Recent Advances in Genetics, Diagnosis, Localization, and Treatment of Pheochromocytoma

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Pheochromocytoma is a rare but important tumor of chromaffin cells that is frequently considered in the evaluation of hypertension, arrhythmias, or panic disorder and in the follow-up of patients with particular genetic diseases. This report provides an update about the genetics, neurochemical diagnosis, localization by imaging, and surgical management of pheochromocytoma. Specific mutations of the RET proto-oncogene cause familial predisposition to pheochromocytoma in multiple endocrine neoplasia type II, and mutations in the von Hippel–Lindau tumor suppressor gene cause familial disposition to pheochromocytoma in von Hippel–Lindau disease. Recent findings demonstrating extraordinarily high sensitivity of plasma levels of metanephrines for detecting pheochromocytoma have led to an algorithm for clinical diagnostic steps. Nuclear imaging approaches, such as $^{123}$I-metaiodobenzylguanidine scintigraphy and $^{6-[^{18}F]}$fluorodopamine positron emission tomography, enhance both diagnosis and localization of the tumor, as described in an algorithm for patients with positive biochemical test results. Since pheochromocytoma is often benign, surgical resection by laparoscopic adrenalectomy can be curative. Areas requiring further work include determining appropriate follow-up of patients with familial pheochromocytoma, elucidating the bases for phenotypic differences, improving both specificity and sensitivity of biochemical tests, optimizing cost-effectiveness of diagnostic imaging, and testing the risk for tumor recurrence after partial adrenalectomy.


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Dr. Karel Pacak (Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development [NICHD] and Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke [NINDS], National Institutes of Health [NIH], Bethesda, Maryland): Pheochromocytomas are chromaffin cell tumors that, although rare, must be considered in patients with hypertension, autonomic disturbances, panic attacks, adrenal incidentalomas, or familial diseases featuring a predisposition to develop pheochromocytoma. Hypertension, whether sustained or paroxysmal, is the most common clinical sign, and headache, excessive truncal sweating, and palpitations are the most common symptoms (1). Pallor is also common, whereas flushing occurs less frequently. Some patients present with severe episodes of anxiety, nervousness, or panic. Patients with a familial predisposition or small incidentally discovered adrenal masses can be normotensive and asymptomatic.

The low pretest prevalence of pheochromocytoma—close to 0.5% among those tested because of hypertension and suggestive symptoms (1) and as high as 4% in patients with adrenal incidentaloma (2)—together with imperfect sensitivity and specificity of commonly used biochemical and imaging tests, can make diagnosis and localization of pheochromocytoma difficult. Effective methods for diagnosis and localization are important because seemingly mild stimuli can provoke the tumor to release large amounts of catecholamines, with severe or fatal consequences. Moreover, surgical removal can cure pheochromocytoma in up to 90% of cases, whereas if left untreated the tumor can prove fatal.

Advances in genetic mutation analysis have greatly improved identification of patients with familial pheochromocytoma, allowing detection of tumors at an early stage, often before typical signs and symptoms occur. These advances provide new insights into the biology and natural history of the disease and highlight inadequacies of commonly used diagnostic tests. In turn, new developments have been made in the management of patients with familial pheochromocytoma and in surgical procedures for preserving normal adrenal cortical tissue in persons with bilateral adrenal tumors. In this paper, we summarize advances in the genetics, biochemical diagnosis, localization, and management of pheochro-
MOLECULAR GENETIC ABNORMALITIES ASSOCIATED WITH PHEOCHROMOCYTOMA

Drs. W. Marston Linehan and McClellan M. Walther (Urologic Oncology Branch, National Cancer Institute [NCI], NIH, Bethesda, Maryland): Pheochromocytomas may be classified as sporadic or familial. Most pheochromocytomas are sporadic. Familial predisposition is seen mainly in patients with multiple endocrine neoplasia type II (MEN II), von Hippel–Lindau disease, neurofibromatosis type 1, and familial carotid body tumors (Table 1). The exact molecular mechanisms by which the hereditary mutations predispose to tumor development remain unknown. Hereditary forms of pheochromocytoma can differ in rate of tumor growth, malignant potential, and catecholamine phenotype.

Cancer Genes

Identification of a cancer gene can help us understand the origin of cancer, such as pheochromocytoma, and elucidate mechanisms of tumor formation and behavior. Moreover, identification of a disease gene provides a method for genetic diagnosis. Phenotypic manifestations of a hereditary cancer syndrome can vary markedly, and genetic tests can confirm the diagnosis when the clinical presentation is complex. Finally, understanding of cancer genes may provide targets for therapy.

The two most studied types of cancer genes are tumor suppressor genes (Figure 1) and oncogenes (7). When mutated, a proto-oncogene becomes “activated,” resulting in an oncogene. This is referred to as a “single hit”; that is, the proto-oncogene undergoes a single activating mutation that turns it into an oncogene (8, 9). Familial predisposition to pheochromocytoma in patients with MEN II results from such a mechanism. In contrast, a tumor suppressor gene is a “loss-of-function” gene, in which inactivation of both copies of the gene causes unregulated cell growth and division. This loss of function can result from mutation of one allele of a tumor suppressor gene and deletion of the second copy (10). Examples of tumor suppressor genes are the retinoblastoma gene, the Wilms tumor gene, the tuberous sclerosis genes, and, in the case of pheochromocytoma, the von Hippel–Lindau gene (11–19).

Pheochromocytoma in Multiple Endocrine Neoplasia Type II: RET Gene

Multiple endocrine neoplasia type II A is characterized clinically by the familial association of medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia. Mucosal ganglioneuromas are also found in some patients (MEN IIb). Pheochromocytoma in MEN II is associated with germline mutation of the proto-oncogene RET. This proto-oncogene becomes an oncogene when an activating mutation occurs (20–25). The activating mutation in the RET gene drives the abnormal cellular proliferation that leads to adrenal medullary hyperplasia and pheochromocytoma. Several RET germ-

### Table 1. Hereditary Forms of Pheochromocytoma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Frequency of Pheochromocytoma, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia type II*</td>
<td>RET oncogene</td>
<td>10q11</td>
<td>30–50</td>
</tr>
<tr>
<td>von Hippel–Lindau disease†</td>
<td>von Hippel–Lindau suppressor gene</td>
<td>3p25</td>
<td>15–20</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Neurofibromatosis type 1</td>
<td>17q11</td>
<td>1–5</td>
</tr>
<tr>
<td>Familial carotid body tumors</td>
<td>Paraganglioma</td>
<td>11q21–23</td>
<td></td>
</tr>
</tbody>
</table>

* Mutations in codons 609, 611, 618, and 620 in exon 10 and codons 631 and 634 in exon 11 are found in most families with multiple endocrine neoplasia type IIA (MEN IIA). Multiple endocrine neoplasia type IIB (MEN IIB) is associated with mutations in codons 918 and 922 in exon 16. In patients with MEN IIA, mutation in codon 634 is one of the most common and accounts for approximately 80% to 85% of all pheochromocytomas (3–5). Mutations in codon 620 are less frequent but are also associated with pheochromocytoma. Very rarely, pheochromocytoma in patients with MEN IIA is associated with mutations in codons 609, 611, 618, and 631 (3–5). In patients with MEN IIB, the mutation in codon 918 is most often associated with pheochromocytoma (3).

† von Hippel–Lindau gene mutations at nucleotides 505, 547, 695, 595, 775, or 695 carry an especially high risk for pheochromocytoma. Family members develop these tumors at a higher frequency and at a younger age than members of families with other mutations (6). In patients with von Hippel–Lindau disease, extra-adrenal or malignant pheochromocytomas are always associated with missense mutations. Of the families with pheochromocytoma, 33% had mutations in codon 187 (nucleotides 712–713). Two different mutations at codon 167 of the von Hippel–Lindau gene result in different clinical manifestations (6). A mutation resulting in the single nucleotide change of arginine to glutamine is associated with the development of renal cancer and pheochromocytoma, whereas mutation resulting in the nucleotide change to tryptophan is associated only with pheochromocytoma.
line mutations are associated with the development of pheochromocytoma, with some variation dependent on the particular mutation (3–5, 26, 27) (Table 1).

Pheochromocytoma in von Hippel–Lindau Disease: the von Hippel–Lindau Gene

Patients with von Hippel–Lindau disease have a germline mutation of the von Hippel–Lindau gene (28). Affected persons can develop early-onset bilateral kidney tumors and cysts, pheochromocytomas, cerebellar and spinal hemangioblastomas, retinal angiomas, pancreatic cysts and tumors, epididymal cystadenomas, and tumors in the endolymphatic sac canal of the inner ear (29–31).

von Hippel–Lindau disease has marked phenotypic heterogeneity. While patients from some families present with central neural, eye, kidney, and pancreatic tumors, patients in other families present mainly with pheochromocytoma (30, 32, 33). Some reports have described families thought to have “familial pheochromocytoma” who proved to have von Hippel–Lindau disease (32, 34–37). Missense mutations in the von Hippel–Lindau gene are associated with the development of pheochromocytoma more than twice as often as are other types of mutations (74% vs. 32%) (6, 33).

Molecular Genetic Diagnosis

von Hippel–Lindau disease and MEN II have a similar prevalence (approximately 1 in 30,000 to 1 in 45,500). Mutations predisposing to pheochromocytoma have greater penetrance in MEN II than in von Hippel–Lindau disease (38, 39). Pheochromocytoma in von Hippel–Lindau families has been reported as familial pheochromocytoma or MEN II (40, 41). Because different kindreds can present with different phenotypes, it can be difficult to distinguish between von Hippel–Lindau disease and MEN II in some patients with familial pheochromocytoma. Patients with bilateral adrenal, recurrent, or multifocal pheochromocytoma should undergo clinical or genetic testing for mutations of the von Hippel–Lindau or RET genes.

The availability of germline testing for both von Hippel–Lindau (42) and RET (15, 20, 23, 40, 43) gene mutations (at OncorMed in Gaithersburg, Maryland, and at the University of Pennsylvania in Philadelphia) has improved the clinical management of patients with hereditary pheochromocytoma. When a patient presents with a family history in which the primary manifestation is pheochromocytoma, the von Hippel–Lindau gene is a likely cause. Some von Hippel–Lindau families present mainly with pheochromocytoma and occult or delayed manifestations in the central nervous system, eye, or other organs. It is less likely that a member of a MEN II family will present predominantly with pheochromocytoma because most of these patients have medullary thyroid carcinoma (44). A small number of families with familial pheochromocytoma have neither von Hippel–Lindau nor RET germline mutations, and the genetic basis for this is currently being studied.

BIOCHEMICAL DIAGNOSIS OF PHEOCHROMOCYTOMA

Dr. Graeme Eisenhofer (Clinical Neurocardiology Section, NINDS, NIH, Bethesda, Maryland): Diagnosis of pheochromocytoma usually requires biochemical evidence of excessive catecholamine production by the tumor, usually achieved from measurements of catecholamines or catecholamine metabolites in urine or plasma. These biochemical approaches, however, have several limitations.

Since catecholamines are normally produced by sympathetic nerves and by the adrenal medulla, high catecholamine levels are not specific to pheochromocy-
Sensitivity of Biochemical Tests

Measurements of plasma levels of normetanephrine and metanephrine have higher sensitivity than other biochemical tests for diagnosis of both sporadic and familial pheochromocytoma (46, 56). In familial pheochromocytoma, periodic screening can lead to early-stage detection before symptoms and signs, when tumors are small and are not secreting large amounts of catecholamines (6). The difficulty of biochemical diagnosis of familial pheochromocytoma is illustrated by our findings of only 46% to 72% sensitivity for commonly used tests in 39 cases of familial pheochromocytoma, compared with a 97% sensitivity for plasma metanephrines (56). In our larger series of 151 patients with mainly sporadic pheochromocytoma, sensitivity of plasma metanephrines was greater than 99%, compared with only 63% to 85% for other tests (Table 2). Plasma metanephrines are also useful for diagnosis of pheochromocytoma in patients with adrenal incidentalomas. In one case of an asymptomatic and normotensive patient with a 5-cm adrenal incidentaloma, elevated plasma levels of metanephrines provided the only biochemical evidence of pheochromocytoma (57).

Specificity of Biochemical Tests

Any of a variety of physiologic, pharmacologic, or pathologic conditions can increase plasma and urinary catecholamine levels (58). Since upper reference limits of biochemical tests are usually established from the 95% confidence intervals of values in a reference population, a certain incidence of false-positive results is expected. In our series of 349 patients in whom pheochromocytoma was excluded, specificities were 80% to 94% (Table 2).

The probability of a positive test result indicating a pheochromocytoma can be estimated by using Bayesian inference in the form of likelihood ratios (59, 60). Probability also depends on the extent of the increase of the test result above normal, established by receiver-operating characteristic curves, in which the frequency of true-positive results at different upper reference limits is plotted against the frequency of false-positive results (46). At higher upper reference limits, although the sensitivity of a test is reduced, the specificity of the test and probability of pheochromocytoma indicated by a positive test result can both approach 100%.

Our experience shows that plasma concentrations of normetanephrine greater than 2.5 pmol/mL or metanephrine levels greater than 1.4 pmol/mL (more than 4- and 2.5-fold above the upper reference limits) indicate a pheochromocytoma with 100% specificity. The few conditions in which plasma metanephrines can reach such levels (for example, monoamine oxidase deficiency)

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Table 2. Sensitivity and Specificity of Biochemical Tests for Diagnosis of Pheochromocytoma*

<table>
<thead>
<tr>
<th>Biochemical Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity at 100% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma metanephrine level</td>
<td>99</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>Plasma catecholamine level</td>
<td>85</td>
<td>80</td>
<td>38</td>
</tr>
<tr>
<td>Urinary catecholamine level</td>
<td>83</td>
<td>88</td>
<td>64</td>
</tr>
<tr>
<td>Urinary metanephrine level</td>
<td>76</td>
<td>94</td>
<td>53</td>
</tr>
<tr>
<td>Urinary vanillylmandelic acid level</td>
<td>63</td>
<td>94</td>
<td>43</td>
</tr>
</tbody>
</table>

* The sensitivities of tests of plasma metanephrines or plasma and urinary catecholamines were determined, respectively, as the percentage of patients with pheochromocytoma who had positive test results for normetanephrine or metanephrine or for norepinephrine or epinephrine. The specificities of tests of plasma metanephrines or plasma and urinary catecholamines were determined as the percentage of patients without pheochromocytoma who had negative test results for both normetanephrine and metanephrine or for both norepinephrine and epinephrine. The sensitivities and specificities of tests of urinary metanephrines reflect tests of urinary total metanephrines (that is, the combined sum of free plus conjugated normetanephrine and metanephrine). The sensitivities at 100% specificity indicate the percentage of patients with pheochromocytoma in whom test results are so high that they unequivocally confirm the presence of a pheochromocytoma. These sensitivities were determined by increasing the upper reference limits for each test to levels at which no patient without pheochromocytoma had a positive test result. Sensitivity was determined for tests in 151 patients, and specificity was determined for tests in 349 patients.
are easily excluded. As illustrated in Table 2, at the higher limits more specific for a tumor, plasma metanephrines are more effective in confirming a pheochromocytoma than other tests.

**Procedural Recommendations**

The most important consideration in choosing an initial biochemical test is the reliability of the test for exclusion of pheochromocytoma. In pheochromocytoma, a missed diagnosis due to a false-negative result can have catastrophic consequences for the patient, while a false-positive result can be refuted by further tests. Because of their uniquely high sensitivity, we recommend plasma metanephrines as the initial biochemical test. Since pheochromocytomas are rare, most tests will prove negative, reliably excluding pheochromocytoma so that no further tests are necessary (Figure 2). This compares favorably with other tests, which do not exclude all pheochromocytomas even when performed in combination (56). A single test of plasma metanephrines also minimizes problems associated with combinations of tests in which higher numbers of false-positive results require additional time and effort for follow-up.

Because the pretest probability of pheochromocytoma is very low, the incidence of false-positive results also has an important effect on diagnosis. As with all biochemical tests, high plasma levels of normetanephrine or metanephrine do not necessarily prove a pheochromocytoma. Thus, because of the low prevalence of pheochromocytoma, the number of false-positive results will probably far exceed the number of true-positive results (Figure 2). Nevertheless, at a 2% pretest probability of pheochromocytoma and at a specificity of 89%, a positive result on an initial test of plasma metanephrines increases the probability of pheochromocytoma to nearly 16%.

As discussed earlier, the probability of whether a positive test result reliably confirms a pheochromocytoma can better be determined by consideration of receiver-operating characteristic curves. Our experience shows that more than 80% of patients with pheochromocytoma have elevated plasma metanephrine levels that indicate a pheochromocytoma with 100% specificity (Table 2, Figure 2). For these patients, the probability of pheochromocytoma is increased to close to 100% by a single test of plasma metanephrines. The immediate task then is to localize the tumor by using imaging studies; further biochemical testing is not necessary.

These considerations show that most patients with pheochromocytoma can be identified immediately by a single test of plasma metanephrines. However, as indicated in the algorithm (Figure 2), many patients have marginally elevated plasma levels of normetanephrine or metanephrine. Among this group, differentiating true-positive from false-positive results remains a problem. In such patients, it is important to review the clinical history and consider possible explanations for a false-positive result. Supplemental biochemical testing is then required, taking care to avoid conditions or medications that might lead to false-positive results.

Additional follow-up biochemical tests should include measurements of plasma catecholamines and repeated measurements of metanephrines (Figure 2). Since metanephrines are produced continuously by a pheochromocytoma, normal plasma levels of normetanephrine and metanephrine in a second test exclude pheochromocytoma, even if results of the first test or other tests are positive. If plasma metanephrines remain positive, then the pattern of alterations in other results can be helpful in planning a strategy for further testing.

The clonidine suppression test is useful for distinguishing between high levels of plasma norepinephrine caused by release from sympathetic nerves and those caused by release from a pheochromocytoma (61–67). A decrease of more than 50% in plasma norepinephrine levels or a decrease after clonidine administration to less than 2.96 nmol/L indicate normal responses, whereas consistently elevated concentrations before and after clonidine administration indicate a pheochromocytoma. When the above criteria for a normal response are used, the test is highly specific. However, in patients with intermittently secreting tumors or those in whom plasma norepinephrine concentrations are normal or only marginally elevated, plasma norepinephrine levels may decrease regardless of a tumor, resulting in a false-negative test result (61–63, 68). False-positive test results can occur in patients taking diuretics or tricyclic antidepressants (61, 69). However, except in these cases, clonidine rarely fails to decrease plasma norepinephrine levels in patients without pheochromocytoma.

The glucagon stimulation test can be useful when high plasma levels of normetanephrine or metanephrine are noted and plasma catecholamine levels are normal or...
moderately elevated. A greater than threefold increase in norepinephrine levels 2 minutes after intravenous administration of glucagon indicates a pheochromocytoma with high specificity (70, 71). However, the test is not sensitive, and a negative test result does not exclude pheochromocytoma.

Because of possible severe hypotension during the clonidine test and hypertension during the glucagon test, both tests are best performed by experienced clinicians. The value of both tests, when judiciously implemented and appropriately interpreted, is that they can indicate a pheochromocytoma with high specificity.

Appropriate biochemical testing, combined with assessment of clinical history, should in most cases provide sufficient evidence to exclude pheochromocytoma or justify imaging studies to locate the tumor. To minimize expensive and unnecessary imaging studies, it would be ideal if biochemical testing could confirm or exclude pheochromocytoma in every patient. In reality, however, follow-up imaging studies are often required in patients for whom biochemical evidence of pheochromocytoma is not definitive.

ADVANCES IN DIAGNOSTIC LOCALIZATION OF PHEOCHROMOCYTOMA

Drs. Karel Pacak and David S. Goldstein (Pediatric and Reproductive Endocrinology Branch, NICHD, and Clinical Neurocardiology Section, NINDS, NIH, Bethesda, Maryland): The diagnosis and treatment of pheochromocytoma depend critically on localization of the tumor. Conventional approaches include computed tomography, magnetic resonance imaging, and scintigraphy after administration of $^{131}$I- or $^{123}$I-labeled metaiodobenzylguanidine.

Computed tomography has good sensitivity (93% to 100%) for detecting adrenal pheochromocytoma (72–75). Sensitivity decreases to approximately 90% for extra-adrenal pheochromocytomas (76). In contrast, magnetic resonance imaging has lower or equal sensitivity for detecting adrenal pheochromocytomas but is superior for detecting extra-adrenal tumors (72, 73). Both imaging methods have poor specificity, as low as 50% in some studies (74). This is an important problem because of the relatively high frequency of adrenal masses that are not pheochromocytomas (74, 77).

Metaiodobenzylguanidine scanning offers superior specificity (95% to 100%) and is helpful in diagnosing...
extra-adrenal tumors. However, it is not sensitive enough (77% to 90%) to exclude pheochromocytoma (49, 74, 76–84). Currently, only $^{131}$I-metaiodobenzylguanidine is commercially available in the United States (85). $^{123}$I-metaiodobenzylguanidine offers superior image quality because the characteristic photon energy is well suited for cameras equipped with low-energy, high-resolution collimators and because it can be used with single-photon emission computed tomography. $^{123}$I-metaiodobenzylguanidine seems especially useful for detecting recurrent or metastatic pheochromocytoma, tumors with fibrosis or distorted anatomy, and tumors in unusual locations (86–88).

The limitations of routinely available imaging methods have led to evaluation of other radiotracers for diagnostic localization of pheochromocytoma (87, 89–91). A few reports noted expression of somatostatin receptors by pheochromocytoma cells (87, 89–91). Scintigraphy after administration of radiolabeled octreotide, an analogue of somatostatin, has had only limited success, depending on anatomic factors, expression of somatostatin receptors, and delivery of the radiopharmaceutical to the tumor cells.

Positron emission tomography is a physiologic method of imaging that depends on selective binding or uptake and retention of radiopharmaceuticals by different tissues. The use of short-lived positron-emitting radionuclides allows administration of large tracer doses, resulting in high count density, superior resolution, and a short imaging time frame. This enables visualization almost immediately after administration of the imaging agent. In contrast, metaiodobenzylguanidine scanning requires imaging for a 24- to 48-hour period (92).

Several imaging agents for positron emission tomography have been used to visualize primary and metastatic tumors (89, 93–96), such as pheochromocytoma (87, 92, 97). Uptake of $^{18}$F-fluorodeoxyglucose by cells with a relatively high metabolic rate can allow successful visualization of pheochromocytoma (91). A case of malignant pheochromocytoma in the anterior mediastinum was localized by positron emission tomography after administration of $^{82}$rubidium, which the body handles similarly to potassium (98). All rapidly metabolizing cells take up both $^{18}$F-fluorodeoxyglucose and $^{82}$rubidium, so neither can detect pheochromocytoma specifically. Thus, these approaches are not recommended for initial localization of pheochromocytoma.

More specific agents, such as $^{11}$C-hydroxyephedrine, might be expected to have less sensitivity than $^{18}$F-fluorodeoxyglucose because of the requirement of uptake by monoamine transporters (91, 92, 99). However, $^{18}$F-fluorodeoxyglucose and $^{11}$C-hydroxyephedrine have similar sensitivities for detection of pheochromocytoma (91). Positron emission tomography with $^{11}$C-hydroxyephedrine has been reported to detect pheochromocytoma rapidly (within 2 to 5 minutes) and clearly in 9 of 10 patients, visualizing more lesions with better contrast than $^{131}$I-metaiodobenzylguanidine (92).

$^{6}$-$^{18}$F-fluorodopamine, a sympathoneural imaging agent developed at the NIH, is a positron-emitting analogue of dopamine and a good substrate for both the plasma membrane and intracellular vesicular transporters in catecholamine-synthesizing cells. This results in a tissue–blood concentration ratio for $^{6}$-$^{18}$F-fluorodopamine of more than 1000 and good visualization of pheochromocytoma tumor cells (100) (Figure 3). In other types of cells, $^{6}$-$^{18}$F-fluorodopamine undergoes rapid metabolism and exit of the metabolites from the cells. Positron emission tomography using $^{18}$F-fluorodeoxyglucose is available for clinical diagnosis at several centers. $^{11}$C-hydroxyephedrine is used at the University of Michigan in Ann Arbor, and $^{6}$-$^{18}$F-fluorodopamine is used at the NIH.

The procedures we recommend for localization of
Pheochromocytoma are outlined in the imaging algorithm (Figure 4). Abdominal computed tomography or magnetic resonance imaging is done first, since both are relatively sensitive tests and have similar sensitivity and specificity in detecting adrenal pheochromocytoma (77). However, because of inadequate specificity, detection of a mass by these tests does not justify a diagnosis of pheochromocytoma. Thus, metaiodobenzylguanidine scanning is done for confirmation. If metaiodobenzylguanidine scanning is positive, the patient can go directly to surgery.

Negative results on metaiodobenzylguanidine scanning do not exclude a pheochromocytoma because the test has imperfect sensitivity. If results of abdominal computed tomography and magnetic resonance imaging are negative, then whole-body evaluation, usually by computed tomography or magnetic resonance imaging, is indicated; metaiodobenzylguanidine scanning results should also be reviewed with attention to the possibility of extra-adrenal pheochromocytoma. Continuous rotation or spiral computed tomography, with its high spatial resolution, is probably preferable here for detecting small thoracic tumors (101). Magnetic resonance imaging may be preferable for detection of juxtacardiac and juxtavascular pheochromocytoma (73).

Neither computed tomography nor magnetic resonance imaging has perfect sensitivity. Therefore, a patient may have a pheochromocytoma even if a mass is not detected by these imaging methods. We have begun to conduct 6-[¹⁸F]fluorodopamine positron emission to-
mography scanning in this setting. Alternative approaches include vena caval sampling for plasma catecholamines and metanephrines and clinical follow-up. At this time, 6-[18F]fluorodopamine positron emission tomography scanning is reserved for cases in which clinical symptoms and signs suggest pheochromocytoma and results of biochemical tests are positive, but conventional imaging studies cannot locate the tumor.

**MANAGEMENT OF PHEOCHROMOCYTOMA**

Dr. McClellan M. Walther (Urologic Oncology Branch, NCI, NIH, Bethesda, Maryland): The definitive treatment for pheochromocytoma is surgical excision of the tumor. Surgery for pheochromocytoma entails several considerations. Induction of anesthesia before surgery, manipulation of the tumor, or other stimulation can cause massive outpouring of catecholamines from the tumor, resulting in hypertensive crisis, stroke, arrhythmias, or myocardial infarction. To prevent these problems, patients with pheochromocytoma must undergo pharmacologic blockade of catecholamine synthesis or effects before surgery (102).

Before the introduction of adrenergic blockade, pheochromocytoma surgical mortality rates ranged from 24% to 50% (103, 104). Routine preoperative pharmacologic blockade with phenoxybenzamine, an -adrenergic receptor blocker, opposes catecholamine-induced vasoconstriction. A -adrenergic receptor blocker is added to oppose the reflex tachycardia often associated with -blockade. -Blockade alone can be dangerous in patients with pheochromocytoma and is contraindicated in this setting because it does not prevent and can actually augment effects of catecholamines at -adrenoceptors.

- -Methyl-para-tyrosine (Merck Sharp & Dohme, West Point, Pennsylvania) competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis (103). Treatment with metyrosine reduces tumor stores of catecholamines, decreases the need for intraoperative medication to control blood pressure, lowers intraoperative fluid requirements, and attenuates blood loss (105). Depletion of tumor catecholamine stores also contributes to decreased ability of the tumor to react to stimulation. The combination of metyrosine, phenoxybenzamine, a -blocker, and liberal salt intake starting 10 to 14 days before surgery leads to better control of blood pressure and decreases surgical risks. Combined medical blockade also allows relaxation of the constricted vascular tree and expansion of the reduced plasma volume, thus avoiding shock after sudden diffuse vasodilation at the time of tumor removal. At midnight before surgery, the patient receives phenoxybenzamine and metyrosine and is assigned to bedrest to avoid orthostatic hypotension. Intravenous fluids are administered for hydration and to ensure adequate blood volume.

After adequate medical blockade and hydration, surgical excision of pheochromocytoma has been performed through a transabdominal incision, with palpation of the contralateral adrenal gland and sympathetic chain to identify possible additional tumors. Patient survival rates of 97.7% to 100% are usual after such procedures (104, 106–113). Residual nonparoxysmal hypertension is found in 27% to 38% of patients after tumor removal (107, 114, 115).

The recent development of laparoscopic surgical techniques has provided an alternative to open surgical procedures (116, 117). Advantages of laparoscopic surgery include less postoperative pain, shortened hospital stay and convalescent period, and improved cosmetic result. Both surgical approaches have similar blood loss and complications (118–126). Laparoscopic surgery is safe, has similar operative time, and shows no difference in blood pressure and heart rate increments when compared with open operations (123–127).

Patients with familial pheochromocytoma are predisposed to multiple or bilateral adrenal tumors. In our series, 64 patients developed 106 pheochromocytomas, of which 47% were bilateral adrenal and 21% were extra-adrenal. Evaluation of different families with von Hippel–Lindau disease has resulted in a clinical classification system (6, 33). Families without pheochromocytoma, classified as von Hippel–Lindau type 1, represent about 44% of von Hippel–Lindau disease families (36). von Hippel–Lindau families with pheochromocytoma (about 56% of von Hippel–Lindau families) are classified as von Hippel–Lindau type 2A or 2B, depending on the absence or presence of renal carcinoma.

Patients with MEN II, identified by screening, present at a younger age and with less frequent symptoms and hypertension (48%) than patients with sporadic pheochromocytoma (128). In contrast to small pheochromocytomas in von Hippel–Lindau disease,
small pheochromocytomas in MEN II detected by screening are often functional; urinary catecholamine excretion is similar to that found in sporadic pheochromocytoma (128).

Pheochromocytomas occur in about 5% of patients with neurofibromatosis type 1 (129). Hypertension in patients with neurofibromatosis type 1 may be essential, renovascular, or, in 20% to 50% of cases, secondary to pheochromocytoma. Solitary adrenal tumors are most common; 9.7% of patients develop bilateral adrenal disease, and 6.3% of patients develop extra-adrenal pheochromocytoma.

Patients with pheochromocytoma secondary to von Hippel–Lindau disease present at a younger age and have fewer symptoms, less hypertension, and smaller and less functional tumors than patients with sporadic pheochromocytoma (6) (Table 3). Pheochromocytoma diagnosed without screening in patients with von Hippel–Lindau disease is associated with a higher incidence of symptoms and hypertension (130). This suggests that smaller, less functional tumors identified by screening account for “silent” pheochromocytomas in patients with von Hippel–Lindau disease (131).

Although adrenalectomy is the established treatment for sporadic pheochromocytoma, the treatment of hereditary forms of pheochromocytoma remains unsettled. Treatment has included follow-up observation of small nonfunctional pheochromocytomas, unilateral adrenalectomy for functional tumors, or prophylactic bilateral adrenalectomy.

Steroid “replacement” therapy after bilateral adrenalectomy often does not suffice for normalizing quality of life. Between 25% and 33% of patients undergoing bilateral adrenalectomy develop Addisonian crisis at some point, and attendant mortality rates are high (132, 133). Moreover, 30% of patients develop clinically significant fatigue, and 48% consider themselves handicapped (133).

In patients with pheochromocytoma, partial adrenalectomy can preserve adrenocortical function and avoid the morbidity of medical adrenal replacement (134, 135). Recently, laparoscopic partial adrenalectomy has been shown to provide clinical results similar to those seen with total adrenalectomy, with less surgical morbidity (103, 134). Although partial adrenalectomy can preserve adrenocortical function, these patients continue to be at risk for recurrent pheochromocytoma. Recurrent pheochromocytoma develops in 20% of patients with von Hippel–Lindau disease a median of 40 months after partial adrenalectomy (136). Patients with MEN II had up to a 33% risk for recurrent pheochromocytoma during 54 to 88 months of follow-up (137, 138). No complications or metastases have been reported secondary to recurrent pheochromocytoma in patients with von Hippel–Lindau disease or MEN II who had partial adrenalectomy (132, 135, 136, 138).

Postoperative follow-up of patients with sporadic and familial forms of pheochromocytoma includes evaluation of plasma metanephrine levels at approximately 6 weeks and again at 6 months after surgery. Because of the high rate of tumor recurrence in familial pheochromocytoma, we recommend yearly follow-up in these patients. Imaging studies should be performed on the basis of follow-up test results.

**Table 3. Comparison of Sporadic Pheochromocytoma and Pheochromocytoma Associated with von Hippel–Lindau Disease**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>von Hippel–Lindau Pheochromocytoma</th>
<th>Sporadic Pheochromocytoma</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29.9</td>
<td>39.7</td>
<td>0.0034</td>
</tr>
<tr>
<td>Symptoms, n/n</td>
<td>6/37</td>
<td>23/26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n/n</td>
<td>3/37</td>
<td>24/26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnostic studies, n/n</td>
<td>23/37</td>
<td>26/26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume, cm³</td>
<td>4.2</td>
<td>35.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine epinephrine level, g/24 h</td>
<td>6.5</td>
<td>14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine metanephrine level, µmol/d</td>
<td>6.59</td>
<td>26.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vanillylmandelic acid level, µmol/d</td>
<td>38</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Future Trends in Diagnosis and Treatment of Pheochromocytoma**

We predict rapid advances in the genetics, diagnosis, localization, and management of pheochromocytoma. The following are key questions for future research in these areas and approaches for answering those questions.

Regarding genetics, how do certain mutations predispose an individual to pheochromocytoma, and how do they lead to the different neurochemical and clinical phenotypes? Is there any identifiable marker for malignant potential or recurrence? Regarding diagnosis and localization, how can tests of plasma metanephrines be made more readily available? In prepaid medical systems,
should these measurements be available systemwide to exclude pheochromocytoma, before other more complex, expensive tests are done? During follow-up of patients with positive biochemical test results, how can we more efficiently and cost-effectually distinguish false-positive from true-positive results? How does 6-[\(^{18}\)F] fluorodopamine positron emission tomography compare with other less expensive and more readily available imaging agents for localization of pheochromocytoma? How can \(^{123}\)I-metaiodobenzylguanidine become more readily available in the United States? Regarding management, how can we improve the treatment of patients with sporadic, familial, recurrent, and malignant pheochromocytoma? Can pheochromocytoma be prevented in genetically predisposed patients?

Some of the above questions may be answered after identification of the specific molecular changes responsible for pheochromocytoma and the mechanisms linking identified germline or somatic genetic alterations to expression of specific tumor-cell phenotypes and clinical features of disease. New techniques, such as complementary DNA microarray analysis and laser-capture microdissection, offer tremendous potential for tracing phenotypic differences in tumors to underlying differences in gene expression and ultimately to the mutations responsible for the tumor. Such findings may lead to improved understanding of mechanisms of tumorigenesis, variations in the rate of disease progression, metastatic potential, tendency to recurrence, metabolic and hemodynamic alterations, variations in sensitivity and specificity of diagnostic tests, and development of and predicted responsiveness to novel treatments. For example, knowledge about expression of specific antigens or proteins, such as membrane catecholamine transporters, could lead to improvements in tumor imaging methods. It could also facilitate novel “magic bullet” therapy by targeting radionuclides, cytotoxins, or vaccines to tumor cells. This may be important, not only for treatment of malignant pheochromocytoma but also for prevention of pheochromocytoma in at-risk patients.

To move advances in disease diagnosis and treatment from the bench to the bedside, rigorous scientific proof of clinical efficacy and economic factors must be considered. The relative lack of availability of \(^{123}\)I-metadiobenzylguanidine in the United States compared with other countries is one example of economic factors outweighing clinical benefits (85). Although pheochromocytoma is a rare tumor, its required consideration at a low pretest probability in large populations makes economic considerations important. To facilitate entry of assays of plasma metanephrines into the diagnostic mainstream, our assay methods are now available on line at www.catecholamine.org/labprocedures. Further advances, such as combining measurements of plasma metanephrines with more established diagnostic procedures (for example, the clonidine suppression test) offer further cost-effective potential for streamlining diagnostic decision making.

More generally, advances in the area of pheochromocytoma research and clinical practice can benefit from an interdisciplinary team approach, involving endocrinologists, clinical chemists, radiologists, nuclear medicine specialists, cardiologists, geneticists, pathologists, experts in basic molecular genetic analyses, and surgeons.

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Acknowledgment: The authors thank Drs. J.W.M. Lenders and B. Zbar for important contributions to the work presented at the Clinical Staff Conference.

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