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

bilateral adrenalectomies. Second, in a study of seventeen such patients treated by us by initial bilateral adrenalectomy, we encountered bilateral gross and/or microscopic disease in 100% of patients. Do you feel that current radiologic findings and intraoperative evaluation are sufficient to rule out adrenal medullary disease adequately, particularly adrenal medullary hyperplasia? A major concern regarding bilateral adrenalectomy has been the possibility of increased morbidity in patients without adrenal glands. In the study of patients with MEN who had previously undergone bilateral total adrenalectomy, we found no such morbidity. In fact, in a study of 15 patients they underwent 8 uneventful full-term pregnancies and 23 operations requiring general anesthesia without incident. These patients were followed for a mean interval of 11 years. To further evaluate the dangers of the anadrenal state, 50 patients undergoing bilateral adrenalectomy for Cushing's disease after unsuccessful transsphenoidal hypophysectomy or for nodular non-ACTH dependent adrenal hyperplasia or for an ectopic ACTH-producing tumor during the period '81 through '91 at our institution were followed for a mean interval of 20 months. We found no instance of a fatal Addisonian crisis in this group of patients. Does the data you presented, Dr. Wells, regarding Addisonian problems justify leaving the opposite adrenal gland in place at the initial operation? One of our MEN patients who was treated previously for medullary thyroid cancer died of a hypertensive crisis during a cesarean section. At autopsy, bilateral pheochromocytomas were found. Are you concerned about this possibility in your patients treated by initial unilateral adrenalectomy? In conclusion, from what I have just said, it is evident that our philosophy is that of initial, bilateral total adrenalectomy. I wonder though, Mr. President, if the correct philosophy requires some flexibility by both of our groups. Should the younger patients be treated by bilateral resection, particularly if malignant tumors have occurred in the family or if the expressivity of the MEN syndrome is that of initial pheochromocytoma and not medullary thyroid carcinoma as is more usual? Shouldn't the older patients, those whose family histories have been relatively benign, whose compliance regarding replacement medication might be suboptimal or who may be from a Third World country, be considered for initial unilateral resection? In this era of cost effectiveness we need to wonder as well about the cost of regular follow-up, raised by Dr. Hanks which will include both radiologic and biochemical evaluation, and balance this against the risk of Addisonian crisis and the necessity of constant medication in the adrenalectomized patients.

DR. GEORGE S. LEIGHT, JR. (Durham, North Carolina): Dr. Wells certainly continues to be a leader in this field and I think we're all indebted to him for his careful analysis of this very difficult group of patients. At Duke University we have subscribed to the same policy as outlined by Dr. Wells for management of these interesting patients. We also have been well satisfied with this approach and will continue to manage the patients in this fashion. In contrast to the patient that Dr. Wells reported today who actually died of acute adrenal insufficiency, we have managed one patient who was initially managed at an outside institution who had undergone bilateral adrenalectomies. She was given a prescription for her cortisone acetate for steroid replacement, but her pharmacist substituted prednisone for the cortisone acetate but at the same dose which would have been appropriate for the cortisone acetate. Needless to say, this patient developed marked Cushing's syndrome with severe hypertension and marked depression. It took numerous months to figure out what was going on in this patient and obviously a long time for the Cushing's to revert after the etiology had been discovered. So this represents obviously a very rare but the opposite type of complication that can occur in patients who are dependent on cortisone replacement. In my experience the most difficult problem and most difficult decision in managing these patients is determining what exactly should be considered a normal adrenal gland. As Dr. Wells has so nicely demonstrated, these patients have adrenal medullary hyperplasia and it can be difficult to distinguish what should be defined as hyperplasia from what is pheochromocytoma. I would ask him what are the modalities that he now ultimately relies upon to make this distinction and do you have any patients in your study who were not thought to have a pheochromocytoma by CT scan who at the time of surgery were found to have pheochromocytoma which required contralateral adrenalectomy? I would also echo the comments of Dr. Hanks and ask what modalities you now rely upon to follow these patients following unilateral adrenalectomy?

DR. TERRY C. LAIRMORE (Closing Discussion): I would like to begin by thanking the discussants for their thoughtful comments and I will begin with Dr. van Heerden's comments. Dr. van Heerden and his colleagues at the Mayo Clinic have had an extensive experience in the management of patients with the MEN type 2 syndromes. In 1975, Dr. Carney was the first to describe bilateral adrenal medullary hyperplasia as the precursor to pheochromocytomas in these patients. In addition, this group has reported, as Dr. Wells said, a family in which malignant pheochromocytomas have clearly occurred. Based on the frequency of bilateral involvement, this group has recommended an aggressive surgical approach with a primary bilateral adrenalectomy for patients with MEN 2A or 2B once a diagnosis of pheochromocytoma is made. Dr. van Heerden's first question relates to the length of follow-up for the group of patients who were treated by unilateral adrenalectomy and who have not developed a contralateral pheochromocytoma. These patients have been followed for a mean interval of 5.2 years as compared with the mean follow-up of nearly 12 years for the group of patients who eventually did develop a pheochromocytoma in the opposite gland. As the former group is followed for 10 years or more, it is reasonable to expect that half or more of these patients will eventually develop a second pheochromocytoma. Although the majority of patients may eventually have bilateral tumors if they're followed for long enough, the critical issue is really what the interval of time would be before the development of the second tumor. For the entire group of 23 patients in our series who had a unilateral resection, even if virtually all of them had contralateral disease at the current length of follow-up, ten of the patients or 43% would have gone more than 10 years before developing a contralateral tumor. Some of the remaining patients may never develop a contralateral tumor. Currently, 48% or nearly half of the patients have no evidence of a new pheochromocytoma 5

years out including two patients who have been followed for 13 and 20 years, respectively. Even for the patients that will eventually require a second adrenalectomy, the morbidity following bilateral adrenalectomy in our data supports having one adrenal gland in place for this period time. In response to Dr. van Heerden's second question, it has been well shown that the adrenal medullary disease in MEN 2 is bilateral at the microscopic level and that virtually all patients have adrenal medullary hyperplasia. Dr. van Heerden has asked whether radiographic imaging and intraoperative evaluation are sufficient to exclude bilateral disease in these patients. The argument is not that the patients do not have adrenal medullary hyperplasia. However, in our opinion patients who are normotensive and without evidence of elevated urinary catecholamines and without evidence of adrenal enlargement on the CT scan should be considered to have a normal adrenal gland with respect to whether it needs to be removed, and this also speaks to Dr. Leight's comments. Finally, Dr. van Heerden has addressed the central issue as well as Dr. Hanks of the risk of the complications after a total adrenalectomy. In a study of 17 patients by the Mayo Clinic group who underwent initial bilateral adrenalectomy who were followed for over 10 years, they found no significant complications related to the need for corticosteroid replacement. These data also agree with the data that Dr. Hanks presented. Our data are at odds with this report in that approximately one quarter of all the patients in our series who had both adrenal glands removed experienced at least one episode of adrenal insufficiency which required hospitalization and the administration of steroids and fluids. Many of these events were associated with noncompliance or a failure to increase the steroid replacement at times of physiologic stress. The point is that a significant proportion of these patients got into trouble including one patient who died. So we would like to emphasize that the adrenal medullary disease in patients with MEN 2 develops in young persons who might be expected to have subsequent pregnancies or other major operations. Finally, the pivotal issue in the controversy, and this was addressed by several of the discussants, involves weighing the risk of the Addisonian state following bilateral adrenalectomy against the risk of complication from an undiagnosed pheochromocytoma left in place. In the present study none of the patients in the group undergoing resection of a unilateral pheochromocytoma have had a hypertensive crisis or other complication that is related to an undiagnosed pheochromocytoma in the remaining gland. For the patients with a unilateral pheochromocytoma our data support that there is a much greater risk of bilateral adrenalectomy than in having a remaining gland with adrenal medullary hyperplasia even though we would concede that a majority of these patients will eventually develop tumors on both sides if followed long enough. The conservative approach of a unilateral adrenalectomy for these patients preserves adrenal cortical function and it prevents the need for daily steroid replacement in these patients who are young and may require that treatment for an extended period of time. We agree that patients with bilateral pheochromocytomas and patients at a significant risk of malignant pheochromocytomas should undergo bilateral adrenalectomy. Finally, Dr. Hanks presented data that concerned the results of unilateral adrenalectomy in a different disease which also involves hereditary pheochromocytomas, the von Hipple-Lindau syndrome. A total of 15 patients in this series who underwent unilateral adrenalectomy were followed for a longer period of time and only a third of them recurred which also supports our conservative approach. In response to how these patients should be followed, we have undertaken an aggressive follow-up plan in which our patients are evaluated at least annually by clinical evaluation, measurement of blood pressure, and measurement of 24-hour urinary excretion rates of catecholamines and their metabolites. The importance of a careful follow-up should be emphasized and is certainly no greater when weighed against that required for a patient who has had both adrenal glands removed.