

# Endocrinology

## ROUNDS™

February 2004  
Volume 4, Issue 2

AS PRESENTED IN THE ROUNDS  
OF THE DIVISION OF  
ENDOCRINOLOGY AND METABOLISM,  
ST. MICHAEL'S HOSPITAL

[www.endocrinologyrounds.ca](http://www.endocrinologyrounds.ca)

## Challenges in Diagnosing Pheochromocytoma

BY JEANNETTE GOGUEN, MD, MED, FRCPC

A pheochromocytoma is a tumour of chromaffin cells of the sympathetic nervous system. Due to its propensity to produce and secrete catecholamines, this disease usually presents with hypertension and other symptoms of catecholamine excess. Although pheochromocytomas are very rare, a tragic outcome can result if the condition is not diagnosed and treated appropriately since fatal cardiovascular events can occur. Furthermore, 10%-13% of pheochromocytomas are malignant. This issue of *Endocrinology Rounds* will focus on the challenges in making an accurate diagnosis of pheochromocytoma, review several recent studies related to its diagnosis, and suggest an approach to minimize the risk of making an incorrect diagnosis (trying to reduce both false positive and false negative diagnoses).

Pheochromocytoma is easy to diagnose when a patient presents with episodes of the classic triad of headache, palpitations, and perspiration, has hypertension, and elevated urinary levels of both catecholamines (Figure 1) and their metabolic byproducts, metanephrines (Figure 2). It is more challenging, however, when the presentation is non-classic and urinary tests are positive. How can you discriminate true positives from the false positives? Measurements of urinary vanillylmandelic acid (VMA) and total metanephrines using spectrophotometry have been available for decades and high performance liquid chromatography (HPLC) is now available. The virtue of HPLC is that it separates out the sub-fractions of catecholamines or metanephrines (eg, metanephrine and normetanephrine) and is used for testing urinary fractionated metanephrines, plasma catecholamines, urine catecholamines, and plasma free metanephrines (o-methylated metabolites of catecholamines). The assay for plasma free metanephrines is technically difficult because its plasma concentrations are 3 orders of magnitude lower than in urine. Several recent studies in large numbers of patients have assessed the usefulness of both the older and newer tests and also examined approaches to dealing with the vexing problem of false positives that occurs whenever there is testing of individuals with a low pre-test probability of a disease, especially when the test specificity is not very high.

Imaging tests are also available, including computed tomography (CT), magnetic resonance imaging (MRI), <sup>131</sup>I-metaiodobenzylguanidine (<sup>131</sup>I-MIBG), and positron emission tomography (PET) scanning, which classically have been used to *locate* a tumour whose existence is inferred based on abnormal biochemical testing. Imaging tests can also be used for their diagnostic value.

### The challenge

In trying to identify the presence of a rare life-threatening tumour with many atypical presentations, the need for high sensitivity (so that a case is not missed) must be balanced with the need for high specificity (to reduce the number of false positives).

### The ideal

You are following a patient that you have identified as being at risk for pheochromocytoma (Table 1). You are aware that these tumours can secrete different proportions of norepinephrine, epinephrine, and metabolites (the metanephrines: normetanephrine and



Leading with Innovation  
Serving with Compassion

**ST. MICHAEL'S HOSPITAL**

A teaching hospital affiliated with the University of Toronto



### Members of the Division of Endocrinology and Metabolism at St. Michael's Hospital

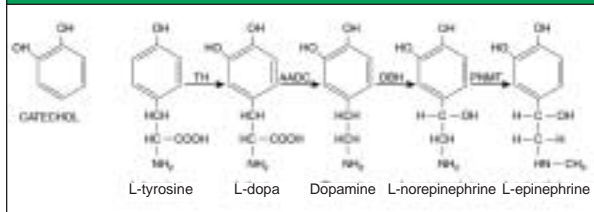
LAWRENCE LETTER, MD (HEAD)  
EDITOR, *ENDOCRINOLOGY ROUNDS*

GILLIAN BOOTH, MD  
ALICE CHENG, MD  
PHILIP CONNELLY, PhD  
CHRISTINE DERZKO, MD  
JEANNETTE GOGUEN, MD  
AMIR HANNA, MD  
SOPHIE JAMAL, MD, PhD  
DAVID JENKINS, MD, PhD  
ROBERT JOSSE, MD  
TIM MURRAY, MD  
DOMINIC NG, PhD, MD  
ROBERT PATTEN, MD  
LETICIA RAO, PhD  
WILLIAM SINGER, MD  
ROBERT VOLPE, MD  
VLAD VUKSAN, PhD  
QINGHUA WANG, MD, PhD  
TOM WOLEVER, MD, PhD  
MINNA WOO, MD, PhD  
ROBERT ZEMAN, MD

**St. Michael's Hospital**  
6121-61 Queen St. E.  
Toronto, Ont. M5C 2T2  
Fax: (416) 867-3696

The opinions expressed in this publication do not necessarily represent those of the Division of Endocrinology and Metabolism, St. Michael's Hospital, the University of Toronto, the educational sponsor, or the publisher, but rather are those of the author based on the available scientific literature. The author has been required to disclose any potential conflicts of interest relative to the content of this publication. *Endocrinology Rounds* is made possible by an unrestricted educational grant.

**Figure 1: Biosynthetic pathways for catecholamines**



Reprinted with permission from: Larsen PR, et al. *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: Saunders; 2003. Copyright: Elsevier Science USA

metanephrine) and that the incidence of adrenal incidentalomas is relatively high (in individuals >50 years, the prevalence is 3%-7%), so you want to confirm the diagnosis with biochemical testing, if possible, before going on to imaging. Which tests should you order?

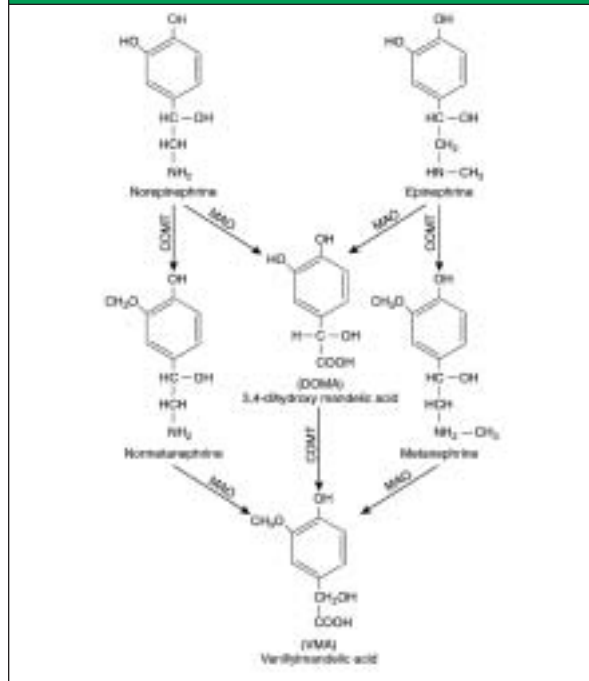
You search the literature and identify a study that was performed in patients similar to your own. In addition to the test being studied, a gold standard test was universally applied to identify all the subjects with the disease. The test itself is safe, available, and affordable, plus it has high sensitivity and specificity, and the results have been confirmed in at least one other study. The likelihood ratios have been calculated (Table 2). The positive likelihood ratio – LR(+) – is the ratio of the rate of true positives divided by the rate of false positives [LR(+) = sensitivity/(1-specificity)].

You perform the test on your patient, first ensuring that all potentially interfering medications have been discontinued. The test is positive. Knowing the pre-test probability (Table 1), the likelihood ratio can now be used to calculate the post-test probability. It is high, so you proceed with imaging to localize the tumour and begin definitive treatment.

### The reality: a literature review

Over the past 2 years, several papers (with large sample sizes), editorials, and reviews have been published that shed light on how best to diagnose pheochromocytoma. Given that a perfect test with 100% sensitivity and 100% specificity does not exist, major tension remains about whether to maximize *sensitivity* or *specificity*. More specifically, there has been a great deal of debate regarding the use of plasma metanephrines for *all* suspected patients (recommended by Eisenhofer at the National Institutes of Health [NIH], which would favour sensitivity), versus 24-hour urine catecholamines and metanephrines in patients with a low pre-test probability of pheochromocytoma (recommended by Young at the Mayo Clinic, which would favour specificity). Several papers have been recently published by these two groups that examined large numbers of subjects who were screened on the basis of clinical suspicion of pheochromocytoma. These papers attempted to determine the best test or combination of tests for diagnosing pheochromocytoma. Unfortunately, in Canada, only urine testing is currently available. Nonetheless, it is valuable to examine these recent studies as they provide useful information about urine testing as well.

**Figure 2: Catabolism of catecholamines**



Reprinted with permission from: Larsen PR, et al. *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: Saunders; 2003. Copyright: Elsevier Science USA

Lenders et al<sup>1</sup> examined results from 1003 patients investigated at 4 referral centres over a 7-year period. Pheochromocytoma was confirmed in 214 (76 hereditary and 138 sporadic), excluded in 644, and the diagnosis was not determined in 145. Therefore, 25% of the subjects screened, in whom the presence or absence of disease could be confirmed, had a pheochromocytoma. The performance of plasma free metanephrines was compared to the performance of urinary total metanephrines, urinary catecholamines, plasma catecholamines, and urinary fractionated metanephrines. The results revealed that the sensitivity and specificity was highest for plasma free metanephrines (97% and 96%, respectively, in hereditary screening compared to 100% sensitivity and 80% specificity in sporadic cases). Using a combination of tests did not improve the diagnostic yield over measuring plasma free metanephrines alone. This group recommends using the most sensitive test available (plasma free metanephrines) and then, patients with borderline positive results must be sorted out as true or false positives.

The major concern about Lenders' study is that a higher proportion of patients were screened due to the presence of hereditary disease than would occur in most clinical settings. As described above, compared to sporadic cases in patients screened for hereditary reasons, plasma free metanephrines had a much higher specificity. While the authors did separate out the data for the two populations (hereditary versus sporadic) to report sensitivity and specificity, they combined both groups for the receiver operator characteristic curves. This approach resulted in the plasma free metanephrine test appearing to perform better than it would in a practice with fewer familial

Table 1: Presentations of pheochromocytoma and prevalence of disease (“pre-test probability”)	
Presentation	Estimated prevalence of a pheochromocytoma in patients with this presentation
Severe drug-resistant or paroxysmal hypertension <sup>9</sup>	0.5-1%
Incidental adrenal mass (asymptomatic) <sup>10</sup> – Imaging characteristics of tumour can add more information	4%
Familial syndromes <sup>11</sup> – MEN 2 A + B – Von Hippel-Lindau – Neurofibromatosis type 1 – Mutations in succinate dehydrogenase genes (SDHB and SDHD)	MEN 2: 50% vonHL: 25% NF-1: 1%
Prior personal history of pheochromocytoma <sup>12</sup>	10% (8% at 5 years, 20% at 10 years post-surgery)

patients. Also, the proportion of patients who actually had the disease was very high, suggesting that the population was already a highly selected one and is, therefore, likely to be different from that in most centres. All the plasma free metanephrine testing was done through one laboratory (the NIH). There is significant concern regarding the practicality of obtaining this test as it is very technically demanding to set up the assay.<sup>2</sup> Plasma free metanephrine tests are not yet available in Canada.

Subsequently, Sawka et al<sup>3</sup> published a retrospective study with a more limited sample size that was composed of 349 consecutive outpatients screened for pheochromocytoma. Of these, 33 had pheochromocytoma and 25% of the 33 had a familial syndrome. Overall, 8.6% of the subjects had a pheochromocytoma, although some may have been missed given that patients were not observed for 2 years to be certain they were disease-free (unlike Lenders<sup>1</sup>). Sawka’s results with plasma free metanephrine testing (97% sensitivity and 85% specificity) were very similar to Lenders et al.<sup>1</sup> This study thus confirms the high sensitivity of plasma free metanephrines in an independent laboratory and in another group of patients. In addition, Sawka was able to obtain a 90% sensitivity and 98% specificity with urine testing by combining urine total metanephrines and urine catecholamines (epinephrine and norepinephrine).<sup>3</sup> For the urine test to be considered positive, only 1 of these 3 components needed to be elevated. Normally, combining tests and requiring only one to be positive for an overall positive test means that sensitivity will be higher than in individual tests, but specificity will fall. Here, they achieved high specificity by raising the cut-point to twice the 95th percentile (other laboratories use the 95th percentile). This also reduced the overall sensitivity. Sawka et al argued that in high-risk patients, a plasma meta-

Table 2: Test characteristics of biochemical and imaging tests:					
Test	Sensitivity	Specificity	LR (+)	LR (-)	Caveats
Plasma-free metanephrine <sup>1,3</sup>	97%	85%	6.3	0.04 <sup>3</sup>	Results for sporadic tumours (even better for familial tumours)
	100%	80%	5.0	0 <sup>1</sup>	
Urine catecholamines + metanephrines <sup>3</sup>	90%	98%	58.9	0.10	Used cutoff of twice the 95th percentile
Urine fractionated metanephrines <sup>1</sup>	100%	45%	1.8	0	
CT scan <sup>7</sup>	95%	≈70%	3	0.07	For adrenal tumours >1 cm
MRI <sup>7</sup>	≈100%	≈70%	3	0.05	For adrenal tumours >1 cm
	≈70% for “lightbulb” sign: hyperintense on T2 weighted image <sup>6</sup>	?	2.3		
<sup>131</sup> I-MIBG <sup>7</sup>	80%	95%-100%	16	0.2	
<sup>123</sup> I-MIBG <sup>7</sup>	90%	95%-100%	18	0.1	

LR = likelihood ratio

nephrine test should be performed; however, in low-risk patients, the combination of urine tests should be performed first because they have a higher specificity, thus reducing the number of false positives.

To address the issue of small sample size in the paper by Sawka, Kudva et al<sup>4</sup> (from the same group at the Mayo Clinic) subsequently published an overview of all of the patients, adding historical data in a case-control design. Pheochromocytomas were confirmed histologically in 147 patients; of these, 75% had sustained hypertension, 78% had paroxysmal symptoms, and 3% were normotensive and asymptomatic. These patients were compared to 881 subjects shown subsequently *not* to have pheochromocytomas who had been evaluated in 1995. The final results produced the same conclusions as the earlier paper and, in the discussion, Kudva remained committed to using urine testing and not the plasma free metanephrine test in low-risk patients.

Eisenhofer et al<sup>5</sup> studied an approach to deal with false positives generated by the very sensitive, but less specific, plasma free metanephrine test. He found the following criteria to be predictive of pheochromocytoma in patients with intermediate plasma free metanephrine results: an increased ratio of metanephrine to epinephrine; or normetanephrine to norepinephrine; or use of the clonidine suppression test to see if normetanephrine is suppressible.

In this study, 16 of 48 patients with pheochromocytoma developed suppressed norepinephrine (= false

negative), but only 2 of 48 patients developed suppressed normetanephrine (= false negative). Therefore, the clonidine suppression test (which was suggested as the solution to the false positive issue by Eisenhofer) has a high incidence of false negatives in the way it is usually done. The substitution of normetanephrine for noradrenaline in the clonidine suppression test results in a reasonable sensitivity. These results need to be confirmed in a separate group of patients.

Imaging studies can also be used to diagnose pheochromocytoma. Ideally, the diagnosis is made biochemically and imaging is used to locate the tumour. Concerns with the use of imaging in the diagnostic approach include the following:

- any adrenal lesion seen could be an incidentaloma (cortical non-secreting adenoma)
- imaging is expensive and often involves radiation exposure
- CT and MRI imaging tend to be sensitive, but not specific
- the lesion may be extra-adrenal and missed by imaging.

However, given that no biochemical test is presently available that effectively deals with potential false positive tests, the alternative is to use imaging studies. Current readily available imaging modalities include CT, MRI, and the <sup>131</sup>I-MIBG scan. Table 2 shows the sensitivities and specificities associated with each test. Tumour imaging characteristics can be very helpful. Suspicious lesions are typically heterogeneous, isodense with liver, and may be hemorrhagic or have cystic components. They are generally vascular and are therefore enhanced with CT. On MRI, the tumour has a very intense “light-bulb” appearance on T2-weighted imaging (approximately 70% sensitivity for this appearance).<sup>6</sup> In contrast, an adrenal cortical adenoma will appear homogeneous and round with a smooth contour and a low density (<10 Hounsfield units) on non-contrast CT. There is limited CT enhancement with contrast.

Reviews by Manger<sup>7</sup> and Ilias<sup>13</sup> discuss <sup>123</sup>I-MIBG scanning and the use of PET scanning with 6-[<sup>18</sup>F]fluorodopamine. These latter 2 agents are much more sensitive than the traditional <sup>131</sup>I-MIBG scan which, while highly specific, suffers from low sensitivity. It is important to be aware that certain medications can interfere with MIBG scanning.<sup>7</sup>

## Issues identified

**Pre-test probability:** Often the pretest probability (the prevalence of pheochromocytoma in patients with a given presentation) is unknown and, therefore, can only be estimated (Table 1). Therefore, even if we know the characteristics of the test, the post-test probability of having the disease can only be estimated. Furthermore, since there are many

presentations of pheochromocytoma, it is impossible to know the pre-test probability for each presentation. Further studies are required to improve our ability to determine this.

**Where do you place the cut-point?** Finding the right balance between sensitivity and specificity can be very difficult. Because of the novelty of diagnosing a pheochromocytoma (and the potential for adverse consequences if the diagnosis is missed), doctors are likely to screen for pheochromocytoma in patients with a low pretest probability of having this illness. This results in many false positives. One can alter the parameters of specificity and sensitivity by raising or lowering the test cut-point (ie, the value set to differentiate between a normal and abnormal test result). Changing the cut-point will always result in one parameter improving at the expense of the other; for instance, if one opts for a higher specificity, sensitivity will fall. Despite the concerns raised by Young’s group at the Mayo Clinic,<sup>3,4</sup> the need for high sensitivity remains the primary goal in a screening test, especially for a disease with a natural history that has a high mortality such as pheochromocytoma. If the test is negative, the disease can be effectively ruled-out (see caveat in the next section below). If the test is strongly positive, the likelihood ratio will be high for that cut-point and the person can be said to have a pheochromocytoma. Young’s group<sup>3,4</sup> has increased the cut-point to twice the 95<sup>th</sup> percentile (upper limit of normal) for urinary catecholamines and metanephrines, thus raising the specificity and reducing the sensitivity. Meanwhile, Eisenhofer’s group accepts the high false positive rate of plasma free metanephrine and goes on to further testing.<sup>5</sup>

**Variation in biochemical test results over time (the “moving target”):** Unlike most other disease states where the tested variable remains constant, the secretion of catecholamines and their products by a pheochromocytoma can be intermittent, leading to false negatives if the patient is studied when asymptomatic. If the tests are negative and there is a high index of suspicion, testing should be repeated when symptoms are present. There appears to be no role for performing a glucagon or histamine challenge as these tests were negative in 542 of 542 patients with suspected false negative baseline tests at the Mayo Clinic.<sup>4</sup>

If tests are positive and it is decided to repeat the test to rule-out a false positive, a subsequent negative test may be misleading because catecholamine secretion may be episodic. Subsequent testing may then be false negative because the tumour is not secreting catecholamines at that time. It also can be misleading because, if we only repeat tests on patients who are positive, there is a greater chance of finding lower results the next time due to chance alone.

**Effect of drugs and acute severe illnesses:** False positives are possible due to drugs that affect the assays. Also, many acute, severe conditions can cause falsely elevated catecholamines (myocardial infarction, ICU setting) in patients where that very condition led to a suspicion of pheochromocytoma.<sup>5</sup>

**Lack of a diagnostic “gold standard” test:** Currently, the only way to confirm whether or not a patient has a pheochromocytoma is with pathology from surgery. In studies, pheochromocytoma cannot be ruled-out in patients called “normals” unless they have been followed for a long time.

**Availability of testing:** Some newer tests are not yet available in Canada (plasma free metanephrines, <sup>123</sup>I-MIBG scan).

**How to interpret multiple test results:** Multiple biochemical tests are customarily done when evaluating a patient for a pheochromocytoma. It is difficult to know which results to favour if some are positive and some negative. Should mixed test results affect our suspicion of pheochromocytoma? For example, urine fractionated metanephrines measure metanephrine and normetanephrine. The test is considered positive if either one (or both) is positive. Measuring individual components will raise the sensitivity and reduce the specificity compared to a test that measures just the combination of the 2 compounds. In contrast, Pauker<sup>8</sup> suggests that if multiple compounds are measured and if epinephrine, norepinephrine, and metanephrine levels are all elevated, the patient is much more likely to have a pheochromocytoma than if only one of the tests is elevated. He suggests that a new likelihood ratio should be calculated that is the product of all of the individual test likelihood ratios.

Pauker’s approach makes two assumptions that do not necessarily hold up in the diagnosis of pheochromocytoma. First, that the different tests are independent of each other, which is unlikely given that some are metabolites of others. Second, that each test has the same likelihood of being present in every patient. This is not true as patients with pheochromocytoma produce different patterns of catecholamines and their metabolites; (eg, some tumours produce only norepinephrine, others only epinephrine, and some tumours produce both). One way to rectify the 2 approaches is to use one likelihood ratio for the biochemistry tests in total,<sup>3,4</sup> and multiply its likelihood ratio by that of any imaging test done, as biochemistry and imaging would be truly independent tests, both of which should be positive in the patient with pheochromocytoma.

### **A suggested approach (when plasma free metanephrine tests are unavailable):**

1. Decide pre-test probability based on history and physical examination (Table 1).

2. Conduct 24-hour urine total metanephrines and catecholamines testing, with urine creatinine measurement to ensure complete collection. Plasma catecholamines are not readily available and do not perform better than urine catecholamines. Urine fractionated metanephrines had very high sensitivity, but low specificity (45%) in the Lenders study.<sup>1</sup>

a. Ensure that the patient is not taking contaminating drugs (including over-the-counter medications) and is not acutely ill. Also, the following can result in false positives for some assays: caffeine and decaffeinated beverages, nicotine, tricyclic antidepressants, antipsychotics, levodopa, drugs containing catecholamines, ethanol, withdrawal from clonidine, phenoxybenzamine, acetaminophen, labetalol, sotalol, buspirone, calcium channel blockers, etc.<sup>4</sup>

b. Examine the patient population used in studies where test characteristics are calculated and decide if they are similar to your own; ie, both of the large studies above had a fairly high percentage of patients with hereditary syndromes, which increases the specificity of the tests. As well, in Lenders study,<sup>1</sup> in particular, a high percentage of screened patients actually had pheochromocytoma.

c. Look at the cut-point your laboratory is using and decide if you want to go with the higher cut-point (twice the upper limit of normal) used in the Mayo group<sup>3,5</sup> to improve specificity at the expense of sensitivity. The likelihood ratios can be used to calculate the post-test probability of pheochromocytoma (Table 2).

3. If the tests are all negative, repeat during symptoms and, if still negative, the disease is ruled out. If the test is strongly positive, the patient likely has pheochromocytoma; therefore, proceed to imaging to localize the tumour.

4. A false positive test should be *suspected* in the following instances when there is:

- only 1 abnormal biochemistry test in a panel of tests
- identification of possible contaminating substances
- intermediate elevation (<2-fold above the upper limit of normal)<sup>3,5</sup>
- a low pre-test probability (eg, if the pre-test probability is 1% and the specificity of the test is 85%, there will be 14 false positive tests for every 1 true positive test)
- a result that is not elevated on repeat testing
- imaging that is not typical for a pheochromocytoma (eg, low Hounsfield units on CT without contrast, the MRI T2 weighted image is not hyperintense)

5. What can be done for a suspected false positive test?

If you suspect a false positive test, you can repeat the test, but a normal value does not necessarily rule out a pheochromocytoma (see #3 above). For almost all patients, proceed to imaging tests for

diagnosis, as well as localization. The caveat with imaging is that an incidentaloma (non-pheochromocytoma) may be identified. If there is still doubt following biochemical testing and MRI or CT, then an <sup>131</sup>I-MIBG scan should be performed; it will be helpful if it is positive. Further testing with venous sampling and PET scanning (if available) may be required to sort out these lesions when the <sup>131</sup>I-MIBG scan is negative. The clonidine suppression test of plasma catecholamines is only helpful if plasma catecholamine testing is available and if catecholamines are not suppressed, it confirms a pheochromocytoma.

## Summary

For all of the reasons outlined in this article, the diagnosis of a pheochromocytoma can be challenging in the subset of patients who do not clearly have the disease. Biochemical testing is becoming more sophisticated but, until new methodologies are widely available, we need to understand the strengths and weaknesses of current tests and to balance optimizing *sensitivity* with optimizing *specificity*. Patients who fall into the "grey zone," where false-positive tests are suspected, will require imaging to help determine if they have a pheochromocytoma.

---

*Jeannette Goguen, MD, MEd, FRCPC, is an Assistant Professor, University of Toronto, Division of Endocrinology, St. Michael's Hospital.*

---

## References

1. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002;287(11):1427-34.
2. Eisenhofer G. Editorial: biochemical diagnosis of pheochromocytoma – is it time to switch to plasma free metanephrines? *J Clin Endocrinol Metab* 2003;88(2):550-2.
3. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 2003;88(2): 553-8.
4. Kudva YC, Sawka AM, Young WF Jr. Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab* 2003;88(10): 4533-9.
5. Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *Clin Endocrinol Metab* 2003;88(6):2656-66.
6. Lucon AM, Pereira MA, Mendonca BB, Halpern A, Wajchenbeg BL, Arap S. Pheochromocytoma: study of 50 cases. *J Urol* 1997;157(4): 1208-12.
7. Manger WM. Editorial: In search of pheochromocytomas. *J Clin Endocrinol Metab* 2003;88(9):4080-2.
8. Pauker SG, Kopelman RI. Interpreting hoofbeats: can Bayes help clear the haze? *N Engl J Med* 1992;327(14):1009-13.
9. Manger WM, Gifford Jr RW. *Clinical and experimental pheochromocytoma*. Cambridge, MA: Blackwell Science;1996.

10. Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab* 2000;85(2):637-44.
11. Kaplan NM. *Kaplan's Clinical Hypertension*. 8th Edition. Philadelphia: Lippincott, Williams & Wilkins; 2002.
12. Plouin PF, Chatellier G, Fofol I, Corvol P. Tumor recurrence and hypertension persistence after successful pheochromocytoma operation. *Hypertension* 1997;29(5):1133-9.
13. Ilias I, Pacak K. Clinical Problem Solving: Current Approaches and Recommended Algorithm for the Diagnostic Localization of Pheochromocytoma. *J Clin Endocrinol Metab* 2004 89:479-491.

## Upcoming Meetings

14 May 2004

### **Banting and Best Diabetes Centre 15<sup>th</sup> Annual Scientific Day**

Vaughan Estate, The Estates of Sunnybrook

2075 Bayview Avenue, Toronto

CONTACT: Tel.: 416-978-4656

Fax: 416-978-4108

Email: diabetes.bbdc@utoronto.ca

4-8 June 2004

### **64<sup>th</sup> Scientific Sessions of the American Diabetes Association**

Orlando, Florida

CONTACT: American Diabetes Association

Tel.: 703-549-1500, ext 2453

Email: meetings@diabetes.org

16-19 June 2004

### **86<sup>th</sup> Annual Meeting of the Endocrine Society**

New Orleans, Louisiana

CONTACT: Tel.: 301-941-0200

Fax: 301-941-0259

Email: endostaff@endo-society.org

Change of address notices and requests for subscriptions to *Endocrinology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to [info@snellmedical.com](mailto:info@snellmedical.com). Please reference *Endocrinology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

---

This publication is made possible by an educational grant from

**Aventis Pharma**

---

© 2004 Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto, which is solely responsible for the contents. Publisher: **SNELL Medical Communication Inc.** in cooperation with the Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto. <sup>TM</sup>*Endocrinology Rounds* is a Trade Mark of SNELL Medical Communication Inc. All rights reserved. The administration of any therapies discussed or referred to in *Endocrinology Rounds* should always be consistent with the approved prescribing information in Canada. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.