Henry Ford Hospital Medical Journal

Volume 35
Number 2 *Second International Workshop on MEN-2*

Article 3

6-1987

Impact of Prospective Screening for Multiple Endocrine Neoplasia Type 2

Robert F. Gagel

Armen H. Tashjian Jr.

Tim Cummings

Nick Papathanasopoulos

Seymour Reichlin

Impact of Prospective Screening for Multiple Endocrine Neoplasia Type 2

Robert F. Gagel,* Armen H. Tashjian, Jr, Tim Cummings, Nick Papathanasopoulos, and Seymour Reichlin

Prospective annual screening for hereditary medullary thyroid carcinoma (MTC) in the J-kindred, currently a 117-member family with multiple endocrine neoplasia type 2A, began in 1969. During the initial screening, 12 patients were found to have MTC. Subsequent screening has detected C-cell abnormalities (C-cell hyperplasia or microscopic MTC) in 22 of 23 additional family members thyroidectomized for abnormal calcium- or pentagastrin-provocative calcitonin (CT) test results. Seven of the initial 12 patients thyroidectomized in 1970 to 1971 and 19 of 23 individuals thyroidectomized since 1971 remain disease-free by all criteria; three patients thyroidectomized since 1971 have had clearly abnormal serum CT measurements on one or more provocative tests. The significance of these abnormal test results is unclear because normal values were obtained when the samples were measured in another CT radioimmunoassay. Urine catecholamine abnormalities have been detected in 19 family members since 1969, resulting in ten bilateral and eight unilateral adrenalectomies. Four of the patients with initial unilateral adrenalectomy required reoperation for a pheochromocytoma in the contralateral gland nine to 13 years later. Hyperparathyroidism has not been observed in any of the family members with early C-cell disease. We conclude that prospective screening for hereditary MTC predicts histologic C-cell abnormalities in affected individuals, and follow-up of these patients provides support for the conclusion that early thyroidectomy is curative in most patients. (Henry Ford Hosp Med J 1987;35:94-8)

Prospective screening for hereditary medullary thyroid carcinoma (MTC) began in 1969 when Melvin et al (1,2) studied J-kindred members, descendants from a large Swedish family affected with this disease (3), to determine whether measurement of serum calcitonin (CT) could correctly predict the presence of MTC. In their initial screening of the family, 12 individuals were found to have abnormal serum CT levels after a provocative calcium (Ca) infusion. Thyroidectomy in each of these individuals showed bilateral foci of MTC (1). Since the initial screening of the family, each unaffected family member over the age of five has been screened with a provocative Ca or pentagastrin test on a regular basis (annually in most cases) to determine whether it is possible to detect hereditary MTC in its earliest stages and effect a cure by total thyroidectomy. Previous reports from this study have shown that prospective screening detects early abnormalities of C-cells prior to the development of metastasis (4,5). Members of this kindred also have been shown to develop parathyroid abnormalities and adrenal medullary disease including pheochromocytoma (2,4) and adrenal medullary hyperplasia (4,6). This report focuses on the clinical course of those individuals prospectively screened for the abnormalities associated with this syndrome and describes the management used in this family.

Patients and Methods

Screening for MTC

The J-kindred is a large family (currently 117 members) with multiple endocrine neoplasia type 2A (MEN-2A) (2). Procedures used for the study of CT secretion in this family have been described (1,2,4,5). Each patient over the age of five has undergone a yearly Ca (15 mg elemental Ca/kg body weight) or pentagastrin (0.5 μg/kg, administered as an intravenous bolus over five seconds) test. Serum CT was measured by radioimmunoassay (RIA) (7) at appropriate time points as described (1,4,5). Basal serum CT concentrations in normal subjects ranged from nondetectable to 380 pg/mL; Ca or pentagastrin-stimulated levels did not exceed 550 pg/mL. Thyroidectomy has been recommended if the patient has shown an abnormal CT secretory response to at least two separate provocative tests. Total thyroidectomy was performed by the method of Crile (8).

Submitted for publication: April 9, 1987.
Accepted for publication: April 29, 1987.
*Address correspondence to Dr. Gagel, Laboratory for Molecular and Cellular Endocrinology, Veterans Administration Medical Center, 2002 Holcombe Blvd, Houston, TX 77030.

Histologic techniques for analysis of thyroid tissue and the criteria used for diagnosis of C-cell hyperplasia or carcinoma have been described (9).

During the past two years a more sensitive CT RIA has been used in addition to the standard assay. The kit for this assay (40-2125) was obtained from Nichols Institute Diagnostics (San Juan Capistrano, CA). This assay has a reported sensitivity of 3 pg/mL, and normal basal values are 3 to 36 pg/mL for men and 2 to 17 pg/mL for women. After a pentagastrin injection, normal stimulated values ranged from 6 to 106 pg/mL in men and 3 to 29 pg/mL in women. Adrenal medullary function was assessed by measurement of urine epinephrine and norepinephrine as described (4). Parathyroid hormone and serum Ca were measured by the Nichols Institute Reference Laboratories (San Juan Capistrano, CA), using a C-terminal RIA (1974 to 1983) and a mid-region assay (1984 to 1986).

Results

Clinical course of patients with MTC and C-cell hyperplasia

Thirty-five family members have been thyroidectomized since the start of prospective screening in 1969 (Fig 1). The operative and pathologic findings in the initial 12 patients (mean age 38.5 years) thyroidectomized between 1969 and 1971 have been reported (1,2). All of these patients had bilateral foci of MTC, seven of 12 with documented local nodal metastasis. An additional 23 patients (mean age 11.8 years) have been thyroidectomized since 1971 for the development of abnormal CT levels after provocative testing. Histologic examination of the thyroid gland showed C-cell hyperplasia in 13 patients, combined microscopic MTC and C-cell hyperplasia in nine patients, and no histologic abnormality in one patient (considered to be a false-positive test result) (4,5). None of the patients had histologic evidence of metastatic disease in local lymph nodes.

The 12 patients thyroidectomized during the initial screening have been followed annually or biannually in most cases (mean follow-up period of 14.5 years) with provocative tests (Ca or pentagastrin). Three of the 12 patients have died. One died secondary to metastatic rectal carcinoma (family tree #3, Fig 1), and another died from metastatic breast carcinoma (family tree #32, Fig 1), although both these patients were thought to have metastatic MTC because of persistent elevations of the serum CT after thyroidectomy. A third patient (family tree #1, Fig 1), as previously reported (6), died of coronary artery disease at age 64 with nondetectable CT levels after provocative testing and no disease detected at autopsy. Of the remaining nine living patients, seven have had consistently normal test results since thyroidectomy, whereas two are considered to have metastatic disease because of elevated CT levels basally or after provocative testing.

The 22 family members thyroidectomized for early C-cell disease between 1972 and 1983 have been followed with annual or biannual testing for a mean of 11 years. Thyroidectomy led to a reduction in the peak serum CT after a provocative pentagastrin test in each case. Nineteen of the 22 patients have had normal test results. Three of the 22 patients have had clearly abnormal CT levels either basally or after a pentagastrin test on one or more occasions, although there was no other clinical evidence of metastatic disease. Aliquots of the serum samples from

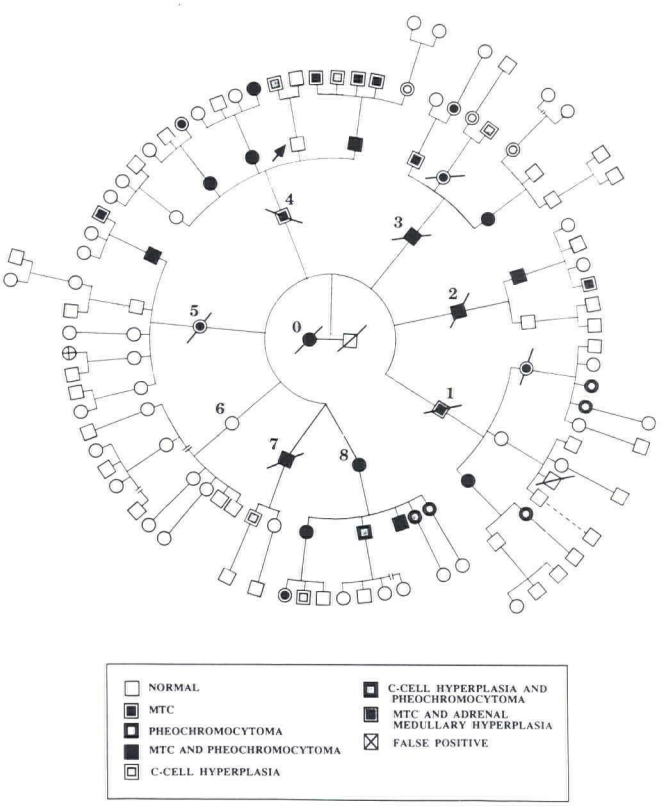

Fig 1—Pedigree of the J-kindred. The numbers 1 through 8 shown for the second generation can be used to identify specific family members. For example, the propositus (marked with an arrow) is the second son of patient #4 (family tree #42) and his two sons would have family tree #421 and #422. A crossbar through the individual symbol indicates the patient is dead. The individual labeled O is the individual born in the 1880s listed as J in the pedigree of the large Swedish kindred shown in Fig 1 of the paper by Telenius-Berg et al (3). This family tree was prepared according to March of Dimes criteria (Grendel Co, PO Box 733, Charleston, SC 29402).

the three patients with abnormal test results and two others with borderline test results from the most recent round of testing were assayed in our standard CT RIA and the Nichols RIA (Table). A comparison of values shows that all of the sera considered to be abnormal in our assay gave normal values when tested in the Nichols assay.

Parathyroid hormone measurements

Parathyroid hyperplasia is a prominent manifestation of the MEN-2A syndrome (2,10-13), and previous studies in this family have demonstrated elevated parathyroid hormone (PTH) values in 40% of family members. In addition, parathyroid hyperplasia was found in ten of the 12 original members thyroidectomized between 1969 and 1971, and four of 12 had a history of renal stones (2). To determine whether clinically apparent parathyroid disease preceded C-cell abnormalities, serum Ca levels were measured in all patients thyroidectomized

Table
Comparison of Abnormal or Borderline Basal or Stimulated Calcitonin Values in Two Radioimmunoassays

Family Tree Number	Type of Sample	Assay 1 (calcitonin pg/mL)	Assay 2
412	S	1,000	6
313	S	890	8
413	B	450	7
422	B	630	5
431	S	650	6

Basal (B) or peak stimulated (S) serum calcitonin during a pentagastrin test.
Assay 1 is our standard calcitonin radioimmunoassay, and assay 2 is the Nichols radioimmunoassay.

for early C-cell abnormalities. The serum Ca concentration was within the normal range in all patients. The serum PTH concentration was normal in seven of nine patients in whom measurements were made and was minimally elevated (< 5% above the upper limit of normal) in two patients. Postoperative PTH concentrations were available on 15 patients a mean of 9.9 years after thyroidectomy and were within the normal range for all patients. The serum Ca concentration has remained normal in all thyroidectomized patients with one exception. A 20-year-old woman (family tree #133, Fig 1) previously thyroidectomized (C-cell hyperplasia) with prethyroidectomy and postthyroidectomy normocalcemia developed hypercalcemia (serum Ca 10.5 to 11.6 mg%) with mid-normal PTH concentrations. She also had symptoms of a pheochromocytoma and urine catecholamine abnormalities. Following bilateral pheochromocytoma removal, her serum Ca normalized, and serum Ca and PTH measurements have remained normal (highest Ca value 10.3 mg) for nine years. We think it likely that the hypercalcemia was caused by the pheochromocytoma because of the immediate drop in the serum Ca after bilateral adrenalectomy.

Adrenal medullary disease

Nineteen patients have developed urine catecholamine abnormalities, which have resulted in ten bilateral adrenalectomies and eight unilateral adrenalectomies. The histologic lesion found at surgery in these patients was pheochromocytoma on a background of diffuse adrenal medullary hyperplasia in all adrenal glands except one in which adrenal medullary hyperplasia was noted. One patient (patient #7, Fig 1, who was thyroidectomized before 1969) with abnormal urine catecholamine levels declined adrenal surgery because of widely metastatic MTC. Postmortem examination showed bilateral pheochromocytomas. Another patient with proven MTC diagnosed before 1969 (patient #13, Fig 1) had been followed for 15 years with normal urine catecholamine levels. During the most recent testing, this 51-year-old woman was noted to have a 24-hour urine epinephrine two times the upper limit of normal. Because she was taking sympathomimetic drugs and theophylline for allergic lung disease, repeat urine catecholamine determinations with the patient off the medications were requested. She died suddenly before the repeat study could be done; a postmortem examination was not performed. Although the exact circumstances surrounding her death are unclear, the single urine catecholamine abnormality and her sudden death suggest the possibility of adrenal medullary disease. A third patient (family tree #1, Fig 1) with proven MTC, not included in these 19 patients because of consistently normal urine catecholamine levels, died of well-documented coronary artery disease at age 64 and at autopsy was shown to have bilateral adrenal medullary hyperplasia (6).

Four of the eight patients who underwent unilateral adrenalectomy have required removal of the contralateral adrenal gland nine to 13 years after initial adrenalectomy because of the development of urine catecholamine abnormalities and symptoms consistent with pheochromocytomas. Fig 2 shows longitudinal urine catecholamine measurements in one of these patients, which indicates that they may go for a prolonged period before requiring contralateral adrenalectomy. The other four patients with unilateral adrenalectomy have been followed for one, 11, 15, and 17 years without developing symptoms of pheochromocytomas or catecholamine abnormalities.

Discussion

Prospective screening for hereditary MTC

The value of prospective screening in the early detection of C-cell abnormalities has been established in this family (4,5) and several other kindreds (14-19). In each of our family members who developed disease, we were able to detect C-cell abnormalities before the development of local metastatic disease. In this family it appears that initiation of screening by the age of five years is adequate for detection of disease (20), but this may not be the case in all kindreds. In another large kindred with MEN-2A, one patient had an abnormal provocative CT test result on initial screening at age six with micrometastasis to local lymph nodes found at surgery (personal communication, Cynthia Torony). We have continued to recommend that screening start at age five in the J-kindred, but recognize that it might be necessary to initiate screening at an earlier age in other kindreds.

The most important finding in this study is absence of detectable disease in 19 of 22 patients a mean of ten years after thyroidectomy for C-cell disease. In the patients with abnormal or borderline values in our RIA, we performed CT measurements using a more sensitive assay and found normal CT values. Studies are currently underway to assay these same samples in the two-site immunoradiometric assay described by Motte et al (21). Although the abnormal values in our standard RIA may be artifactual, a problem seen in all CT RIAs (7,22,23), it will be important to determine whether there is persistent or recurrent MTC because of the possible application of recently described microsurgical approaches to this group of patients (24). Although we are optimistic at this time that thyroidectomy has resulted in a cure for this group of patients, continued follow-up for an additional ten to 20 years will be required before such a conclusion can be firmly stated.

Lack of evidence for parathyroid disease in early hereditary MTC

Our studies show that serum Ca and PTH values are normal prior to and ten years after thyroidectomy. This is in contrast to earlier studies in this and other families with advanced,

untreated MTC in which clinically detectable parathyroid abnormalities have been found in 10% to 20% of affected family members (2,10-13). Our findings make it difficult to support the hypothesis that the C-cell abnormalities in this disease are the result of chronic hypercalcemia caused by hyperparathyroidism, a concept proposed earlier (2,10). The one case of hypercalcemia noted in the patients with early C-cell disease occurred in association with bilateral pheochromocytomas.

Adrenal medullary disease

Management of adrenal medullary disease in this syndrome is difficult, and the correct therapeutic approach is controversial. We have removed only those adrenal glands which had a pheochromocytoma or distinct adrenal medullary enlargement demonstrable by angiography (before 1977), computed tomography, or magnetic resonance imaging scanning. Each patient with documented unilateral disease was offered bilateral adrenalectomy at the time of the primary operation, but all declined. The contralateral adrenal gland is routinely examined at surgery and removed if the operative findings do not confirm the radiologic evaluation. Of eight patients treated with unilateral adrenalectomy, it has been necessary to remove the contralateral adrenal gland in four patients an average of ten years after the primary operation; these results are not dissimilar to those described by other investigators (25). Other investigators have recommended bilateral adrenalectomy at the primary operation because of a family history of adrenal medullary malignancy (26-28) or because of concern about the risks of a second operation to remove the contralateral adrenal gland. We have not observed adrenal medullary malignancy in the J-kindred, and recognize that risks are associated with development of adrenal insufficiency following bilateral adrenal removal and that a different set of risks are associated with the removal of only a single adrenal gland. We have tried to minimize the total risk by combining unilateral adrenalectomy, where appropriate, with yearly postoperative urine catecholamine measurements. Continued follow-up is necessary before firm conclusions can be drawn about the correct management of adrenal medullary disease in this syndrome.

Prospective screening for the several manifestations of MEN-2 has had a positive impact on the quality of life for this family and may prove, with continued follow-up, to have provided a cure for the malignant manifestations of the syndrome.

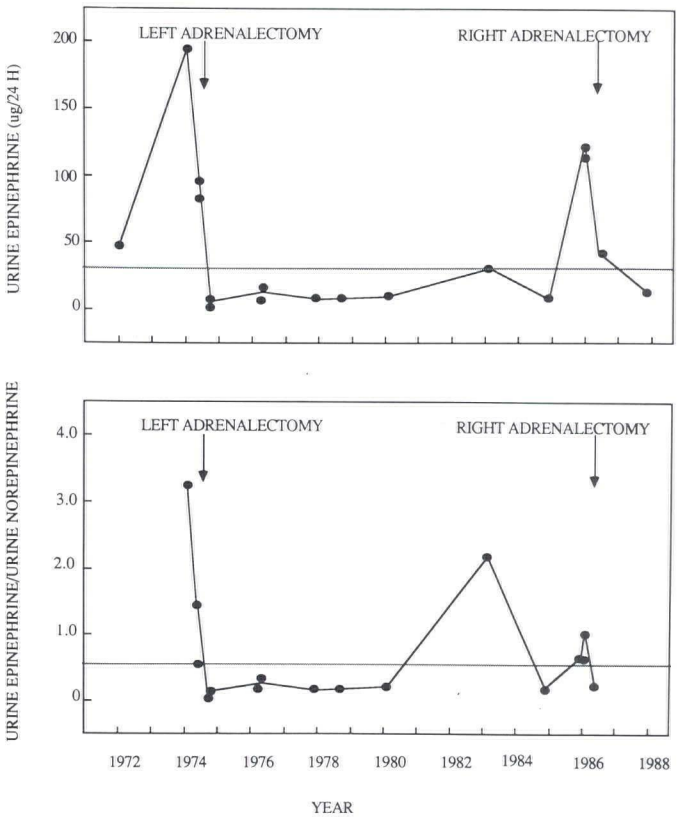

Fig 2—Twenty-four hour urine epinephrine and the epinephrine/norepinephrine ratio in a patient (family tree #22) who had a left adrenalectomy in 1974. After adrenalectomy, the 24-hour urine epinephrine excretion and the epinephrine/norepinephrine ratio returned to normal for nine years before development of symptoms and objective demonstration of a pheochromocytoma led to the removal of the contralateral adrenal gland. Each point in the upper panel shows the results of a single 24-hour urine collection. The points in the lower panel show the epinephrine/norepinephrine ratio calculated by dividing the 24-hour excretion of epinephrine by the 24-hour excretion of norepinephrine as previously described (4,29). The dotted line in each panel shows the upper limit of normal for each measurement.

Acknowledgments

This research was supported by National Institutes of Health grants AM31307, AR10206, M01RR00054, and the Merit Review grant from the Veterans Administration.

References

1. Melvin KEW, Miller HH, Tashjian AH Jr. Early diagnosis of medullary carcinoma of thyroid gland by means of calcitonin assay. N Engl J Med 1971;285:1115-20.

2. Melvin KEW, Tashjian AH Jr, Miller HH. Studies in familial (medullary) thyroid carcinoma. Recent Prog Horm Res 1972;28:399-470.

3. Telenius-Berg M, Berg B, Hamberger B, et al. Impact of screening on prognosis in the multiple endocrine neoplasia type 2 syndromes: Natural history and treatment results in 105 patients. Henry Ford Hosp Med J 1984;32:225-32.

4. Gagel RF, Melvin KEW, Tashjian AH Jr, et al. Natural history of the familial medullary thyroid carcinoma-pheochromocytoma syndrome and the identification of preneoplastic stages by screening studies: A five-year report. Trans Assoc Am Physicians 1975;88:177-91.

5. Graze K, Spiler IJ, Tashjian AH Jr, et al. Natural history of familial medullary thyroid carcinoma: Effect of a program for early diagnosis. N Engl J Med 1978;299:980-5.

6. DeLellis RA, Wolfe HJ, Gagel RF, et al. Adrenal medullary hyperplasia: A morphometric analysis in patients with familial medullary thyroid carcinoma. Am J Pathol 1976;83:177-96.

7. Tashjian AH Jr, Voelkel EF. Radioimmunoassay of human calcitonin: Application of affinity chromatography. In: Jaffe BM, Behrman H, eds. Methods of hormone radioimmunoassay. New York: Academic Press, 1974:199-214.

8. Crile G Jr. The fallacy of the conventional radical neck dissection for

papillary carcinoma of the thyroid. Ann Surg 1957;145:317-20.

9. DeLellis RA, Nunnemacher G, Wolfe HJ. C-cell hyperplasia: An ultrastructural analysis. Lab Invest 1977;36:237-48.

10. Steiner AL, Goodman AD, Powers SR. Study of a kindred with pheochromocytoma, medullary carcinoma, hyperparathyroidism and Cushing's disease: Multiple endocrine neoplasia, type 2. Medicine (Baltimore) 1968;47:371-409.

11. Keiser HR, Beaven MA, Doppman J, Wells SA Jr, Buja LM. Sipple's syndrome: Medullary thyroid carcinoma, pheochromocytoma, and parathyroid disease, studies in a large family. Ann Intern Med 1973;78:561-79.

12. Wells JA Jr, Ontjes DA. Multiple endocrine neoplasia, type II. Annu Rev Med 1976;27:263-8.

13. Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid: A study of the clinical features and prognostic factors in 161 patients. Medicine (Baltimore) 1984;63:319-42.

14. Bigner SH, Mendelsohn G, Wells SA Jr, Cox EB, Baylin SB, Eggleston JC. Medullary carcinoma of the thyroid in the multiple endocrine neoplasia IIA syndrome. Am J Surg Pathol 1981;5:549-72.

15. Sizemore GW, Heath H III, Carney JA. Multiple endocrine neoplasia type 2. Clin Endocrinol Metab 1980;9:299.

16. Sizemore GW, Carney JA, Heath H. Epidemiology of medullary carcinoma of the thyroid gland: 5 year experience (1971-1976). Surg Clin North Am 1977;57:633-45.

17. Linehan WM, Farrell RE, Cooper CW, Wells SA Jr. Analysis of pentagastrin and calcium as thyrocalcitonin secretagogues in the early diagnosis of medullary carcinoma of the thyroid gland. Surg Forum 1977;28:110-2.

18. Emmertsen K, Elbrond O, Nielsen HE, et al. Familial medullary thyroid carcinoma in multiple endocrine neoplasia (MEN) IIa: Diagnosis and problems in treatment. Eur J Cancer Clin Oncol 1982;18:645-50.

19. Jackson CE, Talpos GB, Kambouris A, Yott JB, Tashjian AH Jr, Block MA. The clinical course after definitive operation for medullary thyroid carcinoma. Surgery 1983;94:995-1001.

20. Gagel RF, Jackson CE, Block MA, et al. Age-related probability of development of hereditary medullary thyroid carcinoma. J Pediatr 1982;101:941-6.

21. Motte P, Ait-Abdellah M, Vauzelle P, Gardet P, Bohuon C, Bellet D. A two-site immunoradiometric assay for serum calcitonin using monoclonal antipeptide antibodies. Henry Ford Hosp Med J 1987;35:129-32.

22. Body J-J, Heath H III. Nonspecific increases in plasma immunoreactive calcitonin in healthy individuals: Discrimination from medullary thyroid carcinoma by a new extraction technique. Clin Chem 1984;30:511-4.

23. Deftos LJ, Bury AE, Habener JF, Singer FR, Potts JT Jr. Immunoassay for human calcitonin. II. Clinical studies. Metabolism 1971;20:1129-37.

24. Tisell L-E, Hansson G, Jansson S, Salander H. Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. Surgery 1986;99:60-6.

25. Tibblin S, Dymling J-F, Ingemansson S, Telenius-Berg M. Unilateral versus bilateral adrenalectomy in multiple endocrine neoplasia IIA. World Surg 1984;7:201-8.

26. Carney JA, Sizemore GW, Sheps SG. Adrenal medullary disease in multiple endocrine neoplasia, type 2: Pheochromocytoma and its precursors. Am J Clin Pathol 1976;66:279-90.

27. Lips CJM, Minder WH, Leo JR, Alleman A, Hackeng WHL. Evidence of multicentric origin of the multiple endocrine neoplasia syndrome type 2A (Sipple's syndrome) in a large family in The Netherlands: Diagnostic and therapeutic implications. Am J Med 1978;64:569-78.

28. Sisson JC, Shapiro B, Beierwaltes WH. Scintigraphy with I-131 MIBG as an aid to the treatment of pheochromocytomas in patients with the multiple endocrine neoplasia type 2 syndromes. Henry Ford Hosp Med J 1984;32:254-61.

29. Takai S-I, Miyauchi A, Matsumoto H, et al. Multiple endocrine neoplasia type 2 syndromes in Japan. Henry Ford Hosp Med J 1984;32:246-50.

"Disease is very old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible."
J.M. Charcot (1825-1893)