Secondary Nonrenal Hypertension

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Secondary hypertension is responsible for < 10% of cases of adult hypertension. The suspicion of a secondary cause should be heightened whenever the clinical picture or response to treatment is not typical of those of essential hypertension [1]. The more atypical the picture is, the higher the suspicion of secondary hypertension should be (Table 1). Clues for the presence of secondary hypertension should be sought in the original evaluation of all hypertensive subjects and during the course of treatment. At a minimum, a urinalysis and potassium (K^+), calcium (Ca^{2+}), and creatinine levels should be done on any patient with confirmed hypertension before treatment is initiated. A detailed history of medicinal and recreational drug use is of utmost importance because many of these substances are known to cause blood pressure elevation [2]. A family history of childhood hypertension, renal disease, pheochromocytoma, endocrinopathies, or hypokalemia may be an important clue to the presence of secondary hypertension.

Table 1. The typical picture of essential hypertension.

- Age of onset 25 – 55, older for isolated systolic HTN
- Asymptomatic
- Mild-to-moderate in severity (< 180/110)
- Lack of grade III or IV retinopathy
- Urinalysis, renal function, and potassium are normal
- Controllable with nonpharmacological measures and up to 3 drugs at maximum doses

In some instances essential and secondary hypertension could coexist, and the removal of the secondary cause (such as excessive alcohol consumption) leads to easier control of the essential component. Removing the cause in correctly diagnosed secondary hypertension leads to normalization of the blood pressure unless there is another coexisting factor, or when the secondary hypertension has been long lasting and already caused irreversible damage to the cardiovascular bed and the kidneys.

Mineralocorticoid Hypertension and Liddle Syndrome

Normal Physiology. The activation of the renin-angiotensin system leads to the production of angiotensin (Ang) II which, among other things, binds to a membrane receptor in the zona glomerulosa of the adrenal cortex leading to a series of reactions that end with aldosterone biosynthesis (Figure 1). Aldosterone acts on the distal tubules and cortical collecting ducts of the kidney by occupying an intracellular receptor, the mineralocorticoid or type I receptor, leading to an increase in the number of sodium channels that

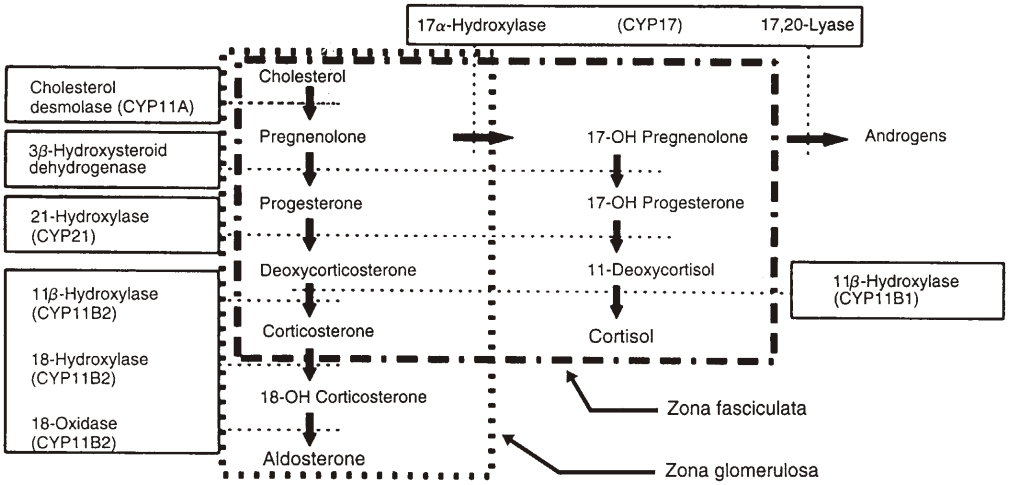

Figure 1. Pathways of adrenal steroid biosynthesis. The conversions occurring in the zonae glomerulosa and fasciculata are marked by broken rectangles. The enzymes responsible for each biosynthetic step are listed in the surrounding boxes. The enzyme CYP11B2 (aldosterone synthase) mediates the last three steps in aldosterone biosynthesis. Deficiencies of CYP11B1 and CYP17 lead to the hypertensive forms of congenital adrenal hyperplasia. Adapted from [3].

are open in the apical membranes of the epithelial cells. Aldosterone also increases potassium conductance into the tubular lumen through specific channels. At the basolateral membrane, aldosterone increases the synthesis of Na^+-K^+-ATPase. The final result is sodium reabsorption and potassium secretion [3].

Under normal circumstances, cortisol is more abundant in the circulation than aldosterone and is capable of binding the mineralocorticoid receptors. However, cortisol is prohibited from activating these receptors because the enzyme 11 -hydroxysteroid dehydrogenase 2 in the endoplasmic reticulum of cells that have mineralocorticoid receptors converts cortisol into the inactive metabolite cortisone (Figure 2) [4].

Mineralocorticoid hypertension and Liddle syndrome share in their pathogenesis an inappropriate increase of sodium (Na^+) reabsorption and potassium and hydrogen ion secretion by the epithelial cells lining the distal tubules and collecting ducts. Hypertension, hypokalemia, and metabolic alkalosis are typical, but the serum potassium might be normal. This group of disorders is caused by one of three mechanisms:

- an excessive production of aldosterone or another substance capable of activating the mineralocorticoid receptor,
- a relative or absolute deficiency of 11 -hydroxysteroid dehydrogenase 2, allowing cortisol to act as a mineralocorticoid (the syndrome of apparent mineralocorticoid excess (AME)), or
- an abnormal Na^+ channel that fails to close in response to deactivation of the mineralocorticoid receptor (Liddle syndrome).

Diagnosis. The usual clue to the diagnosis of mineralocorticoid hypertension is the presence of unprovoked hypokalemia. The workup starts by evaluating renal potassium

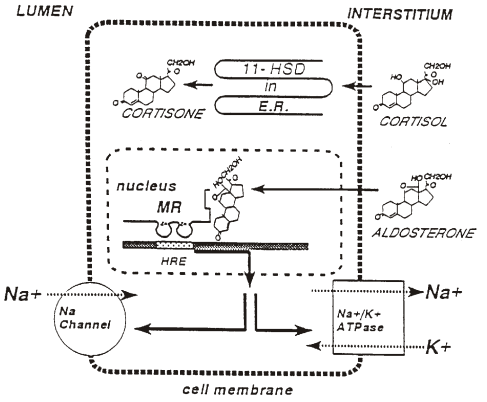

Figure 2. A cell in a renal cortical collecting duct. Aldosterone occupies nuclear receptors (MR) that bind to hormone-response elements (HRE) leading to increased activities of apical sodium channels and the basolateral NA, K-ATPase. The net result is resorption of sodium and excretion of potassium. 11 -hydroxysteroid dehydrogenase, shown in the top, converts the cortisol entering the cell into cortisone, prohibiting it from activation MR. Inappropriate Na^+ reabsorption occurs if there is 1) a defect in the sodium channel (Liddle syndrome), 2) excessive production of mineralocorticoids or 3) insufficient activity of 11-HSD. Adapted from [9].

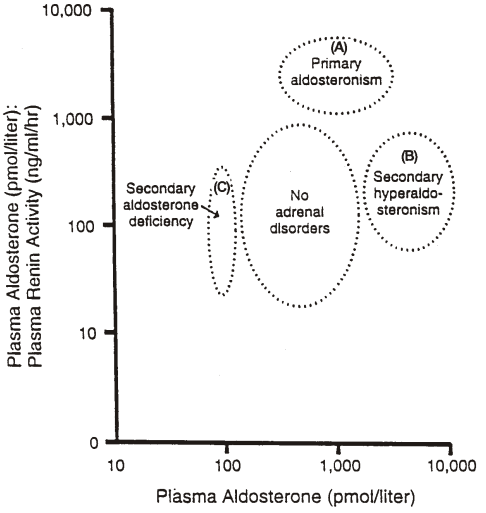

Figure 3. Relation of plasma aldosterone concentration to the ratio of plasma aldosterone to plasma renin activity in mineralocorticoid hypertension. To convert values of plasma aldosterone from ng/dl to pM/l multiply by 27.7. Adapted from [3].

excretion while the patient is hypokalemic. Decreased distal delivery of Na^+ and water may lead to diminished potassium excretion; thus, one has to assure that, at the time of evaluation, Na^+ excretion is 50 mEq/24 hours. Under these circumstances, kaliuria of more than 30 mEq/24 hours, in the absence of diuretic therapy, confirms the diagnosis of a hypokalemic hypertensive syndrome. The next step would be to correct the hypokalemia with potassium chloride supplement and obtain a random ambulatory plasma aldosterone (PA) and plasma renin activity (PRA). From these, a PA/PRA ratio could be calculated. Diuretics, ACE inhibitors, Ang II blockers, -blockers, and possibly calcium channel blockers interfere with these measurements and, according to traditional teachings, should be avoided when these tests are done [5]. Recently, the need to discontinue blood pressure medication has been challenged. The author recommends that at least ACE inhibitors and angiotensin receptor blockers be stopped before testing is done. Spironolactone should not be initiated until these tests are finished. If the patient is already on this drug, it will need to be discontinued for more than a month before renin and aldosterone measurements are done. Plotting the results in the graph in Figure 3 will help in the differential diagnosis and guide further workup [3, 6]. This nomogram is inaccurate in patients with chronic renal failure (CRF).

Primary Hyperaldosteronism

It has been described in all age groups but mostly in the fourth and fifth decades of life.

Hypokalemia is usually the cause for suspecting this diagnosis. The development of a K^+ level below 3 mEq/l during treatment with conventional doses of diuretics, the unresponsiveness of milder degrees of diuretic-induced hypokalemia to potassium supplements, or the addition of potassium-sparing diuretics are also reasons to consider this diagnosis. Hyperaldosteronism should be suspected in patients with resistant or severe hypertension regardless of their potassium levels. About half of the hypertensive patients with unprovoked hypokalemia have primary hyperaldosteronism.

The source of the excess aldosterone is an adrenal adenoma in about one half to two-thirds of cases, bilateral adrenal hyperplasia in the majority of the rest and, rarely, other pathologies, including unilateral adrenal hyperplasia, carcinoma, and ectopic aldosterone-producing tumors [5]. Patients with adenomas tend to be younger at the time of diagnosis and have evidence of more severe disease manifested by higher blood pressure, lower serum K^+, and more profound alkalosis. Most cases are sporadic, but familial forms of both hyperplasia and adenoma exist. Coexistence of primary aldosteronism with pheochromocytoma and fibromuscular hyperplasia of the renal artery has been rarely described.

Hypokalemia, metabolic alkalosis, and, at times, hypomagnesemia are the result of increased K^+, hydrogen (H^+), and magnesium (Mg^{2+}) secretion in exchange of the Na^+ being reabsorbed. Hypokalemia leads to weakness and renal resistance to antidiuretic hormone (ADH) with resultant polyuria and polydipsia. The loss of free water can lead to borderline hypernatremia. Some patients are tachycardic and have signs of a hyperkinetic circulatory state.

Normokalemic primary hyperaldosteronism was reported to be present in 7% to as high as 50% of cases. It is more often associated with hyperplasia than adenoma and may become hypokalemic in the course of the disease, either spontaneously or following the use of diuretics. The search for primary hyperaldosteronism need not be done when the serum potassium is normal except in the cases of resistant or severe hypertension or if a familial form is suspected. Rare cases of normotensive hyperaldosteronism have been described.

Diagnosis. As discussed previously, unprovoked hypokalemia is usually the clue to considering the diagnosis of primary hyperaldosteronism. The workup should start as explained above. At times the picture is very clear, but usually further testing is needed. The purpose of these tests is to try to document that PRA is not stimulable by procedures such as upright posture and use of diuretics and that aldosterone level is not suppressible by procedures such as volume expansion. Many of these tests have been described. Documentation of low PRA (< 1.0 ng/ml/hour) after 2 hours of upright posture with elevated aldosterone levels of > 10 ng/dl following the administration of 2 l of normal saline over 4 hours are usually diagnostic. Aldosterone values between 6 and 10 ng/dl fall in the gray zone and are sometimes seen in hyperplasia. Normal subjects suppress aldosterone levels to < 5 ng/dl. An elevated 24-hour urinary aldosterone level (> 14 g/24 hours) while the patient is on a high sodium diet (as documented by > 250 mEq of Na excretion in the collection) is useful. Failure to suppress aldosterone level after oral captopril is an alternative to salt loading.

Once primary aldosteronism is diagnosed, differentiation between adenoma and hyperplasia needs to be made. This is often difficult, and none of the numerous techniques has a discriminatory power of 100%. The upright posture test, 18-hydroxycorticosterone (18-

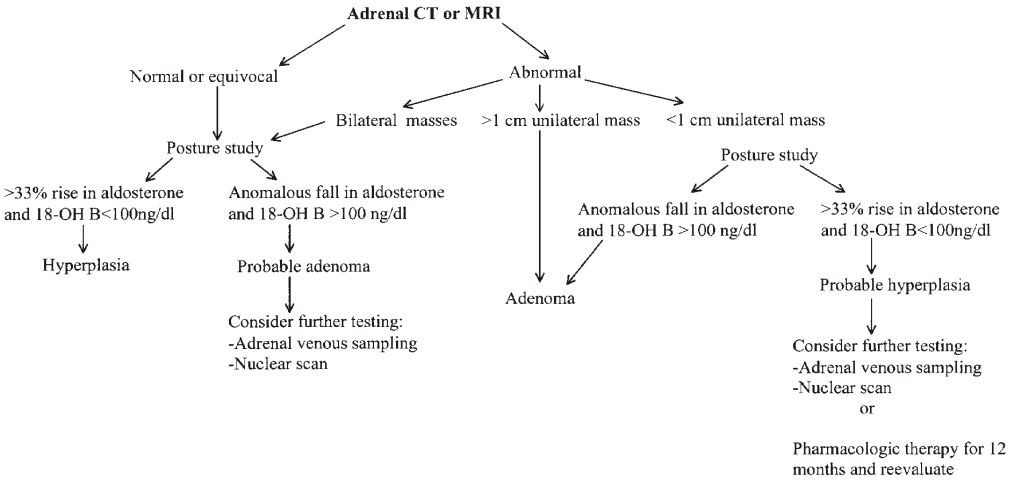

Figure 4. A suggested algorithm for the differentiation between aldosterone-producing adenomas and hyperplasias. 18-OHB ist 18-OH corticosterone. Adapted from [7].

OHB) levels, adrenal venous aldosterone measurements, iodocholesterol nuclear scanning with dexamethasone and adrenal computed tomography (CT) all have good discriminatory power. All adenomas 1.5 cm in diameter, 60% of those between 1 and 1.4 cm, and rarely adenomas measuring < 1 cm can be diagnosed with CT. A suggested scheme is shown in Figure 4.

The 4-hour upright test is based on the concept that adenomas as opposed to hyperplasias do not respond to postural-induced stimulation of the renin-angiotensin system. The sensitivity and specificity of this test for detecting an adenoma are about 80%. 18-OHB is a precursor of aldosterone. Its basal level is usually > 100 ng/dl in adenomas and < 60 ng/dl in hyperplasia. Adrenal venous plasma aldosterone is an invasive and skill-requiring procedure with success rates in some expert hands of no more than 65%. Complications including venous thrombosis and adrenal insufficiency secondary to radiocontrast extravasation into the adrenals can occur. Normal adrenal venous concentration is 200 – 600 ng/dl. In adenomas the ratio of ipsilateral to contralateral aldosterone is usually > 10 : 1. To assure correct catheter placement, adrenocorticotropic hormone (ACTH)-stimulated cortisol levels should be symmetrical. Nuclear imaging, where available, is less invasive. NP-59 scanning is reported to be more advantageous than iodocholesterol. The test is best done with dexamethasone suppression where adenomas remain visible and bilateral hyperplasias fade.

Therapy. Adenomas are best treated surgically. Preoperative therapy with spironolactone may help predict the response to therapy and should ameliorate the hypertension and hypokalemia perioperatively. Postoperatively aldosterone deficiency with hypotension and hyperkalemia may develop but usually resolve within 6 months. In the Cornell series, surgery led to a cure of hypertension in 35% of cases and improvement in 56%. Younger age, lower PRA, and lateralization of aldosterone secretion were associated with higher probability of cure. Enucleation of adenomas, compared to unilateral

adrenalectomy, led in one study to a better reserve adrenocortical function. This is probably of no clinical importance, and the enucleation technique is more complicated. Laparoscopic adrenalectomy is an option that has gained popularity in the recent years and has become the surgical method of choice.

Spironolactone is the treatment of choice for adrenal hyperplasia and in patients with adenomas not treated surgically. Medical management of adenomas has been shown to provide good results and should be considered in patients who are not good surgical candidates, those who elect not to have surgery and whenever differentiation between a hyperplasia and an adenoma is difficult [8]. Doses of 50 – 200 mg/day are used; salt restriction should enhance the response. Other potassium sparing diuretics such as triamterene or amiloride could be used in patients intolerant to spironolactone. Thiazide diuretics, -blockers and calcium channel blockers could be used in addition to spironolactone in the patient that require combination therapy to control their blood pressure.

Glucocorticoid-remediable Aldosteronism (GRA)

GRA is a rare autosomal dominant form of hyperaldosteronism with bilateral hyperplasia characterized by the production of aldosterone in the zona fasciculata and suppressibility of the hyperaldosteronism by glucocorticosteroids [9]. The disease is also called glucocorticoid-suppressible hyperaldosteronism and dexamethasone-suppressible hyperaldosteronism.

Cortisol and aldosterone syntheses require 11 -hydroxylation of steroid intermediates. These steps are normally catalyzed by different isoenzymes, respectively termed steroid 11 -hydroxylase (CYP11B1) in the zona fasciculata and aldosterone synthase (CYP11B2) in the zona glomerulosa. The latter isoenzyme also catalyzes the subsequent 18-hydroxylation and 18-oxidation steps required for aldosterone synthesis (Figure 1).

Subjects with GRA have been shown to have 3 rather than 2 CYP11B genes. The extra gene, located between the other two, is chimeric and contains the regulatory region of the enzyme that promotes the conversion of deoxycortisol to cortisol (11 -hydroxylase or CYP11B1) and the coding sequences of the aldosterone synthase gene (CYP11B2). The former confers a zona fasciculata location and ACTH sensitivity and the latter aldosterone production [9].

Hypertension in most instances occurs in the first two decades of life. Many affected patients, diagnosed by genetic testing, are even normotensive. Serum K^+ is normal in more than half of the cases, but these subjects tend to develop pronounced hypokalemia with the use of diuretics. The high prevalence of normokalemia is thought to be due to a diurnal decline of aldosterone that follows ACTH level. Hemorrhagic strokes and ruptured intracerebral aneurysms are common. Screening for these aneurysms with magnetic resonance angiography is recommended in all patients. Levels of the urinary hybrid steroid 18-oxocortisol are elevated and could be used to make the diagnosis. In a study of 15 patients with this syndrome, all had values of > 40 /g of creatinine. The highest value in 11 normals was 17.4 /g of creatinine. 18-hydroxycortisol levels are also elevated. Genetic testing is available and preferable. The treatment of this condition is the use of glucocorticoids to suppress ACTH production and thus aldosterone production in the zona fasciculata. The starting dose in adults is 1 – 2 mg of dexamethasone daily. This usually

leads to normalization or at least improvement of the blood pressure. When 18-oxocortisol studies and genetic testing are not available, the hypotensive and chemical responses to 0.5 mg of dexamethasone 4 times daily could be used as a diagnostic test.

Tumors Producing Mineralocorticoids Other Than Aldosterone

Tumors producing deoxycorticosterone or 21-deoxyaldosterone rather than aldosterone have been described. The picture is that of mineralocorticoid excess without elevation of the serum aldosterone. These tumors are usually malignant and are easily detectable by CT because of their size. Androgen and estrogen secretion is common.

The Syndrome of Cortisol Resistance

In this familial disease there is partial cortisol resistance with resultant ACTH-induced increased synthesis of steroids with mineralocorticoid activity, androgens, and cortisol. Patients usually have mineralocorticoid hypertension, symptoms of androgen excess, but no cushingoid features. The clinical presentation is extremely variable [10].

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia comprises a group of autosomal recessive disorders that result from deficiencies in enzymes necessary in the synthesis pathways of adrenocortical hormones. Manifestations are the result of inadequate levels of the end products of steroid synthesis, especially cortisol, and the overproduction, in the zona fasciculata, of the precursor steroids proximal to the enzymatic block (Figure 1). Most cases of congenital adrenal hyperplasia are normotensives, but two uncommon syndromes – 11 -hydroxylase deficiency and 17 -hydroxylase deficiency – are often associated with hypertension and hypokalemia. Aldosterone levels are typically low. In both conditions, glucocorticoid therapy, by suppressing ACTH production, corrects the metabolic abnormalities and the hypertension [9].

11 -hydroxylase (CYP11B1) deficiency occurs in about 1 in 200,000 births. Hypertension is present in two-thirds of patients. The onset is often in the first few years of life, and the incidence of end-organ damage is high. Hypokalemia is not common. The ability to synthesize aldosterone is unimpaired, but renin and aldosterone levels are both suppressed. Deoxycorticosterone levels do not correlate well with blood pressure and other substances, including some metabolites of deoxycorticosterone, seem to play a role in the pathogenesis of hypertension. Accumulation of adrenal androgens leads to signs of masculinization at birth and rapid somatic growth during childhood. Levels of deoxycorticosterone and 11-deoxycortisol in the serum and their tetrahydrometabolites in the urine are elevated. Genetic analysis has thus far identified 20 different mutations in the CYP11B1 gene in patients with classical forms of this disorder [9].

17 -hydroxylase (CYP17) deficiency is less common than 11 -hydroxylase (CYP11B1) deficiency. Symptoms of adrenal insufficiency are lacking because corticosterone is a glucocorticoid agonist. Excessive production of deoxycorticosterone leads to

hypertension. The production of sex hormones is impaired. The disease is usually recognized at the age of puberty when symptoms of hypogonadism, primary amenorrhea, and sexual infantilism in females and pseudohermaphroditism in males are noted. Growth is usually not impaired. Elevated progesterone levels and near absence of 17 -hydroxyprogesterone and androgens in the serum and 17-ketosteroids in the urine are diagnostic. Mutations in the CYP17 gene have been identified in many patients with this disorder [11].

Hypokalemic Hyperreninemic Hypertension

In this group of disorders, both the renin and aldosterone are elevated. In some instances, such as diuretic-induced hypokalemia, hypertension and hypokalemia are caused by different mechanisms. In other instances, both hypokalemia and hypertension are a result of stimulation of the renin-angiotensin axis.

Renin-producing Tumors

Renal and extrarenal renin-producing tumors have been described infrequently in the literature [12]. Renin and more impressively prorenin levels are usually extremely high, and the hypokalemia could be severe. Hyponatremia and heavy proteinuria have sometimes been described. Tumors of the juxtaglomerular apparatus, Wilms tumors, rare cases of renal cell carcinomas, and few extrarenal malignancies have been the source of the renin excretion. Renal angiogram is usually needed to rule out renovascular hypertension, which can rarely cause a similar metabolic picture [13]. CT is useful for tumor localization. The hypertensive hypokalemic syndrome responds to treatment of the tumor and ACE inhibitors.

Diuretic-associated Hypokalemic Hypertension

The coexistence of essential hypertension and diuretic-induced hypokalemia is the most common cause of hypokalemic hypertension. In the majority of cases the diagnosis is straightforward. Occasionally a patient with surreptitious diuretic abuse may pose a diagnostic challenge. The syndrome of surreptitious diuretic abuse is classically classified as a cause of normotensive hypokalemia when it needs to be differentiated from Bartter syndrome. However, because essential hypertension is common in the general population and because hypertensives may have easier access to diuretics, it could be seen in association with essential hypertension. Urinary K^+ excretion is elevated, but if the patient stops the diuretic before the urine collection it could be low as a result of the body's appropriate response to conserve K^+. Screening for the presence of diuretics in the urine is available.

Cortisol-induced Mineralocorticoid Excess

This is a group of disorders characterized by excess mineralocorticoid activity exhibited by cortisol. The renal isoform of the enzyme 11 -hydroxysteroid dehydrogenase (11 -HSD2) is either congenitally deficient, chemically inhibited, or overwhelmed by large amount of cortisol, allowing this substance to activate the mineralocorticoid receptors in the distal tubules (Figure 2). In all

these disorders aldosterone, deoxycorticosterone levels, and PRA are low [4].

The Syndrome of Apparent Mineralocorticoid Excess (AME)

In the more common congenital form of AME (type 1), there is a mutation in the gene for the kidney isoform of 11 -hydroxysteroid dehydrogenase (the NAD-dependent isoform) located in chromosome 16q22. The disease is inherited in an autosomal recessive manner. The ratio of the cortisol metabolites tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone, normally about 1 is 8. Clinical manifestations include hypertension and hypokalemia during childhood, intrauterine growth retardation, and failure to thrive. The administration of dexamethasone, by suppressing cortisol production, will correct the hypokalemia, but antihypertensives are often still needed to control the blood pressure. Genetic testing is available. The diagnosis is usually made in children and young adults.

11 -hydroxysteroid dehydrogenase activity is inhibited by licorice or similar compounds. The inhibiting chemical in licorice is a steroid named glycyrrhetinic acid. It works both competitively and by reducing gene expression. Flavonoids present in grapefruit juice have been shown experimentally to inhibit 11 -hydroxysteroid dehydrogenase. The clinical importance of this finding is unknown. Licorice is present in some confectionery items, chewing tobacco, chewing gum, and some drinks, pastis in France and ark al-soos in the Middle East. Carbenoxolone, an antiulcer medication, has a chemical structure similar to that of glycyrrhetinic acid and can cause the same syndrome. The hypertension and hypokalemia should resolve within weeks after the discontinuation of the offending agent. Patients with chronic renal failure, especially those with hypertension, have evidence of decreased activity of 11 -hydroxysteroid dehydrogenase, and this may be one of the mechanisms in the pathogenesis of renal hypertension.

A rarer syndrome called AME type 2 was described. As opposed to AME type 1, the ratio of the cortisol metabolites tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone is normal. Some research has suggested that the hypertensive syndrome seen with the carbenoxolone is an acquired form of this disorder. Explanations of how AME type 2 differs from AME type 1 are discussed elsewhere [4].

Cushing Syndrome

In Cushing syndrome, which is caused by ectopic production of ACTH, and less commonly in other forms of Cushing syndrome, the amount of cortisol produced could overwhelm 11 -hydroxysteroid dehydrogenase, and enough cortisol at the levels of the distal renal tubules will be left to exert mineralocorticoid activity. Evidence also indicates that in this condition there is inhibition of 11 -hydroxysteroid dehydrogenase, possibly by ACTH. More commonly the hypertension of Cushing syndrome is not hypokalemic and is discussed in another chapter.

Liddle Syndrome

In Liddle syndrome the collecting tubule Na^+ channel, which is the path Na^+ takes when entering from the tubule into the cell, fails to close in response to aldosterone suppression caused by volume expansion. The

Table 2. The differential diagnosis of mineralocorticoid hypertension.

Renin Aldosterone Profile *	Syndrome	Steroids Involved	Suppressible by	Genetic Defect	Diagnostic Clues
Zone A	Aldosteronoma	Aldosterone	Surgery	No	See Figure 2
	Idiopathic primary aldosteronism	Aldosterone		No	See Figure 2
	GRA	Aldosterone	Dexamethasone	Yes (AD)	Elevated 18-oxocortisol, 18-hydroxycortisol
Zone B	Renovascular hypertension	Aldosterone	Surgery or angioplasty	No	Renal arteriogram and other tests
	Renin producing tumors	Aldosterone	Surgery	No	Imaging studies, elevated prorenin
	Diuretic abuse	None	Discontinuation	No	History, urine screening for diuretics
Zone C	AME type I	Cortisol	Dexamethasone	Yes (AR)	Intrauterine growth retardation, failure to thrive, elevated (THF + Allo THF)/THE
	Licorice abuse	Cortisol	Discontinuation	No	History, urine screening for glycyrrhetinic acid
	Cushing's syndrome	Cortisol	Surgery, ketoconazole, mitotane	No	Very high cortisol, tumor
	CAH: CYP 11B deficiency	DOC 11-deoxycortisol	Dexamethasone	Yes (AR)	Virilization, high DOC and 11-deoxycortisol, high 17-ketosteroids
	CAH CYP 17 deficiency	DOC 19-nor-DOC	Dexamethasone	Yes (AR)	Hypogonadism, high progesterone and low 17-ketosteriods
	Syndrome of cortisol resistance	DOC	Dexamethasone	Yes (AD)	High cortisol and ACTH, androgen excess, no cushingoid features
	DOC-producing tumors	DOC	Surgery	No	Imaging studies, elevated DOC
	Liddle syndrome	None	Amiloride, triamterene	Yes (AD)	Lack of response to spironolactone, normal cortisol

Adapted from Vallotton MB, Part II, 1996 [15]
* See Figure 3, AD = Autosomal dominant, AR = Autosomal recessive, THF = Tetrahydrocortisol, Allo-THF = Allotetrahydrocortisol, THE = Tetrahydrocortisone, CAH = Congenital adrenal hyperplasia, DOC = Deoxycorticosterone

disease is transmitted in an autosomal dominant fashion. It is caused by mutations in the carboxyl-terminus of the beta or gamma subunits of the renal epithelial Na^+ channel's gene.

Liddle syndrome usually presents itself in childhood with hypertension, hypokalemia, low renin and aldosterone, and normal cortisol levels. Genetic testing of relatives of index cases has shown that the hypertension could be mild and not apparent until adulthood and that hypokalemia is often absent, suggesting that this disease may be underdiagnosed [14]. Liddle syndrome was originally described in whites and Orientals but black individuals were recently found to have it.

The potassium-sparing diuretics triamterene and amiloride directly close the sodium channels and are used in the treatment of Liddle syndrome. Spironolactone is ineffective because the increase of sodium channel activity in this disorder is independent of aldosterone. This feature could help diagnostically. Failure to respond to dexamethasone-induced ACTH suppression distinguishes this syndrome from AME.

Table 2 summarizes features that might be helpful in the differential diagnosis of mineralocorticoid hypertension [15].

Pheochromocytoma

Pheochromocytomas are catecholamine-secreting tumors that arise from neuroectodermal chromaffin cells, which are part of the adrenergic system. Their exact prevalence is unknown, but they are thought to be responsible for less than 0.1% of all cases of hypertension. About 90% of tumors are located in the adrenal medulla. The rest occur in other sites in the abdomen and pelvis such as the organ of Zuckerkandl, paraganglia chromaffin cells, and the urinary bladder, and < 2% above the diaphragm in a paraspinal location, the pericardium, the neck, base of the skull, and other rare sites. The typical pheochromocytomas are sporadic, singular, and benign but some violate one or more of these rules. They occur at any age but more commonly in the fourth and fifth decades. They are more common in females except in the pediatric age group.

Clinical Manifestations. The clinical manifestations of pheochromocytomas result mainly from excess circulating catecholamines and complications of hypertension. Occasionally the secretion of a variety of peptides, local effect of the tumor, and the presence of a coexisting syndrome contribute to the picture. Due to the variation of the rate of catecholamine secretion and its dependence on many exogenous and endogenous stimuli, symptoms and signs tend to be paroxysmal. The frequency of the attacks varies from several per day to one every few months. They typically last less than an hour, but the duration also varies. The onset is abrupt and the resolution is slow.

At least two of the symptoms from the classical triad of headache, tachycardia, and sweating are present in almost all patients with pheochromocytoma. Pallor, dizziness, acute anxiety, tremulousness, pain in the chest and other sites, nausea, vomiting, constipation, symptoms of ischemic bowels, symptoms of dilated cardiomyopathy, weight loss, fever, and other symptoms could also be present. Hyperglycemia is a common laboratory finding in pheochromocytoma. Hypokalemia, hypercalcemia, and lactic acidosis are rarely encountered.

The hypertension in pheochromocytoma is paroxysmal in about 50% of cases and persistent in the other half. Even in this group blood

pressure tends to fluctuate widely. Rarely, patients with predominantly epinephrine-secreting tumors have hypertension alternating with hypotension. Orthostatic hypotension with tachycardia can occur and is attributed to desensitization of the adrenergic receptors and volume depletion.

Some drugs such as -blockers may precipitate a hypertensive attack. This reaction is due to the blockade of the vasodilatory peripheral -receptors with unopposed alpha stimulation. Stressors such as intubation, anesthesia, surgery, and trauma may cause a severe pressor reaction. Unexplained circulatory shock, especially perioperatively, during pregnancy and delivery, and following administration of phenothiazines, may be seen. Bladder pheochromocytomas are associated with painless hematuria, and attacks could be precipitated by bladder distension or micturition.

Occasionally, pheochromocytomas secrete some substances such as vasoactive intestinal peptide (VIP), serotonin, calcitonin, erythropoietin, adrenocorticotropic hormone, parathyroid hormone (PTH)-related protein, and renin leading to some unusual manifestations. Cholelithiasis, for some unexplained reason, is reported to be common.

Two forms of multiple endocrine neoplasia (MEN-2A and MEN-2B) are, in about 40% of cases, associated with pheochromocytoma. Both are inherited in an autosomal dominant fashion. MEN-2A includes medullary thyroid carcinoma or C-cell hyperplasia and hyperparathyroidism, and MEN-2B includes medullary thyroid carcinoma in almost all cases, mucosal neuromas of the lips and tongue, thickened corneal nerves, alimentary tract ganglioneuromatosis, megacolon, and marfanoid habitus. Pheochromocytomas associated with MEN are bilateral in 30% of cases. Malignant disease in familial forms of pheochromocytoma is rare.

Pheochromocytoma is also a feature of von Hippel-Lindau (vHL) disease, which also includes retinal angiomas, hemangioblastoma of the central nervous system (CNS), renal cysts and carcinoma, pancreatic cysts, and epididymal cystadenoma. Bilateral disease is common. Extraadrenal pheochromocytomas are more frequently vHL disease compared to sporadic cases and those associated with MEN-2. Patients with neurofibromatosis type 1 (NF1), tuberous sclerosis (TS), familial carotid body tumors and Sturge-Weber syndrome have increased prevalence of pheochromocytoma.

In a study from Germany [9], 23% of 82 unselected patients with pheochromocytoma were found to be gene carriers of MEN-2 or vHL disease. The authors of this study recommended that every patient with a pheochromocytoma be screened for both MEN-2 and vHL by the pentagastrin test, measurement of serum PTH, ophthalmoscopic examination, MRI of the brain, CT of the abdomen, and ultrasound of the testicles. First-degree relatives of patients with one of these syndromes and of patients with multifocal pheochromocytomas should have pheochromocytoma ruled out regardless of their symptomatology [16].

Diagnosis. Pheochromocytoma should be suspected in patients with severe or refractory hypertension, when one or more of the features detailed above are encountered in a hypertensive patient, or when an adrenal mass is found incidentally in an imaging study. Patients diagnosed with one of the above hereditary disorders and their family members should be screened periodically for the disease. Genetic testing for the RET oncogene of MEN-2 and the von Hippel-Lindau tumor suppressor gene could be done at some research laboratories.

Many conditions may mimic pheochromocytomas, including hyperkinetic hyperten-

Table 3. Drugs and substances that may interfere with the measurements of urinary catecholamines and their metabolites.

Increase Apparent Value	Decrease Apparent Value
Benzodiazepines	Clofibrate
Catecholamines and drugs containing catecholamines	Disulfiram
Chlorpromazine	Ethanol (VMA levels)
Erythromycin	Fenfluramine (large doses), -methyltyrosine
Ethanol (catecholamine and metabolite levels)	MAO inhibitors (VMA levels)
Isoprenolol (Isoproterenol)	Methylglucamine (in renovist. renografin, etc.)
Labetalol	
Levodopa	
MAO inhibitors (metanephrine levels)	
Methyldopa	
Nalidixic acid	
Other fluorescent substances (e.g., quinine, quinidine, bile in urine)	
Rapid clonidine withdrawal	

Manger WM, Gifford RW 1995 Pheochromocytoma: a clinical overview. Adapted from [17], p. 2237.

sion, hyperthyroidism, panic attacks, hypoglycemic reactions, menopause, abuse of street drugs including cocaine and amphetamines, use of medications such as phenylpropanolamine or -agonists, the concomitant use of a monoamine oxidase inhibitor (MAOI), tyramine-containing foods, and clonidine and -blocker withdrawal.

Many tests for diagnosing pheochromocytoma are available. The low pretesting prevalence of pheochromocytoma, even in patients with suggestive features, makes the positive predictive value of highly specific tests also low. The search for pheochromocytoma remains very important due to the severe consequences of missing the diagnosis. The recently developed test for measurement of plasma-free metanephrines, due to its very high sensitivity of 99% and a high speceficity of 89% (at upper reference limits are 0.66 pmol/ml for plasma normetanephrine and 0.30 pmol/ml for metanephrine) should be the diagnostic test of choice [18]. The high sensitivity of the test is due to the fact that free metanephrines, as oppesed to catecholamines, are released continuously from the tumor into the blood. The sensitivity of other tests including urinary studies and plasma catecholamines is much lower. A normal level of both metanephrine and normetanephrine rules out the diagnosis. Patients who have normetanephrine levels that exceed 2.5 pmol/ml or metanephrine levels above 1.5 pmol/ml are confirmed to have pheochromocytoma. If levels are high but neither exceeds these values, then the test should be repeated and a normal value of both rules out the diagnosis. The rest of patients should have a

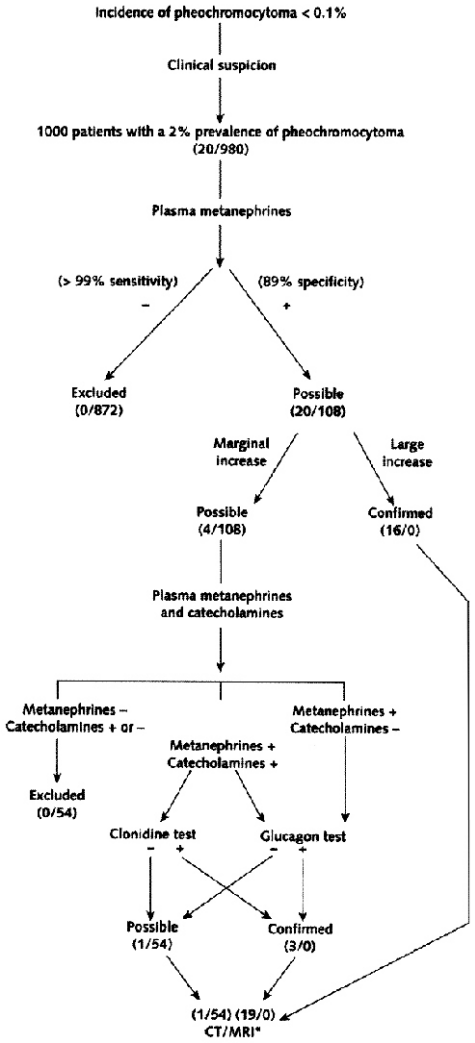

Figure 5. A suggested algorithm for the workup and localization of pheochromocytoma. Adapted from [18]. Used with permission.

diagnostic workup as shown in Figure 5. Plasma metanephrine levels are elevated in monoamine oxidase deficiency. Caffeine and acetaminophen should be avoided prior to testing. Measurement of total plasma catecholamine levels (epinephrine + norepinephrine), requires that blood be drawn via a previously inserted indwelling catheter after the patient has rested in a supine position for 30 min. If plasma tests are not available, urinary tests could be done instead; these tests suffer from low sensitivity making ruling out the diagnosis a difficult task. A combination of these tests increases the sensitivity at the expense of specificity. Many drugs and substances may interfere with the measurement of catecholamines and their metabolites (Table 3).

The clonidine suppression test is used to differentiate between pheochromocytomas and other conditions associated with elevated catecholamines, such as neurogenic hypertension. By suppressing the sympathetic nervous system, clonidine reduces the norepinephrine level by 50% or to a normal value in neurogenic hypertension, but not in patients with pheochromocytoma. -blockers should be discontinued at least 2 days before testing because they can interfere with the suppression of catecholamine concentration in patients with neurogenic hypertension. Drugs that interfere with catecholamine measurements should also be avoided (Table 3), and other antihypertensive medications should be discontinued at least 12 hours before the test. Volume depletion at the time of the test can lead to profound hypotension, and, if present, it should be treated beforehand. The test consists of obtaining baseline plasma catecholamines as described previously followed by administration of 0.3 mg of clonidine orally and then after 3 hours of bed rest another plasma catecholamine determination. Patients without a pheochromocytoma usually suppress the total catecholamine concentration to < 500 pg/ml.

Rarely, the glucagon stimulation test is required to diagnose a paroxysmally secreting tumor. It consists of obtaining a baseline catecholamine specimen, followed by the administration of 1 mg of intravenous (IV) glucagon and a second measurement 2 min

after the infusion. The diagnosis of pheochromocytoma is made if there is a 3-fold rise in catecholamine levels or if the absolute value becomes > 2000 pg/ml. This test is contraindicated if the blood pressure is > 160/105. Premedication with an $_1$-blocker or nifedipine may prevent a hypertensive response without interfering with the measurements. This test should be done under monitored conditions.

Localization Procedures. A CT or MRI of the adrenal gland and abdomen identify 95% of pheochromocytomas. A high signal intensity on MRI is characteristic. Detecting small tumors by these methods may be difficult but usually is not a problem because pheochromocytomas are generally > 3 cm in size.

When the CT or MRI is negative and the diagnosis is still strongly considered, an ^{131}I metaiodobenzylguanidine (MIBG) radionuclide scan may be done. It concentrates in 85% of the tumors and is helpful in detecting small and extraabdominal pheochromocytomas. False positive results may be seen in neuroblastomas, medullary thyroid carcinomas, carcinoids, and small cell carcinomas of the lung. Calcium channel blockers, labetalol, tricyclic antidepressants, sympathomimetics, and tranquilizers can decrease the sensitivity of the test and thus should be discontinued a week before it is done. MIBG scan can detect metastases in malignant pheochromocytomas.

Other methods that could be used for localization include CT or MRI of the chest, neck, head, and pelvis, cystoscopy, and central venous blood sampling. Care should be taken to avoid precipitating an attack whenever an invasive procedure is planned. Fluorodopamine positron emission tomography (PET) scanning has been recently suggested to be highly sensitive for tumor localization.

Treatment. The treatment of pheochromocytoma should be resection of the tumor. Except in rare emergent situations such as uncontrollable malignant hypertension or a hemorrhagic necrosis of a pheochromocytoma, preoperative preparation with alpha blockade is warranted. Phenoxybenzamine, starting at a dose of 10 mg daily and gradually increasing the dose to control the blood pressure and symptoms, should be used preoperatively. An $_1$-blocker like prazosin may be used instead. Excessive alpha blockade should be avoided because it can lead to orthostatic hypotension. After adequate alpha blockade and if tachyarrhythmias are of concern, then -blockers starting at small doses could be used. Cardioselective -blockers are preferable. Alpha-methyl-para-tyrosine reduces tumor stores of catecholamines and should be used preoperatively. Increased salt intake together with pharmacological measures should be initiated two weeks before surgery.

An abdominal approach is preferable to ensure adequate visualization, but if the tumor has been localized by CT or MRI then a flank incision or even a laparoscopic approach may be used. Intraoperative hypertension is treated by phentolamine or nitroprusside. Transient hypoglycemia may occur postoperatively, and it is caused by a rise in insulin level.

Patients with malignant tumors are treated by surgical debulking. Residual tissue may be treated by conventional radiotherapy, chemotherapy, metyrosine, and alpha and beta blockade. The 5-year survival is 35 – 50%. Radiofrequency ablation has been used recently to treat metastatic disease.

Hypertension in Hypothyroidism and Hyperthyroidism

Thyrotoxicosis is associated with an increase of cardiac output and blood volume and a decrease in systemic vascular resistance. A widened pulse pressure and an increase in systolic blood pressure are thus expected, and treatment to a euthyroid state usually leads to normalization of these abnormalities. This diagnosis should be suspected in young patients with systolic hypertension, those with a hyperdynamic state, and those with other suggestive clinical features.

In hypothyroidism the hemodynamic profile is the exact opposite to that seen in hyperthyroidism. Hypertension is seen in as many as 50% of patients, and narrow pulse pressure is characteristic. Depressed glomerular filtration rate (GFR), presumably secondary to decreased renal perfusion, is occasionally seen. Thyroid replacement therapy improves or cures the hypertension [19].

Hypertension in Primary Hyperparathyroidism

The association between hyperparathyroidism and pheochromocytoma was discussed earlier. Even in isolated hyperparathyroidism, the prevalence of hypertension is double that seen in the general population. The nature of this association is not clear. Some of these patients may have coexisting essential hypertension. In some experimental models, hypercalcemia can cause vasoconstriction and an increase in cardiac output, but other factors seem to play a role. Elevated PRA and aldosterone levels in hypertensive hyperparathyroid patients with a significant decrease after parathyroidectomy have been reported.

The diagnosis is suspected when hypercalcemia, spontaneous or after the use of thiazide diuretics, is discovered or during the workup of renal stone disease. Studies on the response of the hypertension to surgical parathyroidectomy have shown conflicting results, with some reporting improvement and others no response or even worsening. The presence or lack of hypertension should not be used as a factor when deciding whether to do a parathyroidectomy.

Hypertension in Acromegaly

Hypertension in acromegaly is present in 40% of cases. High levels of growth hormone lead to sodium retention, cardiomegaly, and an increase in cardiac output. Coarse facial features, large hands, carpal tunnel syndrome, coronary artery disease (CAD), and insulin resistance are some of the clinical features. The diagnosis is made by finding high levels of growth hormone during a glucose tolerance test or elevated insulin-like growth factor I (IGF-I).

Hypertension in Neurological Disorders

Considering the essential role the nervous system plays in the control of blood pressure, it is rather surprising that hypertension in neurological diseases is not that common. Severe

Table 4. Exogenous substance-induced hypertension (Part 1).

Ingredients	Common Use/Abuse	Notes
Steroids		
Glucocorticoids	Replacement therapy and symptomatic treatment of various diseases	Dose-dependent, sustained increase mainly in systolic BP
Mineralocorticoids		
Black licorice	Candy, chewing gum, liquor	Dose-dependent, sustained increase in BP mimicking primary hyperaldosteronism characterized by hypokalemia metabolic alkalosis, and suppressed plasma renin activity and aldosterone levels
Carbenoxolone	Ulcer medication	
9 -fluoroprednisolone	Skin ointments, antihemorrhoid cream	
9 -fluorocortisol	Ophthalmic drops and nasal sprays	
Ketoconazole	Antimycotic	
Estrogen	Contraception, replacement therapy, prostatic cancer	Mild, sustained BP elevation, more common in premenopausal women, severe hypertension has been reported
Progesterone	Contraception, replacement therapy	
Androgens	Anabolic effect	Mild, dose-dependent sustained increase in systolic BP
Danazol (semisynthetic androgen)	(abuse in athletes)	Endometriosis, hereditary angioedema
Anesthetics and Narcotics		
Cocaine	Local anesthetics; street drug	Transient severe increase in BP, especially when used with propranolol
Ketamine hydrochloride	Anesthetic agent	Transient severe increase in BP
Fentanyl citrate	Narcotic analgesic and anesthetic agent	
Scopolamine	Preanesthetic medication, motion sickness	
Naloxone hydrochloride	Opioid overdose	Transient BP evaluation

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Table 4. Exogenous substance-induced hypertension (Part 2).

Ingredients	Common Use/Abuse	Notes
Drugs Affecting the Sympathetic Nervous System		
Phenylephrine hydrochloride	Upper respiratory decongestant; ophthalmic drops	Dose-dependent, sustained increase in BP
Dipivalyladrenaline hydrochloride	Ophthalmic drops	Severe HT has been reported; may precipitate myocardial events and therefore should be used with caution in patients with coronary disease
Epinephrine (with -blocker)	Local anesthetic, anaphylactic reaction, bronchodilatation, decongestant antihemorrhoidal treatment	
Phenylpropanolamine	Anorexic/decongestant	
Pseudoephedrine hydrochloride	Decongestant	
Tetrahydrozoline hydrochloride	Ophthalmic vasoconstrictor drops; ophthalmic vasoconstrictor and nasal decongestant drops	
Oxymetazoline hydrochloride	Decongestant drops	
Caffeine	Analgesia, vascular headache, beverages	Acute transient increases in BP
Metoclopramide	Antiemetic	Transient increase in BP in association with cancer chemotherapy
Alizapride	Antiemetic	
Prochlorperazine	Antiemetic	
Yohimbine hydrochloride	Impotence	Acute, dose-dependent increase in BP
Glucagon	Bowel spasm	Only in patients with pheochromocytoma
Physostigmine	Reverse anticholinergic syndrome	
Ritodrine hydrochloride	Inhibition of preterm labor	Hypertensive crisis has been reported
MAOIs	Antidepressive agents	Mainly with sympathomimetic amines and with certain foods containing tyramine
Tricyclic antidepressants	Antidepressive	More common in patients with panic disorders
Buspirone	Anxiolytic	Mild, dose-dependent increase in BP
Fluoxetine	Antidepressive	In combination with selegiline
Thioridazine hydrochloride	Psychotic and depressive disorder	Massive overdose may cause severe HT

Table 4. Exogenous substance-induced hypertension (Part 3).

Ingredients	Common Use/Abuse	Notes
Ions		
Sodium chloride	Food and Drugs	In salt-sensitive subjects
Lithium	Manic-depressive illness	Acute intoxication can cause severe HT
Calcium	Food and Drugs	
Lead	Industry	
Cadmium	Industry	
Mixed or Unknown Mechanism		
Cyclosporine	Immunosuppressive agent	Dose-dependent mild-to-moderate increase in BP; severe HT has been reported
Alkylating agents	Neoplastic disorder	
Recombinant human erythropoietin	Anemia or renal failure	Dose-related mild increase in BP; hypertensive crisis with encephalopathy has been reported
Bromocriptine mesylate	Suppression of lactation and prolactinoma	Severe HT with stroke has been reported after use for suppression of lactation
Disulfiram	Alcoholism	Slight increase in BP; severe HT may occur in alcoholic-induced liver disease
Alcohol	Various	Dose-dependent, sustained increase in BP
Nicotine	Cigarette smoking	Acute transient increase in BP
Nonsteroidal anti-inflammatory drugs including COX-2-specific inhibitors	Analgesic; anti-inflammatory agent	Mild, dose-dependent increase in BP
Long acting somatostatin	Gastrointestinal disorders	Severe hypertension in subjects with autonomic dysfunction

Adapted from [5].

acute elevation of intracranial pressure (ICP) leads to hypertension with bradycardia (Cushing response) and constitutes a preterminal event. Chronic elevation of ICP does not cause hypertension except when it is very severe.

Tumors of the posterior fossa seem to be more associated with hypertension than supratentorial neoplasms. This is probably related to their proximity to some stretch-sensitive receptor elements in the floor of the fourth ventricle. Rarely, brain lesions lead to a paroxysmal type of hypertension mimicking pheochromocytoma [20]. Neurogenic hypertension can be associated with paroxysmal headache and symptoms of excessive autonomic activity such as tachycardia, diaphoresis, anxiety, tremor, nausea, and vomiting. Flushing of the skin is common and, not unexpectedly, focal neurological signs are usually present. In 38% of the cases, catecholamines and their metabolites are elevated. Patients with features characteristic of pheochromocytoma who have neurological symptoms or signs or who have a negative workup and patients with increased urinary excretion of catecholamines or their metabolites but no evidence of pheochromocytoma on further studies should have an imaging study of the brain to rule out a brain tumor. MRI is preferable because of its superiority in detecting posterior fossa lesions. Similar presentation has been reported after cerebral infarction.

Patients with tranverse lesions of the cervical spinal cord above the origins of the thoracolumbar sympathetic neurons lose central control of their sympathetic outflow. Stimulation of nerves below the injury, as with bladder distension, can cause reflex sympathetic activity via the isolated spinal cord, resulting in hypertension, diaphoresis, flushing, and headache, a syndrome called autonomic hyperreflexia.

Excessive sympathetic nervous activity immediately following severe head injury can lead to a hyperdynamic state with hypertension. Treatment with a short-acting -blocker is preferable to vasodilators, which may further increase ICP.

Hypertension in Sleep Apnea Syndrome

It is estimated that sleep apnea affects 2 – 4% of middle-aged adults and is more prevalent in men. Most commonly it is secondary to upper airway obstruction by the surrounding structures during sleep. Systemic hypertension is seen in 60 – 80% of cases of sleep apnea syndrome. Snoring, sleep fragmentation, daytime somnolence, dysrhythmias, erythrocytosis, large neck size and obesity are other common manifestations. The relation between hypertension and sleep apnea is independent of obesity. It is thought that the repetitive hypoxemia and hypercapnia that result from the obstruction lead to increased sympathetic nervous system tone and neuroendocrine dysfunction with blood pressure elevation and increased risk for cardiovascular complications. Sleep studies should be done in hypertensive patients with a history of habitual snoring associated with daytime somnolence, observed apnea, or some of the other features discussed above. Weight loss, avoidance of CNS suppressant (including some antihypertensives), positive pressure breathing, oral devices, and various surgical interventions are used to treat this condition and usually result in improvement or even cure of the hypertension [21].

Stress and Hypertension

Stress, both physical and emotional, can lead to acute elevation of blood pressure that normalizes with the removal of the stressing situation. Erroneous diagnosis of chronic hypertension and committing the patient unnecessarily to lifelong antihypertensive therapy may result when the role of stressors is ignored. These patients' blood pressure is best treated by removing the cause and usually does not require antihypertensive therapy. Unfortunately, the use of sublingual, short-acting nifedipine to treat the blood pressure under these circumstances remains common despite documented cases of myocardial infarction and ischemic stroke resulting from hypotension and sympathetic overactivation caused by the rapid vasodilatation from this agent. It has been suggested that repeated episodes of stress-induced blood pressure elevation result in sustained hypertension, but this is yet to be proven.

Exogenous Substance-induced Hypertension

Many exogenous substances, including prescription and over-the-counter medications, foods, and substances used for recreational purposes, can raise the blood pressure or interfere with its treatment (Table 4) [2]. The COX-2-specific inhibitors in general have the same renal and hypertensive effects seen with nonsteroidal anti-inflammatory agents. These side effects are reported to be more severe with rofecoxib than celecoxib.

Caffeine and nicotine can transiently elevate the blood pressure, and measurements should not be done within 30 minutes of their use.

Drugs Affecting the Sympathetic Nervous System

Several drugs can directly or indirectly activate the sympathetic nervous system, leading to blood pressure elevation. These reactions are more likely to occur with larger doses of the drugs. The concomitant use of sympathomimetic agents and -blockers can lead to unopposed -adrenergic stimulation and sometimes a severe hypertensive reaction.

Cocaine blocks the reuptake of norepinephrine at sympathetic nerve terminals. Its abuse may cause severe hypertension, renal failure, and myocardial ischemia. During pregnancy it can lead to abruptio placentae and neonatal hypertension. It can also be confused with preeclampsia, because hypertension, headache, blurred vision, and abdominal pain are seen in both conditions. The combined use of cocaine and epinephrine paste in intranasal surgery has been reported to cause severe hypertension, myocardial ischemia, and arrhythmia, even in healthy subjects.

Alcohol

Alcohol consumption could be responsible for up to 11% of chronic hypertension cases seen in men in developed societies and an even higher proportion in some primitive so-

cieties. Women have lower prevalence of alcohol-induced hypertension because, on average, they drink less than men. The hypertensive response to chronic alcohol intake is seen once the consumption exceeds 1 – 2 drinks/day and is dose-related. Population studies suggest that for each standard drink per day, there is a 1 mmHg increase in systolic blood pressure. However, individual responses vary. Older age and obesity increase the hypertensive effect. The pressor response to alcohol develops within a few days of intake and recedes within 1 – 4 weeks of cessation.

The mechanisms involved in alcohol-induced hypertension are poorly understood. A direct vasoconstrictor effect and increased responsiveness of the vascular bed to pressors seem to play a role. Magnesium deficiency, common in alcoholics, can lead to increased intracellular calcium in vascular smooth muscle cells and sympathetic nerve terminals. In an animal model, magnesium supplementation prevented the development of alcohol-induced hypertension. Alcohol increases the secretion of corticotropin-releasing hormone (CRH), which stimulates ACTH production and sympathetic activity. Dexamethasone, which suppresses CRH release, has been shown to blunt the hypertensive reaction caused by acute alcohol administration [21].

Acute alcohol withdrawal and treatment with disulfiram cause hypertensive reactions, but abstinence from alcohol and even dose reduction lead to gradual improvement or normalization of blood pressure.

Psychiatric Medications

Monoamine oxidase inhibitors (MAOI) delay the metabolism of sympathomimetic amines and 5-hydroxytriptophan. They can cause a severe hypertensive reaction when patients taking them consume substances containing tyramine such as aged cheese and red wine, sympathomimetics, or serotonin reuptake inhibitors. Spontaneous hypertensive episodes have been reported. The reaction may mimic pheochromocytoma.

Rarely, tricyclic antidepressants have been reported to cause hypertension via an unclear mechanism. Methylphenidate (Ritalin), used to treat children with attention deficit disorder, has been reported to raise diastolic blood pressure in some children taking it. Buspirone, an anxiolytic, can cause hypertension thought to be the result of $_2$-antagonism caused by one of its metabolites.

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