ANNALS OF SURGERY
Vol. 217, No. 6, 595–603

Management of Pheochromocytomas in Patients with Multiple Endocrine Neoplasia Type 2 Syndromes

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Objective

The authors sought to determine the optimal surgical management of pheochromocytomas that develop in patients with multiple endocrine neoplasia (MEN) type 2 syndromes.

Summary Background data

The performance of empirical bilateral adrenalectomy in patients with MEN 2A or MEN 2B, whether or not they have bilateral pheochromocytomas, is controversial.

Methods

The results of unilateral or bilateral adrenalectomy were studied in 58 patients (49 with MEN 2A and 9 with MEN 2B). Recurrence of disease was evaluated by measuring 24-hour urinary excretion rates of catecholamines and metabolites and by computed tomography (CT) scanning.

Results

The mean postoperative follow-up was 9.40 years. There was no operative mortality and malignant or extra-adrenal pheochromocytomas were not present. Twenty-three patients with a unilateral pheochromocytoma and a macroscopically normal contralateral gland underwent unilateral adrenalectomy. A pheochromocytoma developed in the remaining gland a mean of 11.87 years after the primary adrenalectomy in 12 (52%) patients. Conversely, 11 (48%) patients did not develop a pheochromocytoma during a mean interval of 5.18 years. In the interval after unilateral adrenalectomy, no patient experienced hypertensive crises or other complications related to an undiagnosed pheochromocytoma. Ten (23%) of 43 patients having both adrenal glands removed (either at a single operation or sequentially) experienced at least one episode of acute adrenal insufficiency or Addisonian crisis, including one patient who died during a bout of influenza.

Conclusions

Based on these data, the treatment of choice for patients with MEN 2A or MEN 2B and a unilateral pheochromocytoma is resection of only the involved gland. Substantial morbidity and significant mortality are associated with the Addisonian state after bilateral adrenalectomy.

Patients with multiple endocrine neoplasia (MEN) type 2A (MEN 2A) develop medullary thyroid carcinoma (MTC), pheochromocytomas, and hyperparathyroidism. Patients with MEN 2B also develop MTC and pheochromocytomas. In addition, they develop ganglioneuromatosis and present a characteristic phenotype. Although MTC develops in virtually 100% of patients affected with MEN 2A or MEN 2B, pheochromocytomas develop in only about 50% of patients. Histopathologic studies have demonstrated that the adrenal medullary disease in patients with MEN 2A or MEN 2B is usually bilateral.[1] Diffuse or nodular adrenal medullary hyperplasia both precedes and accompanies the development of pheochromocytomas.[2] Accordingly some clinicians have advocated empirical bilateral adrenalectomy in patients with MEN 2A or MEN 2B even though a pheochromocytoma involves only one gland.[1,3–5] The application of ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy for the early diagnosis of functional as well as anatomic abnormalities[6] of the adrenal medulla has highlighted the diagnostic and therapeutic dilemmas in the management of these patients.

The rationale for bilateral adrenalectomy when either excess catecholamine production or clinical symptoms of pheochromocytoma becomes evident is based on the arguments that: 1) adrenal medullary disease in patients with MEN 2A or MEN 2B is usually diffuse and bilateral; 2) there is a high likelihood of development of a contralateral pheochromocytoma; 3) complications from the adrenal medullary disease are associated with significant morbidity and mortality; 4) pheochromocytomas may be malignant; and 5) there is a low risk of complications from the Addisonian state.

However, the performance of empirical bilateral adrenalectomy in patients with MEN 2A or MEN 2B and pheochromocytomas has been controversial. Other clinicians have recommended a more selective approach[7,8] of resecting an adrenal gland only if there is macroscopic involvement. These authors emphasize that the risk of developing a pheochromocytoma in the opposite gland must be weighed against the risk of producing a permanent Addisonian state by performing a total adrenalectomy.

Resolution of the controversies in the management of pheochromocytomas in patients with MEN 2A or MEN 2B requires a better understanding of the natural history and clinical significance of adrenal medullary disease in these disorders. This study examined the results of unilateral or bilateral adrenalectomy for pheochromocytomas in a large series of patients with MEN 2A or MEN 2B. We sought to determine the optimal surgical management of patients with a pheochromocytoma in only one adrenal gland. The clinical and pathologic characteristics, the frequency with which a contralateral pheochromocytoma developed after unilateral adrenalectomy, the interval between the development of pheochromocytomas in each adrenal gland, and the factors influencing the morbidity and mortality related to unilateral or bilateral adrenalectomy were examined.

MATERIALS AND METHODS

All patients with MEN 2A or MEN 2B who were treated for pheochromocytoma by our group from 1956 to 1990 were included in the study. Almost all of the patients were operated on by a single surgeon, either at the National Institutes of Health (Bethesda, Maryland), Duke University School of Medicine (Durham, North Carolina), or Washington University School of Medicine (St. Louis, Missouri). The clinical history, laboratory values, operative reports and pathology reports of all patients were obtained and reviewed in 1991.

The patients in this study were diagnosed with pheochromocytoma as a result of our annual screening of kindreds with MEN 2A and MEN 2B. Almost all of the patients had clinical signs and symptoms of catecholamine excess. The diagnosis of pheochromocytoma was made by the demonstration of increased urinary excretion rates of catecholamines or their metabolites and by the demonstration of unilateral or bilateral adrenal masses on radiographic imaging studies (arteriography, computed tomographic scanning, magnetic resonance imaging, or MIBG scintigraphy).

Patients with pheochromocytoma were managed by the following strategy. After preoperative preparation with an α-adrenergic antagonist (phenoxybenzamine) for 7–10 days, both adrenal glands were explored through an anterior abdominal approach. Patients with radiographic or macroscopic evidence of bilateral pheochromocytoma had bilateral adrenalectomy. Patients with a unilateral pheochromocytoma, and no evidence of a macroscopic nodule in the contralateral gland by palpation and visualization, were treated by unilateral adrenalectomy. Postoperatively, patients were followed at least annually, and the development of pheochromocytoma in the remaining adrenal gland was documented or excluded by clinical examination, by determination of 24-hour urinary excretion rates of catecholamines and their metabolites, and by radiographic studies.

Supported by NIH grants PO1 CA53524, RR00036, and T32 CA09621.

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Accepted for publication December 17, 1992.

In this study, the intraoperative, perioperative, and postoperative courses of patients treated by bilateral adrenalectomy were compared with those of patients treated by unilateral adrenalectomy. Data were collected by retrospective chart review as well as by interviews with patients and their primary care physicians.

Statistical Analyses

All results are reported as the mean ± the standard error of the mean. Student's *t*-test or a modified *t*-test for unequal variances were used to determine the differences in tumor sizes or age at adrenalectomy between groups. Significance was defined as $p < 0.05$.

RESULTS

Patient Characteristics

A total of 58 patients with either MEN 2A or MEN 2B who had an adrenalectomy for pheochromocytoma during the 34-year period between 1956 and 1990 were included in the study (Table 1). There were 49 patients with MEN 2A from 11 different kindreds and 9 patients with MEN 2B from 5 different kindreds. Of the 58 patients, 33 were female and 25 were male (1.3:1.0 female to male ratio). Ten of the 58 patients died during the follow-up period (Table 2), one from complications of the Addisonian state after bilateral adrenalectomy. The mean period of evaluation after adrenalectomy was 9.4 years (range: 0.7–28.5 yr).

For all patients, the mean age at the first operation for pheochromocytoma was 32.8 ± 1.6 years (range: 4.8–63.7 yr). The mean age at the first operation in patients with MEN 2B was earlier than that in patients with MEN 2A (23.1 ± 3.7 yr vs. 34.4 ± 1.6 yr, $p = 0.014$). All patients in the study with pheochromocytoma also had MTC. For the 56 patients in whom the information was available, the MTC was diagnosed first in 26 (46%) patients, or simultaneously with the pheochromocytoma in 23 (41%) patients. In only 7 (13%) patients was the diagnosis of pheochromocytoma established before the diagnosis of MTC.

Table 1. PATIENT CHARACTERISTICS

	Unilateral Adrenalectomy	Bilateral Adrenalectomy	Total
Number of patients	26	32	58
MEN 2A	23	26	49
MEN 2B	3	6	9
Sex			
Male (%)	10 (38)	15 (47)	25 (43)
Female (%)	16 (62)	17 (53)	33 (57)
Age at operation ± S.E. (yr)	30.4 ± 1.8	34.7 ± 2.4	32.8 ± 1.6

Table 2. MORTALITY DURING OBSERVATION PERIOD

Cause of Death	Number of Patients
Metastatic MTC	6
Myocardial infarction/pulmonary embolism	1
Addisonian crisis	1
Complication of selective arterial catheterization	1
Unknown	1

The signs and symptoms referable to catecholamine excess in the patients in this study are depicted in Table 3. The frequency of the signs and symptoms of pheochromocytoma in the 58 patients with MEN 2A or MEN 2B was similar to that reported by Manger and Gifford in an unselected group of 39 patients.[9] Although it has been thought that the pheochromocytomas in association with MEN 2A or MEN 2B are often insidious or asymptomatic, only 7% of the patients in this study had no symptoms or signs of catecholamine excess.

Operative Treatment

Sixty-nine operations were performed for pheochromocytoma in 58 patients, with low morbidity and no operative mortality (Table 4). The initial operative procedure was bilateral adrenalectomy in 32 patients. Of the 26 patients initially treated by unilateral adrenalectomy, 23 had a normal-sized contralateral adrenal gland evi-

Table 3. SIGNS AND SYMPTOMS OF PHEOCHROMOCYTOMAS

Signs or Symptoms	MEN 2A or MEN 2B Patients n = 58	Unselected* Patients n = 39
Headache	69% (40/58)	72%
Palpitations/tachycardia	62% (36/58)	51%
Hypertension	57% (33/58)	—
Diaphoresis	50% (29/58)	69%
Nausea/vomiting	26% (15/58)	26%
Flushing	21% (12/58)	—
Tremulousness/anxiety	21% (12/58)	26%
Syncope/dizziness	17% (10/58)	3%
None	7% (4/58)	—

*Modified with permission from Manger WM, Gifford RW Jr. Pheochromocytoma. New York: Springer-Verlag, 1977; p 89.

Table 4. OPERATIVE MORBIDITY AND MORTALITY FOLLOWING ADRENALECTOMY FOR PHEOCHROMOCYTOMAS

Total number of adrenalectomies	69
Total number of patients	58
Morbidity	Number of adrenalectomies (%)
Splenectomy	6 (8.7)
Blood transfusion	4 (5.8)
Wound infection	2 (2.9)
Ventricular tachycardia intraoperatively	1 (1.4)
Mortality	0

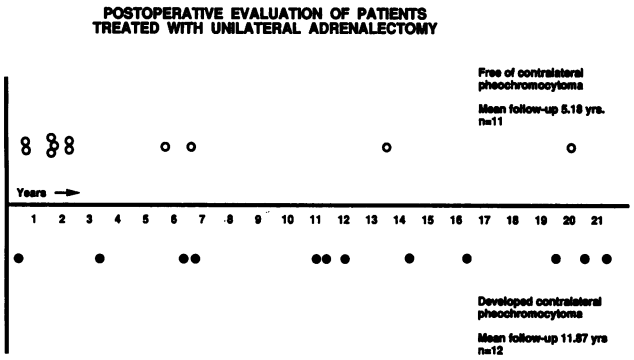

Figure 1. Outcome of unilateral adrenalectomy for pheochromocytoma. The interval of time to either development of a second pheochromocytoma (•) or to the maximum current follow-up (o) are indicated for each patient. The patients free of a contralateral pheochromocytoma during the follow-up period are indicated in the top half of the figure, whereas the patients with a contralateral pheochromocytoma are shown below.

dent on radiographic imaging preoperatively. The normal configuration of the gland was confirmed intraoperatively by palpation and visualization. The remaining three patients in this group had recognized nodular medullary hyperplasia or small pheochromocytomas in the adrenal gland contralateral to the resected pheochromocytoma. The contralateral adrenal glands were left in place in these three patients because all were undergoing chemotherapy for advanced metastatic medullary thyroid carcinoma. These patients were not included in analysis of the frequency of development of a contralateral pheochromocytoma.

During the follow-up period, 11 of the 23 patients who were initially treated with unilateral adrenalectomy (and a clinically normal adrenal gland was left in place) developed a pheochromocytoma in the remaining adrenal gland for which adrenalectomy was performed. One additional patient has a pheochromocytoma in the remaining gland but currently refuses operation. Therefore, a total of 12 (52%) of the 23 patients initially treated with unilateral adrenalectomy developed a pheochromocytoma in the opposite gland with a mean interval of 11.9 years (range: 0.4–21.2 yr) (Fig. 1, Table 5). Conversely, 11 (48%) patients did not develop a pheochromocytoma in the contralateral gland during a mean interval of 5.2 years (range: 0.7–20.6 yr) after the first adrenalectomy.

After unilateral adrenalectomy, none of the 23 patients experienced a hypertensive crisis or other complications related to the presence of an occult or undiagnosed pheochromocytoma. Of the 11 patients who had a unilateral adrenalectomy and did not require removal of the contralateral gland, 2 had uncomplicated pregnancies and 5 others had uncomplicated major operations. Three of the latter operations were thyroidectomies for MTC within a week of adrenalectomy. An additional 5 patients, of the 12 undergoing subsequent contralateral adrenalectomy, had uncomplicated major operations during the interval between the two adrenalectomies.

Recurrence of pheochromocytoma after bilateral adrenalectomy did not occur. However, 10 (23%) of 43 patients having both adrenal glands removed (either at the same time or sequentially) subsequently experienced at least one episode of acute adrenal insufficiency or Addisonian crisis requiring hospitalization and administration of intravenous saline and corticosteroids (Table 6). Of the 32 patients initially treated with bilateral adrenalectomy, 8 (25%) have experienced at least one such episode, and one of these patients died in a rural hospital from unrecognized Addisonian crisis during a bout of influenza.

Pathology

A total of 102 adrenal glands with pheochromocytomas or adrenal medullary hyperplasia were removed in the 58 patients. There were no malignant pheochromocytomas (based on histology or the presence of local or distant metastases), and no extra-adrenal pheochromocytomas were identified. Where the data were available, the mean diameter of the largest tumor nodule was 4.25 ± 0.3 cm (range: 0.4–14.5 cm), n = 79 (Table 7). Pheochromocytomas developed with essentially equal

Table 5. DEVELOPMENT OF A CONTRALATERAL PHEOCHROMOCYTOMA AFTER UNILATERAL ADRENALECTOMY

	Number of Patients (%)	Mean Follow-Up (yr)
No contralateral pheochromocytoma	11 (48)	5.2 ± 1.9
Contralateral pheochromocytoma	12 (52)	11.9 ± 2.0
Total	23	9.4 ± 1.0

Table 6. PATIENTS EXPERIENCING ACUTE ADRENAL INSUFFICIENCY OR ADDISONIAN CRISIS FOLLOWING BILATERAL ADRENALECTOMY

Pt.	Signs/Symptoms	Treatment
1a	Nausea, weight loss, hypotension	Admission, IV saline, hydrocortisone
b	Nausea, vomiting anorexia, headache, dizziness	Admission, IV saline, hydrocortisone
c	Vomiting	Admission, IV saline, hydrocortisone
2	Nausea, dizziness, thirst, weakness	Admission, no treatment; death
3a	Semi-comatose, gasping respirations, undetectable blood pressure	Admission, IV saline, hydrocortisone
b	Nausea, abdominal pain, weakness, hypotension	Admission, IV saline, hydrocortisone
4	Increasing fatigability, nausea	Admission, IV saline, hydrocortisone
5	"Acute adrenal insufficiency"	Admission, IV saline, "steroids"
6	Crisis when steroids tapered to test function of adrenal transplant	
7	Intractable nausea and vomiting	Admission, IV saline
8	Influenza with fever, myalgia, vomiting, weakness	Admission, IV saline, hydrocortisone
9	Repeated hospitalizations for adrenal insufficiency following URTIs	
10	Nausea, vomiting, lightheadedness, postural hypotension	Admission (emergency room), IV saline, hydrocortisone

frequency in the right and left adrenal glands. In this series, right-sided pheochromocytomas were larger than left-sided pheochromocytomas, although the difference was not statistically significant.

The pheochromocytomas in patients with MEN 2A or MEN 2B had a typical pathologic appearance, including polygonal or spindle cells arranged in an alveolar pattern or in sheets within a scant connective tissue framework and a delicate vascular network. The cytoplasm was granular and basophilic, but highly variable, in staining. The nuclei were small, and mitotic figures were infrequent. Microscopic examination of the adrenal glands showed diffuse involvement. The pathology of the adrenal glands removed at unilateral adrenalectomy demonstrated single or multiple pheochromocytomas (nodules $\geq$ 1.0 cm). These findings support previous studies that have described bilateral and diffuse microscopic abnormalities and adrenal medullary hyperplasia as a precursor to the development of pheochromocytomas in patients with MEN 2A or MEN 2B.[1,3–5]

Table 7. PATHOLOGY OF PHEOCHROMOCYTOMAS

	Number of Glands	Mean Diameter (cm)	Range (cm)
Right adrenal	40	4.72 ± 0.47*	0.8–11.0
Left adrenal	39	3.77 ± 0.50*	0.4–14.5
Total	79	4.25 ± 0.30	0.4–14.5

No malignant pheochromocytomas.
No extra-adrenal pheochromocytomas.
* p = not significant.

DISCUSSION

The surgical management of pheochromocytomas in patients with MEN 2A or MEN 2B has been controversial. Many surgeons have recommended bilateral adrenalectomy as soon as a diagnosis of pheochromocytoma is made, whether or not tumors are clearly evident in both adrenal glands. Other surgeons have advocated a more conservative surgical approach, with removal of an adrenal gland only if there is macroscopic or radiographic evidence of a pheochromocytoma.

There is ample histopathologic data to support the contention that adrenal medullary disease in the patient with MEN 2A or MEN 2B is bilateral at the microscopic level. In this report, as well as in nearly all studies where both adrenal glands have been removed,[1,3–5] the adrenal medullae are characterized by the asymmetric development of diffuse or nodular hyperplasia as a precursor to (usually) multicentric pheochromocytomas. Also, adrenal medullary hyperplasia is evident in areas adjacent to the pheochromocytoma at the time of adrenalectomy. However, the natural history of adrenal medullary hyperplasia has not been well defined. Specifically, the frequency with which pheochromocytoma develops in the remaining adrenal gland after unilateral adrenalectomy is not known. Tibblin and associates[7] reported 13 patients with MEN 2A who were studied for a mean of 7.4 years after a unilateral adrenalectomy for pheochromocytoma. In their study, 4 (31%) patients were reoperated on for a pheochromocytoma that developed in the opposite gland at 1, 2, 4, and 10 years after the primary adrenalectomy. The remaining nine (69%) patients were free of persistent or recurrent symptoms of pheochromocytoma during the follow-up period. These authors proposed that the maximum diameter of the largest pheochromocytoma removed at the primary adrenalec-

tomy was related to the development of a second pheochromocytoma in the contralateral adrenal gland. In eight of nine patients in whom a contralateral pheochromocytoma did not develop, the initial tumors were less than 5 cm, whereas in the four patients who had a contralateral pheochromocytoma, the initial tumor had a diameter greater than 5 cm. In review of our data we found a trend similar to that reported by Tibblin and coworkers but there was no statistically significant relationship between the size of the initial pheochromocytoma and the subsequent development of pheochromocytoma in the contralateral adrenal gland.

In the present study, approximately half of the 23 patients initially treated by unilateral adrenalectomy developed a pheochromocytoma in the remaining adrenal gland. However, the mean interval for the development of the contralateral pheochromocytoma was greater than 10 years, and in one patient there was a 21-year interval between the diagnosis of the first and the second pheochromocytomas (Fig. 1). Using ^{131}I-MIBG scintigraphy to sensitively detect adrenal medullary hyperfunction, Jansson and colleagues[8] studied 16 patients with MEN 2A or MEN 2B who did not have symptoms of pheochromocytoma. Included in this group were 8 patients who had been studied for 11 ± 4 years after unilateral adrenalectomy for pheochromocytoma. Seven of these eight patients had accumulation of the radionuclide in the remaining gland, but only two were found to have pheochromocytomas, each less than 2 cm in diameter. All patients were normotensive and lacked symptoms referable to a pheochromocytoma. Although macroscopically normal glands might be expected to show varying degrees of medullary hyperplasia if removed and examined histopathologically, this study and the data of Jansson and colleagues indicate that at least half of such patients appear to remain free of pheochromocytoma or clinically significant catecholamine excess for an extended period.

A second concern of many clinicians in the management of these patients is the risk of malignancy or morbidity from the adrenal medullary disease. Clinical investigators from the Mayo Clinic reported a significant incidence of malignant pheochromocytomas in the MEN type 2 syndromes[1]; however, this has not been the case in most other series.[3,4,7] There were no malignant pheochromocytomas (defined by histopathology and the presence of local recurrence or distant metastases) in our series of 58 patients with MEN 2A or MEN 2B from 16 different families. However, the risk of malignant pheochromocytoma should not be totally discounted and empirical bilateral adrenalectomy should be considered for members of kindreds with a history of malignant pheochromocytoma.

The principal risk of morbidity in these patients is attributable to paroxysms of catecholamine excess. The incidence of such complications varies widely in different series. Carney and associates[1] reported that 5 (29%) of 17 patients in their series died of causes related to hyperfunctional adrenal medullary disease. The most important risks of complications from catecholamine excess (hypertensive crisis, stroke, myocardial infarction) are related to unrecognized pheochromocytoma in patients who undergo surgical procedures or in women during childbirth. Patients with MEN 2A or MEN 2B who have undergone unilateral adrenalectomy for pheochromocytoma and who are enrolled in a structured plan of medical follow-up should have a new or recurrent pheochromocytoma detected early by annual physical examination, measurement of 24-hour urinary catecholamine excretion rates, and computed tomography scanning if indicated. In our series there were no complications attributed to hypertensive crisis in the patients who were serially evaluated after unilateral adrenalectomy.

Patients with MEN 2A or MEN 2B who have bilateral pheochromocytomas should have both adrenal glands removed. The major argument against empirical bilateral adrenalectomy for patients with macroscopic disease in only one gland is the long-term morbidity associated with the anadrenal state. Some have argued that bilateral adrenalectomy and long-term corticosteroid replacement is not associated with a significantly increased risk.[5] However, of the patients treated by bilateral adrenalectomy in the present series, almost 25% had at least one episode of acute adrenal insufficiency or Addisonian crisis requiring admission to the hospital and administration of intravenous saline and corticosteroids. Importantly, one patient died in a rural hospital of unrecognized adrenal insufficiency during a bout of influenza. The long-term morbidity and mortality for patients in this study who had either unilateral or bilateral adrenal-

Table 8. LONG-TERM MORBIDITY AND MORTALITY AFTER ADRENALECTOMY FOR PHEOCHROMOCYTOMAS

Morbidity/Mortality	Number of Patients
After unilateral adrenalectomy	23
Hypertensive crisis from unrecognized pheochromocytoma	0
Development of contralateral pheochromocytoma	12
Mortality	0
After bilateral adrenalectomy	43
Acute adrenal insufficiency or Addisonian crisis	10
Recurrent pheochromocytoma	0
Mortality	1

ectomy for pheochromocytomas are summarized in Table 8.

In patients with MEN 2A or MEN 2B who have a unilateral pheochromocytoma, the treatment of choice is resection of only the involved gland, because 1) approximately half of the patients will not develop a pheochromocytoma in the opposite adrenal gland for at least 10 years, and some perhaps never will; 2) these patients can be studied expectantly because the presence of a second pheochromocytoma is readily detectable by clinical, biochemical, and radiographic evaluation; 3) the occurrence of malignant pheochromocytoma is rare; and 4) substantial morbidity and significant mortality are associated with the Addisonian state.

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Discussion

DR. JOHN B. HANKS (Charlottesville, Virginia): I'd like to congratulate Dr. Wells and Dr. Lairmore on their excellent study. It analyzes one of the perplexing problems in adrenal surgery, that being the efficacy of bilateral adrenalectomy for pheochromocytoma in patients with MEN 2 and 2B patients versus the risk of unilateral adrenalectomy and the development of a later pheochromocytoma, malignant or otherwise. This manuscript is a must reading for any or all of us who are interested in endocrine surgery because it represents the personal experience of one of the truly excellent surgeons, Sam Wells. At the University of Virginia, Dr. Nuzhet Atuck of the nephrology division, has followed 18 patients with pheochromocytoma and with von Hippel-Lindau syndrome. I know that this is a slightly different twist, but I can offer the University of Virginia's experience since 1965 to the present time with Dr. Atuck's blessing because he supports the concepts put forward by Dr. Wells. In this slide you can see that the management of the pheochromocytoma and familial van Hippel-Lindau's disease has taken the same approach that Dr. Wells has advocated. Eighteen patients have been followed. Two patients had bilateral adrenalectomy. In those two patients, there have been no Addisonian crises or any other extra-adrenal pheo development. Fifteen patients or 83% of the group had unilateral adrenalectomy. Five of those 15 or 33% did develop pheo in the remaining adrenal and had those removed. But in 67% or 10 of the 15, there was no pheo in the remaining adrenal, and these patients have been followed for slightly longer than Dr. Well's series for an average of 14.4 years from a range of 2 to 20 years. Interestingly, one patient refused treatment and died at 25 years of coronary artery disease and no further problems with his pheo. I have two questions for Dr. Wells. The first is, would you comment on the tradeoff of the risk of Addisonian crisis in bilateral excision weighed against the risks of surgical mortality of the operation in a clinically active pheo? You've discussed this a bit and clearly your mortality of zero percent is an obvious answer to the question, but obviously those of us that present a pheo to our anesthesiologists are quoted a slight but significant surgical mortality. Secondly, could you emphasize or reemphasize the important concepts of follow-up of these patients not only for the MEN-2 patients but for any of the patients with pheochromocytoma? What are the appropriate parameters to follow with specific regard to specificity and sensitivity, and now, cost effectiveness? Specifically, I'd be curious as to whether you employ MRI T2 scanning or MIBG scans in your follow-up.

DR. JONATHAN VAN HEERDEN (Rochester, Minnesota): Dr. Wells and his colleagues have for many years been leaders in the field of endocrine surgery. This presentation today is certainly no exception. The message just presented is that unilateral adrenalectomy is the procedure of choice in MEN-2 patients with seemingly unilateral disease. Dr. Wells and his coauthors base this conclusion on their experience where 52% of their patients thus treated required contralateral adrenalectomy with a mean follow-up of 11.9 years. They support this surgical philosophy with the finding that no patient developed an adrenal malignancy and that 25% of their anadrenal patients developed a nonfatal Addisonian crisis during hospitalization. I stand corrected. One patient did, in fact, die of an Addisonian crisis. Dr. Wells, I would like to respectfully disagree somewhat with your conclusions and ask a few questions regarding the data presented. First, the 48% of your patients who underwent unilateral resection and have not developed contralateral disease have only been followed for a mean interval of 4.2 years, which is a relatively short time in the evolution of disease in this particular group of patients. Would you predict, and I know this is dangerous, that if followed for the same time period, i.e., 12 years as your group that did develop subsequent contralateral disease, at least half, i.e., six patients might develop disease in the remaining adrenal gland? If so, and this is hypothetical, then 86% of your patients may eventually need