DONALD G. VIDT, MD, AND ALAN BAKST, PHARMD, EDITORS

Pheochromocytoma: current diagnosis and management

WILLIAM M. MANGER, MD, PHD, AND RAY W. GIFFORD, JR, MD

■ **BACKGROUND** Pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells that causes hypertension.

■ **OBJECTIVE** To review the clinical presentation, diagnosis, and treatment of this disease.

■ **SUMMARY** Pheochromocytoma can mimic a number of other diseases, making recognition difficult. Hypertension may be paroxysmal or sustained. The signs and symptoms of pheochromocytoma are mostly due to hypercatecholaminemia, hypertension, complications, or coexisting diseases; however, measurements of catecholamines and their metabolites in the plasma and urine may be normal between "attacks", and other conditions can elevate these values. The clonidine suppression test confers specificity to the clinical and laboratory findings, and magnetic resonance imaging is the most reliable method of locating a tumor. Surgical resection is successful in 90% of patients; however, the disease is fatal if it is not detected and treated.

■ **CONCLUSIONS** Pheochromocytoma should be suspected in patients with paroxysmal or sustained hypertension, particularly if symptoms are present.

■ INDEX TERMS: PHEOCHROMOCYTOMA; HYPERTENSION
■ CLEVE CLIN J MED 1993; 60:365–378

From the National Hypertension Association (W.M.M.), New York, and the Department of Nephrology and Hypertension (R.W.G.), The Cleveland Clinic Foundation.

Address reprint requests to W.M.M., National Hypertension Association, 342 East 30th Street, New York, NY 10016.

FOR THE CLINICIAN, pheochromocytoma is a most fascinating and exciting tumor; for the patient, this pharmacologic bomb poses great risk of death or devastating complications. Pheochromocytoma can be totally removed in 90% of patients who have it, but it will likely prove fatal if unrecognized. The deceptive and treacherous nature of this rare tumor is underscored by the Mayo Clinic experience: of 54 patients who were found to have pheochromocytomas at autopsy, tumors were not suspected in 75% and contributed to death in 55%![1]

With current diagnostic modalities, the presence of a pheochromocytoma can almost always be established or rejected; however, the secret of improved recognition of this endocrine tumor rests on a high index of suspicion. *It is crucial to think of pheochromocytoma in all patients with sustained or paroxysmal hypertension—especially those who are symptomatic.*

CLINICAL PRESENTATION

Because it secretes catecholamines, often episodically, pheochro-

TABLE 1
SYMPTOMS REPORTED BY 76 PATIENTS (ALMOST ALL ADULTS) WITH PHEOCHROMOCYTOMA ASSOCIATED WITH PAROXYSMAL OR PERSISTENT HYPERTENSION*

Symptoms presumably due to excessive catecholamines or hypertension	Paroxysmal (37 patients) %†	Persistent (39 patients) %†
Headaches (severe)	92	72
Excessive sweating (generalized)	65	69
Palpitations with or without tachycardia	73	51
Anxiety, nervousness, fear of impending death, or panic	60	28
Tremulousness	51	26
Pain in chest, abdomen (usually epigastric), lumbar regions, lower abdomen or groin	48	28
Nausea with or without vomiting	43	26
Weakness, fatigue, prostration	38	15
Weight loss (severe)	14	15
Dyspnea	11	18
Warmth or heat intolerance	13	15
Visual disturbances	3	21
Dizziness or faintness	11	3
Constipation (or rarely diarrhea)	0	13
Paresthesia or pain in arms	11	0
Bradycardia (noted by patient)	8	3
Grand mal seizures	5	3
Miscellaneous (A large number of miscellaneous symptoms have been reported. Especially noteworthy are painless hematuria, frequency, nocturia, and tenesmus in pheochromocytoma of the urinary bladder)		
Manifestations due to complications		
Congestive heart failure with or without cardiomyopathy		
Myocardial infarction		
Cerebrovascular accident		
Ischemic enterocolitis with or without megacolon		
Azotemia		
Dissecting aneurysm		
Encephalopathy		
Shock		
Hemorrhagic necrosis in a pheochromocytoma		
Manifestations due to coexisting diseases or syndromes		
Cholelithiasis		
Medullary thyroid carcinoma with or without effects of secretions of serotonin, calcitonin, prostaglandin, or adrenocorticotropic hormone-like substance		
Hyperparathyroidism		
Mucocutaneous neuromas with characteristic facies		
Thickened corneal nerves (seen only with slit lamp)		
Marfanoid habitus		
Alimentary tract ganglioneuromatosis		
Neurofibromatosis and its complications		
Cushing's syndrome (rare)		
Von Hippel-Lindau disease (rare)		
Virilism, Addison's disease, acromegaly, duodenal carcinoid (extremely rare)		
Symptoms caused by encroachment on adjacent structures or by invasion and pressure effects of metastases		

*From Manger and Gifford, reference 4.
†Approximate percent.

mocytoma frequently presents dramatically and explosively with numerous and diverse manifestations that mimic many diseases. Of great diagnostic importance is the presence of sustained or paroxysmal hypertension. Manifestations or "attacks" suggesting hypercatecholaminemia without hypertension are highly atypical. Rarely, hypertension will be absent; this is most common when pheochromocytoma is familial.

One or more symptomatic attacks occur weekly in 75% of patients; however, attacks may occur several times daily or only every few months. Attacks occur abruptly and subside slowly: they last less than 1 hour in 80% of patients, but they may last less than a minute or persist for a week. They may be precipitated by palpation of the tumor, postural changes, exertion, anxiety, trauma, pain, ingestion of foods or beverages containing tyramine (certain cheeses, beers, and wines) or synephrine (citrus fruit), use of certain drugs (histamine, glucagon, tyramine, phenothiazine, metoclopramide, adrenocorticotropic hormone), intubation, anesthesia, operative manipulation, and micturition or bladder distension (with bladder tumors).

The symptoms and signs of pheochromocytoma (*Tables 1* and *2*) are mainly due to hypercatecholaminemia, hypertension, complications, or coexisting diseases or syndromes.

Headaches occur in any part of the head; they may be mild but are usually severe and throbbing (especially during paroxysmal hypertension) and are often accompanied by nausea and vomiting.

Generalized sweating (sometimes drenching) and palpitations with tachycardia (or reflex bradycardia)

occur frequently. Acute anxiety with fear of death is often experienced.

Hypermetabolism may cause considerable weight loss, but some patients, especially those with paroxysmal hypertension, may remain obese. Severe constipation or pseudo-obstruction[2] may occur in patients with sustained hypertension because catecholamines inhibit peristalsis. Ischemic enterocolitis with intestinal necrosis may complicate intense mesenteric artery vasoconstriction caused by hypercatecholaminemia. Secretion of vasoactive intestinal peptide, serotonin, or calcitonin by some pheochromocytomas may cause diarrhea. Severe watery diarrhea may be accompanied by hypokalemia and hypochlorhydria or achlorhydria (Verner-Morrison WDHH or WDHA syndrome).[3] Marked systolic and diastolic hypertension usually occurs with paroxysmal attacks, which occur in 45% of patients; rarely, paroxysms will convert to sustained hypertension. With sustained hypertension, which occurs in 50% of patients, blood pressures may fluctuate widely, and paroxysms may result from variations in circulating catecholamines. The remainder of patients have little hypertension, if any. Very rarely, hypertension alternates with hypotension (with predominantly epinephrine-secreting tumors).

About 5% of patients remain normotensive, especially those with familial pheochromocytoma. Patterns of hypertension in familial disease remain consistent (ie, family members have either sustained or paroxysmal hypertension). Very rarely, a rapid progression in severity and frequency of hypertensive attacks (sometimes alternating with hypotension) may necessitate emergency surgery to remove the tumor.

No close correlation exists between blood pressure and plasma catecholamine concentrations[4]; the sympathetic nervous system contributes to maintenance of hypertension in clinical[5] as well as experimental pheochromocytoma.[6]

Orthostatic hypotension in untreated hypertensive patients suggests pheochromocytoma. When this occurs, blood pressure usually decreases to normotensive levels; rarely, the blood pressure falls to shock levels and is accompanied by tachycardia. Resistance to antihypertensive therapy, paradoxic blood pressure increases during treatment with beta blockers, guanethidine, or ganglionic blockers, or marked pressor responses to conditions mentioned above that may precipitate attacks should suggest pheochromocytoma.

TABLE 2
SIGNS OBSERVED IN PATIENTS WITH PHEOCHROMOCYTOMA*

Blood pressure changes
Hypertension with or without wide fluctuations (rarely paroxysmal hypotension or hypertension alternating with hypotension, or hypertension absent.)
Hypertension induced by physical maneuver such as exercise, postural change, or palpation and massage of flank or mass elsewhere
Orthostatic hypotension with or without postural tachycardia
Paradoxic blood pressure response to certain antihypertensive drugs; marked pressor response with induction of anesthesia
Other signs of catecholamine excess
Hyperhidrosis
Tachycardia or reflex bradycardia, very forceful heartbeat, arrhythmia
Pallor of face and upper part of body (rarely flushing; mottled cyanosis)
Anxious, frightened, troubled appearance
Hypertensive retinopathy
Dilated pupils (very rarely exophthalmos, lacrimation, scleral pallor, or injection; pupils may not react to light)
Leanness or underweight
Tremor with or without shaking
Raynaud's phenomenon or livedo reticularis (occasionally puffy, red, and cyanotic hands in children); skin of extremities wet, cold, clammy, pale, gooseflesh; occasionally cyanotic nail beds
Fever (occasionally very elevated)
Mass lesion (rarely palpable)
Tumor in abdomen or neck [pheochromocytoma, chemodectoma, thyroid carcinoma, or thyroid-swelling (very rare and only during hypertensive paroxysm)]
Signs caused by encroachment on adjacent structures or by invasion and pressure effects of metastases
Manifestations related to complications or to coexisting diseases or syndromes†

*Observed in some of the 76 patients cited in *Table 1*.
From Manger, Gifford. Current concepts of pheochromocytoma. Cardiovasc Med 1975; 3: 289-303.
†See *Table 1*.

Pallor and tachycardia (or reflex bradycardia) frequently occur, and, rarely, flushing is observed during hypertensive paroxysms. Retinopathy is not infrequent when hypertension is severe and sustained, but it rarely occurs when hypertension is paroxysmal. Occasionally, a fine tremor and Raynaud's phenomenon are noted. Slight temperature elevation is common and severe hyperpyrexia may rarely occur.

In children, polydipsia, polyuria, and convulsions may also occur, and, rarely, the hands become puffy, red, and cyanotic. Attacks of pheochromocytoma may be aggravated or may subside during pregnancy

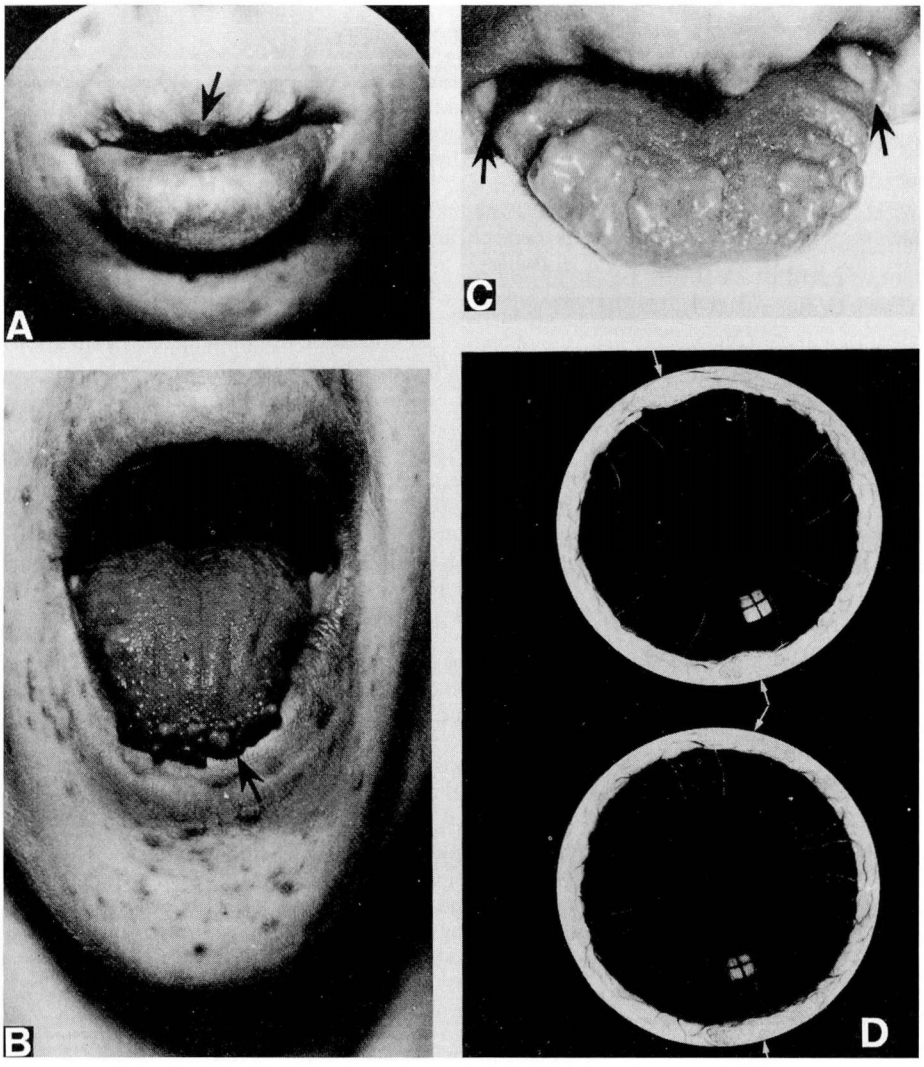

FIGURE 1. Lesions of the lips, tongue, and corneas observed in four patients with multiple endocrine neoplasia, type 3.
(*A*) Diffuse thickening of the lower lip in a patient with medullary thyroid carcinoma (MTC) and pheochromocytoma. Thickening of upper lip is less prominent but is irregular and accentuated centrally (arrow) and produces a bumpy appearance.
(*B*) Multiple sessile confluent nodules stud tip of tongue in a patient with MTC without evidence of pheochromocytoma. Slightly elevated plaque-like lesions, more evident on right (arrow) are present along margins of tongue.
(*C*) Several large nodules are present on anterior third of tongue in patient with MTC without pheochromocytoma. Intraoral conical projections at angles of mouth are just visible bilaterally (arrows). From Carney JA, Sizemore GW, Lovestedt SA. Mucosal ganglioneuromatosis, medullary thyroid carcinoma, and pheochromocytoma: multiple endocrine neoplasia, type 2b. Oral Surg Oral Med Oral Pathol 1976; 41:746–747.
(*D*) Thickened corneal nerve of right and left eyes and thickened perilimbal neuromas are visible on either side of each limbus (arrows). (Drawing from Robertson DM, Sizemore GW, Gordon H. Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. Trans Am Acad Ophthalmol Otolaryngol 1975; 5:733.)

and can be confused with eclampsia; shock may occur with labor or after delivery and may mimic a ruptured uterus. Tumors in the bladder may cause painless hematuria, and attacks may occur during micturition or bladder distension.

ASSOCIATED ENTITIES

Ten percent of pheochromocytomas are familial as indicated by their occurrence in families and by their coexistence with multiple endocrine neoplasia (MEN). Coexistence with medullary thyroid carcinoma (MTC) or C-cell hyperplasia and sometimes parathyroid neoplasms or hyperplasia constitutes MEN type 2. Coexistence of pheochromocytoma, MTC, mucosal neuromas, thickened corneal nerves, alimentary tract ganglioneuromatosis, and, often, a marfanoid habitus constitutes MEN type 3 (*Figure 1*). Hyperparathyroidism occurs in 50% of patients with MEN type 2 but rarely in MEN type 3.

MTC involves both thyroid lobes and frequently spreads to cervical and mediastinal nodes. Serotonin, prostaglandin, and calcitonin may be released from MTC and may cause severe diarrhea; adrenocorticotropic hormone-like substances may be secreted by MTCs or pheochromocytomas and can cause Cushing's syndrome. Patients with pheochromocytoma should be screened for

MTC or premalignant C-cell hyperplasia and hyperparathyroidism. MTC may occur years before pheochromocytoma.[4,7] Hypercalcitoninemia suggests MTC or C-cell hyperplasia; however, hypercalcitoninemia occurs in other conditions and occasionally in pheochromocytoma.[8,9] Similarly, hypercalcemia may not indicate MEN, since it may result from a parathyroid-like hormone released from some pheochromocytomas.[10] Therefore, reevaluation for MEN should be performed after removal of a pheochromocytoma.

Neurofibromatosis (Von Recklinghausen's disease), often with "café-au-lait" spots, occurs in 5% of patients with pheochromocytoma, whereas the incidence of pheochromocytoma in neurofibromatosis is 1%. Coexistence of neurofibromatosis, pheochromocytoma, and somatostatin-rich duodenal carcinoid was reported in one patient.[11] Rarely, pheochromocytoma coexists with von Hippel-Lindau disease (cerebellar hemangioblastoma plus retinal angioma) or acromegaly. The high incidence of cholelithiasis (up to 30%) in patients with pheochromocytoma remains unexplained.

APUD is an acronym indicating cells having similar cytochemical behavior (ie, they produce amines by *a*mine *p*recursor *u*ptake and *d*ecarboxyla-

TABLE 3
DIFFERENTIAL DIAGNOSIS OF PHEOCHROMOCYTOMA*

All hypertensive patients (sustained and paroxysmal) when cause is unknown
Anxiety, panic attacks, psychoneurosis, tension states
Hyperthyroidism
Paroxysmal tachycardia
Hyperdynamic beta-adrenergic circulatory state
Menopause
Vasodilating headache (migraine and cluster headaches)
Coronary insufficiency syndrome
Acute hypertensive encephalopathy
Diabetes mellitus
Renal parenchymal or renal arterial disease with hypertension
Focal arterial insufficiency of the brain; cerebral vasculitis
Intracranial lesions (with or without increased intracranial pressure)
Autonomic hyperreflexia
Diencephalic seizure; Page's syndrome; dopamine surges
Toxemia of pregnancy (or *eclampsia with convulsions*)
Hypertensive crises associated with monoamine oxidase inhibitors
Carcinoid
Hypoglycemia
Mastocytosis
Familial dysautonomia
Acrodynia
Neuroblastoma; ganglioneuroblastoma; ganglioneuroma
Acute infectious disease; *acute abdomen* (cardiovascular catastrophe)
Unexplained shock
Neurofibromatosis (with or without renal arterial disease)
Fatal familial insomnia
Rare causes of paroxysmal hypertension (*adrenal medullary hyperplasia; acute porphyria; lead poisoning*; tabetic crisis; encephalitis, *clonidine withdrawal*; hypovolemia with inappropriate vasoconstriction; pulmonary artery; fibrosarcoma; pork hypersensitivity; dysregulation of hypothalamus; *baroreflex failure; tetanus; Guillain-Barré syndrome; pseudopheochromocytoma*: factitious-induced by certain illegal, prescription and nonprescription drugs)
Fortuitous circumstances simulating pheochromocytoma
Conditions sometimes associated with pheochromocytoma
  Coexisting disease or syndromes
    Cholelithiasis
    Medullary thyroid carcinoma
    Hyperparathyroidism
    Mucosal neuromas
    Thickened corneal nerves
    Marfanoid habitus
    Alimentary-tract ganglioneuromatosis
    Neurofibromatosis
    Cushing's syndrome
    Von Hippel-Lindau disease
    Polycythemia
    Virilism, Addison's disease, acromegaly
  Complications
    Cardiovascular disease†
    Cerebrovascular disease
    Renovascular disease
    Circulatory shock
    Renal insufficiency
    Hemorrhagic necrosis of pheochromocytoma†
    Dissecting aneurysm†
    Ischemic enterocolitis with or without intestinal obstruction

*Conditions in italics may have increased excretion of catecholamines and/or metabolites
From Manger and Gifford, reference 4 with modification.
†May present as an abdominal or cardiovascular catastrophe.

TABLE 4
INDICATIONS FOR SCREENING PATIENTS FOR PHEOCHROMOCYTOMA*

- Hypertension (sustained or paroxysmal) with the following:
  - Symptoms *(Table 1)* and signs *(Table 2)* or coexisting disease or syndromes *(Table 3)*
  - Group 3 or 4 retinopathy of unknown cause
  - Weight loss
  - Hyperglycemia
  - Hypermetabolism without hyperthyroidism
  - Cardiomyopathy
  - Resistance to antihypertensive therapy
  - Orthostatic hypotension (without antihypertensive drugs)
  - Unexplained fever
- Persons with marked hyperlability of blood pressure
- Recurrent attacks of symptoms and signs of pheochromocytoma even if hypertension not demonstrated
- Severe pressor response during or induced by the following:
  - Anesthesia induction
  - Intubation
  - Surgery
  - Angiography
  - Parturition
  - Antihypertensive therapy
  - Precipitating factors listed under "Clinical Presentation" in text
- Unexplained circulatory shock – especially:
  - During anesthesia
  - During pregnancy, delivery, or in puerperium
  - During operation or postoperatively
  - Following administration of phenothiazine drugs
- Family history of pheochromocytoma, especially if hypertensive (also screen siblings and children)
- Hypertension with disease or complications sometimes associated with pheochromocytoma *(Table 1)*
- Hyperlabile blood pressure or severe hypertension during pregnancy or apparent preeclampsia or eclampsia
- Transient abnormal electrocardiogram during hypertensive episodes
- Imaging evidence of suprarenal mass

*Adapted from Manger WM, Gifford RW Jr. Hypertension secondary to pheochromocytoma. Bull NY Acad Med 1982; 58: 139-158.

tion.[12] The term "neurocristopathies" designates the constellation of embryogenetically related diseases such as pheochromocytoma, neuroblastoma, neurofibromatosis, MTC, carcinoids, Hirschsprung's disease, nonchromaffin paragangliomas, melanotic progonoma, MEN, and neurocutaneous melanosis. The common denominator in these conditions is apparently an aberrant neural crest development[13]; the presence of enolase[14] and chromogranin A[15] in some of these tumors and the fact that some of these conditions produce catecholamines support this concept.

DIFFERENTIAL DIAGNOSIS

Many conditions can produce manifestations suggesting pheochromocytoma (*Table 3*). Most of these conditions can be excluded on clinical grounds, and most of these are discussed in detail elsewhere.[4] Preoperative diagnosis of pheochromocytoma requires demonstration of substantial elevations of catecholamines or their metabolites in plasma or urine. Neural crest tumors, increased intracranial pressure, hypoglycemia, convulsions, clonidine withdrawal, baroreflex failure, surreptitious catecholamine administration, or consumption of certain illegal and prescription drugs may also cause substantial elevations of these substances, but few conditions increase them to levels occurring with pheochromocytoma. Physicians should be aware that many types of stress can significantly elevate these concentrations as well.[4]

Consumption of certain controlled and illegal substances (amphetamine, cocaine, phencyclidine [PCP], lysergic acid diethylamide [LSD]) and of some prescription and nonprescription drugs containing phenylpropanolamine may cause manifestations mimicking pheochromocytoma. Factitious manifestations in emotionally disturbed persons who have access to prescription and illicit drugs should be considered in the differential diagnosis. Hemorrhagic necrosis in a pheochromocytoma may present as an acute abdomen or cardiovascular catastrophe.

DIAGNOSIS

Since 95% of patients are symptomatic, all patients with sustained or paroxysmal hypertension who have manifestations suggesting pheochromocytoma should be screened, unless the cause of hypertension is known. Asymptomatic patients with hypertension of unknown cause should be screened if they have laboratory or electrocardiographic abnormalities caused by hypercatecholaminemia, radiographic or magnetic resonance imaging (MRI) evidence suggesting pheochromocytoma, or diseases sometimes coexisting with pheochromocytoma (*Table 1*). Other indications for screening are listed in *Table 4*. Screening should be performed by measuring 24-hour urinary metanephrine excretion or plasma catecholamine concentrations. Urinary catecholamine and vanillylmandelic acid measurements are less reliable.

TABLE 5
PHEOCHROMOCYTOMA "PEARLS"
(FACTS WORTH MEMORIZING)*

6 Hs†	Hypertension
	Headache
	Hyperhidrosis
	Heart consciousness
	Hypermetabolism
	Hyperglycemia
95% will have	Headache or hyperhidrosis or palpitation
Rough rule of 10	10% familial
	10% bilateral (adrenal)‡
	10% malignant
	10% multiple (other than bilateral adrenal)‡
	10% extra-adrenal
	10% occur in children
Multiple endocrine neoplasm syndrome, type-2 triad	Medullary thyroid carcinoma
	Bilateral-familial pheochromocytoma (frequent)
	Hyperparathyroidism (about 50%)
Multiple endocrine neoplasm syndrome, type-3 sextet	Medullary thyroid carcinoma
	Bilateral-familial pheochromocytoma (frequent)
	Mucosal neuromas
	Thickened corneal nerves
	Marfanoid habitus
	Alimentary tract ganglioneuromatosis (very rarely hyperparathyroidism)
4 Cs	Cholelithiasis
	Cushing's syndrome (very rare)
	Cutaneous lesions
	Cerebellar hemangioblastoma (very rare)
Manifestations may appear during pregnancy!	

*Adapted from Manger and Gifford, reference 4.
†The term "triad of Hs" was used by Dr. John E. Howard and refers to hypertension, hyperglycemia, and hypermetabolism (without hyperthyroidism) occurring in patients with pheochromocytoma. We have extended this category to include 6 Hs.
‡Adults and children combined.

TABLE 6
LABORATORY FINDINGS SOMETIMES
PRESENT IN PHEOCHROMOCYTOMA*

- Fasting hyperglycemia (two thirds of patients with sustained hypertension)
- Glycosuria
- Impaired glucose tolerance
- Increased basal metabolic rate (>20%) (three fourths of sustained hypertensive patients)
- Increased plasma free fatty acid concentrations (mainly in sustained hypertensive patients)
- Increased triglycerides
- Hypercholesterolemia
- Anemia or polycythemia; increased white blood cell count; usually erythrocyte sedimentation rate normal (occasionally increased platelet count)
- Decreased plasma or total blood volume, or both
- Increased blood urea but rare (<60 mg/dL in 95%); with or without proteinuria (rarely slight increase in serum creatinine)
- Hyperreninemia with or without aldosteronism
- Hypokalemia
- Increased serum glucagon concentration
- Hypercalcemia (caused by pheochromocytoma)
- Hypoinsulinemia (rarely hyperinsulinemia and hypoglycemia)
- Hyperamylasemia
- Lactic acidosis (decreased pH, decreased PO_2, increased phosphorus)
- Increased serum PTH-like substance, adrenocorticotropic hormone, vasoactive intestinal peptide, calcitonin, serotonin, gastrin, opioids, melanocyte-stimulating hormone, atrial natriuretic peptide, somatostatin (all rarely elaborated by pheochromocytoma)

If associated with:
- Cushing's syndrome
  - Increased serum adrenocorticotropic hormone (from pheochromocytoma or medullary thyroid carcinoma)
  - Increased plasma cortisol
  - Increased urinary steroids
- Hyperparathyroidism
  - Increased serum calcium
  - Increased serum parathyroid hormone
  - Decreased serum phosphate
- Medullary thyroid carcinoma
  - Increased serum thyrocalcitonin
  - Increased serum prostaglandin (E_2 and $F_{2\alpha}$)
  - Increased serum serotonin
  - Increased urinary 5-hydroxyindoleacetic acid
  - Increased serum histaminase
  - Increased adrenocorticotropic hormone concentration

*Modified from Manger and Gifford, reference 4.

Unrecognized pheochromocytoma in pregnancy carries a high risk of maternal and fetal mortality. Manifestations may first appear in pregnancy, remit after delivery, and return in a subsequent pregnancy.

Table 5 contains facts helpful in evaluating patients for pheochromocytoma.

Laboratory and electrocardiographic abnormalities

Laboratory abnormalities sometimes caused by pheochromocytoma and coexisting conditions are enumerated in *Table 6* and are reviewed elsewhere.[4] Hyperglycemia, hypermetabolism, increased free fatty acid concentrations, and hypercholesterolemia may result from hypercatecholaminemia. Hypovolemia occurs in the majority of patients, primarily those with sustained hypertension. Rarely, pheochromocytomas (or an associated cerebellar hemangioblastoma) secrete erythropoietin and cause polycythemia.

TABLE 7
EFFECTS OF DRUGS AND INTERFERING SUBSTANCES ON EXCRETION OF CATECHOLAMINES AND THEIR METABOLITES*

Upper limit of normal (adult) (mg/24 h)		Effects	
		Increase apparent value	Decrease apparent value
Catecholamines		Catecholamines	Fenfluramine (large dose)
Epinephrine	0.02	Drugs containing catecholamines	Alpha-methyltyrosine
Norepinephrine	0.08	Isoproterenol	
Total	0.10	Levodopa	
Dopamine	0.40	Methyldopa	
		Labetalol†	
		Tetracyclines†	
		Erythromycin†	
		Chlorpromazine†	
		Other fluorescent substances (eg, quinine, quinidine, bile in urine)†	
		Rapid withdrawal from clonidine	
		Ethanol	
Metanephrines		Catecholamines	Methylglucamine (in radiopaque agents)
Metanephrine	0.4	Drugs containing catecholamines	
Normetanephrine	0.9	Monoamine oxidase inhibitors	Fenfluramine (large doses)
Total	1.3	Benzodiazepines	Alpha-methyltyrosine
		Labetalol†	
		Rapid clonidine withdrawal	
		Ethanol	
Vanillylmandelic acid	6.5	Catecholamines (minimal increase)	Clofibrate
		Drugs containing catecholamine (minimal increase)	Disulfiram
			Ethanol
		Levodopa	Monoamine oxidase inhibitors
		Labetalol†	Fenfluramine (large doses)
		Nalidixic acid†	Alpha-methyltyrosine
		Rapid clonidine withdrawal	

*As determined by most reliable assays. Modified from Manger et al, reference 31.
†Probably spurious interference with fluorescence and high-pressure liquid chromatography assays.

Severe catecholamine-induced ischemia involving multiple organs may result in lactic acidosis[16] and elevations of pancreatic, hepatic, and cardiac enzymes.[17] Hypertension may be exacerbated by elevated plasma concentrations of renin, angiotensin II, and aldosterone resulting from catecholamine stimulation of renal $beta_1$-adrenergic receptors or, rarely, from renal artery spasm or compression by a pheochromocytoma or coexisting neurofibroma.[4,18]

Arrhythmias or electrocardiographic changes suggesting myocardial ischemia, damage, or strain may develop; although nonspecific, their transient appearance during paroxysms suggests pheochromocytoma in the absence of other causes. Permanent electrocardiographic changes can result from hypertension, coronary atherosclerosis, or catecholamine cardiomyopathy. Catecholamine cardiomyopathy may occur in patients with sustained or only paroxysmal hypertension or, rarely, with normotension.[19]

Biochemical tests

Concentrations of plasma catecholamines and excretion of urinary metanephrines are invariably elevated when pheochromocytoma causes sustained hypertension; when hypertension is only paroxysmal, measurements of catecholamines and their metabolites in plasma and urine may be normal during normotensive periods. If hypertension is paroxysmal, one must obtain blood during spontaneous or provoked hypertension or collect urine following a hypertensive episode to establish the preoperative diagnosis.

Pharmacologic tests

Some patients with essential or neurogenic hypertension have borderline or moderate elevations of plasma or urinary catecholamines or their metabolites (plasma catecholamine concentrations may be 500 to 2000 pg/mL under basal conditions). Often, these patients even have manifestations suggesting pheochromocytoma.

Diagnostic specificity is conferred by suppressing the sympathetic nervous system with clonidine; this reduces plasma norepinephrine by 50% or to normal concentrations in neurogenic hypertensive patients, but not in patients with pheochromocytoma.[20,21] Changes in the plasma epinephrine concentration are a less reliable diagnostic guide; rarely, significant increases in epinephrine consistent with pheochromocytoma have been observed during clonidine suppression.[21] The test is quite safe, although clonidine's vagotonic effect can cause marked hypotension, particularly in the presence of beta blockade; patients should remain recumbent until this drug effect subsides. Beta blockers should be discontinued 48 hours before testing since they can prevent significant suppression of plasma catecholamine concentrations by clonidine in patients with neuro-

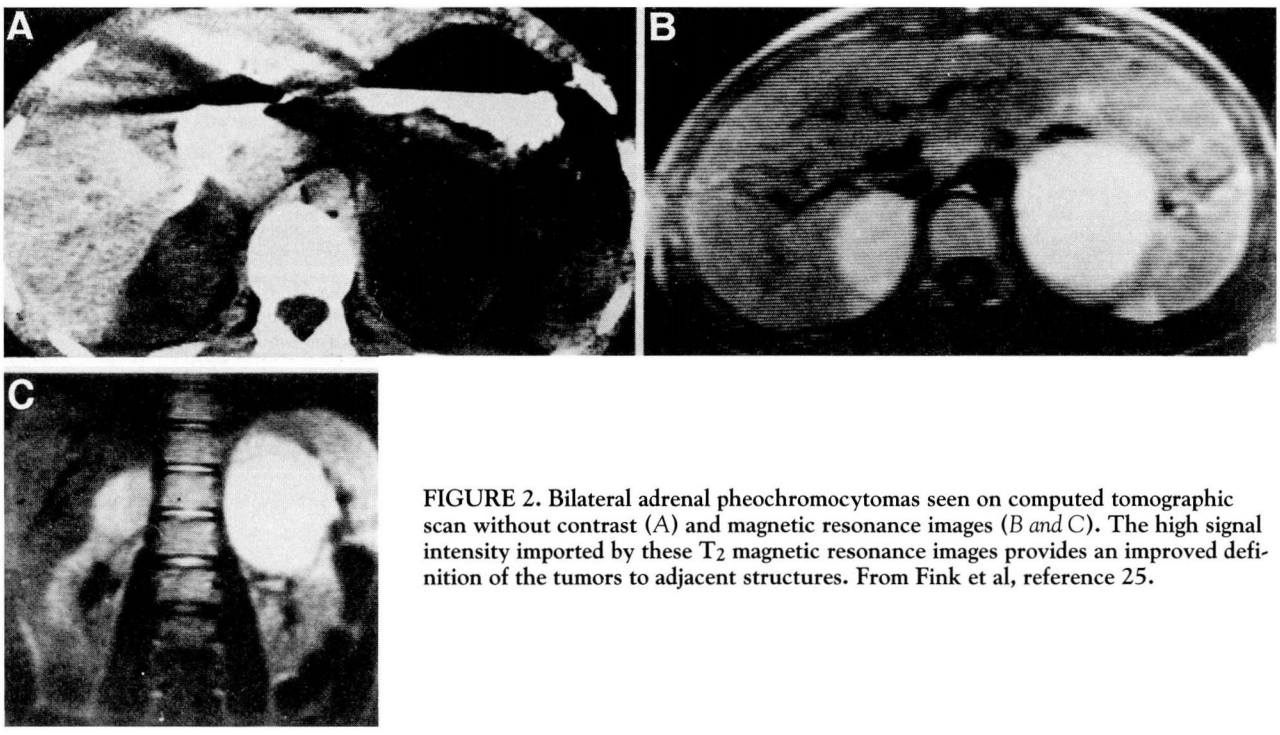

FIGURE 2. Bilateral adrenal pheochromocytomas seen on computed tomographic scan without contrast (*A*) and magnetic resonance images (*B and C*). The high signal intensity imported by these T_2 magnetic resonance images provides an improved definition of the tumors to adjacent structures. From Fink et al, reference 25.

genic hypertension and falsely suggest the presence of a pheochromocytoma. A few drugs (eg, isoproterenol, methyldopa, levodopa) cause significant spurious elevations of plasma catecholamine concentrations determined radioenzymatically; however, a variety of drugs may interfere with high-pressure liquid chromatographic catecholamine assays (*Table 7*). A catecholamine assay of blood drawn via an indwelling catheter from a patient who has been recumbent for 1 hour usually differentiates neurogenic from pheochromocytic hypertension; the clonidine suppression test is reserved for patients whose catecholamine concentrations remain elevated despite 1-hour recumbency.

Elevated catecholamine concentrations in platelets[22] and decreased numbers of beta-adrenoceptors on leukocytes[23] have been reported in pheochromocytic, but not neurogenic, hypertension.

Rarely, a provocative test with glucagon combined with plasma catecholamine measurement is required to establish the presence of a paroxysmally secreting pheochromocytoma. Testing is safe when performed with precautions to counteract hypertensive crises, arrhythmias, or hypotension; it is contraindicated when blood pressure is greater than 160/105 mm Hg or if sudden pressure elevations may be hazardous. Creating an alpha-adrenergic blockade or administering 10 mg of nifedipine orally prior to testing prevents a hypertensive response without influencing a diagnostic plasma catecholamine elevation.

Measurement of 24-hour urinary total metanephrines (metanephrine plus normetanephrine) is a highly reliable screening test, since these are elevated in about 95% of patients with pheochromocytoma.

Table 7 gives upper limits for normal excretion of catecholamines and their metabolites and indicates substances that can affect their determinations. We are unaware of drugs (except for metyrosine) that lower excretion of catecholamines or metabolites to normal levels in patients with pheochromocytoma; however, radiopaque media containing methylglucamine can cause false-negative results for metanephrines.

PREOPERATIVE LOCALIZATION

Pheochromocytomas arise from chromaffin cells in the adrenal medulla (90% of tumors), the organ of Zuckerkandl and other extra-adrenal sites in the abdomen, chest (< 2% of tumors), and neck (< 0.1% of

tumors), and in such exotic sites as the base of the skull, middle ear, and spermatic cord. Multiple and extra-adrenal pheochromocytomas are more common in children (35%) than adults (8%). If a significant fraction of plasma or urinary catecholamines is epinephrine or its metabolite (metanephrine), the pheochromocytoma is probably in the adrenal area, or, rarely, in the organ of Zuckerkandl; however, imaging studies must establish tumor location.

Imaging

Computed tomography (CT) identifies 95% of pheochromocytomas and reveals adrenal lesions 1 cm or larger and extra-adrenal lesions 2 cm or larger. Intravenous and oral contrast media may be needed for optimal interpretation. CT is noninvasive and superior to angiography, which is now rarely indicated. It reliably demonstrates chest lesions, although intrapericardial pheochromocytomas may be missed.[24]

MRI is the most reliable method of locating a pheochromocytoma. A high signal intensity on MRI is characteristic of pheochromocytoma (*Figure 2*).[25] Rarely, other benign or malignant lesions may mimic pheochromocytoma.[26] MRI probably identifies more than 95% of tumors. It is noninvasive and does not produce artifacts like those caused by surgical clips in CT. It is superior to CT in detecting extra-adrenal lesions and some cardiac[27] and familial adrenal pheochromocytomas.

The radiopharmaceutical agent metaiodobenzylguanidine I 131 (MIBG) concentrates in 85% of pheochromocytomas, and MIBG scintigraphy is highly specific for diagnosing pheochromocytoma and locating tumors.[28] It is especially helpful in detecting very small tumors, tumors in unusual locations (eg, in the pericardium[29]), and, perhaps, adrenal medullary hyperplasia (experience of E.L. Bravo). MIBG uptake may occur in neuroblastoma, MTC, carcinoid, and small-cell carcinoma of the lung. Drugs such as labetalol, reserpine, calcium antagonists, tricyclic antidepressants, sympathomimetics, cocaine, adrenergic neuron blockers, and tranquillizers may inhibit uptake and should be discontinued a week before scintigraphy.[30]

CT, MRI, and scintigraphy with MIBG may locate bladder pheochromocytomas, but cystoscopy should be performed only after alpha-adrenergic blockade. Experience locating pheochromocytomas in the neck and base of the skull is limited; however, MRI and MIBG scintigraphy may prove most reliable.

Because scintigraphy with MIBG produces images of the entire body, it is particularly valuable in detecting metastases. Scanning with technetium 99 may demonstrate bone metastases missed by MIBG. Liver metastases can be detected with MRI or CT. Metastases usually involve the lymph nodes, liver, lungs, and bones, but not the brain.

Central venous blood sampling

When all attempts to locate a pheochromocytoma have failed, blood sampling for catecholamine assay from various sites in the vena cava may locate an abdominal tumor or indicate a thoracic or cervical lesion.

The algorithm in *Figure 3* can be followed if pheochromocytoma is suspected.

PREOPERATIVE EVALUATION AND MANAGEMENT

MTC, C-cell hyperplasia, and hyperparathyroidism must be excluded in all patients with pheochromocytoma and in relatives of patients with familial pheochromocytoma.[31,32] Diagnosis and treatment of these conditions should be delayed until after the pheochromocytoma is removed.

Malignant hypertension, acute cardiovascular or abdominal complications (eg, hemorrhagic necrosis of a pheochromocytoma), or acceleration in the frequency and severity of hypertensive crises may necessitate immediate medical or surgical therapy, or both, but this does not often happen.

Hypertensive crises are usually aborted by a rapid intravenous bolus of phentolamine (5 mg); if there is no response, the dose can be repeated every 2 minutes until the blood pressure is adequately reduced. Since phentolamine's effect is transient, repeated hypertensive crises (eg, those during surgery) are best controlled by infusing sodium nitroprusside or phentolamine (100 mg of either drug in 500 mL 5% dextrose in water) at a rate that normalizes blood pressure. Nitroprusside can cause thiocyanate toxicity if the infusion is prolonged or if renal function is impaired. Blood pressure should be lowered cautiously to avoid myocardial ischemia.[33]

If immediate surgery is needed, hypovolemia is corrected by infusion of appropriate intravenous fluids within 18 hours preoperatively to minimize postoperative hypotension.

Abdominal palpation and stressful procedures should be performed cautiously, and drugs should be

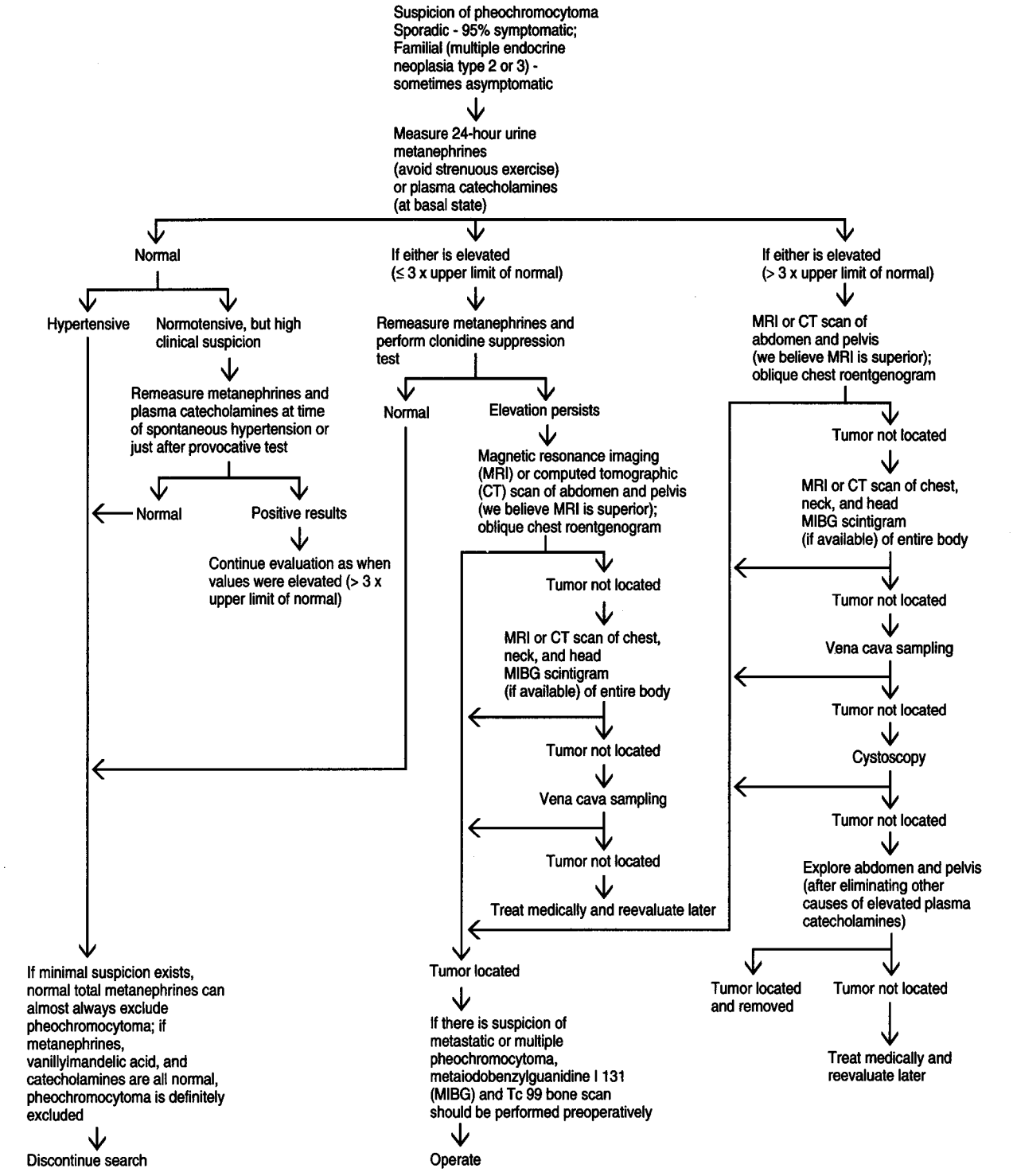

FIGURE 3. Algorithm for diagnosis of pheochromocytoma. From Manger WM, Gifford RW Jr. Pheochromocytoma. (In: Laragh JH, Brenner BM, Kaplan NM, editors. Endocrine mechanisms in hypertension. New York: Raven Press, 1989:1639–1659.)

available to combat hypertensive crises, hypotension, and arrhythmias. Morphine and phenothiazines should be avoided, since they may precipitate hypertensive crises or shock.

Adrenergic blockade

Preoperative alpha blockade with phenoxybenzamine (10 to 20 mg twice daily) or prazosin (starting with 1 mg and increasing to 1 or 2 mg two or three times daily) for a week or longer and continuing until surgery usually minimizes preoperative manifestations, reverses hypovolemia, and promotes smooth anesthetic induction and relatively stable blood pressure during surgery. However, blockade is optional unless patients have severe sustained or paroxysmal hypertension or cardiovascular complications. Moreover, the dosage should be kept low enough to avoid orthostatic hypotension because higher dosages would prevent the blood pressure elevation caused by intra-abdominal palpation (which aids the surgeon in locating tumors), and prevent recognition of additional pheochromocytomas (which, without blockade, cause persistence of hypertension after tumor removal).

Extensive experience at the Cleveland Clinic revealed that preoperative alpha-adrenergic blockade with phenoxybenzamine or large doses of prazosin was not essential for successful surgical management and a satisfactory outcome for patients with pheochromocytoma.[34]

Preoperative beta blockade (propranolol 10 to 40 mg two or three times daily), if not contraindicated, is used for hazardous supraventricular arrhythmias, tachycardia, or angina. To rapidly control tachycardia due to atrial fibrillation or flutter, intravenous esmolol (a rapid-acting cardioselective $beta_1$-blocker) may be effective. Ventricular arrhythmias are treated with lidocaine (50 to 100 mg intravenous bolus). *Beta blockers should never be given without first creating alpha blockade, since beta blockade used alone can cause marked hypertension.* This occurs particularly with nonselective beta blockers (eg, propranolol, nadolol), since they inhibit the vasodilating effects of epinephrine. Cardioselective beta blockers (eg, metoprolol, atenolol) have less vascular effect and are more appropriate.

Labetalol (an alpha-beta blocker) is effective in treating some patients with pheochromocytomas[35]; however, we prefer not to use it, since it sometimes causes hypertension.[36,37]

OPERATIVE AND POSTOPERATIVE MANAGEMENT

In expert hands, operative mortality is low (0 to 4%). Preoperatively, a tranquilizer is given to allay anxiety, which could trigger catecholamine release. Fentanyl and droperidol may stimulate tumor catecholamine secretion and are to be avoided. We avoid atropine since it may induce tachycardia in the presence of hypercatecholaminemia. Before endotracheal intubation, muscle relaxants are administered and electrocardiographic and intra-arterial pressure monitoring is initiated. Isoflurane is the preferred anesthetic, although enflurane is suitable.

During intubation and surgery, it is critical to treat hypertensive crises promptly with intravenous phentolamine or nitroprusside and to control arrhythmias with intravenous propranolol (esmolol may be preferable) or lidocaine, or both. Intraoperative replacement of blood loss will prevent postoperative hypotension.

Since intra-abdominal tumors may be multiple and extra-adrenal, an anterior transperitoneal incision is mandatory. Intra-abdominal neurofibromatosis, vascular lesions, and cholelithiasis may require additional surgery. We avoid bilateral prophylactic adrenalectomy, although some authorities recommend it when an adrenal pheochromocytoma occurs in MEN syndromes; their rationale is the great likelihood that both adrenals are, or will become, involved.

Hypercalcitoninemia and hypercalcemia are reevaluated after the pheochromocytoma has been removed; return of serum calcium and calcitonin concentrations to normal levels rules out other endocrine neoplasms as their cause.

Pheochromocytomas of the head, neck, chest, and bladder require special surgical procedures; otherwise, management is similar to that for intra-abdominal tumors. Pheochromocytomas discovered during pregnancy should be removed when the diagnosis is made; however, if the pregnancy is carried to term, cesarean section is advisable to avoid the stress of labor.

Close postoperative monitoring is mandatory. Hypovolemia and hemorrhage at operative sites can cause hypotension and require volume replacement. Fluid overload, pain, hypoxia, hypercapnia, urinary retention, or residual pheochromocytoma can cause postoperative hypertension. Inadvertent renal artery ligation can cause hyperreninemia; however, hypertension would probably not appear for several

days or weeks postoperatively.

Severe hypoglycemia with central nervous system manifestations has occurred within 2 hours after surgery. It is a transient phenomenon caused by a rise in insulin levels; alpha blockers may augment it by reducing inhibition of insulin secretion by catecholamines. Beta blockers can impair recovery from hypoglycemia by reducing gluconeogenesis and glycogenolysis, and they mask hypoglycemic signs by preventing tachycardia and tremor; in some cases sweating may also be impaired.[38] Blood glucose should be monitored for several hours postoperatively, and hypoglycemia should be treated promptly. Initiating an infusion of 5% dextrose and water immediately after tumor removal and continuing it for several hours prevents hypoglycemia.[31,39] Transient hyperinsulinemia with hypoglycemia was reported following glucose tolerance tests in two patients with pheochromocytoma.[19]

Why 25% of patients remain hypertensive following tumor removal is unclear; coexisting essential hypertension may be a partial explanation. Five-year survival with benign pheochromocytomas is 95% but varies from 36% to 50% with malignant tumors.

LONG-TERM MEDICAL MANAGEMENT

If a pheochromocytoma cannot be totally removed, as much as possible is resected to reduce the amount of catecholamine-secreting tissue.

Conventional radiotherapy of bone metastases may be effective. Irradiation with MIBG may cause tumor regression and may decrease catecholamine secretion in 25% of malignant pheochromocytomas; however, since all patients treated with MIBG relapsed within 2 years, this therapy has been curtailed in the United States.

Combination intravenous chemotherapy with cyclophosphamide, vincristine, and dacarbazine temporarily reduces tumor mass, catecholamine excretion, and symptoms in 50% of patients with malignant pheochromocytoma.[40] Since damaged cells may release catecholamines, treatment of hypertensive crises is sometimes required during chemotherapy.

Alpha and beta blockers can control manifestations of hypercatecholaminemia for many years, and beta blockers may prevent catecholamine-induced cardiomyopathy.[41] Metyrosine decreases catecholamine synthesis and minimizes manifestations of hypercatecholaminemia, and it appears useful in treating catecholamine-induced cardiomyopathy.[42]

Nifedipine (10 mg orally) is especially effective in promptly resolving hypertensive crises. It can suppress clinical symptoms without altering plasma catecholamine concentrations,[43] although a significant decrease in norepinephrine excretion occurred in one patient with pheochromocytoma.[44]

Somatostatin can be useful in hypersecretory diarrhea.[45] In one of our patients, large intravenous doses of somatostatin partially controlled severe secretory diarrhea caused by marked elevation of plasma vasoactive intestinal peptide and calcitonin concentrations.

SUMMARY

Pheochromocytoma can be difficult to recognize: the key to diagnosing it is suspecting it in patients with paroxysmal or sustained hypertension, especially those with any manifestations suggesting hypercatecholaminemia. Measurements of catecholamines and their metabolites in plasma or urine provide definitive information in about 95% of patients with pheochromocytoma, but the clonidine suppression test may be needed to rule out neurogenic hypertension. Rarely, a provocative test may be required to stimulate a quiescent tumor. MRI or CT imaging or scintigraphy with MIBG can be used to localize tumors, but MRI appears the most reliable. Management requires expertise; surgical resection is successful in 90% of patients.

ACKNOWLEDGMENT

The preparation of this report was supported by the National Hypertension Association, Inc.

REFERENCES

1. **St. John Sutton MG, Sheps SG, Lie JT.** Prevalence of clinically unsuspected pheochromocytoma: review of a 50-year autopsy series. Mayo Clin Proc 1981; **56**:354–360.
2. **Mullen JP, Cartwright RC, Tisherman SE, Misage JR, Shapiro AP.** Case report: pathogenesis and pharmacologic management of pseudo-obstruction of the bowel in pheochromocytoma. Am J Med Sci 1985; **290**:155–158.
3. **Viale F, Dell'orto P, Moro E, Gozzaglio L, Goggi G.** Vasoactiveintestinal polypeptide, somatostatin- and calcitonin-producing adrenal pheochromocytoma associated with the watery diarrhea (WDHH) syndrome. Cancer 1985; **55**:1099–1106.
4. **Manger WM, Gifford RW Jr.** Pheochromocytoma. New York: Springer-Verlag, 1977.

5. **Bravo EL, Tarazi RC, Fouad FM, Textor SC, Gifford RW Jr, Vidt DG.** Blood pressure regulation in pheochromocytoma. Hypertension 1982; **4(Suppl II)**:II-193–II-199.
6. **Prockocimer PG, Maze M, Hoffman BB.** Role of the sympathetic nervous system in the maintenance of hypertension in rats harboring pheochromocytoma. J Pharmacol Exp Ther 1987; **241**:870–874.
7. **Raue F, Frank K, Meybier H, Ziegler R.** Pheochromocytoma in multiple endocrine neoplasia. Cardiology 1985; **72(Suppl 1)**:147–149.
8. **Sizemoroe GW.** Medullary thyroid carcinoma. Thyroid Today 1982; **5**:106.
9. **Weinstein RS, Ide LF.** Immunoreactive calcitonin in pheochromocytoma. Proc Soc Exp Biol Med 1980; **165**:215–217.
10. **Heath H III, Edis AJ.** Pheochromocytoma associated with hypercalcemia and ectopic secretion of calcitonin. Ann Intern Med 1979; **91**:208–210.
11. **Wheeler MH, Curley IR, Williams ED.** The association of neurofibromatosis, pheochromocytoma, and somatostatin-rich duodenal carcinoid tumor. Surgery 1986; **100**:1163–1168.
12. **Pearse AGE.** Cytochemical evidence for the neural crest origin of mammalian ultimobranchial C cells. Histochemie 1971; **27**:96–102.
13. **Bolande RP.** The neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. Hum Pathol 1974; **5**:409–429.
14. **Lloyd RV, Shapiro B, Sisson JC, et al.** An immunohistochemical study of pheochromocytomas. Arch Pathol Lab Med 1984; **108**:541–544.
15. **O'Connor DT, Burton D, Deftos LJ.** Immunoreactive human chromogranin A in diverse polypeptide hormone producing human tumors and normal endocrine tissue. J Clin Endocrinol Metab 1983; **57**:1084–1086.
16. **Bornemann M, Hill SC, Kidd GS.** Lactic acidosis in pheochromocytoma. Ann Intern Med 1986; **105**:880–882.
17. Fifer MA, Koerner FC. A 34 year old man with hypertension and episodes of flushing, nausea and vomiting. Case 6, 1986 Case Records of the Massachusetts General Hospital. N Engl J Med 1986; **314**:431–429.
18. **Kohara K, Mikami H, Ogihara T, et al.** Extra-adrenal pheochromocytoma manifesting renovascular hypertension. J Clin Hypertens 1987; **3**:303–309.
19. **Heramalsu K, Takahashi K, Kanemoto N, Arimori S.** A case of pheochromocytoma with transient hyperinsulinemia and reactive hypoglycemia. Jpn J Med 1987; **26**:88–90.
20. **Bravo EL, Tarazi RC, Fouad FM, et al.** Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. N Engl J Med 1981; **305**:623–626.
21. **Karlberg BE, Hedman L.** Value of clonidine suppression test in the diagnosis of pheochromocytoma. Acta Med Scand Suppl 1986; **714**:15–21.
22. **Weiffler AJ, Julius S.** A diagnostic test in patients with elevated plasma catecholamines. N Engl J Med 1982; **306**:890–894.
23. **Valet P, Damase-Michel C, Chamontin B, et al.** Adrenoceptors in the diagnosis of pheochromocytoma. Lancet 1987; **2**:337.
24. **Jebara VA, Uva MS, Farge A, et al.** Cardiac pheochromocytomas. Ann Thorac Surg 1992; **53**:356–361.
25. **Fink IJ, Reinig JW, Dwyer AJ, Doppman JL, Linehan WM, Keiser HR.** MR imaging of pheochromocytomas. J Comput Assist Tomogr 1985; **9**:454–458.
26. **Baker EM, Spritzer C, Blinder R, Herfkens RJ, Leight GS, Dunnick NR.** Benign adrenal lesions mimicking malignancy on MR imaging: report of two cases. Radiology 1987; **163**:669–671.
27. **Stowers SA, Gilmore P, Stirling M, et al.** Cardiac pheochromocytoma involving the left main coronary artery presenting with exertional angina. Am Heart J 1987; **114**:423–427.
28. **Sisson JC, Frager MS, Valk TW, et al.** Scintigraphic localization of pheochromocytoma. N Engl J Med 1981; **305**:12–17.
29. **Saad MF, Frazier OH, Hickey RC, Samaan NA.** Intrapericardial pheochromocytoma. Am J Med 1983; **75**:371–376.
30. **Khafagi FA, Shapiro B, Fig LM, Mallette S, Sisson JC.** Labetalol reduces iodine-131 MIBG uptake by pheochromocytoma and normal tissue. J Nucl Med 1989; **30**:481–489.
31. **Manger WM, Gifford RW Jr, Hoffman BB.** Pheochromocytoma: a clinical and experimental overview. Curr Probl Cancer 1985; **9**:5–89.
32. **Graze K, Spiler IJ, Tashjian AH, et al.** Natural history of familial medullary thyroid carcinoma: effect of a program for early diagnosis. N Engl J Med 1978; **299**:980–985.
33. **Friedman E, Mandel M, Katzelson D, Sack J.** Pheochromocytoma and hydralazine-induced myocardial ischaemia in a 14-year-old boy. Eur J Pediatr 1986; **145**:318–320.
34. **Boutros AR, Bravo EL, Zanettin GG, Straffon RA.** Perioperative management of 63 patients with pheochromocytoma. Cleve Clin J Med 1990; **57**:613–617.
35. **Rosei EA, Brown JJ, Lever AF, et al.** Treatment of pheochromocytoma and of clonidine withdrawal hypertension with labetalol. Br J Clin Pharmacol 1986; **3(Suppl 3)**:809–815.
36. **Briggs RS, Birtwell AJ, Pohl JE.** Hypertensive response to labetalol in pheochromocytoma [letter]. Lancet 1978; **1(8072)**:1045–1046.
37. **Reach G, Thibonnier M, Chevillard CP, et al.** Effect of labetalol on blood pressure and plasma catecholamine concentrations in patients with pheochromocytoma. Br Med J 1980; **280**:1300–1301.
38. **Meeke RI, O'Keefe JD, Gaffney ID.** Pheochromocytoma removal and postoperative hypoglycemia. Anesthesia 1985; **40**:1093–1096.
39. **Pullerits J, Reynolds C.** Pheochromocytoma: a clinical review with emphasis on pharmacologic aspects. Clin Invest Med 1982; **5**:259–265.
40. **Averbuch SD, Steakley CS, Young RC, et al.** Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med 1988; **109**:267–273.
41. **Rosenbaum JS, Ginsburg R, Billingham ME, Hoffman BB.** Effects of adrenergic receptor antagonists on cardiac morphological and functional alterations in rats harboring pheochromocytoma. J Pharmacol Exp Ther 1987; **241**:354–360.
42. **Imperato-McGinley J, Gautier T, Ehlers K, Zullo MA, Goldstein DS, Vaughan DE Jr.** Reversibility of catecholamine-induced dilated cardiomyopathy in a child with a pheochromocytoma. N Engl J Med 1987; **316**:793–797.
43. **Favre L, Vallotton MB.** Nifedipine in pheochromocytoma [letter]. Ann Intern Med 1986; **104**:125.
44. **Serfas D, Shoback DM, Lorell BH.** Pheochromocytoma and hypertrophic cardiopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. Lancet 1983; **2**:711–713.
45. **Moreau JP, De Feudis FV.** Minireview—pharmacological studies of somatostatin and somatostatin-analogues: therapeutic advances and perspectives. Life Sci 1987; **40**:419–437.