

Pheochromocytoma: State-of-the-Art and Future Prospects

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This review provides current understanding of the pathophysiology of pheochromocytoma and the wide range of associated clinical manifestations that have led to earlier recognition of the disease. In addition, it reviews optimal screening methods and localization techniques that have enhanced the clinician's ability to make the diagnosis with greater certainty. This article will also discuss alternative antihypertensive regimens and innovative anesthetic and surgical procedures that have made successful management more promising than ever before.

Areas requiring further development include additional clinical experience with the measurement of plasma metanephrines that have been shown to have high sensitivity and specificity in the diagnosis of sporadic and familial pheochromocytoma, optimizing cost effectiveness of diagnostic imaging, improving the ability to predict and treat malignant pheochromocytoma, and elucidating not only the surgical approach but, perhaps with rapid advances in molecular genetics, ways of preventing familial pheochromocytoma. (*Endocrine Reviews* 24: 539–553, 2003)

- I. Introduction
- II. Prevalence
- III. Clinical Presentation
- IV. Pathophysiology
 - A. Role of the sympathetic nervous system (SNS)
 - B. Role of other neurohumoral agents
 - C. Hemodynamic characteristics
- V. Clinical Pathology
- VI. Diagnosis
 - A. Priority of evaluation
 - B. Biochemical testing
 - C. Pharmacological testing
- VII. Localization
- VIII. Treatment
 - A. Medical therapy
 - B. Surgical therapy
- IX. Future Prospects
 - A. Diagnostic localization techniques
 - B. Diagnosis and management of genetic abnormalities associated with pheochromocytoma
 - C. Malignant pheochromocytoma

cal pathways and urinary studies for catecholamines and their metabolites were established in the 1960s (1, 2). These studies coupled with the introduction of sensitive and specific radioenzymatic (3) and HPLC techniques (4) that detected catecholamines in small biological samples provided an accurate method to solidify the diagnosis. The development and rapid implementation of computerized tomography (CT) (5) and scintigraphy (6) produced a quantum leap forward in the ability to image the adrenal gland and localize these tumors. Simultaneously, better understanding of the pathophysiology of pheochromocytoma and its varied clinical presentations, advances in antihypertensive drug therapy, and anesthetic and surgical techniques have radically changed our overall approach to the diagnosis and treatment of pheochromocytoma.

This article reviews these developments with the objective of developing current perspectives in the identification and management of pheochromocytoma. It will emphasize current approaches as well as discuss the potential for future research and development in the field.

I. Introduction

OUR ABILITY TO diagnose and treat pheochromocytoma has been enhanced by striking advances in our knowledge of human catecholamine metabolism, by the development of sensitive and specific chemical techniques for assaying catecholamines in biological fluids, and by advances in noninvasive localizing techniques. The biochemi-

II. Prevalence

The prevalence of pheochromocytoma is not precisely known. Among the general population in Olmsted County, Minnesota (7), pheochromocytoma occurs in about 1–2 per 100,000 adults per year. This figure suggests that if 20% of the adult population is hypertensive, approximately five pheochromocytomas would be expected to be found among 100,000 hypertensives each year. In countries other than the United States, a lesser incidence has been noted (8). More recently, in a large series of patients screened biochemically for suspicion of pheochromocytoma, the incidence has been reported to be as high as 1.9%, occurring equally in men and women (9). In an autopsy series compiled from Sydney, Melbourne, and Auckland, McNeil *et al.* (10) found one pheochromocytoma per 2301 autopsies. With improved recogni-

Abbreviations: CgA, Chromogranin-A; CT, computerized tomography; E, epinephrine; MEN, multiple endocrine neoplasia; ¹²³I-MIBG, ¹²³iodinated-metaiodobenzylguanidine; MRI, magnetic resonance imaging; NE, norepinephrine; NPY, neuropeptide Y; POB, phenoxybenzamine; RET, rearranged during transfection; SDHB, succinate dehydrogenase subunit B; SDHD, succinate dehydrogenase subunit D; SNS, sympathetic nervous system; VHL, von Hippel-Lindau disease; VMA, vanillylmandelic acid.

tion and the routine use of CT for abdominal complaints, it is likely that more tumors will be discovered. In approximately 10% of patients, the tumor is discovered incidentally during CT or magnetic resonance imaging (MRI) of the abdomen for unrelated symptoms (11).

III. Clinical Presentation

The diverse manifestations of this tumor reflect variations in the hormones it releases, their patterns of release, and in the individual-to-individual differences in catecholamine sensitivities. There is no correlation between circulating levels of the catecholamines or even existence of hypertension in these patients (Fig. 1 and Ref. 12). Indeed, some patients may have long periods of normotension despite high circulating catecholamines, and sudden increases in blood pressure may not be associated with further elevations in plasma catecholamines (Fig. 2 and Ref. 13). In general, the hypertension is paroxysmal in 48% of patients, persistent in 29%, and 13% have normal blood pressure. Norepinephrine (NE)-secreting tumors are usually associated with sustained hypertension. Tumors that secrete relatively large amounts of epinephrine (E) together with NE are associated with episodic hypertension. Pure E-producing tumors can produce hypotension rather than hypertension (14). Large (>50 g) cystic pheochromocytomas are often asymptomatic because the secreted catecholamines are metabolized within the tumor, and, therefore, only a small amount, if any, of free catecholamines is released into the circulation (2).

The most common set of symptoms comprises attacks of headaches (80%) described as intense and global, palpitations (64%), and diaphoresis (57%). In one study (15), the symptomatic triad of headache, sweating attacks, and tachycardia in a hypertensive patient was found to have a sensitivity of 90.9% and specificity of 93.8%. However, about 8% of patients may be completely asymptomatic; such patients are usually those with familial forms of the disease or with large, cystic tumors (2).

Other disorders can often dominate the clinical picture. These include endocrine (hypercalcemia, Cushing's syndrome, thyroid carcinoma), metabolic (diabetes mellitus, lactic acidosis), surgical (acute abdomen), cardiovascular (shock, myocarditis, dilated cardiomyopathy, cardiac ar-

rhythmias, pulmonary edema, heart failure), and neurological (altered mental status, stroke, seizures, focal neurological signs and symptoms) disorders. For a more detailed discussion of these associated clinical manifestations, the reader is referred to a previous review (16).

The fact that pheochromocytoma can present in many ways may explain why these tumors are not often considered in the differential diagnosis. In a series from Mayo Clinic, 41 of 54 autopsy-proven cases were unsuspected clinically during life (17). Of the 13 (of the 54 cases) correctly diagnosed before death, four cases were discovered incidentally at laparotomy for unrelated conditions. Of those diagnosed after death, only 54% had had hypertension. Headache (27%),

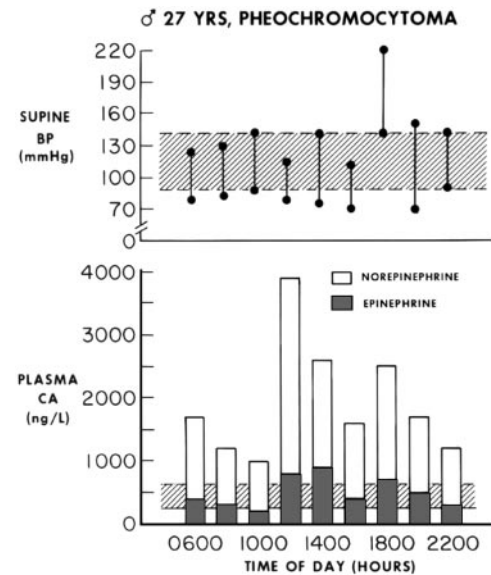
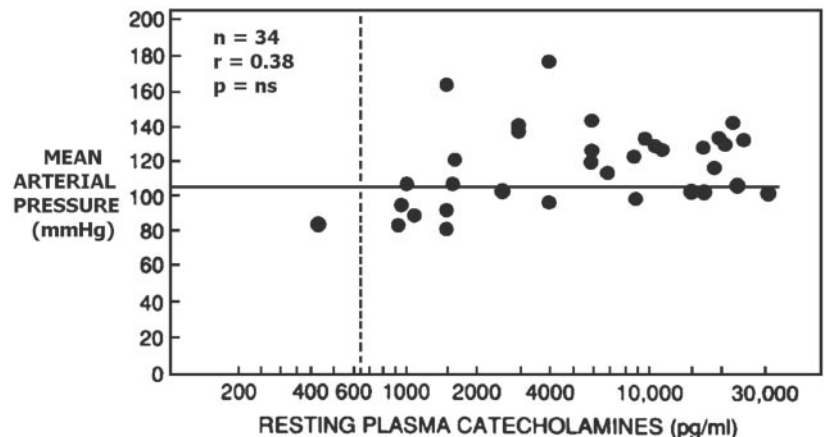


FIG. 2. Depicts plasma catecholamine concentration and simultaneously recorded arterial blood pressure in a patient with adrenal pheochromocytoma. Each blood pressure shown is the average of at least three determinations taken 1 min apart. The cross-hatched area defines the upper limits for systolic blood pressure (140 mm Hg) and diastolic blood pressure (90 mm Hg). For plasma catecholamines, the cross-hatched area represents the mean (260 pg/ml) and +2 SD (580 pg/ml) of values obtained in 26 normotensive patients. All measurements were taken in the fasting state, after 30 min of supine rest, at 2-h intervals from 0600–2200. [Reproduced with permission from E. L. Bravo: *Ann NY Acad Sci* 970:1–10, 2002 (13).]

FIG. 1. Relationship between the height of arterial blood pressure and circulating catecholamine (NE and E) levels in pheochromocytoma. [Reproduced with permission from E. L. Bravo *et al.*: *N Engl J Med* 301: 682–686, 1979 (12). © Massachusetts Medical Society.]



diaphoresis (17%), and palpitations (17%) were much less common than in patients whose tumors were diagnosed before death. Twelve patients were older than 68 yr; in nine of these elderly patients, the diagnosis was unsuspected. In a retrospective study from Australia, 17 of 46 confirmed cases were diagnosed at autopsy (18). Of these, 14 died of cardiovascular complications that were attributed to their disease. Most of the tumors discovered at autopsy were found in patients 60 yr or older. Stenstrom and Svardsudd (8) reported that, in 439 patients with pheochromocytoma registered in Sweden from 1958 to 1982, the incidence increased continuously with advancing age both for men and women. In 184 cases (40%), the diagnosis was made at autopsy. Pheochromocytoma was an incidental finding in 60 cases (14% of all cases). The average age at diagnosis in those whose disease was discovered before death was 48.5 yr, significantly lower than the average age of those diagnosed only at autopsy, which was 65.8 yr. Similarly, Krane (19) found that, of 32 patients with pathologically confirmed tumors, 11 patients had tumors that were clinically unsuspected. In a more recent report, McNeil *et al.* (10) found no difference in the prevalence of pheochromocytoma between autopsy series before and after 1990.

These observations indicate that a high percentage of patients with pheochromocytoma may present with minor or no signs and symptoms, and that some patients with pheochromocytoma still remain undiagnosed despite advances in diagnostic techniques. Furthermore, elderly patients appear to present a special diagnostic challenge. A contributory factor to the delay in the antemortem diagnosis of pheochromocytoma in the elderly may be a decrease in baroreceptor function with age. Additionally, most elderly patients have concomitant disease, the signs and symptoms of which can confound the diagnosis. Cardiac and neurological symptoms are often attributed to coronary artery and cerebrovascular disease from atherosclerosis.

IV. Pathophysiology

A. Role of the sympathetic nervous system (SNS)

The hypertension of pheochromocytoma has been thought to result solely from the action of circulating catecholamines on cardiovascular adrenergic receptors. Under these conditions, the activity of the SNS is thought to be normal or depressed reflexly because of baroreceptor resetting, and neurally released NE is considered of minor physiological import in comparison to the effects of markedly elevated plasma catecholamine levels. However, clinical studies suggest that the SNS is intact and may play a role in blood pressure regulation in pheochromocytoma. In patients with pheochromocytoma, blood pressure does not correlate with circulating catecholamines (12), sympathetic reflexes are intact (20), and blood pressure and heart rate are significantly reduced by clonidine (a centrally acting α_2 -agonist that inhibits neurally mediated catecholamine release) despite maintained high circulating catecholamines (21).

Johnson *et al.* (22) investigated the role of the SNS in the maintenance of elevated blood pressure in an animal model of hypertension similar to pheochromocytoma, *i.e.*, contin-

uous infusion of NE in chronically maintained rats. They demonstrated the following: first, continuous infusion of NE resulted in an increase in plasma NE from 330–13,000 pg/ml and an increase in plasma E from 115–265 pg/ml, levels that are similar to the increase in patients with pheochromocytoma. In addition, NE content in the aorta and heart increased significantly. Systolic blood pressure increased from 112 ± 4 to 166 ± 3 mm Hg with no significant change in heart rate. Second, NE infusions that elicited a slow rise in pressure cause sympathetic nerve activity to increase by 20–30%. Third, administration of bretylium, a drug that blocks the neuronal release of NE, caused systolic blood pressure to fall to control levels and heart rate to increase markedly. These findings were interpreted to mean that, as in pheochromocytoma patients, the SNS is markedly enhanced and that SNS function is integral to the maintenance of elevated blood pressure in this form of catecholamine-induced hypertension.

The paradoxical elevation of sympathetic activity during elevation of circulating catecholamines is postulated to be due to at least three mechanisms: 1) loading of sympathetic vesicles with catecholamine. Tissue catecholamine content increases during catecholamine infusion, presumably reflecting a loading of noradrenergic terminal vesicles with neurotransmitter; 2) increased sympathetic neuronal impulse frequency; and 3) a selective desensitization of presynaptic α_2 -adrenergic receptors. Because presynaptic α_2 -receptors inhibit release of neuronal NE (23), selective desensitization would result in enhanced release of neuronal NE during nerve stimulation.

Neuronal control of blood pressure was also demonstrated in rats implanted with a pheochromocytoma. Eliminating sympathetic nerve activity by pithing caused a greater reduction of blood pressure in pheochromocytoma-bearing rats than in age-matched unimplanted rats (24). Furthermore, Prokocimer *et al.* (25) found that both clonidine and chlorisondamine, a ganglion blocker, markedly decreased blood pressure in intact rats with pheochromocytoma. Moreover, the observation that the blood pressure in pithed rats with pheochromocytoma is further reduced by phentolamine, an α_1 -adrenergic antagonist, suggests that high concentrations of circulating catecholamines also are involved in the maintenance of the elevated blood pressure.

The above observations have important pathophysiological and clinical implications. Because of enhanced SNS activity and excessive stores of NE in sympathetic nerve terminals, any direct or reflexly mediated stimulus to the SNS could release excessive quantities of NE into the synaptic cleft and produce a hypertensive crisis. The easier access of NE released from the postganglionic neuron at its receptor site on effector cells can result in marked symptoms with relatively small increments in circulating NE. These findings can account not only for the observation that spontaneous or evoked crises in blood pressure can occur without additional increases in the elevated plasma catecholamine levels but also for the demonstration that blood pressure may be normal despite high circulating catecholamine levels (Fig. 2).

The studies of Grassi *et al.* (26) contrast with these findings and conclusions. They showed that patients with pheochromocytoma had lower muscle sympathetic nerve traffic than

patients with essential hypertension and that, after surgical removal of tumors, nerve traffic increases. These findings are not in agreement with the demonstration that clonidine, a centrally acting α_2 -agonist, decreases blood pressure similarly in both essential hypertension and pheochromocytoma patients, (21) and that chronic infusions of NE led to an increased preganglionic cervical sympathetic nerve firing rate (22). The studies also have several limitations. First, the muscle sympathetic nerve activity values of the patients with pheochromocytoma were not clearly less than those reported in normotensive patients (27). Second, muscle sympathetic nerve activity provides an index of central sympathetic outflow that is restricted to the skeletal muscle and therefore does not allow one to conclude that in pheochromocytoma central sympathetic drive is similarly inhibited throughout the body (28).

B. The role of other neurohumoral agents

Angiotensin II does not appear to play a direct role because the administration of clonidine reduces arterial blood pressure without significantly decreasing plasma renin activity (PRA) (21). As already discussed, neurally released NE plays a significant role in blood pressure regulation. More recently, excess NE has also been found to impair both endothelium-dependent and -independent vasodilation in patients with pheochromocytoma (29). Neuropeptide Y (NPY) levels are increased in plasma and tumors of patients with pheochromocytoma (Fig. 3 and Ref. 30–32). NPY has potent direct and indirect cardiovascular effects. It increases coronary and peripheral vascular resistance independently of α -adrenergic mechanisms by interacting with vascular G protein-coupled receptors (33, 34). In some vascular beds, NPY has no direct vasoconstrictor effects but potentiates NE-induced vasoconstriction (35–37). Thus, NPY released from pheochromocytoma might be partly responsible for the hypertensive episodes that occur in pheochromocytoma patients receiving α -blockade. Indeed, Lundberg and Tatemoto (34) reported that preoperative blockade with 200 mg phenoxybenzamine (POB) daily did not prevent the hypertensive response induced by surgical manipulation of an adrenal pheochromocytoma when both plasma NE and NPY levels were significantly increased. Likewise, Hauptman *et al.* (38) reported a pheochromocytoma patient resistant to α -adrenergic blockade.

C. Hemodynamic characteristics

Because systemic administration of NE plus E increases cardiac rate and systemic vascular resistance, enhances cardiac contractility, and decreases venous compliance, the concept has evolved that pheochromocytoma is associated with a hyperkinetic, vasoconstrictive, hypovolemic form of hypertension. Although it is clear that the hypertensive crisis of pheochromocytoma mimics the hemodynamic responses to acute administration of catecholamines, it is less clear whether sustained exposure to high circulating catecholamines produces a hemodynamic profile characteristic of systemically administered hormones. We examined the hemodynamic features of 24 untreated patients with surgi-

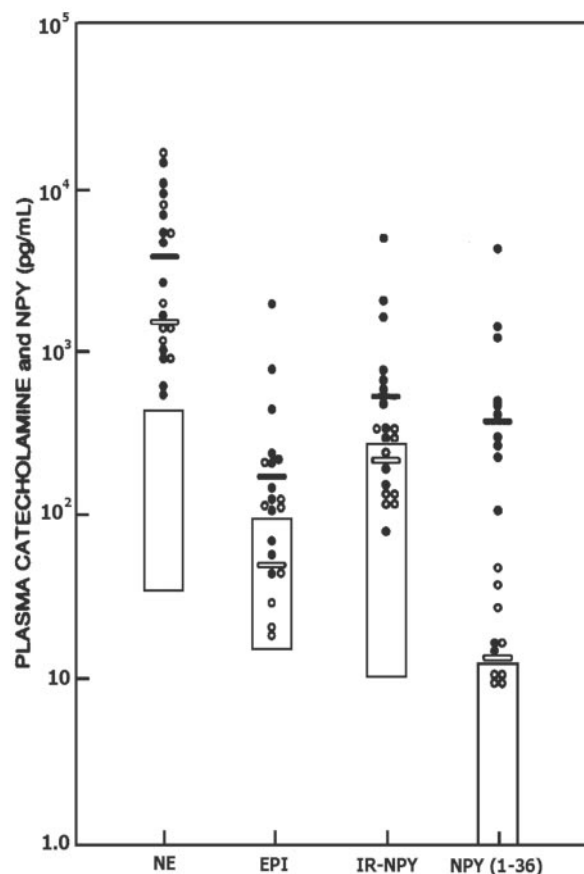


FIG. 3. Levels of plasma NE, E (EPI), immunoreactive NPY (IR-NPY), and NPY (1–36) (determined by RIA coupled to reverse-phase HPLC) in patients with an adrenal (closed circle) or extraadrenal (open circle) pheochromocytoma. The rectangles in each lane indicate the normal range (NE, 126–402, 218; EPI, 24–78, 42; IR-NPY, 10–271, 174; NPY (1–36), <10–12, 10; range and median for the respective peptides). The median for each group is indicated by the transverse bars (solid bar, adrenal pheochromocytomas; hollow bar, extraadrenal pheochromocytomas). [Reproduced from P. deS Senanayake *et al.*: *J Clin Invest* 96:2503–2509, 1995 (30).]

cally proven pheochromocytoma during steady-state periods and compared them with 24 untreated essential hypertensive patients individually matched for gender, age, body surface area, and arterial blood pressure (20). We found that, despite having 10-fold higher levels of circulating catecholamines, pheochromocytoma patients have hemodynamic features similar to patients with essential hypertension. In addition, in individual patients, the ratio of circulating NE to E had no relation to the hemodynamic profile, and blood volume values were no different between the two groups. In both groups, increased peripheral vascular resistance was primarily responsible for the maintenance of hypertension.

V. Clinical Pathology

In a retrospective study of 132 patients with proven pheochromocytoma treated at the Cleveland Clinic from 1980–1994, we found that adrenal tumors are rarely associated with extraadrenal tumors, are uncommon in patients

younger than 20 yr old, and were the most common form in patients 60 yr or older (Fig. 4). In addition, these tumors were associated with familial syndromes [*i.e.*, multiple endocrine neoplasia (MEN) type 2A, von Hippel-Lindau disease (VHL), von Recklinghausen's neurofibromatosis] and other endocrinopathies (*i.e.*, ACTH excess syndrome and hyperparathyroidism) in 14% of cases. Bilateral adrenal tumors were usually found in patients with familial syndromes. On the other hand, extraadrenal tumors, which comprised 23% of all cases, were associated with multifocal lesions in 19%, were rarely associated with familial syndromes, were the predominant tumors in patients younger than 20 yr old, and were uncommon in patients 60 yr or older. Other studies have shown that the younger the patient, the more likely it is that the syndrome is familial, the tumors are multiple and extraadrenal, and the hypertension persistent (39).

The prevalence of malignancy (defined as focally or locally invasive, with or without metastatic disease) was present in 19% of all cases and was more prevalent in tumors greater than 5.0 cm in diameter than in tumors 5.0 cm or less in diameter (76 vs. 24%). However, when each tumor type was considered separately, the prevalence of malignancy in sporadic adrenal pheochromocytoma was 9.2% ($n = 9$); for extraadrenal tumors, the prevalence was 52% ($n = 16$). In a separate report, the prevalence of malignant pheochromocytoma in 251 patients with MEN type 2A was 4.4% (40).

Thus, adrenal and extraadrenal pheochromocytoma are clinically and pathologically dissimilar, necessitating different approaches to diagnosis and treatment.

VI. Diagnosis

Perhaps the single most critical element in the management of pheochromocytoma is simply to seriously consider it in the differential diagnosis. Because of the deceptive and varied manifestations of pheochromocytoma, the optimal pretreatment evaluation rests on the demonstration of excessive and inappropriate catecholamine production. However, laboratory testing should complement clinical judgment and not replace it. Certain clinical settings provide insight into a patient's diagnosis: first, in patients with overt

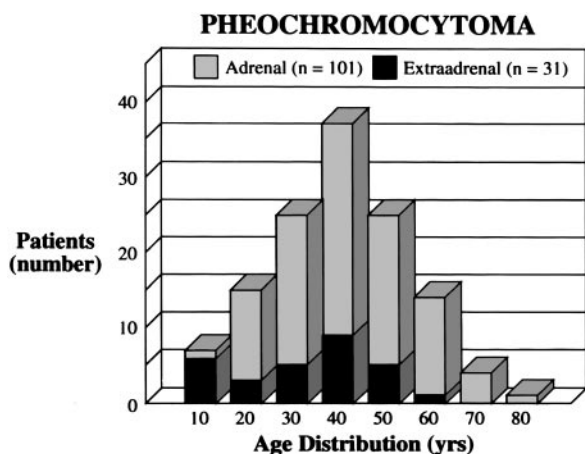


FIG. 4. Incidence of adrenal and extraadrenal pheochromocytomas according to age.

signs and symptoms, the plasma catecholamines are usually at least 2000 pg/ml (41); second, patients with overt signs and symptoms and plasma catecholamines less than 1000 pg/ml at the time of sampling do not have the disease; third, in asymptomatic patients, normal values of plasma catecholamines do not rule out the disease. Pheochromocytomas may develop in about 50% of patients with MEN types 2A and 2B, in 25% of patients with VHL type 2, and in 5% of patients with von Recklinghausen's disease (neurofibromatosis) (42–44). In a review of 118 articles, Walther *et al.* (45) found that, in patients with Recklinghausen's disease and hypertension, a pheochromocytoma was identified in more than a third.

A. Priority of evaluation

An important rule to follow is to consider any patient for screening who has manifestations even remotely suggestive of a pheochromocytoma. Certain groups of patients deserve careful inquiry, painstaking observation, and scientific testing. These include patients with episodic symptoms of headaches, tachycardia, and diaphoresis (with or without hypertension); family history of pheochromocytoma or a MEN syndrome, VHL, or von Recklinghausen's disease; incidental suprarenal or abdominal masses; unexplained paroxysms of tachy-/bradyarrhythmias and/or hypertension during intubation, induction of anesthesia, parturition, or prolonged and unexplained hypotension after an operation; adverse cardiovascular responses to ingestion, inhalation or injection of certain drugs including anesthetic agents, histamine, glucagon, tyramine, TRH, ACTH, antidopaminergic agents, naloxone, succinylcholine chloride, phenothiazine, β -blockers, guanethidine, tricyclic antidepressants, and mecholyl; spells or attacks occurring during exertion, twisting and turning of the torso, straining, coitus, or micturition.

B. Biochemical testing

The availability of large numbers of hormone assays and the need to exclude with certainty a potentially lethal disease with an unpredictable course have led to various approaches to biochemical testing. Because pheochromocytomas are a heterogeneous group of hormone-secreting tumors, no single analysis can achieve 100% accuracy. Readily available biochemical tests include 24-h urinary fractionated metanephrines (normetanephrine and metanephrine), 24-h urinary catecholamines (NE and E), and plasma concentrations of NE and E—all analyzed by HPLC. Spectrophotometric assays of urinary "total" metanephrines and urinary vanillylmandelic acid (VMA) have been employed extensively in clinical practice. A promising new biochemical test has been developed recently to detect pheochromocytoma. This technique involves the determination of free metanephrines in plasma by HPLC with electrochemical detection (46). Reference ranges depend on the population studied (*i.e.*, normotensive or hypertensive) and may vary from laboratory to laboratory.

1. *Plasma catecholamines.* Figure 5 depicts plasma concentrations of NE (A) and E (B) in patients found to have either an adrenal or extraadrenal pheochromocytoma (47). It is clear

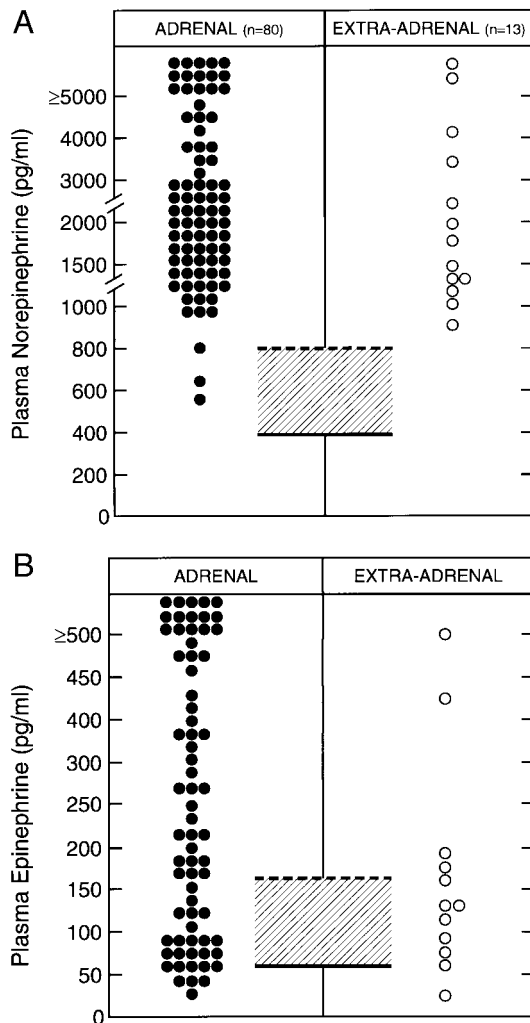


FIG. 5. A, Plasma NE values in pheochromocytoma. The cross-hatched area represents the mean (425 pg/ml) and the 95% upper confidence limits (811 pg/ml) of values obtained from 104 patients with essential hypertension. B, Plasma E values in pheochromocytoma. The cross-hatched area represents the mean (59 pg/ml) and the 95% upper confidence limits (135 pg/ml) of values obtained from 104 patients with essential hypertension. [Reproduced with permission from J. W. Lenders *et al.*: *Clin Chem* 39:97–103, 1993 (46). © Elsevier.]

that the majority of patients with pheochromocytoma have elevated plasma NE values. Only three patients had plasma values that fell within the 95% upper confidence limits for values obtained in 104 patients with essential hypertension (*i.e.*, 811 pg/ml). None had values that fell within the 95% upper confidence limits for gender- and age-matched 58 normotensive subjects (*i.e.*, 402 pg/ml).

Plasma E values were less predictable and had little value in predicting the location of a tumor. Thirty percent (24 of 80) of patients with adrenal pheochromocytomas had plasma E values below the 95% upper confidence limits (*i.e.*, 135 pg/ml), whereas 38% (5 of 13) of patients with extraadrenal tumors had plasma values above the 95% upper confidence limits.

In a larger series of 130 patients who had plasma catecholamine measurements (personal observations), nine (6.9%) had plasma NE and E values within the essential

hypertensive range, 13 (10%) had increases in plasma E only, 56 (43%) had increases in plasma NE only; the rest had increases in plasma concentrations of both NE and E, with NE predominating.

It is useful to record the blood pressure during plasma sampling for catecholamine measurements. Normal plasma catecholamine values obtained when the patient is normotensive and asymptomatic do not exclude the presence of a pheochromocytoma. However, normal plasma catecholamine values in a hypertensive and symptomatic patient make the diagnosis of pheochromocytoma highly unlikely.

2. *Urinary free catecholamines and metabolites.* Urinary free NE and E and the two major metabolites of the catecholamines, metanephrines (normetanephrines and metanephrines) and VMA are commonly assayed to detect the presence of a pheochromocytoma. These tests are relatively easy to perform and are usually readily available. In most circumstances, a diagnosis can be confirmed or excluded on the basis of properly collected 24-h urine samples. For example, the demonstration of urinary NE at least 156 $\mu\text{g}/24\text{ h}$, urinary total metanephrines at least 1.8 mg/24 h, and urinary VMA at least 11.0 mg/24 h makes the diagnosis highly probable.

Large (>50 g) cystic tumors may present with large quantities of urinary catecholamine metabolites but with near normal circulating NE and E. Crout and Sjoerdsma (2) showed that these tumors release mainly metabolized catecholamines into the circulation as reflected by a relatively high ratio of metabolites to free catecholamines in urine.

In MEN syndromes, Gagel *et al.* (40) found either 24-h urinary E excretion or the calculated ratio of E to NE to be a very sensitive screening test. The 24-h urinary NE was of little value in predicting the diagnosis of pheochromocytoma in these patients. However, Neumann *et al.* (43) reported that no biochemical test was completely diagnostic for pheochromocytoma patients. The sensitivity of the tests used to detect pheochromocytoma was as follows: urinary NE 86%, urinary E 33%, urinary VMA 64%, plasma NE 58%, and plasma E 33%. Thus, these investigators found NE production a better biochemical marker in predicting pheochromocytoma in those patients.

3. *Serum chromogranin-A in pheochromocytomas.* Serum chromogranin-A (CgA) is an acid-soluble protein that is costored and coreleased with catecholamines from adrenal medullary and sympathetic neuronal vesicles during exocytosis (48). It has been advocated as a specific diagnostic test in the differential diagnosis of pheochromocytoma (49) and has been suggested as an alternative to catecholamines because neither its secretion nor its measurement is influenced by drugs commonly used in the treatment of pheochromocytoma. However, although it is relatively sensitive (86%) in the diagnosis of pheochromocytoma, it has poor diagnostic specificity. This is, in large part, due to the fact that the kidneys play a major role in the clearance of CgA from the circulation so that even mild degrees of renal impairment can lead to significant increases in serum concentration of CgA. In a recent study (50), the overall specificity of serum CgA in the diagnosis of pheochromocytoma was only 74%; among hypertensive patients with creatinine clearance less than 80

ml/min, the diagnostic specificity of serum CgA was only 50% and the positive predictive value was 38%. However, when combined with elevated plasma catecholamines in patients with creatinine clearance at least 80 ml/min, the diagnostic specificity and positive predictive values improved to 98 and 97%, respectively.

4. Plasma metanephrines. Because the elevated plasma levels of free metanephrines in patients with pheochromocytoma are produced independently of catecholamine release by tumors, and because some tumors do not secrete catecholamines but metabolize catecholamines to free metanephrines, the measurement of plasma free metanephrines has been advocated as the best marker for the presence of pheochromocytoma than the parent amines (51). In an earlier study of 52 patients with benign and malignant pheochromocytoma, Lenders *et al.* (52) reported a test sensitivity and negative predictive value of 100% for each. Later, Eisenhofer *et al.* (53) reported a test sensitivity and specificity of 97 and 96%, respectively, in 35 patients with hereditary forms of pheochromocytoma. Raber *et al.* (54) provided similar results in 17 patients, most with MEN 2A.

More recently, a multicenter cohort study (55) examined the diagnostic utility of several biochemical tests in 214 patients with proven pheochromocytoma (138 sporadic, 48 VHL, 23 MEN-2, 3 neurofibromatosis type 1) and in 644 patients in whom the diagnosis was suspected but excluded. In this study, the measurement of plasma free metanephrines was clearly superior to plasma catecholamines in the diagnosis of hereditary and sporadic pheochromocytoma (Table 1). However, the test specificity of plasma free metanephrines was only 82% in sporadic pheochromocytoma. Of the urine measurements, test sensitivity for urinary fractionated metanephrines was similar to plasma free metanephrines, but lacked specificity for both hereditary (82%) and sporadic (45%) disease. In sporadic pheochromocytoma, urinary catecholamines had excellent sensitivity (97%), and total metanephrines the best specificity (89%). Sensitivity and specificity values at different upper limits were highest for plasma free metanephrines using receiver operating characteristics of curves (Fig. 6, A and B). Combining different tests did not improve the diagnostic yield beyond that of a single test of plasma free metanephrines. The above considerations have led the authors to recommend against use of multiple biochemical tests to exclude pheochromocytoma in favor of a single test of plasma free metanephrines.

As presented, the results clearly show the diagnostic su-

periority of plasma free metanephrines over currently available tests in the diagnosis of pheochromocytoma. Nonetheless, it is important to point out certain limitations of the study. First, urine tests were performed less frequently than plasma free metanephrines in individual patients; this may account for the poor performance of urine tests when compared with plasma free metanephrines. This is especially evident for the low test sensitivity of urinary total metanephrines and the low test specificity of urinary fractionated metanephrines (Table 2). Second, all plasma free metanephrine assays were performed in a single research facility; its performance in other clinical laboratories must be determined. A preliminary report (56) from another laboratory showed that the test is highly sensitive but less specific than urinary total metanephrines and catecholamines in the detection of pheochromocytoma, with a false-positive rate of about 15%. Third, more patients under various clinical settings should be studied. Finally, the test is not readily available for routine use.

5. Recommendations for biochemical testing. The availability of tests in any given center will necessarily determine the nature of the investigation in an individual patient, and debate over the relative merits of various tests will continue. When performed under appropriate clinical settings, currently available tests can establish the diagnosis in greater than 95% of cases. For example, the combination of resting plasma catecholamines (NE plus E) at least 2000 pg/ml and urinary metanephrines (NMN + MN) at least 1.8 mg/24 h has a diagnostic accuracy of close to 98% in both sporadic and hereditary pheochromocytoma. In 109 confirmed cases in whom all four tests were performed, we found (our personal observations) that assays of plasma catecholamines and urinary metanephrines have the lowest false-negative rates (7%), and assays of urinary NE and E the next higher (14%). Urinary VMA measurements have high false-negative rate (41%) and should not be used for screening purposes. However, all four tests have excellent specificity when elevated.

When available, the measurement of plasma free metanephrines should be performed, especially when hereditary pheochromocytoma is suspected. It has a reported test sensitivity and specificity of 97 and 96%, respectively, in this patient population. In sporadic pheochromocytoma, the test has a reported sensitivity of 99% and a specificity of 82% (Table 1). In this study, the measurement of urinary fractionated metanephrines is equally sensitive (97%) but has a

TABLE 1. Sensitivities and specificities of plasma tests in the diagnosis of hereditary and sporadic pheochromocytoma

Plasma (nmol/liter)	Upper reference limit	Sensitivity (%)		Specificity (%)	
		Hereditary	Sporadic	Hereditary	Sporadic
Free metanephrines		97 (74/76)	99 (137/138)	96 (326/339)	82 (249/305)
Normetanephrine	0.6				
Metanephrine	0.3				
Catecholamines		69 (52/75)	92 (126/137)	89 (303/339)	72 (220/304)
Norepinephrine	2.9				
Epinephrine	0.5				

Sensitivity was calculated from patients with pheochromocytoma and false-negative test results for both normetanephrine and metanephrine or for both NE and E. Numbers in parentheses indicated true-positive over true-positive plus false-negative results. Specificity was calculated from patients without pheochromocytoma and with false-positive test results for either normetanephrine or metanephrine or for either NE or E. Numbers in parentheses indicate true-negative over true-negative plus false-positive results. [Derived from Ref. 55.]

FIG. 6. A, Plasma free metanephrines vs. plasma or urinary catecholamines and VMA. B, Plasma free metanephrines vs. urinary fractionated metanephrines and total metanephrines. Relationships between rates of true-positive test (*i.e.*, sensitivity) and rates of false-positive test results were calculated at different upper reference limits for each of the tests. The areas under the receptor operated curves for plasma catecholamines (0.927), urinary catecholamines (0.931), urinary total metanephrines (0.919), and urinary VMA (0.896) were all significantly lower ($P < 0.001$) than the area for plasma free metanephrines (0.985). The area under the receptor operated curve for urinary fractionated metanephrines (0.960) was also lower ($P = 0.01$) than that for plasma free metanephrines. [Modified from J. W. Lenders *et al.*: *JAMA* 287:1427–1434, 2002 (55). © American Medical Association. All rights reserved.]

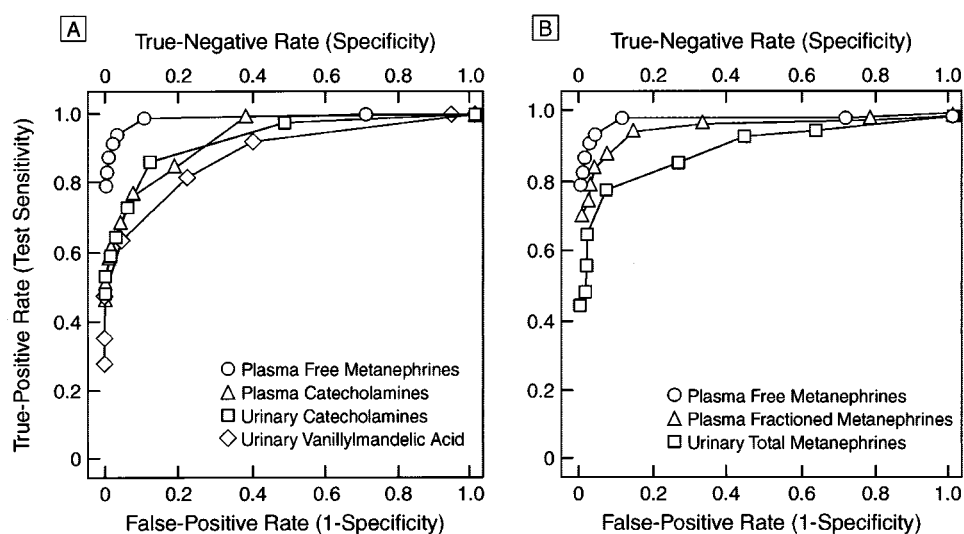


TABLE 2. Sensitivities and specificities of urine tests in the diagnosis of hereditary and sporadic pheochromocytoma

Urine ($\mu\text{mol/d}$)	Upper reference limit	Sensitivity (%)		Specificity (%)	
		Hereditary	Sporadic	Hereditary	Sporadic
Fractionated metanephrines		96 (26/27)	97 (76/78)	82 (327/288)	45 (73/164)
Normetanephrine					
Women	1.7				
Men	3.0				
Metanephrine					
Women	0.7				
Men	2.0				
Catecholamines		79 (54/68)	97 (91/107)	96 (312/324)	75 (159/211)
NE	0.5				
E	0.5				
Total metanephrines	6.0	60 (27/45)	88 (61/69)	97 (91/94)	89 (79/89)
Vanillylmandelic acid	40.0	46 (30/65)	77 (66/58)	99 (310/312)	86 (132/153)

Sensitivities and specificities were calculated as in Table 1. [Derived from Ref. 55.]

test specificity of only 45% (Table 2). However, the test specificity of urinary total metanephrines is highest at 89%.

Because pheochromocytomas are a heterogeneous group of hormone-secreting tumors with variable metabolism, it is prudent to recommend that, for 100% diagnostic accuracy, multiple tests be performed. Whether the measurement of plasma free metanephrines should be the sole diagnostic test for pheochromocytoma remains to be determined.

6. Clinical situations that may alter measured levels of catecholamines and metabolites. Certain clinical situations may increase both plasma catecholamines and urine catecholamine metabolites to levels often seen in the presence of pheochromocytoma. These disorders include: 1) acute clonidine withdrawal, 2) acute alcohol withdrawal, 3) monotherapy with pure arterial vasodilators, hydralazine or minoxidil, 4) acute myocardial ischemia or infarction, 5) acute cerebrovascular accident, 6) cocaine abuse, and 7) severe congestive heart failure, class 3 or 4. Intravenously administered dopamine, oral dopaminergic drugs, and acute hypoglycemia produce significant elevations in plasma E concentrations. Drugs that inhibit central sympathetic outflow (*e.g.*, clonidine, methyl dopa, bromocriptine, haloperidol) decrease plasma catecholamines in normal and hypertensive subjects, but have little effect on the excessive catecholamine secretion by pheochromocytoma. Drugs that tend to

increase plasma catecholamines (*e.g.*, POB, phentolamine, theophylline, prazosin, β -blockers, and diuretics) do so only slightly and rarely approach values usually encountered in pheochromocytoma. Blood samples should be collected using a large bore scalp vein needle with patients fasting overnight and supine for at least 20 min before sampling.

Labetalol, a commonly used antihypertensive agent, can increase plasma catecholamines and urinary metanephrines determined by HPLC to values seen in pheochromocytoma patients (57). In addition, a urinary metabolite of buspirone, an anxiolytic drug, is artificially measured as metanephrine, resulting in marked increase in measured metanephrine excretion (58).

The measurement of plasma free metanephrines is influenced by many of the same stimuli and drugs that influence plasma catecholamines. In addition, acetaminophen has been shown to cause spurious increases in plasma free metanephrines, and subjects should be instructed to avoid taking the drug for at least 5 d before blood sampling.

C. Pharmacological testing

Basal concentrations of plasma catecholamines are usually severalfold higher in patients with pheochromocytoma than

in other subjects (Fig. 5 and Ref. 41), even when taking into account normal variations due to postural change, exercise, and emotional arousal. When blood specimens are drawn under standardized conditions, a total level of plasma catecholamines of at least 2000 pg/ml is diagnostic of pheochromocytoma; one less than 500 pg/ml essentially rules it out. Concentrations in between, especially those exceeding 1000 pg/ml in medically stable patients, suggest the need for further testing and confirmation by pharmacological evaluation. In such cases, the goal is to separate pheochromocytoma patients with relatively low levels of biosynthetic activity from nonpheochromocytoma patients with increased sympathetic outflow. Either a stimulation test, to provoke catecholamine secretion (59) from a tumor with low secretory activity, or a suppression test, to inhibit sympathetic outflow (60), is usually employed.

A provocative test is employed (usually glucagon) when the clinical findings are highly suggestive of pheochromocytoma, but the blood pressure is normal or slightly increased and plasma catecholamines are between 500 and 1000 pg/ml (41). If a sudden rise in blood pressure is a concern, a calcium channel antagonist can be used to blunt the hypertensive response without interference with plasma catecholamine determinations. A positive glucagon stimulation test requires at least a 3.0-fold increase and/or more than 2000 pg/ml in total plasma catecholamines. The glucagon test has high specificity (100%) but low sensitivity (81%). A suppression test (clonidine) is used in patients with plasma catecholamines between 1000 and 2000 pg/ml, with and without hypertension (60). A normal clonidine suppression test requires a fall of plasma catecholamines from baseline of at least 50% and below 500 pg/ml. When the test is performed in patients with plasma catecholamines of at least 1000 pg/ml, the false-positive and false-negative rates are 2%. (For details of these tests, please refer to a previous review by the author. Ref. 61.)

VII. Localization

Biochemical confirmation of the diagnosis should be followed by radiological evaluation to locate the tumor, not the other way around. An understanding of the clinicopathological behavior of these tumors may help localize them more precisely. As already alluded to, adrenal tumors are common in patients 60 yr or older, are rarely associated with extraadrenal tumors, and may be bilateral when occurring in

patients with familial syndromes. On the other hand, extraadrenal tumors are predominant tumors in patients younger than 20 yr old, are often multifocal, and are rarely, if ever, associated with familial syndromes. Thus, age and the presence or absence of family history are important considerations when determining the type and location of pheochromocytomas. Most tumors (95%) occur within the abdomen (61). The most common extraadrenal locations are the superior and inferior paraortic areas (75% of extraadrenal tumors), the bladder (10%), the thorax (10%), and the head, neck, and pelvis (5%) (62).

CT and MRI are equally sensitive (98 and 100%, respectively), but have lower specificities of 70 and 67%, respectively (16). ¹²³Iodinated metaiodobenzylguanidine (¹²³I-MIBG) has excellent specificity (100%), but sensitivity of only 78%. In the biochemically confirmed patient, MRI provides the highest sensitivity among current imaging techniques. Pheochromocytomas appear hyperintense to the liver on T₂ weighted image, whereas benign tumors appear isointense (Fig. 7). If no tumor is detected, MIBG scintigraphy should be employed (Fig. 8). Arteriography and/or venous sampling for plasma concentrations are hardly ever indicated except in situations in which the clinical and biochemical evidence points strongly to pheochromocytoma yet the non-invasive techniques persistently fail to localize the tumor sites. A recommended diagnostic approach is shown in Fig. 9.

VIII. Treatment

A. Medical therapy

Appropriate antihypertensive drugs are used to manage hypertension, to control associated cardiovascular symptoms, and to prepare patients for operation. The question debated most often regarding medical therapy of pheochromocytoma is whether antihypertensive regimens other than complete and long-lasting α -blockade are just as effective and safe.

In the absence of controlled studies of large groups of pheochromocytoma patients, the use of nonspecific α -blockade, specifically POB, has a mostly theoretical pharmacological basis. The preoperative use of POB was mainly advocated to counteract the sudden release of massive quantities of catecholamines during surgical intervention (63, 64). Yet, hypertensive crises (defined as systolic blood

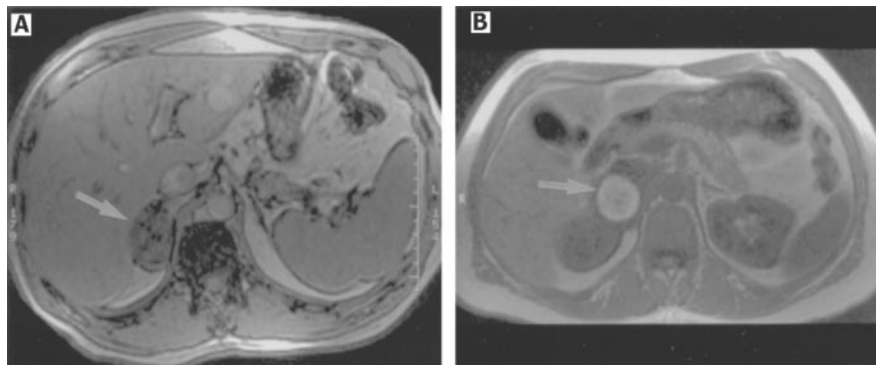


FIG. 7. A benign adrenal adenoma (A) and an adrenal pheochromocytoma (B) as imaged by MRI-T₂.

FIG. 8. Localization of pheochromocytoma employing ^{123}I -MIBG. A, Uptake of ^{123}I -MIBG by a right adrenal pheochromocytoma 48 h after injection of the radioisotope. K, Kidney. B, Uptake of ^{123}I -MIBG by metastatic sites in bones in a patient with malignant adrenal pheochromocytoma. [Reproduced with permission from E. L. Bravo *et al.*: Adrenal medullary tumors: pheochromocytoma. In: Mazzaferri EL, Samaan NA, eds. Endocrine tumors. Boston: Blackwell Scientific Publishers; 1426–1448, 1993 (108).]

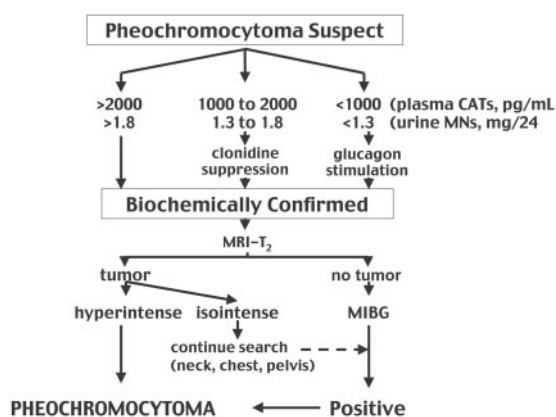
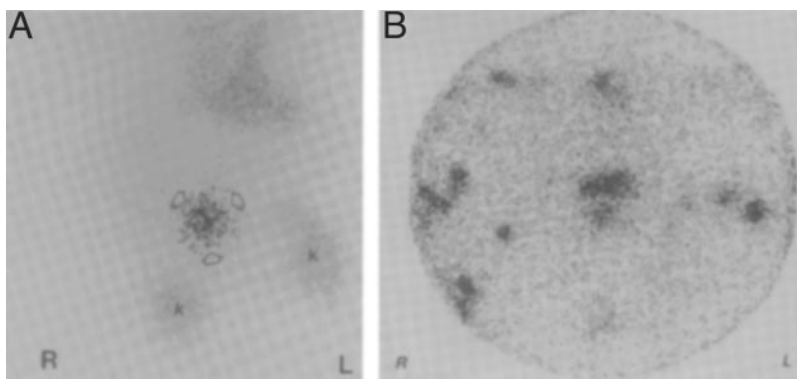


FIG. 9. A simplified algorithm for the diagnosis and localization of pheochromocytoma. [Reproduced with permission from E. L. Bravo: *Cardiol Rev* 10:44–50, 2002 (109). © Lippincott Williams and Wilkins.]

pressure higher than 250 mm Hg) were reported in most patients when the tumor was manipulated whether or not α -blockade was used (65). Newell *et al.* (66) also reported that preoperative adrenergic blockade did not prevent severe intraoperative hypertension and that prolonged periods of preparation were not more effective in preventing intraoperative tachycardia and ventricular arrhythmias. In 63 consecutive patients with pheochromocytoma treated at the Cleveland Clinic over a span of 10 yr, Boutros *et al.* (67) reported similar perioperative results whether or not patients received preoperative α -blockade. Similarly, in a study of 114 patients who underwent removal of pheochromocytoma, fewer perioperative complications were observed in those not given α -blockers (68). These studies suggest that the need for the use of POB or other drugs that produce profound and long-lasting α -blockade in preparing pheochromocytoma patients for the surgical removal of the tumor is no longer necessary. This is, in large part, attributable to advances in anesthetic and monitoring techniques and the availability of fast-acting drugs capable of correcting sudden changes in cardiovascular hemodynamics.

When α -blockade is needed to control symptoms, prazosin, terazosin, or doxazosin (selective α_1 -receptor antagonists) can be used to circumvent some of the disadvantages of POB. Because they do not block presynaptic α_2 -receptors, this class of drugs does not enhance NE release and, therefore, does not produce reflex tachycardia (69). They also have a shorter

duration of action, permitting more rapid adjustment of dosage and a reduced duration of postoperative hypotension.

Calcium channel antagonists have been shown to control blood pressure and symptoms in pheochromocytoma (70–73). They relax arteriolar smooth muscle and decrease peripheral vascular resistance by inhibiting NE-mediated release of intracellular calcium and/or transmembrane calcium influx in vascular smooth muscle (74). In doses of 30–90 mg/d, nifedipine gastrointestinal transport system (GITS) normalizes blood pressure in hypertensive patients and prevents the hypertensive response to provocative challenge (Fig. 10 and Ref. 75). In more resistant cases, calcium channel antagonists can be combined with specific α_1 -receptor antagonists with successful control of blood pressure. These agents have also been used exclusively to control circulatory fluctuations during resection of a pheochromocytoma (76, 77). Calcium channel antagonists have other advantages: they do not produce overshoot hypotension or orthostatic hypotension and therefore may be used safely in patients who are normotensive but have occasional episodes of paroxysmal hypertension; they are useful in managing patients with cardiovascular complications because they prevent catecholamine-induced coronary vasospasm and myocarditis.

Thus, appropriately used calcium channel antagonists and selective α_1 -receptor blockers are effective and safe without the adverse effects associated with nonspecific, complete, and prolonged α -blockade with POB.

B. Surgical therapy

Precise localization of pheochromocytoma, the availability of new medications and procedures to safeguard intraoperative hemodynamics, and the introduction of innovative surgical techniques have all combined to dramatically change the surgical approach to pheochromocytoma. Until recently, pheochromocytoma was removed only through an open approach. With technological advances and experience in minimally invasive surgery, the tumor can now be removed safely and successfully with laparoscopic surgery. Table 3 shows perioperative hemodynamic variables in 14 pheochromocytoma patients who underwent laparoscopic surgery compared with 20 patients who underwent the traditional open approach. In this study (78), the intraoperative hemodynamic values during laparoscopic adrenalectomy were comparable to those of open surgery. However, in patients

undergoing laparoscopy, intraoperative hypotension was less severe (mean lowest blood pressure 98/57 mm Hg *vs.* 80/50 mm Hg, $P = 0.05$), and hypotensive episodes were less frequent (median 0 *vs.* 2 episodes, $P = 0.005$). The median estimated blood loss was 100 ml (range, 100–200 ml) in the

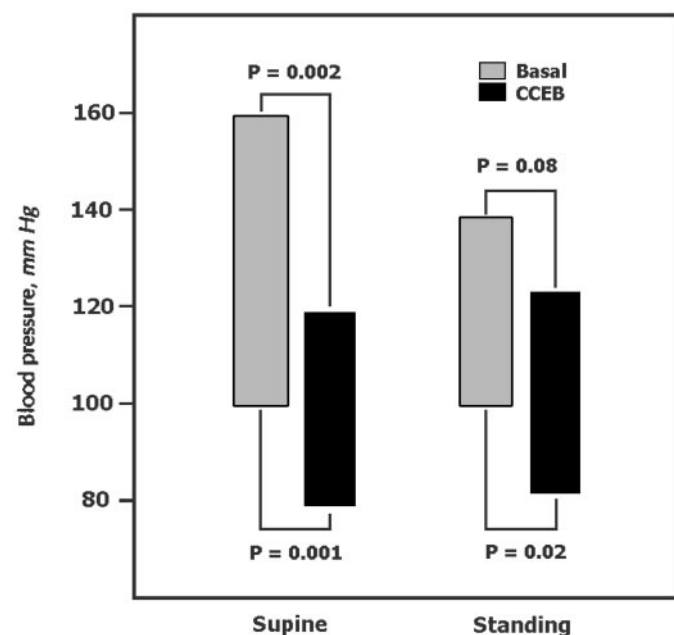


FIG. 10. Blood pressure response to calcium channel antagonists in pheochromocytoma. Bars represent the mean systolic and diastolic blood pressures from 10 patients with surgically diagnosed pheochromocytoma. CCEB, Calcium channel entry blocker. Patients received either verapamil-SR (120–240 mg daily; $n = 5$) or nifedipine-XL (30–90 mg daily; $n = 5$) for 6–8 wk. The blood pressure values reported here were obtained immediately before drug administration and before the surgical procedure. Calcium channel antagonist maintained blood pressure at normal levels, and patients were symptom-free throughout the study period. Before drug treatment, patients had reduction in systolic blood pressure with standing. This reduction was completely eliminated during treatment. [Reproduced with permission from E. L. Bravo. Secondary hypertension: adrenal and nervous systems. In: Hollenberg NK, ed. Atlas of heart diseases. Philadelphia: Current Medicine; 118–143, 2001 (75).]

TABLE 3. Perioperative hemodynamic variables

	Open ($n = 20$)	Laparoscopic ($n = 14$)	P value
Mean preoperative blood pressure (mm Hg) ^a	140 ± 18/78 ± 10	144 ± 13/74 ± 14	0.50
Highest blood pressure (mm Hg) ^a	191 ± 33/98 ± 25	194 ± 19/106 ± 19	0.50
Hypertension ^b	0.5 (0–5)	1.0 (0–3)	0.41
SBP ≥ 200 mm Hg	0 (0–4)	0 (0–2)	0.70
Lowest blood pressure (mm Hg) ^a	88 ± 14/50 ± 13	98 ± 19/57 ± 8	0.05
Hypotension, episodes	2.0 (0–6)	0 (0–2)	0.005
Highest heart rate, bpm	104 ± 15	101 ± 24	0.78
Heart rate ≥ 110 bpm ^b	0 (0–3)	0 (0–3)	0.36
Lowest heart rate, bpm	61 ± 11	60 ± 9	0.81
Heart rate Ω 50 bpm ^b	0 (0–1)	0 (0–5)	0.81
Patients requiring treatment for hypertension ^c , n	17.0	13.0	0.63
Patients requiring treatment for hypotension ^d , n	9.0	1.0	0.02

^a Systolic and diastolic blood pressure presented as the standard deviation; P value based on the test.

^b Median number of episodes for one patient, with the range in parentheses; P value based on the Jackson-Whitney U test.

^c Includes patients who intraoperatively received at least one of the following treatments: nitroglycerin, sodium nitroprusside, β -blocker, α/β -blocker, or a calcium channel antagonist.

^d Includes patients who intraoperatively received at least one of the following treatments: phenylephrine, dopamine, or epinephrine. [Reproduced with permission from J. Sprung *et al.*: *Urology* 55:339–343, 2000 (78). © Elsevier Science.]

laparoscopy group and 400 ml (range, 150–1500 ml) in the open group ($P = 0.001$). Surgery time was no different between the two groups (196 ± 69 min for open *vs.* 177 ± 59 min for laparoscopy). Patients who underwent laparoscopy had a faster postoperative course: time to ambulation 1.4 *vs.* 4 d ($P = 0.002$), resumed oral food intake sooner (median 1 *vs.* 3.5 d, $P = 0.001$), and duration of hospitalization was much shorter (median 3 *vs.* 7.4 d, $P = 0.001$). In addition, patients resumed normal physical activity faster (within 5–7 d), and the cosmetic results were far better compared with the open approach.

IX. Future Prospects

A. Diagnostic localization techniques

Other radiotracers have been evaluated for the localization of pheochromocytoma. ¹²³I-MIBG offers superior image quality compared with ¹³¹I-MIBG, and seems suited for detecting recurrent or metastatic tumors, especially those with fibrosis or distorted anatomy or in unusual locations (79, 80). ¹²³I-MIBG is not routinely used and is available only in a few centers. Expression of somatostatin receptors by pheochromocytoma cells led to evaluation of radiolabeled octreotide, an analog of somatostatin; it has had only limited success (81).

Positron emission tomography scanning is a physiology-based method of imaging dependent on selective binding or uptake and retention of radiopharmaceuticals (82). The use of short-lived positron-emitting radionuclides allows administration of large tracer doses, resulting in high count density and superior resolution compared with that of single photon emitters. ¹⁸F-Fluorodeoxyglucose (83, 84) and ¹¹C-hydroxyephedrine (85) have been used to localize pheochromocytoma. However, both agents cannot detect pheochromocytomas specifically. 6-[¹⁸F]Fluorodopamine is a positron-emitting analog of dopamine. In catecholamine-synthesizing cells, 6-[¹⁸F]fluorodopamine is transported actively and avidly by both plasma membrane NE transporter and the vesicle monoamine transporter. Preliminary studies suggest that positron emission tomography scanning with 6-[¹⁸F]fluorodopamine visualizes pheochromocytomas almost immedi-

ately with a high degree of sensitivity and specificity (86). However, this test is in its initial stages of testing, is expensive, and is technically demanding.

B. Diagnosis and management of molecular genetic abnormalities associated with pheochromocytoma

Molecular medicine makes it possible to differentiate sporadic from hereditary disease, which will affect medical management not only for the patient, but also for the family. When hereditary, pheochromocytoma can be a component of MEN-2, caused by mutation of the RET gene; VHL disease caused by mutation of the VHL tumor-suppressor gene; and, rarely, neurofibromatosis type 1 (87–91). Recently, mutations of the gene for succinate dehydrogenase subunit D (SDHD) and subunit B (SDHB) were identified for another related neuroendocrine disease, familial paragangliomas of the neck, or globus tumors (92–94). Molecular identification of a mutation in any of these genes could lead to surveillance, early diagnosis of tumors, and more effective treatment before onset of clinical disease.

In a recent study, Neumann *et al.* (95) reported that almost one fourth of patients with apparent sporadic pheochromocytomas may be carriers of mutation. Among 271 patients with pheochromocytoma without a family history of the disease, 66 (24%) were found to have mutations. Of these 66, 30 had mutations of VHL, 13 of RET, 11 of SDHD, and 12 of SDHB. Younger age, multifocal tumors, and extraadrenal tumors were significantly associated with the presence of a mutation; none had associated signs and symptoms at presentation. It is recommended that patients with apparent sporadic pheochromocytoma undergo routine analysis of mutations of RET, VHL, SDHD, and SDHB to identify pheochromocytoma-associated syndromes that would otherwise be missed.

The measurement of plasma metanephrines promises to be the best screening biochemical test for pheochromocytoma in patients with a familial predisposition to these tumors (55). The high sensitivity (97%) of measurements of plasma normetanephrine and metanephrine is accompanied by a high level of specificity (96%). This provides early detection before signs and symptoms occur, when tumors are small and not secreting large amounts of catecholamines. The surgical approach to hereditary forms of pheochromocytoma remains unsettled. Treatment has included follow-up observation of small nonfunctional pheochromocytomas, unilateral adrenalectomy for functional tumors, and cortical-sparing adrenalectomy (96–98). Routine prophylactic bilateral adrenalectomy is not warranted in familial pheochromocytoma (99, 100).

C. Malignant pheochromocytoma

Successful surgical excision of an apparently benign tumor may be followed by a diagnosis of malignancy as long as 15 yr later (101). There are, as yet, no good ways to predict which tumors will progress to malignancy. Prognostic factors that have been suggested for future malignant course include large tumor size, local tumor extension at the time of surgery, and the DNA ploidy pattern with DNA diploid being benign

and DNA aneuploidy and tetraploidy having a more aggressive nature (102). An initial report suggests that inhibin/activin β -B subunit expression may help distinguish between benign and malignant disease; expression was absent or weak in malignant tumors, but was strong or moderate in almost all benign adrenal pheochromocytomas (103). Another study also suggested that the lack of NPY mRNA expression may distinguish malignant from benign pheochromocytoma (104). However, extraadrenal tumors already have low NPY mRNA expression (30).

Although the survival rate is less than 50%, malignant pheochromocytomas can be slow growing, and patients may have minimal morbidity and survive for as long as 20 yr (101). Whenever possible, surgical excision or debulking of accessible tumors should be attempted. For control of cardiovascular manifestations, calcium channel antagonists and postsynaptic α_1 receptor blockers with and without β -blockade have been used effectively (see Section VIII.A). Patients with advanced and aggressive tumors have been treated with either chemotherapy (consisting of cyclophosphamide, vincristine, and dacarbazine) (105) or tumor irradiation with ^{131}I -MIBG (106). Both have had limited therapeutic success and have not produced significant, long-lasting benefit even with repeated administration. Radiofrequency ablation of hepatic and bone metastasis have shown promise in some selected patients (107).

Note Added in Proof

Since the submission of this manuscript, current developments have arisen that warrant further study (110–113).

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