Pheochromocytoma is a tumor of chromaffin cells that usually presents as hypertension. The tumor has potentially life-threatening consequences if it is not promptly diagnosed, located, and removed. Evidence of excessive production of catecholamines is essential for diagnosis of the tumor. Traditional tests have relied on measurements of the 24-hour urinary excretion of catecholamines (norepinephrine and epinephrine) or of the products of catecholamine metabolism (1-4).

Because of the common problems of incompleteness and inconvenience associated with 24-hour urine collections, clinicians have long sought a diagnostic test based on sampling of antecubital venous blood. Measurements of plasma catecholamines are useful in this respect (4, 5). However, patients with a pheochromocytoma can have plasma concentrations of catecholamines that fall within the range of those in patients with essential hypertension (4, 6) (that is, false-negative results). In addition, emotional distress or pathologic conditions other than pheochromocytoma (such as heart failure) can produce abnormally high catecholamine concentrations (7, 8) (that is, false-positive results). Glucagon stimulation and clonidine suppression testing can enhance the accuracy of plasma catecholamine determinations in the diagnosis of pheochromocytoma (9, 10). These tests, however, can still yield false-negative or false-positive results (9-11); they also require considerable time and effort. The search has continued for a simple, highly sensitive and specific blood test with which to confirm the presence of the tumor in patients with pheochromocytoma. We studied the diagnostic accuracy of tests for specific catecholamine metabolites for this purpose, notably the metanephrines—normetanephrine and metanephrine.

An understanding of why plasma metanephrines may be particularly useful for diagnosis of pheochromocytoma requires an understanding of catecholamine metabolism. Norepinephrine and epinephrine are first metabolized intraneuronally by deamination to dihydroxyphenylglycol or extraneuronally by O-methylation to the metanephrines (12). Because most dihydroxyphenylglycol is formed from norepinephrine leaking from neuronal stores and little is formed from circulating catecholamines (13, 14), plasma levels of this metabolite are relatively insensitive to the release of catecholamines into the circulation from a pheochromocytoma (6, 15). The formation of most methoxyhydroxyphenylglycol from dihydroxyphenylglycol (14) and the formation of most vanillylmandelic acid from methoxyhydroxyphenylglycol within the liver (16) explains

---

**Objective:** To examine whether tests for plasma metanephrines, the O-methylated metabolites of catecholamines, offer advantages for diagnosis of a pheochromocytoma over standard tests for plasma catecholamines or urinary metanephrines.

**Design:** Cross-sectional study.

**Setting:** 3 clinical specialist centers.

**Patients:** 52 patients with a pheochromocytoma; 67 normotensive persons and 51 patients with essential hypertension who provided reference values; and 23 patients with secondary hypertension and 50 patients with either heart failure or angina pectoris who served as comparison groups.

**Measurements:** Plasma concentrations of catecholamines (norepinephrine and epinephrine) and metanephrines (normetanephrine and metanephrine) were measured in all patients. The 24-hour urinary excretion of metanephrines was measured in 46 patients with pheochromocytoma.

**Results:** Pheochromocytomas were associated with increases in plasma concentrations of metanephrines that were greater and more consistent than those in plasma catecholamine concentrations. No patient with a pheochromocytoma had normal plasma concentrations of both normetanephrine and metanephrine. The sensitivity of these tests was 100% (52 of 52 patients [95% CI, 94% to 100%]), and the negative predictive value of normal plasma concentrations of metanephrines was 100% (162 of 162 patients). Tests for plasma catecholamines yielded eight false-negative results and a sensitivity of 85% (44 of 52 patients [CI, 72% to 93%]). The negative predictive value of normal plasma concentrations of catecholamines was 95% (156 of 164 patients). Tests for urinary metanephrines yielded five false-negative results and a sensitivity of 89% (41 of 46 patients [CI, 76% to 96%]). Because no statistical difference was noted in the number of false-positive results between tests for plasma metanephrines (15%) and tests for plasma catecholamines (18%), the specificities of the two tests did not differ.

**Conclusions:** Normal plasma concentrations of metanephrines exclude the diagnosis of pheochromocytoma, whereas normal plasma concentrations of catecholamines and normal urinary excretion of metanephrines do not. Tests for plasma metanephrines are more sensitive than tests for plasma catecholamines or urinary metanephrines for the diagnosis of pheochromocytoma.


From the National Institutes of Health, Bethesda, Maryland; St. Radboud University Hospital, Nijmegen, the Netherlands; and the University of Göteborg, Göteborg, Sweden. For current author addresses, see end of text.
why a test for vanillylmandelic acid is also a poorer marker for pheochromocytoma than other tests (17). In contrast, preferential metabolism of circulating catecholamines compared with neuronal catecholamines by extraneuronal pathways (14) suggests that the metanephrines—as extraneuronal metabolites—may provide good markers for release of catecholamines from a pheochromocytoma. Furthermore, substantial production of metanephrines within adrenal tissue (18) suggests that metanephrines may be produced within the tumor itself.

In humans, metanephrines are extensively sulfate-conjugated (18, 19). Assays of metanephrines in urine depend on measurements after deconjugation to free metanephrines (19) so that measurements represent the sum of free and conjugated metabolites (total metanephrines). In contrast, good sensitivity of the assay for plasma metanephrines (20) enables measurements of both free and total metanephrines.

We compared the sensitivity, specificity, and positive and negative predictive values of tests for plasma free and total metanephrines with those of tests for plasma catecholamines and urinary total metanephrines. Study participants included a relatively large sample of patients with pheochromocytoma, patients with essential hypertension or secondary hypertension from causes other than pheochromocytoma, and patients with either heart failure or angina pectoris in whom sympathetically mediated catecholamine release would be expected to be increased.

Methods

Patients

Fifty-two patients with a histologically proven pheochromocytoma were studied. Thirty patients were studied retrospectively, and 22 were studied before the final diagnosis was made. The pheochromocytoma was benign in 39 patients and malignant in 13. Sixty-seven healthy, normotensive persons and 51 patients with either heart failure or angina pectoris in whom sympathetically mediated catecholamine release would be expected to be increased were studied. No patients with heart failure and 15 with secondary hypertension, arterial blood was obtained through an indwelling arm arterial catheter. Blood samples were collected into precooled tubes containing heparin or EGTA and glucose and were centrifuged within 30 minutes to separate the plasma, which was stored frozen until assayed. All plasma catecholamine and urinary metanephrine assays were done within 2 weeks of sample collection. Seven of the 52 pheochromocytoma samples were assayed for plasma metanephrines after being stored at −80°C for more than 2 years (range, 2 to 8 years), whereas the remaining 45 samples were assayed within 2 years of collection (22 samples within 4 weeks). In 46 of the 52 patients with pheochromocytoma, a 24-hour urine collection was obtained, with 30 mL of 6-M hydrochloric acid used as a preservative.

Blood and Urine Samples

All patients refrained from ingesting methylxanthine-containing food products and from smoking after midnight on the day before blood sampling. Blood was collected from an indwelling catheter in an antecubital vein after the patients had rested supine for 20 minutes. In 39 patients with heart failure and 15 with secondary hypertension, arterial blood was obtained through an indwelling arm arterial catheter. Blood samples were collected into precooled tubes containing heparin or EGTA and glucose and were centrifuged within 30 minutes to separate the plasma, which was stored frozen until assayed. All plasma catecholamine and urinary metanephrine assays were done within 2 weeks of sample collection. Seven of the 52 pheochromocytoma samples were assayed for plasma metanephrines after being stored at −80°C for more than 2 years (range, 2 to 8 years), whereas the remaining 45 samples were assayed within 2 years of collection (22 samples within 4 weeks). In 46 of the 52 patients with pheochromocytoma, a 24-hour urine collection was obtained, with 30 mL of 6-M hydrochloric acid used as a preservative.

Analytic Methods

Plasma metanephrines were assayed at the National Institutes of Health (NIH) using liquid chromatography with electrochemical detection (20). Concentrations of total metanephrines (the sum of concentrations of free and sulfated metanephrines) were measured after incubation of 0.25 mL of plasma with 0.1 units of sulfatase (Sigma Chemical Company, St. Louis, Missouri) at 37°C for 30 minutes. The detection limits were 0.013 nmol/L for normetanephrine and 0.019 nmol/L for metanephrine. At a plasma normetanephrine concentration of 0.31 nmol/L and a metanephrine concentration of 0.21 nmol/L, the interassay coefficients of variation were 12.2% for normetanephrine and 11.2% for metanephrine. As previously reported (20), the presence of acetaminophen in samples of plasma can substantially interfere with measurements of plasma normetanephrine concentrations.

Therefore, this analgesic must not be used by patients for several days before blood samples are collected. No analytic interference of various other drugs with this assay has been shown (20).

Plasma catecholamines were assayed using liquid chromatography. Electrochemical detection was used for quantification at the NIH (21), and fluorometric detection was used at St. Radboud University Hospital, Nijmegen, the Netherlands (22). At the NIH, the detection limits were 0.006 nmol/L for norepinephrine and 0.010 nmol/L for epinephrine. At a plasma norepinephrine concentration of 2.4 nmol/L and an epinephrine concentration of 0.39 nmol/L, the interassay coefficients of variation were 6.5% for norepinephrine and 11.4% for epinephrine. At St. Radboud University Hospital, the detection limits for norepinephrine and epinephrine were 0.002 nmol/L and 0.003 nmol/L, respectively. At plasma concentrations of 1.02 nmol/L for norepinephrine and 0.15 nmol/L for epinephrine, interassay coefficients of variation were 9.5% for norepinephrine and 7.2% for epinephrine.

Urinary concentrations of metanephrines were measured according to a previously described method (23); the upper reference limit of the normal range for the 24-hour urinary output of metanephrines was 6.8 μmol/d.

Table 1. Patient Characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotension</th>
<th>Essential Hypertension</th>
<th>Secondary Hypertension</th>
<th>Heart Failure or Angina Pectoris</th>
<th>Pheochromocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>67</td>
<td>51</td>
<td>23</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Mean age ± SD (range), y</td>
<td>39 ± 12 (20–72)</td>
<td>43 ± 13 (16–69)</td>
<td>48 ± 14 (20–69)</td>
<td>57 ± 11 (34–81)</td>
<td>39 ± 13 (11–71)</td>
</tr>
<tr>
<td>Male/female, n/n</td>
<td>40/27</td>
<td>24/27</td>
<td>14/9</td>
<td>42/8</td>
<td>28/24</td>
</tr>
<tr>
<td>Study center (NIH/SR/SH), n/n/n</td>
<td>36/31/0</td>
<td>1/50/0</td>
<td>17/15</td>
<td>13/7/50</td>
<td>41/11/0</td>
</tr>
</tbody>
</table>

* NIH = National Institutes of Health; SH = Sahlgrens Hospital; SR = St. Radboud University Hospital.
Because plasma concentrations of catecholamines and metanephrines were not normally distributed, only medians and ranges are presented for these concentrations. Differences in plasma concentrations of metanephrines and catecholamines among patients with pheochromocytoma and other groups were tested using the Kruskal-Wallis test. We assessed relations among variables using the Spearman rank correlation coefficient.

Normal distributions of plasma concentrations of catecholamines and metanephrines were obtained after logarithmic transformation of the data. Thus, upper reference limits, defined as the 97.5th percentile, were determined after logarithmic transformation of individual values for the combined data from normotensive persons and those with essential hypertension (118 persons). The 97.5th percentiles were calculated from the antilogarithm of the mean plus 2 standard deviations of the transformed data. A false-negative result of a test for plasma metanephrines in a patient with pheochromocytoma was defined as plasma concentrations of both nor-metanephrines and metanephrines that were below their respective upper reference limits. Similarly, a false-negative result of a test for plasma catecholamines was defined as plasma concentrations of norepinephrine and epinephrine that were below their respective upper reference limits. A false-positive result of a test for plasma metanephrines was defined as a plasma concentration of either normetanephrine or metanephrine that was equal to or above the upper reference limits. Similarly, a false-positive result of a test for plasma catecholamines was defined as a plasma concentration of either norepinephrine or epinephrine that was equal to or greater than the upper reference limits. We calculated the sensitivity and specificity (with 95% CIs), pretest and post-test probabilities, and positive and negative predictive values for each analyte (24).

Differences in tumor-associated elevations in plasma catecholamine concentrations and free and total metanephrine concentrations were assessed from the fold-increases in plasma concentrations of compounds in patients with pheochromocytoma that were greater than median values in the normotension and essential hypertension reference group. We computed mean ± SE fold-increases after logarithmic transformation of individual fold-increases. We estimated differences among fold-increases by analysis of variance; post hoc tests were done with the Schef~ F-test.

Receiver-operating characteristic curves were constructed from the relation between the rates of true-positive and false-positive results (that is, sensitivity compared with 1 minus the specificity) for diagnosis of pheochromocytoma that are based on different upper reference limits for each analyte (25). These curves enabled us to compare the sensitivity and specificity of tests for plasma metanephrines for diagnosing pheochromocytoma with those of tests for plasma catecholamines, as a function of different upper reference limits for each analyte. The areas under the receiver-operating characteristic curves for plasma catecholamines and metanephrines were calculated as summary measures of the diagnostic power that were independent of upper reference limits. We calculated the difference between the two areas and tested them according to the method of Hanley and McNeil (26).

Results

Plasma Concentrations of Catecholamines and Free and Total Metanephrines

Plasma concentrations of free normetanephrine and metanephrine in the normotension and hypertension reference groups were not normally distributed until the data were logarithmically transformed (Figure 1). Ranges of plasma concentrations of normetanephrine and metanephrine were wider and the values were considerably higher \((P < 0.001)\) in patients with pheochromocytoma than in any other patient group (Table 2).

In each group, plasma concentrations of total metanephrines were much higher than concentrations of free metanephrines; only a small proportion (<7%) of the normetanephrine or metanephrine in plasma was in the free form (Table 2). Like the free metanephrines, ranges of plasma concentrations of total metanephrines were much wider and the values much higher \((P < 0.001)\) in patients with pheochromocytoma than in any other patient group. Similarly, ranges of plasma concentrations of norepinephrine and epinephrine were wider in patients with pheochromocytoma than in other groups, but only norepinephrine concentrations were consistently higher \((P < 0.001)\) in patients with pheochromocytoma than in other groups.

Accuracy of Tests for Plasma Metanephrines

The upper reference limits were 0.66 nmol/L for plasma normetanephrine and 0.30 nmol/L for metanephrine. Only 1 of the 52 patients with pheochromocytoma had a plasma concentration of normetanephrine within the normal range (Figure 2, top), that is, a false-negative result.
However, this patient (patient 42; Table 3) also had an elevated plasma metanephrine concentration. Thus, when both metabolites were considered in the diagnosis rather than plasma normetanephrine alone, the number of false-negative results was reduced from 1 to 0, yielding a sensitivity and negative predictive value of 100% (Table 4). In 29 of the 191 patients (15%) without pheochromocytoma, a test for plasma normetanephrine or metanephrine yielded false-positive results (Figure 2). Six of these 29 false-positive results were obtained in patients with renal artery stenosis or renal failure, and 16 were obtained in patients with heart failure.

Accuracy of Tests for Plasma Catecholamines

The upper reference limits were 3.00 nmol/L for normetanephrine and 0.54 nmol/L for epinephrine. In contrast to the one patient with pheochromocytoma and a false-negative result of the plasma normetanephrine test, 10 patients had false-negative plasma norepinephrine test results (Figure 2, top). Of these 10 patients, 2 had elevated plasma epinephrine concentrations (patients 32 and 34; Table 3); thus, the number of false-negative results was reduced from 10 to 8 when the diagnosis was based on plasma concentrations of both norepinephrine and epinephrine rather than on norepinephrine concentrations alone. This resulted in a sensitivity of 85% (Table 4). Tests of plasma catecholamines yielded false-positive results in 35 (18%) of the 191 patients without pheochromocytoma (Figure 2). In 19 of these 35 patients, results of tests for plasma metanephrines were also false-positive. Seven of these 35 false-positive results were obtained in patients with renal artery stenosis or renal failure, and 21 were obtained in patients with heart failure.

Accuracy of Tests for Urinary Metanephrines

Twenty-four-hour urine specimens were obtained from 46 of the 52 patients with pheochromocytoma and were not obtained from patients in any other group. The median urinary excretion rate of metanephrines in these patients was 24.2 μmol/d (range, 2.1 to 242 μmol/d). Use of an upper reference limit of 6.8 μmol/d for the urinary excretion of metanephrines in normotensive persons (23) yielded false-negative results in 5 of the 46 patients and a sensitivity of 89% (95% CI, 76% to 96%); all 5 patients had increased plasma concentrations of metanephrines, but only 3 had increased plasma concentrations of catecholamines. Creatinine excretion among the 5 patients with normal urinary excretion of metanephrine was within the normal range (1 to 2.5 g/d). Use of an upper reference limit of 9.5 μmol/d in hypertensive patients (4)
yielded 10 false-negative results and a sensitivity of 78% (CI, 64% to 89%).

Accuracy of Tests for Plasma Metanephrines Compared with Tests for Catecholamines

Tumor-associated elevations in plasma normetanephrine concentrations were 153% greater than those in plasma norepinephrine and 64% greater than those in plasma concentrations of total normetanephrine (Figure 3, top). Tumor-associated elevations in plasma metanephrine concentrations were 70% greater than those in epinephrine concentrations but did not differ from those in total metanephrine concentrations (Figure 3, bottom). Increases in plasma concentrations of total normetanephrine were 54% greater than increases in plasma concentrations of norepinephrine, whereas increases in total metanephrine concentrations were 46% greater than increases in epinephrine concentrations.

Among the 11 patients with phaeochromocytoma and equivocal results of tests for normetanephrine or norepinephrine (Table 3), 17 positive results were obtained for tests for metanephrines (normetanephrine, 10 results; metanephrine, 7 results); only 4 positive results were obtained for tests for catecholamines (norepinephrine, 1 result; epinephrine, 3 results). In 7 of these 11 patients, plasma normetanephrine or metanephrine concentrations were elevated more than three times the upper reference limits for metanephrines; no patients had elevations in plasma norepinephrine or epinephrine concentrations greater than three times the respective upper reference limits.

Receiver-operating characteristic curves, which show the relation between rates of true-positive and false-positive results at different decision thresholds (that is, at different upper reference limits of plasma concentrations of metanephrines and catecholamines), confirmed the superiority of tests for plasma metanephrines over tests for plasma catecholamines for the diagnosis of phaeochromocytoma, regardless of the reference limits used to define an abnormal test result (Figure 4, top). The area under the curve for plasma metanephrines \(0.977 \pm 0.015\) was greater than that for plasma catecholamines \(0.917 \pm 0.027\) \((P = 0.03)\).

The relation between pretest and post-test probabilities—estimated from the sensitivity and specificity values listed in Table 4—show that as the prevalence rate (that is, the pretest probabilities) increases, the post-test probabilities similarly increase for diagnoses that are based on plasma concentrations of metanephrines and catecholamines (Figure 4, bottom). The negative predictive value of tests for plasma metanephrines for the diagnosis of phaeochromocytoma remained constant at 100% for all prevalence rates, whereas the negative predictive value of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metanephrines</td>
<td>100 (52/52) (94 to 100)</td>
<td>85 (162/191) (79 to 90)</td>
<td>64 (52/81)</td>
<td>100 (162/162)</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>98 (42/43) (68 to 100)</td>
<td>82 (112/137) (74 to 88)</td>
<td>63 (42/67)</td>
<td>99 (112/113)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>85 (44/52) (72 to 93)</td>
<td>82 (156/191) (75 to 87)</td>
<td>56 (44/79)</td>
<td>95 (156/164)</td>
</tr>
</tbody>
</table>

* "Metanephrines" refers to free normetanephrine and metanephrine. "Total metanephrines" refers to sulfonated and free normetanephrine and metanephrine. The sensitivity of (total) metanephrines for diagnosis of phaeochromocytoma was calculated from patients with both a false-negative plasma (total) normetanephrine test result and a false-negative (total) metanephrine test result. The specificity of catecholamines was calculated from patients with both a false-negative plasma norepinephrine test result and a false-negative epinephrine test result. The specificity of metanephrines was calculated from patients with either a false-negative plasma (total) normetanephrine test result or a false-negative (total) metanephrine test result. The specificity of catecholamines was calculated from patients with either a false-negative plasma norepinephrine test result or a false-positive plasma epinephrine test result.
tests for plasma catecholamines decreased with increasing prevalence rates.

In terms of positive and negative predictive values, measurement of plasma concentrations of total normetanephrine and metanephrine provided no advantage over measurement of free metanephrine concentrations (Table 4). However, measurements of plasma concentrations of total metanephrines provided greater sensitivity for the diagnosis of pheochromocytoma than measurements of plasma concentrations of catecholamines.

Patient and Tumor Characteristics in Relation to Neurochemical Indices

Four patients with pheochromocytoma had von Hippel-Lindau disease, and six had multiple endocrine neoplasia. Two of the patients with von Hippel-Lindau disease had normal plasma concentrations of catecholamines but elevated plasma normetanephrine concentrations (patients 43 and 50; Table 3). One of these patients was asymptomatic; initial testing was done after an adrenal mass was noted during computed tomography for an unrelated condition. In this patient, an elevated plasma normetanephrine concentration provided the only other indication for a tumor; results of all other neurochemical tests (those for plasma catecholamines, urinary metanephrines, clonidine suppression, and glucagon stimulation) were negative. Because of these negative results and for personal reasons, the patient did not have surgery until 11 months later. At this time, she became symptomatic and had elevated plasma concentrations of catecholamines and urinary metanephrines in addition to consistently elevated plasma concentrations of metanephrines. All patients with multiple endocrine neoplasia were symptomatic, but two had normal plasma concentrations of catecholamines (patients 48 and 49; Table 3). Both these patients had grossly elevated plasma concentrations of metanephrines.

In only one patient (patient 42; Table 3) did plasma concentrations of metanephrines provide a tumor marker that was inferior to that provided by plasma catecholamine concentrations. This patient was unusual, presenting with Cushing disease secondary to an adrenocorticotropicin-secreting pheochromocytoma.

Thirty-two pheochromocytomas were located in the adrenal glands, and 19 were located at extra-adrenal sites. Patients with the adrenal tumors had higher plasma concentrations of metanephrine than patients with extra-adrenal tumors (0.61 nmol/L compared with 0.27 nmol/L; \(P = 0.03\)). Similarly, plasma concentrations of epinephrine were higher in patients with adrenal tumors than in those with extra-adrenal tumors (0.34 nmol/L compared with 0.14 nmol/L; \(P = 0.01\)). In contrast, plasma concentrations of norepinephrine were higher in patients with extra-adrenal tumors (22.3 nmol/L compared with 8.40 nmol/L; \(P = 0.009\)). Plasma normetanephrine concentrations did not differ among patients with adrenal and extra-adrenal tumors (5.83 nmol/L compared with 5.44 nmol/L; \(P = 0.30\)).

We found strong positive relations between the size of the tumor and plasma concentrations of normetanephrine (\(r = 0.61; P < 0.001\)), plasma concentrations of metanephrine (\(r = 0.45; P = 0.007\)), and urinary excretion of metanephrines (\(r = 0.64; P < 0.001\)). No association was seen between tumor size and plasma concentrations of norepinephrine (\(r = 0.12; P = 0.48\)) or epinephrine (\(r = 0.14; P = 0.42\)).

Discussion

Because a pheochromocytoma secretes catecholamines directly into the circulation, any of several means to detect the tumor by assays of plasma or urinary catecholamines and their metabolites should theoretically prove adequate. However, the occurrence of false-nega-
The relation between pretest probability (that is, prevalence) and post-test probability shows the effect of prevalence of pheochromocytoma on positive predictive values for given test results of plasma metanephrines and catecholamines. Curves were constructed from estimates of the true-positive (sensitivity) and false-positive (1 - specificity) rates obtained using upper reference limits determined from the mean plus 1, 1.5, 2.0, 2.5, 3.0, or 3.5 SDs. The different upper reference limits (nmol/L) for plasma catecholamines and metanephrines are tabulated below:

<table>
<thead>
<tr>
<th></th>
<th>Catecholamines</th>
<th>Metanephrines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Norepinephrine</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>1.0 SD</td>
<td>1.93</td>
<td>0.24</td>
</tr>
<tr>
<td>1.5 SD</td>
<td>2.41</td>
<td>0.36</td>
</tr>
<tr>
<td>2.0 SD</td>
<td>3.00</td>
<td>0.54</td>
</tr>
<tr>
<td>2.5 SD</td>
<td>3.75</td>
<td>0.79</td>
</tr>
<tr>
<td>3.0 SD</td>
<td>4.66</td>
<td>1.18</td>
</tr>
<tr>
<td>3.5 SD</td>
<td>5.85</td>
<td>1.76</td>
</tr>
</tbody>
</table>

The relation between pretest probability (that is, prevalence) and post-test probability shows the effect of prevalence of pheochromocytoma on positive (upper curve) and negative (lower curve) predictive values for given test results of plasma metanephrines (○) and plasma catecholamines (●).

Figure 4. Receiver-operating characteristic curves (top) and the relation between pretest probability (that is, prevalence) and post-test probability (bottom). Receiver-operating characteristic curves show the relative changes in rates of true-positive and false-positive results for the diagnosis of pheochromocytoma as a function of different upper reference limits for plasma metanephrines (○) and catecholamines (●). Curves were constructed from estimates of the true-positive (sensitivity) and false-positive (1 - specificity) rates obtained using upper reference limits determined from the mean plus 1, 1.5, 2.0, 2.5, 3.0, or 3.5 SDs. The different upper reference limits (nmol/L) for plasma catecholamines and metanephrines are tabulated below:

Because no test can be completely sensitive, one may ask what our findings of 100% sensitivity and 100% negative predictive value for tests for plasma metanephrines actually mean and in which clinical settings they would apply. In our study, 100% sensitivity resulted from the consideration of normotensive persons and those with essential hypertension as a single reference group. When we considered only persons with essential hypertension as the reference group, one false-negative result occurred, and the sensitivity decreased to 98% (CI, 90% to 100%). However, as shown by the receiver-operating characteristic curves, the sensitivity of tests for metanephrines for the diagnosis of pheochromocytoma remained higher than that of tests for catecholamines, regardless of changes in the upper reference limits. For a disease such as pheochromocytoma, in which a missed diagnosis could have life-threatening consequences for a patient, the diagnostic test should exclude false-negative results as efficiently as possible. The results show that measurements of plasma concentrations of metanephrines provide a method of excluding the presence of a tumor that is superior to measurements of plasma catecholamines.

Although pheochromocytoma may be excluded by normal plasma concentrations of metanephrines, an abnormal test result does not always positively confirm the presence of a tumor. We found elevated plasma concentrations of metanephrines in a few patients with secondary hypertension or cardiac failure. Elevated concentrations of total metanephrines have also been reported in patients with renal failure (27). When plasma concentrations of metanephrines are increased in the presence of either heart failure or kidney disease, additional diagnostic techniques, including imaging studies, are necessary.

Positive and negative predictive values depend on the prevalence or pretest probability of a disease. The predictive values reported here correspond to a 21% prevalence rate of pheochromocytoma—a much higher rate than that in the overall population of patients with hypertension and probably higher than the rate in the hypertensive patients referred to most specialist centers. The negative predictive value of normal plasma concentrations of metanephrines was superior to that of normal plasma catecholamines regardless of prevalence rates (Figure 3, bottom), a disparity that increased with increasing prevalence. Even at the highest prevalence rates, normal plasma concentrations of metanephrines almost exclude diagnosis of pheochromocytoma. This means that in a general practice setting or in patients in whom pheochromocytoma is strongly suspected (for example, patients at a referral center who have hypertension, headache, and adrenal mass), normal plasma concentrations of metanephrines may exclude the diagnosis of pheochromocytoma.
concentrations. It is the free, not the conjugated, meta-

In conclusion, normal plasma concentrations of meta-

patients must explain this observation is that the assay technique used (23) is a

metanephrines rules out this explanation. Another possi-

108 15 July 1995 •

(34); however, only concentrations of tests for plasma total metanephrines for the diagnosis of aauLcai a

of pheochromocytoma that has been shown previously

mephrines excludes a diagnosis of pheochromocytoma, and

urinary metanephrines be less sensitive than a test for plasma concentrations of the same compounds? One ex-

planation is that a small percentage of patients in any

large-scale study would be expected to provide an incomplete urine collection; this would yield false-negative re-

results. However, the normal creatinine excretion in the patients with false-negative results of tests for urinary

metanephrines rules out this explanation. Another possible

explanation is that the assay technique used (23) is a
colorimetric method. An assay for urinary metanephrines

that uses the high-performance liquid chromatography

technique might be superior to the colorimetric tech-

nique. Finally, individual differences in the renal conver-
sion of metanephrines to methoxyhydroxyphenyglycol and

vanillylmandelic acid might be responsible for some of the false-negative results.

Plasma catecholamines were assayed at two centers,

whereas plasma metanephrines were assayed at one cen-
ter. The involvement of different laboratories in our study

could have resulted in wider distributions and higher up-

per reference limits for plasma catecholamines than might

have been obtained had measurements been done in one

laboratory. This in turn could have resulted in more false-
negative results for plasma catecholamines determined in
two laboratories than would have occurred in one. How-
ever, separate analysis of the data for the two centers

indicated a 14.6% rate of false-negative results for cat-

eholamines assayed at St. Radboud University Hospital

compared with 18.2% for those assayed at NH. In addi-
tion, the reference limits of 3.00 nmol/L for norepineph-

rine and 0.54 nmol/L for epinephrine obtained in our

study were substantially lower than those of other studies

(4, 6, 10). Because many of the patients with equivocal
catecholamine test results had plasma concentrations of
catecholamines well below the upper reference limits, a

substantial reduction in these limits would be required to

influence the results.

In conclusion, normal plasma concentrations of meta-
nephrines exclude a diagnosis of pheochromocytoma, and

normal plasma catecholamines or urinary metanephrines
do not. Tests for plasma metanephrines are more sensi-
tive than tests for plasma catecholamines or urinary meta-
nephrines for the diagnosis of pheochromocytoma.

Acknowledgments: The authors thank Dr. Irwin J. Kopin for his support
and critical review of the manuscript and Dr. André Verbeek for his
assistance in the statistical analysis.

Requests for Reprints: Jacques W.M. Lenders, MD, Division of General
Internal Medicine, Department of Internal Medicine, St. Radboud Uni-
versity Hospital, Geert Grooteplein Zuid 8, 6525 GA, Nijmegen, the
Netherlands.
Current Author Addresses: Drs. Lenders, Jacobs, and Thien: Division of General Internal Medicine, Department of Internal Medicine, St. Radboud University Hospital, Geert Grooteplein Zuid 8, 6525 GA, Nijmegen, the Netherlands. Dr. Kloppenborg: Division of Endocrinology, Department of Internal Medicine, St. Radboud University Hospital, Geert Grooteplein Zuid 8, 6525 GA, Nijmegen, the Netherlands. Mr. Willemsen: Laboratory of Experimental and Chemical Endocrinology, St. Radboud University Hospital, Geert Grooteplein Zuid 8, 6525 HB, Nijmegen, the Netherlands. Drs. Eisenhofer and Goldstein: Clinical Neuroscience Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room SN214, Bethesda, MD 20892. Dr. Keiser: Hypertension-Endocrine Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Building 10, Room 8C103, Bethesda, MD 20892. Dr. Friberg: Department of Heart and Lung Disease, Division of Clinical Physiology, Sahlgrens Hospital, University of Göteborg, Göteborg, Sweden.

References