Hypothesis: Multiple endocrine neoplasia type 1 (MEN 1) syndrome is an autosomal dominant disorder caused by germline mutations in the MEN1 gene and characterized by multiple endocrine tumors, most notably in the parathyroid glands, pituitary, and pancreas. The syndrome demonstrates variable expressivity and considerable genetic heterogeneity. Patient data were examined for possible associations between genotype and phenotype.

Design: We reviewed recorded medical data from 1975 to 2001 on patients with MEN 1 and compared specific types and locations of MEN1 gene mutations with manifestations of the syndrome.

Patients and Results: We identified 109 affected patients from 24 MEN 1 kindreds. The phenotypic expression of MEN 1 in affected individuals included hyperparathyroidism in 74%, pancreatic endocrine tumors in 51%, and pituitary tumors in 35%. Twelve of 14 insulinomas occurred in patients with pituitary tumors. Mutation analysis was completed in 14 of 24 kindreds (80 of the 109 patients). Mutations were most common in exons 2 (31%), 9 (15%), and 10 (23%). All 21 patients with frameshift mutations (and known pancreatic endocrine tumor status) had such tumors. Pituitary tumors were associated with frameshift mutations in exon 2.

Conclusions: The type and location of MEN1 mutations may be associated with the phenotypic expression of specific tumors. Such information may assist in the genetic counseling and surveillance of at-risk patients. A specific genotype-phenotype correlation is unlikely because of the heterogeneity of the mutations in the MEN1 gene.

Arch Surg. 2002;137:641-647
PATIENTS AND METHODS

STUDY GROUP

The study included 109 affected individuals from 24 unrelated MEN 1 kindreds retrieved from the MEN 1 database in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center. This database was developed by review of medical records from 1975 to 2001. The clinical diagnosis of MEN 1 was based on accepted criteria as previously published.30 Forty-seven (43%) of the 109 patients were seen in consultation at our institution; information from the remaining 62 patients (57%) was obtained by patient interview and telephone follow-up.

For the 47 patients examined at our institution, the presence or absence of hyperparathyroidism, PETs, pituitary neoplasms, carcinoid tumors, neoplasms of the adrenal glands, and other phenotypic characteristics of MEN 1 was determined from review of operative and pathology reports, radiographic imaging studies, and/or laboratory analysis. The presence of hyperparathyroidism was confirmed by (1) elevated levels of serum calcium and intact parathyroid hormone with or without a history of clinical symptoms secondary to hypercalcemia or (2) histologic documentation of parathyroid hyperplasia after parathyroidectomy. Patients judged to have a PET included those who had a pancreatic neoplasm found at operation or identified on computed tomographic images. In the absence of operative/pathologic or computed tomographic evaluation of the pancreas, the presence or absence of a PET was not confirmed. The type of PET was defined as functioning or nonfunctioning. Functioning tumors were those associated with a clinical syndrome or an elevation (greater than 2 times the upper limit of normal) of serum levels of pancreatic peptides. In the absence of a clinical syndrome attributable to peptide hypersecretion, patients with mild elevations (less than 2 times the upper limit of normal) of gastrin, pancreatic polypeptide, glucagon, or vasoactive intestinal peptide were considered to have nonfunctioning tumors. The diagnosis of insulinoma was based on results of an observed fast with serum glucose level less than 45 mg/dL (2.5 mmol/L) and a concomitant insulin level greater than 6 µU/mL (42 pmol/L).

For the 62 patients determined to have MEN 1 by patient interview, confirmation by laboratory, radiographic, and pathologic data was incomplete. It is reasonable to assume that the frequency of MEN 1 and specific manifestations of MEN 1 in the kindreds studied is underestimated.

MUTATION ANALYSIS OF MENV1 GENE

Mutation analysis was limited to the proband within each kindred; once a mutation was identified in the proband, all blood relatives with documented MEN 1 were assigned the same genotype. For mutation analysis, blood was collected from affected individuals with informed consent. DNA was isolated from whole blood with a kit (QIAGEN blood or tissue kit; QIAGEN Inc, Chatsworth, Calif). Polymerase chain reaction assays and sequence analysis were performed as previously described.30 In all cases, a detected mutation was confirmed by sequencing the opposite strand of a second sample and by restriction digestion where possible.

STATISTICAL ANALYSIS

The statistical associations of the site (exon) or the type of mutations with clinicopathologic variables were assessed by χ2 and Fisher exact tests. Associations of continuous variables with different groups of mutations were assessed by the nonparametric Mann-Whitney test. All analyses were performed with the StatView (version 5.01) statistical software package (Abacus Concepts Inc, Berkeley, Calif). Differences were considered statistically significant at P<.05.

RESULTS

Of the 109 affected individuals, 67 (61%) were alive, 28 (26%) were dead (most deaths were from MEN 1–related complications), and vital status was unknown for the remaining 14 (13%). The mean age of the 67 living individuals was 43 years (median, 42 years; range, 19-69 years). The mean age at the time of death for the 24 individuals in whom the age at death was known was 50 years (median, 50 years; range, 27-86 years); the age at death was unknown for 4 individuals.

The phenotypic expression of MEN 1 in all 109 individuals is summarized in Table 1. The most common manifestations of disease were hyperparathyroidism (74%), PETs (51%), and pituitary tumors (35%). As seen in Table 1, the frequency of observed phenotype was based on the extent of evaluation. For the 47 patients treated at our institution, the mean age at the time of clinical presentation with a first manifestation of MEN 1 was 29 years (median, 29 years; range, 9-53 years). The first manifestation of MEN 1 was hyperparathyroidism in 30 (64%) of these 47 patients.

The presence or absence of a PET was confirmed in 66 of the 109 individuals (in 43 of the 47 patients treated at our institution and in 23 of the remaining 62 affected relatives). Among these 66 individuals, PETs were found in 56 (85%). The type of PET was known for 45 of 56 patients. Fifty-two different types of PETs were found in these 45 patients, including 24 gastrinomas (46%), 15 insulinomas (29%), 9 nonfunctioning tumors (17%) (5 with elevation of pancreatic polypeptide), and 4 glucagonomas (8%).

The associations of hyperparathyroidism, pituitary tumors, carcinoid tumors, adrenal neoplasms, lipomas, and cutaneous angiofibromas with the types of PETs were
shown in Table 2. Table 2 includes tumors from individuals in whom the presence or absence of disease was verified by medical evaluation or interview. Of interest, 12 (86% [representing 8 different kindreds]) of 14 insulinomas occurred in patients with pituitary tumors (P = .03).

At present, mutation analysis is complete in 14 of the 24 kindreds (80 [73%] of the 109 patients). A germline mutation in menin was identified in 79 of the 80 patients. Table 3 summarizes the 13 identified MEN1 germline mutations, as well as the type of mutation and exon location. Among the 13 kindreds with an identified MEN1 mutation, mutations were most common in exons 2 (31%), 9 (15%), and 10 (23%). The positions of the mutations in the MEN1 gene are illustrated in the Figure.

The mutation type and location in patients for whom both the MEN1 mutation and the presence or absence of a specific type of tumor were known are shown in Table 4. The presence or absence of hyperparathyroidism was known in 83 (76%) of the 109 patients; hyperparathyroidism was present in 81 (98%). The MEN1 mutation was known for 60 of the 83 patients with known parathyroid status; hyperparathyroidism was present in 59 (98%). Hyperparathyroidism was not associated with any specific type or site of MEN1 mutation.

The presence or absence of PETs was known in 66 (61%) of the 109 patients; PETs were present in 56 (85%). The MEN1 mutation was known for 49 of the 66 patients with known PET status; PETs were present in 43 (88%). All (100%) of the 21 patients with known PET
and MEN1 mutation status who had frameshift mutations had PETs, whereas 22 (79%) of 28 patients with all other types of MEN1 mutations had PETs ($P = .03$).

The presence or absence of a pituitary tumor was known in 62 (57%) of the 109 patients; pituitary tumors were present in 38 (61%). The MEN1 gene mutation was known for 49 of the 62 patients with known pituitary status; pituitary tumors were present in 29 (59%). Fourteen (48%) of the 29 patients with pituitary tumors had frameshift mutations in exon 2 (representing 2 of 9 kindreds); frameshift mutations in exon 2 were not found in any of the 20 patients without pituitary tumors ($P < .001$).

The presence or absence of a bronchial or thymic carcinoid tumor was known in 47 (43%) of the 109 patients; bronchial or thymic carcinoid tumors were present in 8 (17%). The MEN1 gene mutation was known for 36 of the 47 patients with known carcinoid status; bronchial or thymic carcinoid tumors were present in 5 (14%).

The presence or absence of an adrenal tumor was known in 47 (43%) of the 109 patients; adrenal tumors were present in 8 (17%). The MEN1 mutation was known for 35 of the 47 patients with known adrenal status; adrenal tumors were present in 8 (23%). There was an even distribution of mutation type and location among the 8 adrenal tumors.

The type and location (exon) of MEN1 mutations present in the 43 patients with PETs are shown in Table 4. These 43 patients had a total of 50 PETs (some patients had more than 1 type of PET). Of these PETs, 26 (52%) were associated with frameshift mutations, 19 (38%) with nonsense mutations, 3 (6%) with deletions, and 2 (4%) with missense mutations. Of interest, all 4 glucagonomas were associated with frameshift mutations in exon 2 ($P = .004$).

Twenty-five patients with PETs were treated surgically at our institution. Surgical procedures consisted of distal pancreatectomy with or without enucleation of tumors in the head of the pancreas or the uncinate process in 18 patients, enucleation or nonanatomic resection of tumors in 2 patients, pancreaticoduodenectomy in 2 patients, and total pancreatectomy in 3 patients. Because of tumor recurrence in the pancreatic head, completion total pancreatectomy was performed in 5 (28%) of the 18 pa-

Table 4. Mutation Types and Locations in Affected Individuals With and Without Specific MEN 1 Manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Total</th>
<th>Frameshift (n = 27)</th>
<th>Nonsense (n = 41)</th>
<th>Missense (n = 6)</th>
<th>Deletion (n = 6)</th>
<th>Exon of MEN1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (n = 27) 9 (n = 7) 10 (n = 13) Other (n = 32)</td>
</tr>
<tr>
<td>HPT Present</td>
<td>59</td>
<td>20</td>
<td>31</td>
<td>3</td>
<td>5</td>
<td>20 4 10 25</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>PET Present</td>
<td>43</td>
<td>21</td>
<td>17</td>
<td>2</td>
<td>3</td>
<td>18 4 7 14</td>
</tr>
<tr>
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<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0 0 3 3</td>
</tr>
<tr>
<td>Pituitary tumors Present</td>
<td>29</td>
<td>16</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>15 2 2 10</td>
</tr>
<tr>
<td>Absent</td>
<td>20</td>
<td>2</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td>1 2 8 9</td>
</tr>
<tr>
<td>Carcinoid tumor Present</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1 0 3 1</td>
</tr>
<tr>
<td>Absent</td>
<td>31</td>
<td>11</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>9 3 6 13</td>
</tr>
<tr>
<td>Adrenal tumor Present</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2 2 2 2</td>
</tr>
<tr>
<td>Absent</td>
<td>27</td>
<td>8</td>
<td>17</td>
<td>1</td>
<td>1</td>
<td>8 1 7 11</td>
</tr>
</tbody>
</table>

*Includes only patients in whom both the MEN 1 mutation and the presence and absence of the specific manifestation were known. Abbreviations are explained in the first footnote to Table 1.
patients who underwent initial distal pancreatectomy. Lymph node metastases were found in 10 (45%) of the 22 patients who underwent surgery that included resection of 1 or more lymph nodes for pathologic analysis. Synchronous liver metastases (at the time of surgery) were found in 2 (8%) of the 25 patients who had surgery, and metachronous liver metastases developed in 2 (9%) of the remaining 23 surgically treated patients.

The presence or absence of metastatic neuroendocrine carcinoma in either regional lymph nodes or distant organs was known for 26 (58%) of the 45 patients in whom the type of PET was known. Metastatic disease in regional lymph nodes and/or distant organs was found in 16 (62%) of these 26 patients. Twelve (86%) of 14 patients with gastrinoma had lymph node or distant metastases. In contrast, metastases were found in only 4 (33%) of 12 patients with PETs other than gastrinoma (P = .01). The mutation type and location was known for 22 of the 26 patients. No significant correlation was found between the presence or absence of metastatic disease (lymph node or distant organ) and the type or site of mutation in patients with PETs.

In the present study, we determined the phenotypic expression of MEN 1 in 109 affected kindred members from 24 unrelated families. We attempted to define the relationship between the mutations in the MEN1 gene and the associated neuroendocrine neoplasms. We identified a mutation in 13 families, each with a unique germ-line mutation (Table 3). We did not detect a mutation in 1 of the 14 probands in whom analysis was completed. The inability to detect a MEN1 germ-line mutation in some patients with MEN 1 is expected, as large deletions and/or mutations in the promoter regions or untranslated regions of the gene may not be detected. Of the mutations we identified, Y276X is a novel nonsense mutation in exon 6, and 275_286delIGCTTCAC-CGCC is a novel deletion in exon 2. The remaining 11 mutations identified in our patients were previously reported.3,7,14,26,29,37 Mutations 354_356delGAA, 247_250delCTGT, 1216_1217insA, and 210_211delCC have been renamed by means of standardized nomenclature38 and were previously reported as K119del, 357del4, 1325insA, and 320del2, respectively.

Consistent with previous reports, many MEN1 mutations in this study were nonsense or frameshift mutations, which eliminate the function of 1 copy of the gene and result in a truncated menin protein.3,14,26 As expected, the mutations found in our patients were scattered throughout the coding region of the MEN1 gene.3,14,29,29 Bassett and colleagues26 have suggested that mutation hot spots exist in exons 2, 3, and 10; in the present study, MEN1 mutations were most common in exons 2, 9, and 10.

Several previous reports have failed to demonstrate a direct genotype-phenotype correlation in patients with MEN 1. There are 2 possible reasons for this. First, a wide spectrum of mutations in the MEN1 gene has been identified in different families with the same clinical manifestations of MEN 1. For example, several kindreds from Newfoundland and Tasmania have been identified as having a distinct MEN1 phenotype characterized by a high prevalence of prolactinomas, late-onset hyperparathyroidism, and a rare occurrence of pancreatic neoplasms.26,33-35,39,40 This variant of MEN1 (MEN1Burin) has been reported in at least 5 kindreds. However, these 5 kindreds do not all have the same MEN1 mutation. Second, previous studies have observed the same MEN1 mutation in different kindreds with different clinical manifestations of MEN1.26,33-35

Bartsch et al30 suggested that the type or site of mutation might predict the biological behavior of PETs in patients with MEN 1. In their study, 55% of patients with nonfunctioning or frameshift mutations of the C- or N-terminal regions of exons 2, 9, or 10 had malignant tumors, compared with only 10% of patients with all other mutations of the MEN1 gene. However, most patients considered to have metastatic disease had lymph node metastases but no distant organ metastases. In fact, only 1 patient with a nonsense or frameshift mutation in exon 2, 9, or 10 had a distant organ metastasis (lung).

Other studies suggesting a possible genotype-phenotype association in patients with MEN 1 include a report by Calender et al31 in which patients with MEN 1 and triple-organ involvement or aggressive phenotypes had truncating mutations. In addition, a mild variant form of MEN1 called familial isolated hyperparathyroidism has been associated with missense mutations occurring mainly between exons 3 and 7.31,32,42

In the present report, all patients with frameshift mutations had PETs (Table 4). Furthermore, glucagonomas appeared to be associated with frameshift mutations in exon

<table>
<thead>
<tr>
<th>PET Tumor Type</th>
<th>Total (N = 50)</th>
<th>Frameshift (n = 26)</th>
<th>Nonsense (n = 19)</th>
<th>Missense (n = 2)</th>
<th>Deletion (n = 3)</th>
<th>2 (n = 23)</th>
<th>9 (n = 4)</th>
<th>10 (n = 6)</th>
<th>Other (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>20</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>PPomas</td>
<td>5</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nonfunctioning</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Function status unknown</td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Includes 50 individual tumors from 43 patients in whom MEN1 mutation analysis was known. PPomas indicates pancreatic polypeptide tumors.

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2. A significant association was also found between pituitary tumors and frameshift mutations in exon 2, while bronchial and thymic carcinoids were more frequently associated with mutations in exon 10 (Table 4). However, our data did not demonstrate a significant association between the specific type or location of MEN1 mutation and the development of metastatic disease in patients with PETS. The small number of patients with lymph node and distant organ metastases in our study limits this analysis.

In contrast to MEN 1, MEN 2 is characterized by a strong genotype-phenotype correlation. The biological aggressiveness of medullary thyroid carcinoma can be predicted on the basis of the specific mutation in the RET proto-oncogene. In addition, specific codon mutations are associated with classic MEN 2B, MEN 2A, and familial medullary thyroid carcinoma. Most important, knowledge of the specific RET mutation guides the recommendation for the timing of thyroidectomy in at-risk patients. Such data are not yet available for patients with MEN 1, specifically those with PETS.

Our findings suggest that the specific mutation type and location in an individual family with MEN 1 may be associated with the clinical manifestations of the MEN 1 syndrome. A more specific genotype-phenotype correlation is probably not possible because of the heterogeneity of the mutations reported in the MEN1 gene. Initial reports such as this will improve our overall understanding of the molecular genetics of MEN 1. At present, guidelines for the operative treatment of patients with MEN 1–associated neoplasms are not based on information about the specific MEN1 mutation; however, this information may be helpful for the screening and genetic counseling of at-risk patients.

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REFERENCES

DISCUSSION

Jon A. Van Heerden, MD, Rochester, Minn: This presentation and the ensuing manuscript that is excellent are no exception. As emphasized in the preceding presentation this morning, we as surgeons continue to understand the diseases we deal with on a daily basis better by an improved understanding, by us, of the molecular biology and the genetic mutations associated with these diseases. Because of this better understanding, we are today able to, for example, advise a total thyroidectomy on a healthy preschool child, with no physical abnormalities, based solely on genetic mutations, in this case, a positive RET proto-oncogene mutation, and fully expect a 100% long-term cure. What a wonderful advance, and wouldn’t it be surgical utopia if this became a reality for a wide array of malignancies we deal with on a daily basis.

The Houston group has told us, however, that we are not doing nearly as well in those rare patients with MEN 1, who, as you know, have a propensity to develop pancreatic endocrine tumors. MEN patients are in fact prone to premature death, with an important cause of death being metastatic islet cell tumors. Liver metastases were present in 15% of their patients and lymph node metastases in a staggering 45% of their patients. We, and others, have in fact found that the 20-year survival of MEN patients was about 64% in comparison to 81% of a matched non-MEN patient population group. Almost one third of the deaths in this group were due to metastatic islet cell tumors.

Most importantly, I think, the authors have shown a correlation between frameshift mutations, in particular exons, with specific pancreatic endocrine tumors, glucagonomas and PPomas in particular. This interesting finding is in keeping with the recent publication in Surgery by investigators from Germany, headed by Mathias Rothmund, who found that patients with truncating nonsense or frameshift mutations in the N- or C-terminal regions of the MEN1 gene, which are exons 2, 9, and 10, had a higher rate of malignancy. 55% vs 10%, and a shorter disease-free interval, 26 vs 92 months, than those MEN patients without these genetic mutations.

May I ask the authors 2 simple questions? What is your advice to a 19-year-old totally asymptomatic MEN 1 patient who has a normal CT scan of the abdomen, whose father died of metastatic glucagonoma at age 40, and who has a frameshift mutation on exon 2? Is this patient a candidate for a prophylactic total pancreatectomy?

Secondly, because of the rarity of these patients and in view of the small numbers in your study, and the small numbers worldwide, should we perhaps assemble all MEN 1 patients, perhaps with the help of the International Association of Endocrine Surgeons, in an attempt to determine the relationship between MEN 1 phenotype and tumor aggressiveness?

Richard A. Prinz, MD, Chicago, Ill: I would like to ask a variation of Dr Van Heerden’s first question. Have you done this gene mutation analysis prospectively in patients with MEN 1 who are at risk of developing islet cell tumors? If you have, how has it helped to tailor your screening and imaging in these patients to facilitate early diagnosis and treatment of an islet cell tumor?

Geoffrey B. Thompson, MD, Rochester: You grouped all the gastrinomas under the heading of pancreatic endocrine tumors. Generally, in MEN 1 patients, we think of the gastrin excess as coming from duodenal microcarcinoids. That has been our experience as well as others elsewhere. I am curious what the breakdown was for these tumors (duodenal vs pancreatic), and is there any correlation between the duodenal and pancreatic gastrin-producing tumors and the type or types of mutations seen?

Edwin L. Kaplan, MD, Chicago: I share Dr Van Heerden’s point of view that we should have an international database. I want to ask one question. When studied by immunohistochemistry, many pancreatic endocrine tumors contain more than one peptide. How do you classify these tumors?

Dr Lee: Thank you all for your kind comments and cogent questions. I will answer some of the easier questions first. Dr Kaplan asked how we classified patients whose tumors stained for multiple peptides by immunohistochemistry. These patients were classified on the basis of clinical hormone production rather than on the basis of immunohistochemical markers.

We were asked how many of our gastrinoma patients had duodenal tumors. Duodenotomy was performed in 4 gastrinoma patients and islet cell tumors were identified and enucleated in 3 of these 4 patients. Duodenal tumors were found in an additional 5 patients who underwent pancreaticoduodenectomy or total pancreatectomy.

Dr Van Heerden asked about an international registry of MEN 1 patients. We certainly would support the development of an international registry as Dr Van Heerden has described. The number of patients and kindreds seen at any individual institution, even those such as ours with a dedicated clinical and basic science research program in MEN 1, is relatively small. Our presentation today, as well as recent publications of other groups, demonstrate that it is very difficult to get at genotype-phenotype correlations using data from any single institution, so we would certainly support development of such an international registry.

Dr Prinz and Dr Van Heerden asked related questions regarding screening and prophylactic surgery for patients from MEN 1 kindreds, particularly in kindreds in which the pancreatic neuroendocrine disease has been relatively aggressive. The issue of prophylactic surgery goes to the heart of our presentation and the difficulty in getting good data about associations between genotype and phenotype. We think the example of MEN 2 is an excellent one where prophylactic thyroidectomy has really changed the way that we manage these patients and the natural history of the disease. We don’t think we are there yet with regard to MEN 1 and surgical treatment of pancreatic neuroendocrine disease. For MEN 1 patients who have hyperparathyroidism, where the aggressiveness of hyperparathyroidism does appear to be kindred-specific, we and others have begun to tailor our surgical treatments for those patients based on the aggressiveness of the hyperparathyroidism in the kindred and the individual patient. However, we do not recommend yet prophylactic total pancreatectomy for any of our patients with MEN 1. The way that we would manage a patient such as Dr Van Heerden described would be to do an initial thin-cut, high resolution, contrast-enhanced CT scan. We would also add endoscopic ultrasound to look at the pancreas and the duodenum at the time of initial presentation. We would follow a patient like this, in the absence of better data, with annual CT scans as well as measurements of plasma peptide hormone levels. At the first clinical evidence for a pancreatic endocrine tumor, we would consider operation. We would not wait until the tumor reached an arbitrary size, 2 cm for example. The operation that we would do would be an operation such as Dr Norman Thompson has described, that is, a distal pancreatectomy, enucleation of tumors in the pancreatic head, and a peripancreatic and portal lymph node dissection.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
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