result in primary hypertension.

Secondary Changes Maintaining Hypertension

The longer the duration of hypertension, the greater the tendency of resistance vessels to "adapt" to the elevated blood pressure with media hypertrophy and increased wall-to-lumen ratio (vessel remodeling), which makes the vessels even more susceptible to vasoconstrictors. Thus, the primary (or secondary) mechanism eventually becomes less relevant, because the altered vascular structures themselves serve to perpetuate the condition. Secondary changes also occur in the kidney. Even before clinically evident nephrosclerosis develops, renal blood flow (RBF) declines and renal vascular resistance increases. As a consequence, the salt-excreting capacity of the kidney further decreases , making the hypertension more volume dependent over time. This is the reason that low-renin hypertension is predominant in long-standing hypertension and in older patients. In addition, compliance of large vessels including the aorta declines, impairing the *windkessel* function of the aorta, leading to further increase of systolic blood pressure.

Management

Nonpharmacological Approaches

Multiple Risk Reduction

The purpose of hypertension treatment is to reduce stroke and cardiovascular risk. Thus, hypertension treatment must necessarily consider other risk factors. A person's genetic makeup, age and gender cannot be changed. Volitional risk factors must therefore be addressed. The most important of these is smoking, which constitutes the single leading cardiovascular risk factor. Numerous approaches have been advocated; nicotine-containing gum and patches to wean the addicted patient from smoking have been shown to be effective in randomized trials. The nicotine content of these aids does not influence cardiovascular risk, and patients with preexisting heart disease can use them safely.

The evidence associating cholesterol with heart disease is overwhelming, and several secondary and primary prevention trials have clearly shown that lowering cholesterol lowers cardiac events and mortality. Any dietary approach for hypertension should simultaneously consider cholesterol intake. In the Scandinavian simvastatin trial, stroke also occurred less frequently in the treatment group than in the control group. The value of lowering cholesterol by medication can be estimated from the Sheffield risk tables, which consider age, gender, cigarette smoking, hypertension, diabetes mellitus, and left ventricular hypertrophy on ECG [12].

Diabetes mellitus (DM) is a leading risk factor for stroke and heart disease, and currently half the dialysis patients in the United States and Europe have DM as their primary diagnosis. The incidence of diabetes mellitus is increasing incrementally in all industrialized nations. A fasting blood sugar of 7 mmol/L (125 mg/dL) or a glycosylated hemoglobin level > 7% are sufficient for the diagnosis. Hyperglycemia in diabetic patients must be controlled by diet or medication and control of body mass index is crucial [13].

Weight Control

Weight control is the most important nonpharmacological approach to lower blood pressure [14]. Randomized, controlled trials have documented that weight loss lowers blood pressure. The reduction in blood pressure occurs with the loss of the first few kilograms. The mechanism by which obesity raises blood pressure is not known for certain; however, increased cardiac output and increased sympathetic tone appear to be important. In studies examining various nonpharmacological interventions simultaneously, weight loss was superior to any manipulation of electrolyte intake. The reduction in mean blood pressure to be expected is in the range of 5 – 8 mm Hg. Weight loss is also the most important nonpharmacological approach to DM and has a beneficial influence on cholesterol. The obesity epidemic warrants new novel approaches to weight loss. The discovery of genes responsible for appetite such as leptin will hopefully open new therapeutic options in the future. Currently, no weight loss program has been shown to be consistently successful in the long term, and individual approaches should be attempted. Crash diets, fad diets, complete fasts, and other unbalanced diets should be avoided, because they are generally effective only in the short term. There is good evidence that weight loss with subsequent weight gain is worse than doing nothing at all, making a change in lifestyle necessary to maintain weight reduction.

Aerobic Exercise

Aerobic exercise alone will lower blood pressure if performed approximately 2 times 30 minutes weekly, provided that the intensity provides 70 – 80% of the maximal work load. Such a load will necessarily increase the aerobic capacity. Several specific benefits can be attributed to exercise: patients with severe hypertension on multiple drug regimens can experience regression of left ventricular hypertrophy after regular aerobic exercise that increases aerobic capacity, drug dosage can be reduced in some patients, and improved health consciousness and body image may reinforce lifestyle changes such as smoking cessation.

Reduction of Alcohol Intake

A high alcohol intake (> 30 g ethanol/day) increases blood pressure. In patients whose blood pressure suddenly becomes difficult to control, the possibility of increased alcohol intake should always be considered. Cleverly designed randomized controlled studies have shown that alcohol can increase blood pressure chronically and that lowering alcohol intake can reduce blood pressure. Patients should be encouraged to curtail their alcohol intake to the equivalent of no more than 2 glasses of wine or beer per day.

Reduction of Salt Intake

Randomized, prospective trials have shown that by reducing salt intake, mean arterial blood pressure may be decreased by 5 – 8 mm Hg. Not all patients exhibit a decrease in blood pressure; patients may be divided into salt-sensitive and salt-resistant individuals. The theoretical possibility that salt-resistant persons might exhibit an increase in blood pressure after lowering their salt intake has not been convincingly demonstrated. Thus, all hypertensive patients should be encouraged to reduce their dietary salt intake to < 100 mmol sodium (2.5 g sodium or 5 g table salt) per day. Sodium ingested in the form of other nonchloride salts, such as sodium bicarbonate in mineral water and baking powder has not been shown to increase blood pressure. Ninety-eight percent of sodium is ingested as the chloride salt. Less than one-third of the daily intake is ingested as salt added to the food in cooking or from the salt shaker. The bulk of dietary salt is present in prepared packaged foods. Thus, persons wishing to decrease their salt intake must check food labels accordingly.

Potassium Intake

Increased potassium intake may lower blood pressure in some individuals and decrease the risk of stroke independent of blood pressure-lowering effects. Improved short-term blood pressure regulation and a saluretic effect might mediate these beneficial effects. Because potassium is present in fruits and vegetables, an increase in folic acid can also be expected, which would have the added desirable effect of lowering homocysteine levels. High homocysteine levels have been convincingly associated with increased cardiovascular risk.

Calcium Intake

Increased calcium intake decreases the propensity to develop preeclampsia in pregnant women and may also decrease blood pressure in some hypertensive individuals, in addition to its reduction of osteoporosis risk. Lowering

the dietary salt intake decreases the daily urinary calcium excretion, which may also help maintain calcium homeostasis.

The United States Joint National Committee (JNC) has listed potential benefits of increasing dietary potassium to 3000 mg/day, calcium to 800 – 1000 mg/day, and magnesium to 350 – 400 mg/day, and recommends use of these electrolytes as an effective pharmacological strategy. However, the JNC does not recommend electrolyte supplements unless patients are unable to maintain these levels of intake in their diets.

In summary, the hypertensive patient will benefit from a low calorie, low fat, low salt, high potassium, high calcium diet and an active lifestyle. Such a diet will necessarily be rich in complex carbohydrates as provided by ample amounts of fruits and vegetables. A brief review of nonpharmacological approaches is shown in Table 3. Although nonpharmacological measures have limited value for the treatment of hypertension if applied alone, they may greatly reduce the amount of medication required and even serve as a preventative measure.

Table 3. Life-style Modifications to Lower Blood Pressure, Decrease Cardiovascular Risk, Decrease Medication Requirements, and Possibly Avoid Hypertension*

– STOP smoking!
– Lose weight; desired BMI is 24
– Perform aerobic exercise, preferably daily. Brisk walking 30 – 45 min/day is better than "occasional" jogging
– Limit alcohol intake to 30 g ethanol/day (2 beers, 2 glasses of wine, 1 whiskey-containing drink)
– Reduce salt intake to < 2.5 g (100 mmol) sodium or < 5 g salt daily.
– Increase intake of (fresh) fruits and vegetables, improve potassium, magnesium, and calcium intake
– Modify diet further to consider other risk factors, decrease cholesterol and saturated fat intake

*In accordance with the fifth report of the Joint National Committee and the recommendations of the German Antihypertension League.

Antihypertensive Medications

Four large clinical trials, the Australian Management Committee study, the Oslo study, the Hypertension Detection and Follow-up program, and the Medical Research Council study, showed that patients whose diastolic blood pressure ranged from 90 – 104 mm Hg benefit from drug treatment. Stroke, aortic dissection, heart failure, and cardiac hypertrophy occurred less frequently in treated patients than in control subjects and 2 of the studies showed a reduction in mortality. Elderly patients also benefit from antihypertensive treatment. The Medical Research Council study and the Scandinavian STOP Hypertension study both demonstrated that stroke can be sharply curtailed in the elderly. One of the studies showed a reduction in cardiovascular events, as well as improved mortality. Systolic hypertension is also worth treating. The Systolic Hypertension in Elderly Patients (SHEP) study documented that controlling systolic hypertension reduces stroke and cardiovascular events.

Thus, clinical trials suggest that patients with diastolic blood pressures of 105 mm Hg or greater should be treated aggressively. Patients with blood pressures between 90 – 104 mm Hg can benefit from treatment, as do patients with isolated systolic hypertension. Finally, advancing age should be viewed as an opportunity rather than an impediment for treatment. The level to which blood pressure should be reduced for the greatest risk-reduction benefit is not known. A study currently in

progress is addressing the question of whether diastolic pressures of 90, 85, or 80 mm Hg should be the goal.

Diuretics

Diuretics have been employed in every medication outcomes trial to date. They are proven to reduce stroke and improve cardiovascular risk in hypertensive patients. The most recent (1997) recommendation of JNC stated that diuretics should be considered in the initial treatment of hypertension, unless specifically contraindicated [15]. Such is seldom the case. Significant hypokalemia is unlikely if the diuretic dose is maintained at a low level, and hydrochlorothiazide 25 mg daily is usually sufficient to treat hypertension. Thiazides may be combined with a potassium-sparing diuretic such as amiloride, triamterene, or spironolactone. Hypokalemia should be avoided since it may induce ventricular irritability. Thiazide diuretics may lead to glucose intolerance and increased uric acid serum concentrations. Both are unlikely at the suggested dosage. Hypercalcemia rarely occurs with thiazide diuretics and, if present, suggests hyperparathyroidism. Because thiazides decrease urinary calcium excretion, they are ideal for the treatment of patients with kidney stones, who have a higher incidence of hypertension than the general population, as well as for the treatment of hypertensive osteoporosis patients. Thiazides may increase LDL cholesterol and triglyceride levels, however, the HDL cholesterol level and the ratio of total cholesterol to HDL cholesterol remain unchanged. The changes appear transient and their contribution to cardiovascular risk is unknown [16]. Thiazide diuretics have been shown to be more effective than furosemide in lowering blood pressure in several prospective studies, even when furosemide is given twice daily. Thus, there is no reason to treat hypertensive patients with loop diuretics unless they have reduced renal function (serum creatinine > 3 mg/dl) or salt retention. Potassium-sparing diuretics are less potent than hydrochlorothiazide and should not be given alone, together with ACE inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs), since hyperkalemia may ensue. Diuretics are inexpensive, given once daily, and can conveniently be combined with other medications – all features contributing to compliance. Subjective side effects include sexual dysfunction, which in one study occurred even more frequently than during beta blocker therapy.

Beta Blockers

Beta blockers were also included in all medication outcomes trials to date. They are also proven to reduce stroke and to improve cardiovascular risk in hypertensive patients. The JNC concluded that like diuretics, beta blockers should be considered in the initial treatment of hypertension, unless specifically contraindicated. Beta blockers have also been shown to reduce mortality after myocardial infarction and recently to reduce cardiovascular mortality after any major surgery in patients at cardiovascular risk. Beta blockers are, along with nitrates, the drug of choice for angina pectoris. Thus, the argument to use beta blockers in the treatment of essential hypertension is compelling. Beta blockers are effective as initial therapy, particularly in young and middle-aged patients, 50 – 75% of whom respond. The response rate for older patients is somewhat lower. Beta blockers also function well combined with other medications. The blood pressure-lowering action of beta blockers is still not entirely clear, however beta blockers reduce cardiac output and

reduce renin release. At higher doses, a renin-independent central nervous system effect is also operative.

Beta blockers have several disadvantages. They are contraindicated in persons with asthma and difficult to use in patients with chronic lung diseases. They diminish aerobic exercise tolerance to some degree, although they do not interfere with the benefits of aerobic exercise. Beta blockers should be used with caution in patients with congestive heart failure, although several recent trials have shown beta blockers to be beneficial in the treatment of congestive heart failure and more studies addressing this issue are under way. Beta blockers should not be given to patients with atrioventricular conduction disturbances and should not be combined with verapamil. Beta blockers may make intermittent claudication worse. They may induce depression and nightmares in some patients. They may make hypoglycemic episodes less noticeable in diabetic patients receiving insulin by blocking the expected tachycardia and diaphoresis. Diabetic patients should be warned accordingly. Beta blockers may increase the ratio of total cholesterol to HDL cholesterol, although the effect on cardiovascular risk is unknown.

Different types of nonselective and selective beta blockers are available from which to choose. Propranolol, nadolol, and timolol are nonselective beta blockers. The latter 2 are long-acting. Atenolol and metoprolol are selective beta blockers, while celiprolol is highly selective. Some beta blockers, such as pindolol, also have an intrinsic sympathomimetic activity, which may obviate the cardioprotective effect offered by beta blockers in coronary heart disease. Labetalol combines both alpha- and beta-blocking properties. This drug is effective in the oral or intravenous treatment of hypertensive emergencies and may be used for the treatment of known or suspected pheochromocytoma. Labetalol is also helpful in the treatment of preeclampsia and related syndromes. Carvedilol is a beta blocker that has some alpha- and calcium channel-blocking activities.

Alpha Blockers

Alpha blockers, such as prazosin, terazosin, and doxazosin block smooth muscle post-synaptic alpha1 receptors. Urapidil is an alpha blocker that also has a central mode of action, and may be given parenterally. Alpha blockers do not usually induce a reflex increase in cardiac output and renin release, and may be combined with other drugs. Alpha blockers are generally well tolerated. Rarely, a patient may experience sudden syncope, usually postural after the first dose of prazosin. The mechanism is unexplained. Physicians frequently begin prazosin treatment with a 1 mg evening dose taken with the patient already supine. Postural hypotension may occur in 2% of patients; special care must be taken in patients with previous syncope and in the elderly. Alpha blockers may be particularly helpful in patients with known or suspected pheochromocytoma and also in patients with Raynaud's phenomenon. Alpha blockers cause at least a short-term reduction in serum lipids of unknown significance. They are associated with retrograde ejaculation in some patients. Alpha blockers are also particularly useful in patients with benign prostatic hypertrophy. In a recent trial alpha blockers were more effective in alleviating this condition than inhibitors of dihydrotestosterone.

Angiotensin-converting Enzyme (ACE) Inhibitors

ACE inhibitors inhibit the production of Ang II, inhibit the degradation of bradykinin,

and increase serum concentrations of Ang (1 – 7). They are very successful in reducing blood pressure. Moreover, ACE inhibitors have revolutionized the treatment of congestive heart failure and increase survival after myocardial infarction, even in patients with good left ventricular function. The short-acting ACE inhibitor captopril was the first of this class available and was given to patients in doses up to 300 mg/day, although such doses are rarely indicated. The recommended starting dose in moderate to severe hypertension is 25 mg 2 – 3 times daily. ACE inhibitors all have characteristic side effects, including cough, upper respiratory congestion, allergy-like symptoms, and dysgeusia. Rarely, angioneurotic edema may occur. Such effects have been attributed to bradykinin. Proteinuria is said to occur in 1% of patients; however, careful investigations of putative ACE inhibitor-induced proteinuria did not convincingly show that the ACE inhibitor was responsible. ACE inhibitors may increase creatinine levels, particularly in patients with a solitary kidney with vascular stenosis. Reversible granulocytopenia was reported with captopril after its introduction, possible related to high doses. ACE inhibitors are contraindicated during pregnancy or in women intending to become pregnant because of teratogenicity. An important side effect of ACE inhibitors is hyperkalemia, particularly in patients with some decrease in renal function (e.g. DM) who are simultaneously receiving a potassium-sparing diuretic, NSAID, beta blockers, and digitalis. This effect is termed secondary hypoaldosteronism and is an expected pharmacological action rather than a side effect.

Certain captopril-related side effects were attributed to the presence of a free sulfhydryl group; other ACE inhibitors have been introduced without this sulfhydryl group. Similar side effects have been observed with enalapril and lisinopril. Additional ACE inhibitors available include benazepril, fosinopril, quinapril, and ramipril. With few exceptions, the indications, dosage range, duration, and side effects of these ACE inhibitors are similar to those outlined above. Fosinopril is eliminated by both the kidneys and liver, and consequently no dosage adjustment is necessary with reduced renal function. Ramipril is the ACE inhibitor with the best documentation regarding blood pressure reduction 24 hours after administration.

Prospective trials in patients with diabetic nephropathy and patients with a variety of renal diseases indicate that ACE inhibitors favorably influence the progression of chronic renal disease. In these trials, patients received their usual antihypertensive agents and were then randomized to either the ACE inhibitor or a placebo tablet. The blood pressure values of the ACE inhibitor-treated patients were slightly lower than in the control group, suggesting that blood pressure lowering is the most important aspect. Impressive data have also been accrued regarding the reduction of proteinuria and microalbuminuria in patients with type II DM. ACE inhibitors are also effective in the regression of ventricular hypertrophy. The action of ACE inhibitors is potentiated by a low-salt diet, thiazide diuretics, and loop diuretics.

Angiotensin Receptor Antagonists and Renin Inhibitors

The renin-angiotensin cascade can be inhibited at various places. Ang II has two major receptors. The AT-1 receptor mediates smooth muscle cell contraction, renal sodium reabsorption, aldosterone release, and central effects of drinking and salt appetite. Effective blockers of the AT-1 receptor have been introduced. These small nonpeptide molecules are well absorbed orally and very well tolerated.

Angiotensin receptor antagonists do not cause angioneurotic edema and have no effect on bradykinin elimination that can cause cough or respiratory symptoms. Thus, the 15% of patients who have difficulty tolerating ACE inhibitors may be effectively treated with angiotensin receptor antagonists. Angiotensin receptor antagonists result in increased PRA and increased production of Ang II. Theoretically, the AT-2 receptor is more likely to be occupied when the AT-1 receptor is blocked. The functions of the AT-2 receptor have not been clarified, however, it may exert an antiproliferative effect on vascular tissue. Two AT_2 receptor blockers, losartan and valsartan, have been introduced into clinical practice. A double-blind prospective trial showed that losartan lowered blood pressure as effectively as enalapril.

Calcium Channel Blockers

Calcium channel blockers work by inhibiting calcium influx via the L-type, voltage-dependent calcium channel on vascular smooth muscle cells. Verapamil is also particularly effective in the cardiac conduction system. As a class, the drugs can be considered arteriolar vasodilators. The claims that calcium channel blockers are specifically helpful in the elderly, black patients, and salt-sensitive hypertension patients have not been backed up by prospective clinical trials.

Nifedipine was the first of the dihydropyridine calcium channel blockers introduced. A short duration of action (only 4 – 6 h) means that it must be given 3 – 4 times daily. Side effects include flushing, headaches, and postural hypotension. Although often used to treat hypertension, short-acting nifedipine was never approved for this indication by the United States Food and Drug Administration. Furthermore, although advocated for the treatment of hypertensive emergencies by some, recent considerations suggest that its use in this clinical setting is not without problems [17]. Longer-acting forms of nifedipine lack these undesirable side effects. Additional long-acting dihydropyridines are now available, including amlodipine, felodipine, isradipine, and nicardipine. The side effects and efficacy seem similar to those of long-acting nifedipine. Both short- and long-acting calcium channel blockers may cause pedal edema. The edema probably results from increased intracapillary pressure from peripheral arteriolar dilatation and is not related to primary renal salt retention.

Diltiazem (a benzothiazepine) and verapamil (a phenylalkylamine) are nondihydropyridine calcium channel blockers. They differ from the dihydropyridines by their chronotropic properties. Verapamil particularly is associated with constipation, and patients should be alerted. Verapamil and diltiazem should be used with extreme caution in patients with conduction abnormalities or on beta blockers.

New types of calcium channel blockers are being introduced that not only inhibit voltage-dependent L-type calcium channels, but also T-type calcium channels. Mibefradil is such a compound, and has a greater affinity for the T-type calcium channel than the L-type calcium channel. Mibefradil dilates both coronary and peripheral arteries, with a slight decrease in heart rate. Nevertheless, mibefradil leads to no decreased inotropic effects. The drug's half life is sufficiently long to permit once daily administration. A placebo-controlled trial in patients with hypertension showed a 15 – 18 mm Hg blood pressure decrease at higher doses compared to a 3 – 5 mm Hg reduction for placebo.

The calcium channel blockers have been used as first-line antihypertensive drugs. They possess excellent blood pressure-lowering ef-

ficacy. Calcium channel blockers have a natriuretic action and are not associated with salt and water retention, making them very popular with physicians. Recently calcium channel blockers, particularly short-acting nifedipine, have come under attack. In retrospective, case-control, observational studies, patients receiving nifedipine, verapamil, and diltiazem experienced increased numbers of adverse cardiovascular events compared to patients not receiving these drugs. Numerous confounding variables played a role in these studies and iron-clad conclusions cannot be drawn. In a prospective trial comparing isradipine to hydrochlorothiazide, adverse cardiovascular events were, if anything, more common ($p=0.07$) in the isradipine group than in the control group. Prospective comparative trials involving calcium channel blockers and ACE inhibitors, neither of which have as yet been shown to reduce morbidity and mortality in patients with hypertension, will hopefully clarify these issues. Finally, the use of short-acting nifedipine in patients with hypertensive urgencies or emergencies has been challenged on the basis of frequent complications, such as acute stroke. The use of nifedipine in this setting should be re-evaluated.

Centrally Acting Agents

Clonidine, moxonidine, methyldopa, and guanabenz act in the central nervous system. Initially, an $alpha_2$-adrenergic agonist action was postulated, but current thinking favors activation of imidazoline receptors. Clonidine can be extremely effective in patients with severe hypertension or renin-dependent disease. It acts by decreasing sympathetic output from the central nervous system. Side effects include dry mouth, drowsiness, delayed alertness, depression, and impotence, and are dose related. A convenient transdermal patch is available. Clonidine has specific usefulness in treating patients with cocaine-related effects, methamphetamine effects, and hyper reactivity associated with withdrawal states. The patch is also very convenient in this therapeutic setting. Anecdotal information suggests that clonidine may also help hypertensive smokers attempting to quit. Methyldopa has been safely and reliably used for decades. The drug has a particular niche in the treatment of hypertension in pregnancy, primarily because of its long track record rather than on the basis of controlled clinical data. Methyldopa may also act by serving as a false neurotransmitter. Centrally-acting agents, particularly Clonidine, have been associated with substantial rebound hypertension if suddenly discontinued. Moxonidine, which binds selectively to imidazole receptors in the rostral ventrolateral medulla, has fewer side effects and less tendency to cause a withdrawal syndrome, although it also should be withdrawn with caution.

Guanethidine and Guanadrel

These drugs deplete catecholamines from nerve endings. The compounds have a wide dose-response range and are not associated with sedation. Side effects include orthostatic hypotension and diarrhea. In today's practice, these drugs are primarily of historic interest.

Reserpine

Reserpine has a long history and was included in the initial controlled trials which indicated that antihypertensive treatment decreases stroke and cardiovascular risk. Reserpine in higher doses may initiate sudden severe depression; it should be administered only to emotionally stable patients who have

been informed. Depression is unusual with doses ≤ 0.25 mg/day. Once-a-day treatment is effective. Reserpine's efficacy and low cost suggest that its world-wide role should be reconsidered.

Vasodilating Agents

Hydralazine and minoxidil are vasodilators that probably work by facilitating potassium entry into vascular smooth muscle cells. Minoxidil is more potent. Both drugs cause reflex tachycardia and renal salt and water retention and should thus be used together with a beta blocker and loop diuretic. Hydralazine may cause a lupus-like syndrome (usually sparing the kidneys) when given at doses > 200 mg/day. Minoxidil causes hair growth, a side effect for which the drug is marketed as a topical agent. Minoxidil is effective in severe refractory hypertension and should be considered in patients requiring three or more drugs to control their blood pressure.

Agents Under Development

Nonpeptide, orally absorbable renin inhibitors have been developed, which may offer a new means to alter the renin-angiotensin system. Remikiren, enalkiren and zankiren are examples. Neutral endopeptidase inhibitors, such as candoxatrilat, candoxatril, and sinoxpidan lower blood pressure by preventing the degradation of atrial natriuretic peptide, resulting in natriuresis and vasodilatation. Endothelin inhibitors are being developed that are capable of blocking the action of endothelin at its specific receptor site. NO inducing compounds, such as L-arginine, could decrease peripheral vascular resistance by promoting NO production. Renomedullary depressor lipids, such as medulipin, are being considered to promote vasodilatation, sympathetic nervous system suppression, and natriuresis. New potassium channel openers, such as pinacidil, cromakalim, and levcromakalim, are being developed to hypopolarize cells, alter calcium flux, and reduce vascular smooth muscle tone.

Choice of Drugs

Surprisingly, the antihypertensive efficiency of all antihypertensive drugs when given singly is similar, decreasing blood pressure by about 8 mm Hg, compared to placebo. This result is probably related to the many different feedback loops controlling blood pressure simultaneously. Interference with any one system results in counter-regulatory mechanisms, which limit the effect of any single agent.

The most recent JNC (1997) recommendation reversed a previous stand and suggested that antihypertensive treatment should commence with diuretics and beta blockers. If necessary, the two drugs could be combined. Cost and documented efficacy of risk reduction stemming from prospective clinical trials played a role in the JNC recommendation. The recommendation is controversial; the International Society of Hypertension and the German Antihypertension League published different recommendations. These expert groups suggested that thiazides, beta blockers, ACE inhibitors, alpha blockers, and calcium channel blockers are all first line agents [18]. Initial treatment could commence with any of these drugs, with addition of a second as needed.

A trial is in progress testing the efficacy of five drug classes in terms of stroke and cardiovascular event reduction. The results of this trial will not be available for several years to come. Thus, initial treatment decisions re-

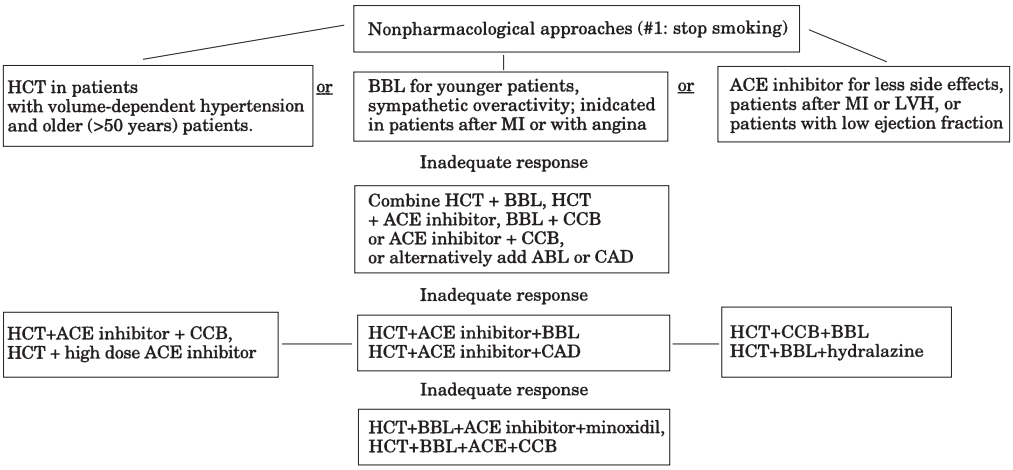

Figure 4. A simplified approach to the treatment of hypertension*. Suggestions are flexible and are intended as examples. HCT = hydrochlorothiazide (or equiv), BBL = beta blocker (combined beta + alpha blocker acceptable), ACE = angiotensin converting enzyme inhibitor, CCB = calcium channel blocker, ABL = alpha$_1$-blocker, CAD = centrally acting drug.

main essentially empirical and are based on blood pressure-lowering effects, a surrogate endpoint, since the primary concern is decreasing the incidence of stroke and cardiovascular disease. In recent years, physicians have frequently chosen to begin treatment with an ACE inhibitor or a calcium channel blocker because of perceived decreased side effects, even though the best "hard end point" data are available for diuretics, beta blockers and reserpine. Diuretics have waned in popularity because of concerns about hypokalemia and their lipid-raising potential. The TOMHS study examined the effects of monotherapy in patients with mild hypertension followed for 4 years, compared to a nonpharmacological intervention [19]. The drugs administered in the trial included an ACE inhibitor (enalapril), beta blocker (acebutolol), diuretic (chlorthalidone), calcium channel blocker (amlodipine), and an alpha blocker (doxazosin). The drugs were more effective than the nonpharmacological intervention; however, the antihypertensive effect was not significantly different among the regimens: about 6 – 8 mm Hg. Side effects were few and not significantly different from placebo. Regression of left ventricular size was monitored echocardiographically in the patients and interestingly, the thiazide diuretic was comparable to the other drugs, in this respect.

A decision tree is suggested in Figure 4. In terms of monotherapy, treatment should begin with a thiazide diuretic or a beta blocker. Young patients with autonomic hyperactivity, patients with angina pectoris, or patients who have had a myocardial infarction should receive a beta blocker. Older patients, or patients with salt-sensitive, volume-dependent hypertension do well with a low dose of hydrochlorothiazide. In patients with reduced ventricular function (even mild heart failure), an ACE inhibitor should be given. Two-drug therapy is best accomplished by combining a thiazide

diuretic with a beta blocker or an ACE inhibitor. A long-acting calcium channel blocker can be conveniently combined with a centrally acting drug or an ACE inhibitor. A dihydropyridine can also be combined with a beta blocker. The combination of a calcium channel blocker with a diuretic is said not to be particularly effective because both exert a natriuretic action; however, the scant controlled data addressing this issue are not convincing. Interestingly, different classes of calcium channel blockers can be combined to achieve an even greater blood pressure-lowering effect.

Severe hypertension may require three or more drugs. A diuretic, high-dose ACE inhibitor, and a calcium channel blocker or beta blocker can be considered. An alpha blocker or a centrally-acting drug may be a valuable addition. If the hypertension is refractory, physicians should not refrain from prescribing minoxidil in combitnation with a beta blocker and a diuretic to avoid reflex tachycardia and salt and water retention.

Several points need to be kept in mind. Compliance to life-long drug therapy is always problematic. A single daily dose has the best chance for success. Even twice daily dosage is questionable. Thus, formulations must be selected that allow for single daily dosing. Requirement for such a formulation is a > 50% "peak to trough" ratio of blood pressure-lowering effect, which means that at least half the maximal potency must be retained after 24 hours. Physicians must ask about side effects. Patients seldom volunteer information about impotence, depression, and nightmares, and may not recognize cough. The young male patient with impotence may simply not take his medicine. The spouses of the patients should be asked about side effects as well, as their answers are often illuminating. The nonpharmacological approaches should be regularly stressed. If hypertension continues or recurs, the physician should consider increased alcohol intake, excessive salt intake, noncompliance, or secondary hypertension. The latter (e.g. renal artery stenosis) occasionally develops superimposed on essential hypertension. Patients should be taught the names of their medicines. They should be able to recognize each tablet, know their dosage schedules, and have these written down and readily available. It is surprising what human beings will ingest without question.

Home blood pressure monitoring by the patients themselves has become popular. Inexpensive sphygmomanometers, or wrist blood pressure measuring devices, are available and the practice of home monitoring is helpful. However, the devices are not all reliable and should be regularly compared to a mercury column sphygmomanometer in the physician's office. Furthermore, blood pressure monitoring can become a fetish and an obsession. As a result, patients frequently juggle their medicines on their own without informing their physicians. Patients must understand that antihypertensive treatment is a life-long, marathon treatment of a risk factor designed to protect against stroke and heart attack. A momentary blood pressure value is of only marginal interest. Finally, patients must be made aware that hypertension, with the exception of malignant hypertension, is asymptomatic. The lay public and many physicians are firmly convinced that hypertension is responsible for headache, dizziness, nose bleeds, flushing, tinnitus, and other perturbations of daily life. A prospective study examining this issue showed no difference in the appearance of such symptoms in hypertensive patients and a normotensive control population.

Last but not least, long-term use of antihypertensive drugs is safe and well tolerated. In a study of 5,485 hypertensive patients, no

deaths attributable to the therapy were reported, fewer than 1% of patients required hospitalization for side effects, and only 9% had side effects sufficiently severe to require a change in pharmacological therapy.

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