MULTIPLE ENDOCRINE NEOPLASIA

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Pluriglandular neoplasia has been recognized at least since the turn of the century (1). Beginning with a "report of eight cases in which parathyroids, pituitary, and pancreatic islets were involved" by Underdahl, Woolner and Black in 1953 (2), multiple endocrine neoplasia (MEN) has emerged as a distinct clinical phenomenon. Studies of patients with MEN syndromes and of their families have revealed several important features. First, family pedigrees of most cases demonstrate numerous members with similar patterns of endocrine gland involvement. As initially suggested by Wermer in 1954 (3), it is now clearly established that familial aggregation is the result of a single autosomal gene mutation transmitted in a dominant mode with a high degree of penetrance. The expressivity of the mutation within and among families may be quite varied however (Fig. 1). Second, at least three patterns of endocrine gland involvement are currently recognized. These are (a) parathyroid hyperplasia associated with pancreatic islet cell adenoma or carcinoma and adenoma or hyperplasia of the anterior pituitary; (b) medullary carcinoma of the thyroid associated with pheochromocytoma and parathyroid hyperplasia, and (c) medullary carcinoma of the thyroid associated with pheochromocytoma and multiple mucosal neuromas. These syndromes are designated MEN I (Wermer's syndrome), MEN II (or IIa) (Sipple's syndrome), and MEN III (or IIb) (multiple mucosal neuroma syndrome), respectively. Overlap of syndromes has been observed but for the most part such cases are sporadic with no evidence of familial involvement (4-5). [One exception in which overlap may occur is a familial association of pheochromocytoma with pancreatic islet cell tumor (6-8).] Third, evidence to date suggests that each component of the various syndromes develops independently of the others. That is, for example, in MEN II patients with parathyroid hyperplasia, the parathyroid abnormality arises as a primary disorder and not in response to stimulation by calcitonin produced by the medullary thyroid carcinoma. However, modulations by one disorder of the clinical expression of another may occur in certain instances. Fourth, the spectrum of pathologic findings in involved endocrine glands in patients with MEN range from hyperplasia to adenoma to carcinoma. (Thus in many cases multiple endocrine *neoplasia* is not a precise term.) For several of the disorders it is established that adenomas or carcinomas evolve from antecedent hyperplasia (9, 10). Furthermore within any one gland adenomas or carcinomas are usually multicentric. Fifth, screening relatives of MEN patients who are at high risk for developing endocrine tumors is crucial to detect involvement at an early stage of the disease, before metastases (medullary thyroid carcinoma) or complications of excessive hormonal secretion (gastrin, catecholamines, parathyroid hormone) have developed.

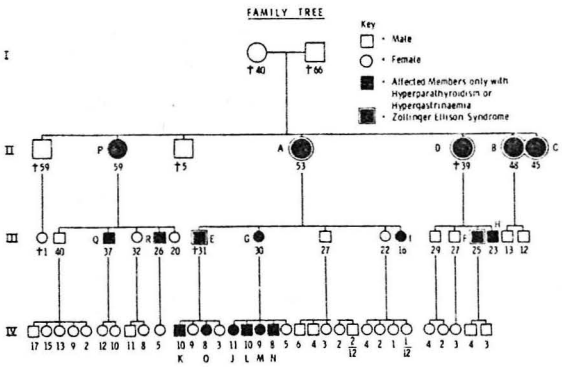

Fig. 1A Pedigree of a family with MEN I.

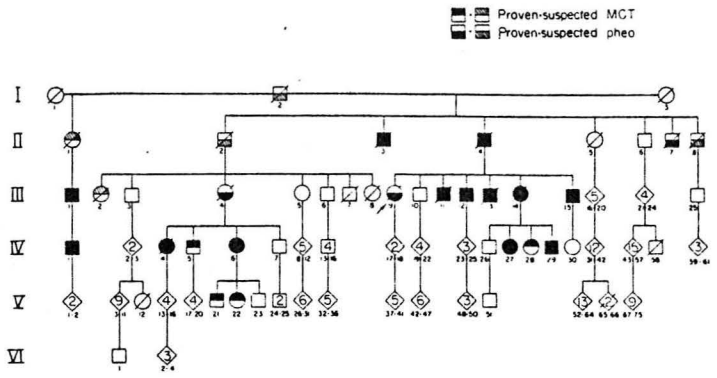

Fig. 1B Pedigree of a family with MEN II.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE I (WERMER'S SYNDROME)

The principal features of MEN I are hyperparathyroidism, tumors of the pancreatic islet cells, and anterior pituitary adenomas. Pancreatic and pituitary tumors may be secretory or nonsecretory. Carcinoid tumors, primarily bronchial and duodenal, as well as subcutaneous and visceral lipomas occur with increased frequency in patients with MEN I and therefore are also considered integral components of the syndrome. Adrenocortical lesions (adenomas and hyperplasia) as well as thyroid disease are reported in patients with MEN I but these lesions are commonly seen in routine autopsy series (11, 12), and are probably in most instances not related to the underlying genetic disorder.

The clinical expression of each of the 3 major components of MEN I within and among affected families is highly variable. However, evidence of hyperparathyroidism is essentially always present at the time diagnosis is established (Table I) (13). [Members of MEN I kindreds with hyperparathyroidism alone and kindreds with isolated familial hyperparathyroidism (probably a form fruste of MEN I) (14, 15) are not considered in Table I.] Of 122 cases reported in the literature between 1963 and 1979 (reviewed in reference 13) 97 percent had hyperparathyroidism. Only a third had involvement of all 3 endocrine glands at the time the report was made. Pancreatic tumors occurred in 82 percent and pituitary tumors in 54 percent of cases. It is likely however that combined pituitary, parathyroid, and pancreatic disease is eventually present in virtually all affected patients with MEN I as indicated by a thorough review of autopsy findings (16).

Table 1. Pattern of gland involvement in MEN I .

Pattern of involvement	Number of cases	%
Parathyroids, pituitary and endocrine pancreas	40	33
Parathyroids and endocrine pancreas	56	46
Parathyroids and pituitary	22	18
Pituitary and endocrine pancreas	4	3

Symptoms of endocrine disease typically appear during the third to fifth decade (Fig. 2) but screening programs may identify affected but asymptomatic individuals at an earlier age. In such programs asymptomatic hypercalcemia is the most frequently detected abnormality but asymptomatic fasting hypergastrinemia and unrecognized pituitary disease may be uncovered as well (13, 17). Morbidity and mortality in patients with MEN I are primarily related to the pancreatic component of the disorder, specifically to complications of gastrin-secreting tumors (Table II) (13).

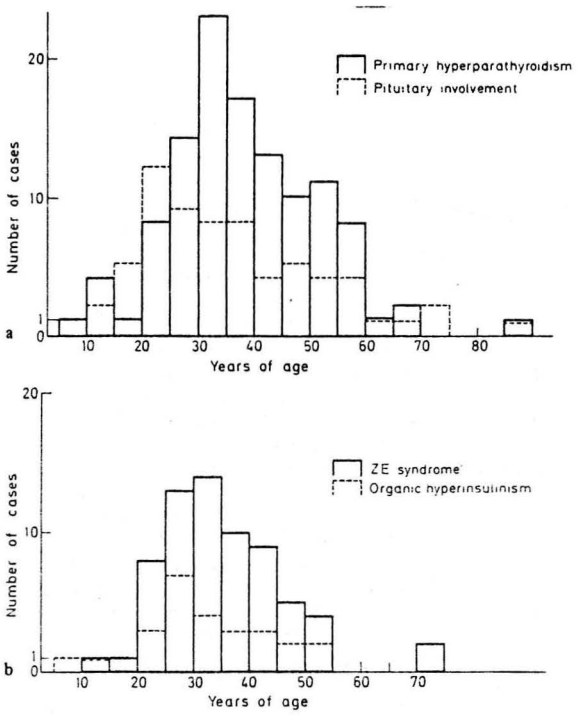

Fig. 2 Age at onset of disease or detection of abnormality in patients with MEN I.
a. Primary hyperparathyroidism and pituitary involvement.
b. ZE syndrome and organic hyperinsulinism.

MEN I is a rare disorder with an estimated prevalence of between 0.02 to 0.2 per thousand (13). Its importance however is magnified by its transmission as an autosomal dominant mutation with high penetrance. Each first-degree relative of an affected patient has a 50 percent risk of inheriting the disease. Family histories obtained from identified patients usually do not provide an accurate estimate of the magnitude of involvement with MEN I in the family.

Table II. Causes of death related to MEN I.

Cause of death	Patients	%
Ulcer complications (perforation, bleeding)	12	33
Following laparotomy for (sub) total gastrectomy and/or pancreatectomy	7	19
Sequel of other operations	3	8
Metastatic tumors, cachexia	4	11
Hyperparathyroid crisis	4	11
Pituitary tumor	3	8
Infections	2	6
Hypoglycemic coma	1	3

Hyperparathyroidism

Approximately 10 to 15 percent of cases of primary hyperparathyroidism occur in a familial pattern (14, 18), and most if not all of these represent patients with MEN I or II (14, 15). Many MEN I families have members whose only endocrinologic disorder at the time of study is hyperparathyroidism (14, 15, 19-22). There are other families in whom hyperparathyroidism is the sole endocrine disorder (23-28). Such families most likely are affected with the same gene mutation responsible for MEN I, but in whom expression of the mutation is limited to the parathyroid glands. Alternatively, reports of familial hyperparathyroidism may be due to incomplete analysis of kindred members or examination of very small kindreds such that pancreatic and/or pituitary involvement are undetected.

Multiple parathyroid gland involvement, described in more than 80 percent of cases, is the characteristic finding in MEN I/familial hyperparathyroidism (13, 20-23). Of patients with primary hyperparathyroidism who do have multiple gland involvement, a high proportion have MEN (29). Both hyperplasia and multiple adenomas are reported but pathologic distinction between the two is frequently tenuous. It is the consensus of most investigators that hyperplasia -- diffuse, asymmetric, or nodular -- is the primary parathyroid lesion in patients with MEN I. True adenomas, when they do occur, may have evolved from antecedent hyperplasia.

Hyperparathyroidism is responsible for initial symptoms of MEN I in only 20 to 30 percent of patients (13). The spectrum of symptoms and signs of hyperparathyroidism in MEN I is similar to that observed in sporadic primary hyperparathyroidism (30). Urolithiasis is found in approximately 45 percent of patients and evidence of osteitis fibrosa in approximately 25 percent; about 50 percent have asymptomatic hypercalcemia. Symptoms of acid peptic disease, related either to the hyperparathyroidism per se or to a gastrin-secreting tumor, are also frequent in patients with MEN I-associated hyperparathyroidism. It has been postulated that in some MEN I patients with hypergastrinemia increased gastrin secretion is secondary to hypercalcemia. However, patients with hypercalcemia due to sporadic primary hyperparathyroidism with and without peptic ulcer disease have normal fasting serum gastrin levels (31). Thus, the presence of hypercalcemia in an MEN I patient with gastric hyperacidity does not affect the interpretation of an elevated serum gastrin; hypergastrinemia and peptic ulcer disease in such a patient is not due to hypercalcemia but to a gastrin-secreting tumor.

Diagnosis of hyperparathyroidism is established as in sporadic hyperparathyroidism -- documentation of hypercalcemia associated with an inappropriately elevated serum parathyroid hormone (PTH) level. However those kindreds in which MEN I is suspected on the basis of familial hypercalcemia without evidence of pancreatic or pituitary involvement must be differentiated from kindreds with familial hypercalcemic hypocalciuria (FHH) (32). Findings of onset of hypercalcemia during the first decade of life; lack of clinical evidence of PTH excess; hypocalciuria; and hypomagnesemia are most consistent with the diagnosis of FHH.

The indications for parathyroidectomy in patients with MEN I-associated hyperparathyroidism are similar to those with sporadic disease. Evidence of bone disease, a history of urolithiasis, mental status changes, and/or a serum calcium greater than 11.5 mg/dl are indications for prompt surgical intervention. Although asymptomatic patients with sporadic primary hyperparathyroidism who have only mild hypercalcemia are frequently followed without immediate parathyroidectomy, asymptomatic MEN I patients should probably be definitively treated at the time diagnosis is established for two reasons. First, hyperparathyroidism in many such MEN I patients is detected at a young age as part of family screening studies; therefore they are at risk for development of complications of hyperparathyroidism for a much longer period of time. Second, although hypercalcemia associated with sporadic hyperparathyroidism does not cause hypergastrinemia (31), it is still possible that prolonged hypercalcemia in MEN I patients may be a stimulus for tumor development in genetically predisposed islet cells. Serum gastrin levels do fall (though not to normal) following parathyroidectomy in patients with MEN I and Zollinger-Ellison syndrome (ZES) (33, 35). Because of the high frequency of multiple parathyroid gland involvement in MEN I the surgical procedure in all cases should be subtotal parathyroidectomy. However, even with subtotal parathyroidectomy 4 of 12 patients with MEN I-associated hyperparathyroidism in a recently reported series had persistent or recurrent hypercalcemia; 3 others developed permanent hypoparathyroidism (36). Similar experience has led some surgeons to advocate total parathyroidectomy with autotransplantation of parathyroid tissue into forearm musculature (37), particularly in MEN I patients with parathyroid hyperplasia (36). Regardless of surgical approach, long-term follow-up of parathyroid status is mandatory.

Pancreatic Islet Cell Tumors

Most of these tumors secrete gastrin or insulin and produce distinct clinical syndromes of hormone excess; some are nonsecretory but many of these undoubtedly escape detection (Table III). Some islet cell tumors secrete pancreatic polypeptide, a peptide hormone for which there are no recognized clinical sequelae of overproduction. Other tumors are the site of ectopic hormone production; both ACTH (38) and calcitonin (39) are recognized as secretory products of pancreatic tumors. Although not reported in patients with MEN I, Cushing's syndrome and acromegaly may in some patients be the result of pancreatic tumor secretion of corticotropin releasing factor (CRF) and growth hormone releasing factor (GHRF) (40, 41) respectively. Even though most pancreatic tumors secrete only one hormone and thereby produce one distinct clinical syndrome, cells containing other peptide hormones are usually located by immunohistochemical techniques within the tumor (42). As is the case with other tumors associated with MEN syndromes, pancreatic tumors are frequently multicentric. Although not recognized clinically in most cases, islet cell hyperplasia or nesidioblastosis may precede tumor development (43-45).

Table III. Pancreatic involvement in MEN I.

Clinical syndrome	A Percentage of cases
Zollinger-Ellison syndrome	67
Organic hyperinsulinism	29
ZE s. and organic hyperinsulinism	9
Glucagon-secreting tumors	4
ZE s. associated with hyperglucagonism	2
ZE s. associated with hyperinsulinism and hyperglucagonism	1
WDHA syndrome	1
Cushing's syndrome	2
Asymptomatic (?) tumors	10

A, Present series of 100 out of 122 MEN I cases (82%) reported in the literature 1963–1979

Gastrinoma. Approximately two-thirds of islet cell tumors in patients with MEN I secrete gastrin. The virulent peptic ulcer disease associated with gastrinomas -- the Zollinger-Ellison syndrome — is the most frequent cause of morbidity and mortality in MEN I (13, 46). The prevalence of MEN I in patients with ZES varies markedly among clinical series (47-49), but has been reported to be as high as 60 percent. Thus all patients with documented ZES should be screened for evidence of MEN I. In two European series all ZE patients with MEN I had hyperparathyroidism (48, 50).

Clinical sequelae of hypergastrinemia are the same in patients with MEN I-associated disease as in those with sporadic ZES. In both groups the availability of serum gastrin measurements has enabled diagnosis at an earlier and therefore less severe stage of the disease. Some MEN I patients with asymptomatic hypergastrinemia have been detected through family screening studies (17, 51). Multiple primary tumors are frequently present in both sporadic ZES (40-60 percent) and MEN I-associated ZES (approximately 70 percent), and are located either in the pancreas or duodenal wall. Carcinoma may be slightly more common in those with sporadic disease (50 to 70 percent vs. approximately 40 percent) (13).

Diagnosis of ZES is established by documenting coexistent hypergastrinemia and gastric hyperacidity in patients who do not have a retained gastric antrum or antral G-cell hyperplasia. The criteria considered essential for diagnosis have changed considerably since the gastrin radioimmunoassay has become generally available (Table IV: 1955-1970 vs. 1971-1978 patients) (49). A gastrin level was instrumental in diagnosis in 95% of the patients evaluated during the years 1971-1978 by Deveney et al. All patients with basal gastrin levels greater than 300 pg/ml had ZES (Fig. 3) (49). However 22 patients with gastrinomas had serum gastrin levels between 75 and 300 pg/ml, a range in which some duodenal ulcer patients without gastrinoma also fell. Identification of ZE patients who have basal gastrins in this intermediate range is most often possible utilizing a provocative test with either intravenous calcium (Fig. 4) or secretin (Fig. 5). In this series of Deveney et al., an increment in gastrin concentration of greater than 400 pg/ml at

any point during the 3-hour calcium infusion or an increase of 110 pg/ml or more after secretin injection was diagnostic of ZES (49). Ninety to 95% of ZE patients have a positive response to one or both agents. Similar results with secretin provocative testing have been obtained in a series restricted to MEN I-associated ZES patients (51). Duodenal ulcer patients as well as patients with retained antrum or antral G-cell hyperplasia have negligible gastrin responses to calcium or secretin. Patients with the latter syndrome may in fact have a decrease in serum gastrin following secretin (51); they are further distinguished from ZE patients by a marked response of gastrin to a standard test meal stimulus, a response also observed in duodenal ulcer patients (Fig. 6).

Table IV. Factors essential for diagnosis of ZE syndrome.

Finding	Number of Patients 1955–1970 (27 Patients)	1971–1978 (38 Patients)
History of virulent ulcer disease	15 (56%)	9 (24%)*
Upper gastrointestinal x-rays	5 (19%)	9 (24%)
Family history	5 (19%)	2 (5%)
MEA	13 (47%)	5 (13%)*
Gastric analysis		
All patients	11 (41%)	22 (58%)
Unoperated patients	6/6 (100%)	20/23 (87%)
Basal gastrin level	3 (11%)	36 (95%)*
Provocative test for gastrin	1 (4%)	18 (47%)*
Demonstration of tumor	16 (43%)	2 (5%)*

* $p < .05$.

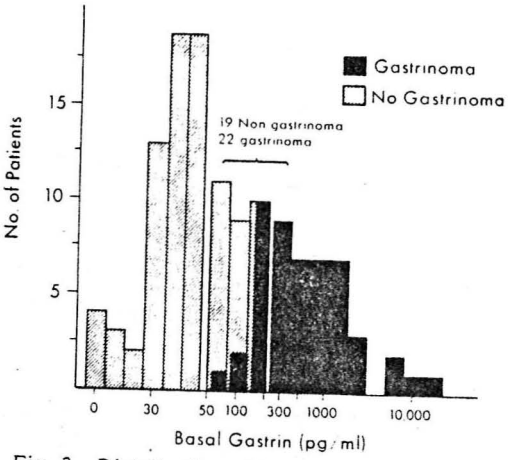

Fig. 3 Distribution of basal gastrin levels in patients with and without gastrinoma.

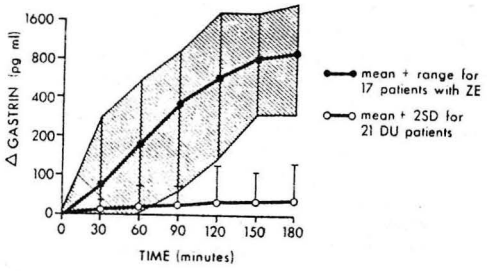

Fig. 4 Gastrin response to intravenous infusion of calcium gluconate (4 mg Ca^{++}/kg·h for 3 hours) in patients with and without ZE syndrome.

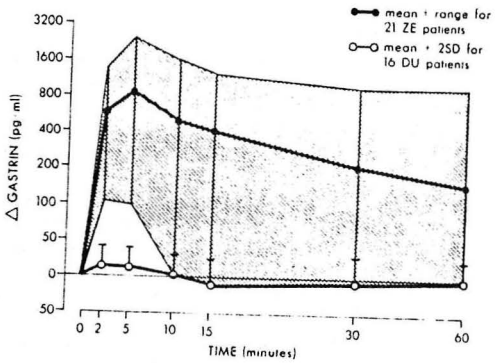

Fig. 5 Gastrin response to intravenous injection of secretin 2U/kg.

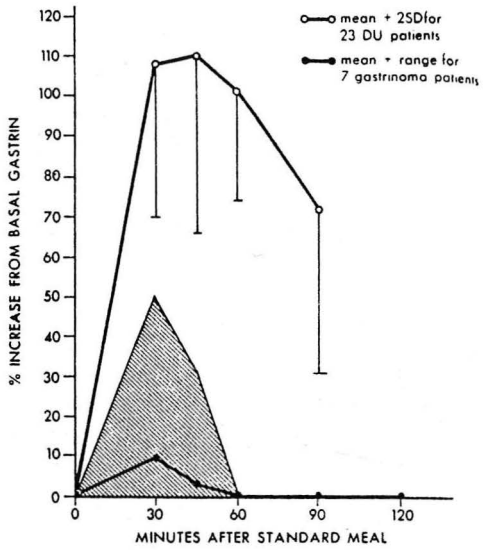

Fig. 6 Gastrin response to a standard test meal (30 g protein, 20 g fat, 25 g carbohydrate) in patients with and without gastrinoma.

Effective treatment of patients with ZES, both sporadic and MEN I-associated, usually necessitates total gastrectomy. In the less frequent circumstance that a solitary gastrinoma is identified in the body or tail of the pancreas, tumor excision is curative (unless the lesion is malignant and has already metastasized). In 30 to 60 percent of patients a tumor is not identified at laparotomy (49). Attempts at preoperative localization with angiography and computed tomography are typically unsuccessful (52, 53). Selected patients with ZES may be effectively treated with an H_2 receptor blocking drug such as cimetidine or ranitidine (54, 55). However prolonged follow-up of patients treated with such drugs is not yet available and short-term treatment failures have been reported (49, 55). Optimal management of the patient with asymptomatic hypergastrinemia is not clear. Laparotomy soon after detection of the elevated gastrin has been tentatively recommended for such patients since morbidity may be prevented or delayed if a solitary tumor is identified and resected (13). As described earlier, although gastrin levels usually decrease to some extent in hyperparathyroid-ZE patients following parathyroidectomy and normalization of serum calcium, serum gastrins still remain elevated.

Insulinoma. Insulin-secreting tumors account for approximately one-third of islet cell neoplasms in MEN I. Occasional patients (about 10 percent of MEN I patients with pancreatic tumors) have both gastrin- as well as insulin-secreting tumors with clinical features of ZES and hyperinsulinism (56, 57). These combined tumors may arise synchronously or metachronously. Multiplicity of insulin-secreting tumors is a much more prevalent finding in patients with MEN I-associated insulinoma (75-90 percent of patients with MEN I have more than one tumor) than in unselected cases (multiple tumors found in only 10 percent) (13); this contrasts with the high frequency of multiple gastrin-secreting tumors in both sporadic and MEN I-associated ZES. Malignancy is less common in insulin-secreting tumors than in gastrinomas (25 percent versus 40 percent), but the percentage of

malignant insulinomas in patients with MEN I is somewhat greater than in those with sporadic insulinoma (5-15%) (13, 58). The prevalence of MEN I among all patients with insulinoma is quite low -- approximately 4 percent (58); this finding also contrasts with the high prevalence of MEN I among patients with ZES. The familial occurrence of insulinomas without other evidence of MEN (59) may, as in families with isolated hyperparathyroidism, be a form fruste of MEN I.

Diagnosis of insulinoma is pursued in patients with a history of symptoms suggestive of hypoglycemia. Documentation of fasting hypoglycemia associated with an inappropriately elevated plasma insulin level is necessary to make the diagnosis. An insulin:glucose ratio greater than 0.3 is highly suggestive of hyperinsulinism. During a fast the insulin:glucose ratio in a patient with an insulinoma increases instead of decreases. Occasionally measurement of plasma proinsulin and/or C-peptide may be necessary to confirm the diagnosis. Hypoglycemia due to hypopituitarism in a patient with MEN I and a large pituitary tumor is unusual. Preoperative localization of the insulinoma with selective angiography or computed tomography may be helpful (53), but even in the case of a single tumor visualized in the tail or body of the pancreas, distal pancreatectomy is probably the initial procedure of choice in a patient with MEN I because of the frequency of multiple tumors. If hypoglycemia persists following pancreatectomy because of residual pancreatic or metastatic disease, diazoxide may be useful in managing the patient. Follow-up total pancreatectomy should be offered patients in whom there is no evidence of metastases. In the case of metastatic disease a trial of streptozotocin or DTIC (60) may provide palliation.

Other pancreatic tumors. Hyperglucagonemia is not an uncommon finding in patients with MEN I (43, 61). However in only a few MEN patients has a glucagonoma actually been demonstrated (62), and none has had the typical skin eruption, glossitis or stomatitis characteristically associated with glucagon-producing tumors. The only finding referable to an elevated glucagon level in some patients is glucose intolerance or frank diabetes mellitus; frequently there are no clinical endocrinologic correlates of hyperglucagonemia or of histologically demonstrated α cell adenomas (56, 61-63). Even in MEN I patients who do have hyperglycemia, consideration should be given to possibilities other than glucagonoma to explain glucose intolerance -- these include excess secretion of growth hormone or cortisol as well as primary diabetes mellitus. Usually patients with hyperglucagonemia have concomitant hypergastrinemia and/or hyperinsulinemia with clinical evidence of ZES and hyperinsulinism (61). Gastrinomas and insulinomas frequently do contain glucagon-immunoreactive cells, so that hyperglucagonemia in patients with either of these tumors is not necessarily due to a glucagonoma per se. Furthermore hyperglucagonemia in some patients may be associated with α cell hyperplasia with or without evidence of tumor elsewhere in the pancreas.

Vasoactive intestinal peptide (VIP)-secreting pancreatic tumors have not been rigorously documented in patients with MEN I by demonstration of elevated serum or tumor content of VIP. However one of the original 9 patients with watery diarrhea, hypokalemia, and achlorhydria (WDHA) reported by Verner and Morrison did have a pituitary adenoma in addition to an islet cell tumor (64). Another patient with the WDHA syndrome who was subsequently reported had hyperparathyroidism, 2 islet cell tumors, and a family history suggestive of MEN (65).

Elevated serum levels of pancreatic polypeptide (PP) have been reported in a high percentage of patients with MEN I-associated pancreatic tumors (66). No clinical correlate of elevated PP levels is recognized, but it has been suggested that measurement of PP is a useful screening procedure for detection of otherwise silent pancreatic neoplasms in MEN families (66). However there are some factors

that mitigate against its proposed usefulness as a screening tool. First, elevated serum PP levels, as in the case of hyperglucagonemia, may be due to PP cell hyperplasia without tumor (67). Second, in many MEN I patients in whom elevated PP levels have been found, hypergastrinemia with ZES or hyperinsulinemia with hypoglycemia has also been present (67, 68). In one recent series no MEN I patient had elevated serum PP levels who did not have a previously recognized pancreatic tumor (68). Thus, diagnosis of pancreatic tumor is usually established by clinical features of excess hormonal secretion and does not rely on measurement of a serum PP level.

Pituitary Adenomas

Although the incidence of pituitary adenomas in several large series of patients with MEN I is 50 to 60 percent (13, 46), it is likely, based on a careful autopsy series, that the incidence of these tumors is much higher (16). Clinical manifestations, as in patients with non-MEN-associated lesions, depend on both tumor size as well as secretory status. Prolactin secretion has been documented in a high proportion of patients with adenomas (69-72); in nonselected series prolactinomas account for as many as 60 to 70 percent of pituitary tumors. Many if not most tumors characterized as chromophobe prior to the capability to detect prolactin in serum and tissue are prolactin-secreting (73). Growth hormone-secreting tumors are also relatively frequent in patients with MEN I, accounting for 20 to 27 percent of cases with adenomas (13, 46). ACTH secretion by a pituitary tumor in MEN I is rare (13). Hypopituitarism is present in about a fourth of MEN I patients with adenomas (13) and can be attributed either to pituitary compression by tumor, or, in the case of isolated hypogonadotropism in patients with prolactin-secreting tumors, to hyperprolactinemia (74).

Diagnosis of pituitary tumor is based on demonstration of excess prolactin, growth hormone or ACTH and/or radiographic evidence of tumor by computed tomography. Some MEN I patients with acromegaly are reported to have eosinophilic hyperplasia rather than a distinct adenoma. This observation raises the possibility that acromegaly in such cases may be secondary to stimulation of growth hormone secretion by a GHRF-producing pancreatic tumor. This phenomenon has not been documented in a patient with MEN however.

Management of a pituitary tumor is similar in MEN I patients as in non-MEN I-associated cases. Definitive treatment of all growth hormone-and ACTH-secreting tumors is mandatory; hypophysectomy, by a transsphenoidal approach if feasible, is usually the initial approach. Residual tumor requires management with radiation therapy postoperatively. Endocrine deficiencies, the result of tumor or of treatment, require appropriate replacement therapy. Nonsecreting or prolactin-secreting pituitary macroadenomas (tumors with a diameter greater than 10 mm), with or without suprasellar extension, should be managed in a similar manner. Optimal management of patients with prolactin-secreting microadenomas must be individualized and consists of either transsphenoidal hypophysectomy, bromocriptine, or close follow-up without specific treatment.

Other Endocrine Disorders

Adrenocortical hyperplasia or adenomas, only rarely associated with increased glucocorticoid or mineralocorticoid secretion, are reported in approximately 25 to 40 percent of patients with MEN I (13, 46). However that primary adrenal involvement is a direct consequence of the MEN mutation is not unequivocally established. Incidental, nonfunctional adrenal adenomas are recognized in up to 9 percent of autopsy cases (75), and in one autopsy survey, incidental adrenocortical lesions were found in about one-third of cases (11).

Furthermore the rare functioning lesions of the adrenals in patients with MEN I such as adrenocortical hyperplasia associated with hypercortisolism are most often the result of pituitary or ectopic ACTH secretion. Aldosteronism due to aldosterone-producing adenomas has been described in at least 2 patients with concomitant parathyroid or pituitary adenomas but no family history of MEN (76, 77). One other patient with MEN I and aldosteronism had diffuse adrenal hyperplasia (46). Primary involvement of the thyroid is most likely not a specific feature of MEN I. Diffuse and nodular hyperplasia, follicular adenomas, and colloid goiter have all been reported in patients with MEN I (13, 46) but without significant enrichment over the incidence of such lesions in the general population.

Carcinoid Tumors

Carcinoid tumors occur in 5 to 9 percent of patients with MEN I (13). The most frequent sites of origin of the tumor when associated with MEN I are the bronchus, duodenum, and thymus (78-83). Both benign and malignant neoplasms are described. Although elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) levels have been reported in some patients in whom measurements were obtained prior to tumor removal (or prior to death), carcinoid syndrome with typical flushing attacks is rarely described (83). Other features of MEN I, i.e. hypercalcemia, peptic ulcer disease, hypoglycemia, so dominate the clinical picture that diagnosis of carcinoid tumor is usually not established until histological examination of tissue obtained at surgery or autopsy is completed. In addition to serotonin, carcinoid tumors may secrete calcitonin (81) and ACTH (83). Ectopic secretion of the latter may account for some of the cases of Cushing's syndrome in MEN I.

Nonendocrine Tumors in MEN I

Numerous reports of patients with MEN I include descriptions of subcutaneous, frequently multiple, lipomas. Occasionally visceral lipomas -- pleural and retroperitoneal — have been described. Most investigators attribute this finding to the MEN mutation.

Other nonendocrine tumors reported in patients with MEN I such as gastrointestinal polyps and renal adenomas, are most likely fortuitous occurrences.

Family Screening in MEN I

Early identification of patients affected with MEN I may reduce morbidity and mortality from the disorder. This is particularly important with respect to the gastrinoma component of the syndrome. Although most patients with MEN I-associated ZES have hypercalcemia at the time of diagnosis, it is probably prudent to initiate screening of close relatives of all ZE patients whether they are hypercalcemic or not. One protocol that has been recommended is to screen relatives of patients with MEN I approximately every 2 years beginning about age 15 and continuing through age 65 (Fig. 7) (84). Attention should be focused on all first- and second-degree relatives. If an abnormality is detected on screening, the interval between examinations is decreased to once per year for early detection of other associated endocrinopathies.

Screening history and physical examination are directed toward eliciting symptoms and signs of hypercalcemia, peptic ulcer disease, and hypoglycemia; stigmata of acromegaly and hypercortisolism; evidence of hypopituitarism and symptoms/signs of an expanding mass in the suprasellar area; a history of galactorrhea-amenorrhea in women; and presence of subcutaneous lipomas. Specific laboratory evaluation is based on findings of history and physical examination but in all individuals a serum calcium, fasting serum gastrin, serum

prolactin, and a coned view of the sella should be obtained.

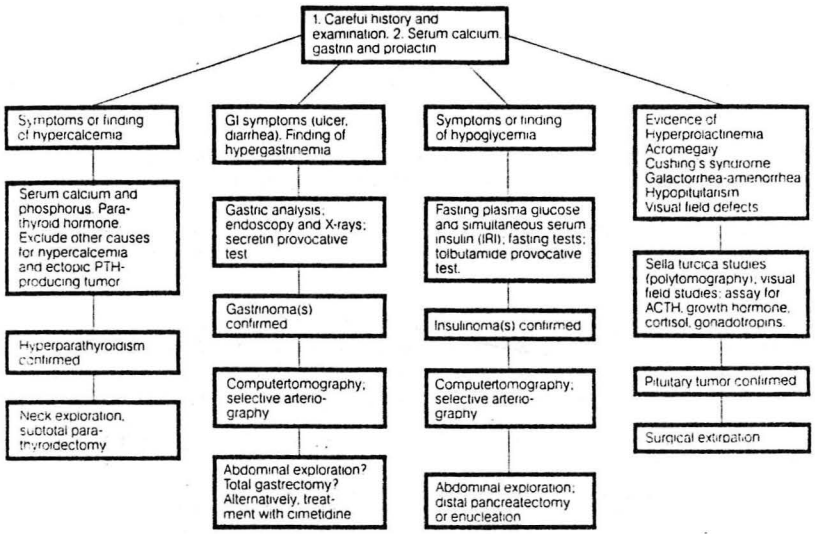

Fig. 7 Screening procedure for MEN I family member.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE II (SIPPLE'S SYNDROME)

The components of the MEN II syndrome are medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism. Although coexistence of thyroid cancer and pheochromocytoma was initially reported approximately 50 years ago (85), the focus on this association was not intensified until Sipple's observation in 1961 that there was at least a 14-fold increase of pheochromocytoma in patients with thyroid carcinoma (of all types) (86). Recognition of the familial nature of this association is attributed to Cushman whose report of one pedigree with MTC and pheochromocytoma appeared in 1962 (87). Williams in 1965 pointed out that MTC was the type of thyroid cancer in all families with what he termed the 'medullary tumor syndrome' (88). The same year Schimke and Hartmann proposed that the pheochromocytoma-medullary thyroid carcinoma was the result of an autosomal dominant mutation (89). Steiner et al. in a 1968 review suggested "multiple endocrine neoplasia, Type 2" as the designation of this syndrome to formally differentiate it from the "multiple endocrine adenomatosis-peptic ulcer disease" complex that they termed "multiple endocrine neoplasia, Type 1" (90).

MTC is the hallmark of MEN II, occurring in essentially all affected families. Pheochromocytoma, although it may dominate the clinical picture in some families, is reported in 40 to 50 percent. Parathyroid adenoma and/or hyperplasia is described in from 40 to 80 percent of affected patients undergoing parathyroid exploration, but hypercalcemia is a clinical feature in only a subfraction (91).

MTC, pheochromocytoma, and parathyroid involvement are multicentric in patients with MEN II as is the case with parathyroid disease and pancreatic tumors in MEN I. Furthermore documentation that hyperplasia (of C-cells and of adrenal medullary tissue) precedes tumor formation in MEN II is more firmly established than is the case with endocrine tumors associated with MEN I.

The diagnosis of MTC usually antedates that of pheochromocytoma, but biochemical evidence of increased adrenal medullary activity may be present relatively early in the clinical course. In some families pheochromocytoma is the dominant feature of the syndrome, but in greater than 60 percent of cases with documented MTC and pheochromocytoma there are no symptoms of increased catecholamine secretion (92). Both MTC and pheochromocytoma figure prominently as causes of death in patients with MEN II. The virulence of the MTC however varies from family to family as well as among members of the same family (93).

As is the case with MEN I, MEN II is also a very rare disorder. Again, however, because it is transmitted as an autosomal dominant, its clinical significance is greatly magnified. Means of screening family members at risk of developing MTC and possibly pheochromocytoma are currently available, enabling diagnosis at a preclinical and curable stage of the disease.

Medullary Thyroid Carcinoma

MTC is the result of neoplastic transformation of the C-cells of the thyroid. These cells are normally found scattered singly or in small groups among thyroid follicular cells and produce the 32 amino acid peptide calcitonin. Originally termed parafollicular, C-cells are now recognized to occupy an intrafollicular position (94). Their embryologic origin is the primitive neural crest and not the foregut endoderm that gives rise to the follicular cells of the thyroid. The C-cells are concentrated within the mid- and, to a lesser extent, upper third of the lateral lobes of the thyroid (Fig. 8) (9).

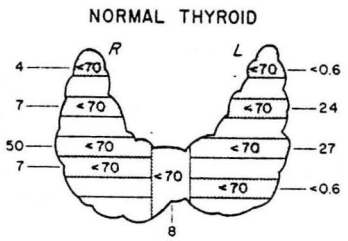

Fig. 8 Calcitonin content of sections of a normal human thyroid gland. Values inside the gland are MRC mU/g determined by bioassay. Values outside the gland are MRC mU/g determined by radioimmunoassay.

MTC accounts for approximately 10 percent of all thyroid neoplasms; about 80 to 90 percent of cases occur sporadically and the remaining 10 to 20 percent as a familial disorder (92). Familial MTC may occur as a component of MEN II or MEN III, or without associated endocrine neoplasia. The latter cases, also transmitted in an autosomal dominant pattern, may represent limited expression of the same mutation responsible for MTC in MEN-associated disease.

The transformation of normal C-cells to MTC in patients with MEN II has been well characterized histologically (Fig. 9) (94). The earliest detectable abnormality, identifiable only by immunoperoxidase staining for calcitonin, is a focal C-cell hyperplasia (CCH). Continued proliferation of C-cells gives rise to diffuse, and eventually nodular hyperplasia. In this latter stage no identifiable follicular elements can be recognized. Only after the proliferating C-cells have penetrated the follicular basement membrane is the lesion characterized as MTC. A biochemical marker of this transition from hyperplasia to carcinoma has been identified by Baylin and coworkers (95, 96). The enzyme histaminase, a protein usually found in mature cells of the intestinal mucosa, kidney, and placental decidual cells, is identified by immunoperoxidase staining in clusters of C-cells located within foci of microscopic and gross MTC but not in areas of CCH. CCH is multicentric in patients with MEN II, a finding that explains the multiplicity of MTC in this disorder. In any one gland microscopic and gross carcinoma coexist with areas of CCH remote from the carcinoma.

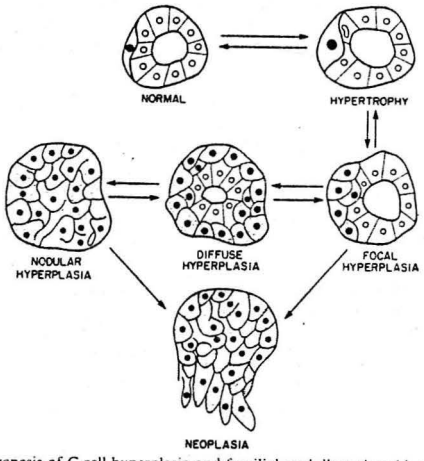

Figure 9. Histogenesis of C cell hyperplasia and familial medullary thyroid carcinoma. The C cells have stippled cytoplasm and dark nuclei, and follicular cells have clear cytoplasm and light nuclei. The C cells gradually replace the follicular and colloidal elements, ultimately invading the interstitium to form medullary thyroid carcinoma.

MTC that remains undetected and untreated at an early, preclinical stage progresses to clinically overt disease over a variable period of time. Clinical features of MTC are related to extent of local tumor growth in the neck, to symptoms from distant metastases, and to effects of secretory products of the tumor. Maintenance of normal thyroid function is the rule. CCH and MTC less than approximately 0.7 cm in diameter are clinically occult, whereas patients with MTC greater than 1.5 cm in diameter have clinically palpable disease (97). One or more nodules, typically in the mid-to upper portions of the lateral lobes, in a normal-sized or enlarged thyroid may be present. In patients with palpable disease there is nothing on physical examination of the thyroid that allows distinction of MTC from other thyroid nodules. Larger tumors may produce local symptoms such as dysphagia and a sensation of pressure in the neck and may erode into larynx, trachea, or esophagus (92). Palpable lesions appear as cold nodules on radioiodine scans. In patients with advanced disease plain radiography of the neck may disclose dense, irregular calcification within the involved portions of the thyroid as well as in lymph nodes harboring metastases (98).

Metastasis of MTC to cervical lymph nodes occurs during very early stages of the disease. Lesions as small as several millimeters in diameter have been associated with regional node metastases (97). However larger tumors (greater than 1.5 cm in diameter) are much more likely to have metastasized to cervical nodes. Distant metastases -- to mediastinal nodes and soft tissue, lung, liver, trachea, adrenal, esophagus and bone -- almost always arise from these larger primary lesions (97). Death directly related to MTC is generally attributed to widespread dissemination of the tumor. The virulence of MTC varies remarkably from patient to patient, such that some patients have a rapid downhill course and die within months of diagnosis whereas others with extensive local disease may survive for decades after initial appearance of the tumor. A recent study by Lippman and coworkers strongly suggests that differentiation of patients with virulent MTC from those with indolent disease is possible at the time of diagnosis by examining the pattern of tissue staining for calcitonin (99). Thyroids from all patients with CCH and microscopic MTC demonstrated a homogeneous distribution of cells staining for calcitonin within involved areas and staining activity was strong. Distant metastases from all patients who had died of disseminated MTC were only weakly reactive on calcitonin staining, and the distribution of calcitonin-positive cells was markedly heterogeneous. More significant from a prognostic standpoint, those patients with regional disease who had tumors that demonstrated intense staining for calcitonin and a homogeneous cellular distribution of calcitonin-positive cells were all clinically well on follow-up examination, whereas those with regional MTC who had a patchy localization of calcitonin within their primary tumors had either died of metastatic disease within 0.5 to 5 years of initial surgery or had documented distant metastases. No other clinical or histologic characteristics distinguished these 2 groups of patients with regional MTC.

MTC produces a variety of biologically active substances and enzymes (Table V). Of these substances only calcitonin (100) and L-dopa-decarboxylase (101) are produced both by the normal C-cell as well as by MTC. The only clinical manifestation that may be directly attributed to increased calcitonin levels is a secretory diarrhea that occurs in approximately 30 percent of patients with MTC (102, 103). Serotonin and prostaglandins have also been implicated as contributing factors to the diarrhea but most patients with MTC and diarrhea have normal serum prostaglandin and urinary 5-HIAA levels (104, 105). Ectopic ACTH secretion by MTC is well recognized; because of the indolent and prolonged course of many patients with MTC, ACTH secretion by this tumor may result in features of Cushing's syndrome indistinguishable from those seen with hypercortisolism due to increased pituitary ACTH secretion or to primary adrenal neoplasms (106-109).

TABLE V

Medullary Thyroid Carcinoma - Secretory Products

Calcitonin
L-Dopa decarboxylase
Serotonin
Prostaglandins
ACTH
Histaminase
Carcinoembryonic antigen

The availability of the calcitonin radioimmunoassay has radically altered the approach to diagnosis and management of patients with MTC, particularly of those with MEN-associated disease (110, 111). Basal plasma calcitonin levels are elevated in essentially all patients with MTC who have palpable thyroid disease, and in most instances the degree of elevation correlates directly with tumor mass (Fig. 10) (112). In patients with small, nonpalpable tumors basal calcitonin levels may be either normal or elevated. Most patients with microscopic carcinoma and all with CCH have normal basal calcitonin levels that increase following provocative stimuli. Serum histaminase (113-115) and carcinoembryonic antigen (116, 117) are also elevated in some patients with MTC but, since they are unaffected by provocative stimuli, these proteins are not as sensitive tumor markers as calcitonin, particularly in early disease. Elevation of histaminase is most frequently associated with metastatic disease (114).

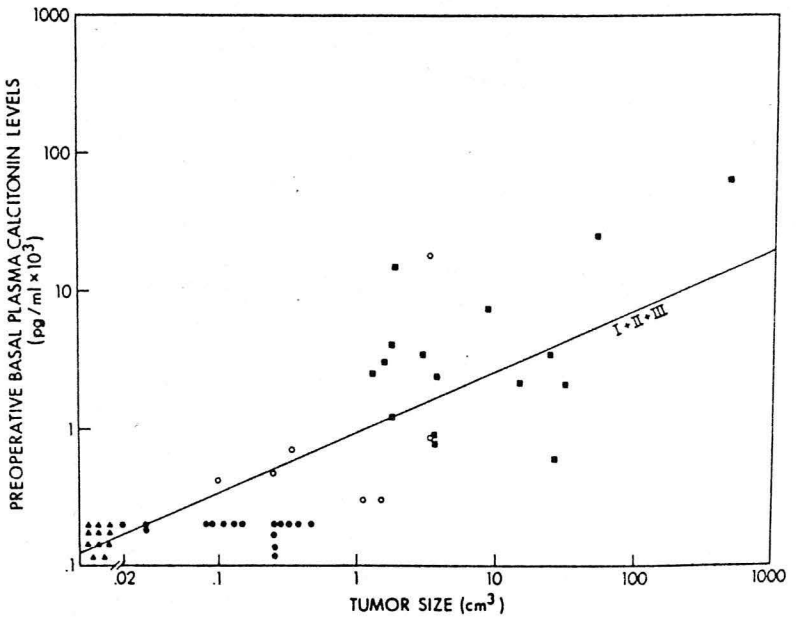

Fig. 10 Correlation of tumor size to preoperative basal calcitonin levels.

Detection and treatment of MTC at an early stage has a profound impact on its clinical course. Total thyroidectomy is curative if disease is detected while still confined to the thyroid — either as a premalignant lesion (CCH) or as small tumor foci. Since CCH and early MTC are clinically occult and since palpable nodules of MTC cannot be distinguished clinically from other types of thyroid nodules, preoperative diagnosis requires measurement of plasma calcitonin. Diagnostic criteria in calcitonin testing established by Wells and coworkers (118, 119) are (1) a normal basal level of calcitonin (less than 200 pg/ml) that stimulates following a short calcium-pentagastrin infusion to greater than 300 pg/ml or (2) an elevated basal calcitonin level (greater than 300 pg/ml); if the elevation of basal calcitonin is minimal (in the range of 300 to 600 pg/ml) a further 5-fold stimulation following

calcium-pentagastrin must be demonstrated before diagnosis can be made. A comparison of results of provocative testing using calcium alone, pentastrin alone, and calcium plus pentagastrin reveals greater and more consistent calcitonin stimulation with the combined stimuli (Fig. 11) (118). Furthermore some patients respond to one stimulus but not the other. In this protocol 2 mg elemental calcium/kg is infused over 50 to 60 seconds followed immediately by pentagastrin 0.5 μg/kg injected over 5 to 10 seconds. Plasma for calcitonin is obtained at 0, 1, 2, 3, 5, and 10 minutes after the injection. Since the peak level of calcitonin with the combined stimuli occurs consistently between 2 and 3 minutes, basal, 2-, and 3-minute samples are sufficient. Using the criteria outlined by Wells et al. no false-positive and very few false-negative tests are observed. Furthermore the absolute level of calcitonin following calcium-pentagastrin correlates with extent of disease as defined by presence or absence of regional lymph node metastases and presence of microscopic or gross disease (119). Specific values for normal and stimulated calcitonin levels vary with the specific antibody used in the radioimmunoassay. With a sensitive assay used at the Mayo Clinic, calcitonin is routinely detected under basal conditions in all normal individuals at a level of 30 to 80 pg/ml (120).

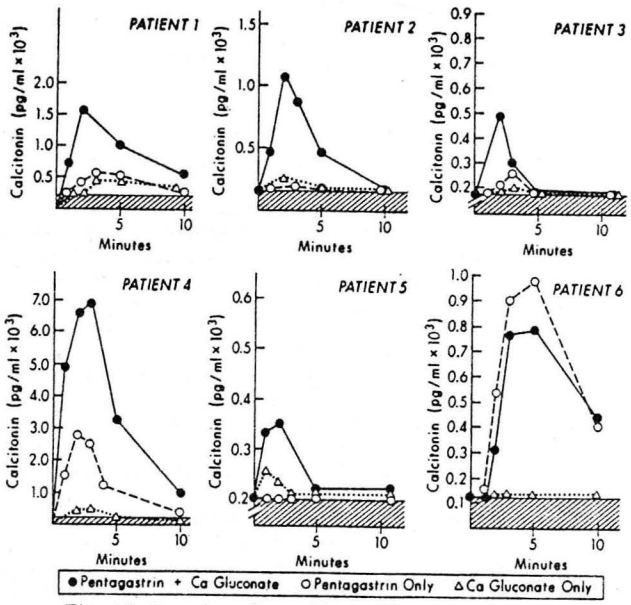

Fig. 11 A comparison of various provocative tests for calcitonin secretion in 6 patients with familial MTC (C cell hyperplasia or microscopic MTC).

Screening family members at risk by measuring calcitonin levels has changed considerably the profile of patients at the time MTC is detected. The effects of calcitonin testing on stage of disease and age at diagnosis in one kindred with MEN II are depicted in Figure 12 (94). Prior to 1970, when the diagnosis of MTC could be made only after a palpable thyroid lesion had appeared, all patients had advanced local disease with regional or distant metastases. Mean age of patients was 50 years. Patients identified between 1971 and 1981 as part of a prospective study of calcitonin testing were not only much younger (mean age 15 years) but also had much less advanced disease. Half of the patients had CCH and/or microscopic

MTC and none had metastatic disease (94). Similar results have been obtained in other MEN II kindreds evaluated in a similar manner (112, 121).

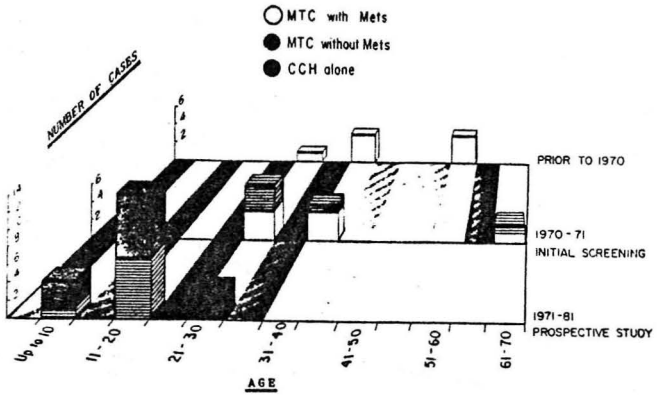

Fig. 12 Effects of calcitonin testing on stage of MTC and age at time of surgery in a kindred with MEN II.

Treatment of MTC confined to the neck is total thyroidectomy, since multicentric disease is demonstrable from the earliest stage in 80 to 100 percent of cases (122, 123). Surgery should be performed when disease is first detected either clinically or by an elevated calcitonin level (122). (The presence of pheochromocytoma must be rigorously excluded before thyroidectomy. If pheochromocytoma is identified, adrenalectomy must precede thyroid surgery.) Because cervical node metastasis occurs early in the course of MTC, all patients with disease that is palpable or that is clinically occult but grossly visible on cut section of the thyroid should undergo resection of lymph nodes in the central compartment of the neck, from the hyoid bone to the sternal notch and from jugular vein to jugular vein, along with removal of a midjugular node from each side. Lateral cervical lymph node dissection is performed if clinically involved nodes are identified or if metastasis is found in the midjugular node, but a radical procedure with removal of jugular vein, accessory nerve and sternocleidomastoid is not recommended unless these structures are involved with tumor (122-124).

Efficacy of thyroidectomy and lymphadenectomy can be assessed postoperatively by measurement of plasma calcitonin. A normal provoked calcitonin following surgery is indicative of cure in most cases; only infrequently does an initially normal level increase at a later time (Table VI) (112). Some investigators however report in some patients a delayed fall in calcitonin over a period of 2 to 6 months following surgery with maintenance of normal levels thereafter (125). The likelihood of achieving normal calcitonin levels postoperatively is a function of stage of disease at the time of diagnosis. All patients with CCH and microinvasive MTC (126), and more than 95 percent of patients with clinically occult disease whose preoperative stimulated calcitonin levels are less than 1000 pg/ml have normal calcitonins postoperatively (119). Of all patients with clinically occult disease, only 17 percent have evidence of residual or recurrent disease over a 3- to 5-year postoperative follow-up period. On the other hand 63 percent of patients with clinically detectable disease at preoperative evauation have persistent calcitonin elevation postoperatively (112). Most of these latter patients do very well and have no evidence of residual disease at postoperative follow-up. Unless

localized neck recurrence develops at a later time, it is recommended that such patients be followed without aggressive reoperation, chemotherapy or radiation therapy (122, 127). In two reported cases administration of radioiodine to patients with postoperative elevations of calcitonin but absence of clinical disease has been reported to return stimulated calcitonin levels to normal or close to normal (128, 129). Although the iodine is not taken up by the MTC it is postulated that radioiodine concentration in nearby follicular cells is sufficient to destroy adjacent tumor cells. If clinical recurrence in the neck is detected on follow-up, resection is performed at that time (121).

TABLE VI. *Stimulated Plasma Calcitonin Levels Postoperatively*

	One Week		One Year		Positive Conversion
	+	−	+	−	
Group I	1	14	1	14*	1 (5 yr)
Group II	0	4	0	4*	1 (3 yr)
Group III	9	9	9	9*	1 (5 yr)

Chemotherapy for metastatic disease and external radiation for control of aggressive local disease have not been very effective in patients with MTC. Of the chemotherapeutic agents tried, only doxorubicin (130) and DTIC (60) have been associated with any effect on the tumor. In patients with refractory diarrhea, tumor debulking may be palliative (122).

Pheochromocytoma

Approximately 5 percent of cases of pheochromocytoma are familial (131), and of these familial cases, about 20 percent are associated with MTC (132). Pheochromocytoma is reported in from 40 to 50 percent of patients with MEN II. It typically develops in older patients, such that the incidence of pheochromocytoma in MEN II increases with advancing age. In contrast to sporadic cases, of which approximately 10 percent of tumors are bilateral and 10 percent extraadrenal, bilateral pheochromocytomas are very frequent in MEN II, occurring in 60 to 70 percent of patients with this adrenal tumor, whereas extraadrenal lesions are very rare (133-135). Malignant pheochromocytoma is also much less common when associated with MEN II than when the tumor occurs sporadically (133).

Just as C-cell hyperplasia is the initial recognizable thyroid lesion in patients with MTC, bilateral adrenal medullary hyperplasia has been identified in MEN II patients prior to and concomitant with development of pheochromocytoma (10, 136, 137). Diffuse adrenal medullary hyperplasia with expansion of medullary tissue into the body and tail of the gland and a decrease in the corticomedullary ratio gives rise to nodular hyperplasia. Nodules greater than 1 mm in diameter are designated pheochromocytomas (Fig. 13) (136, 137).

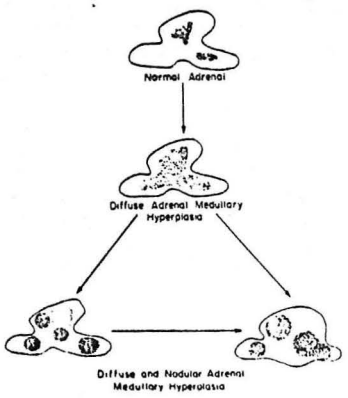

Fig. 13 Histogenesis of adrenal medullary abnormalities in patients with MEN II.

Symptoms and signs of excess catecholamine secretion in MEN II patients with pheochromocytoma may be characteristic and severe or mild to nonexistent. Diagnosis, based on standard measurements of plasma and/or urinary catecholamines and their metabolites, may require serial determination of catecholamines, metanephrines, and vanillylmandelic acid (VMA) before pheochromocytoma is documented since biochemical abnormalities may be intermittent. Serial measurements may also reveal a progressive rise in these levels, in which case monitoring frequency should be increased (135, 138). The sensitivity of the clonidine suppression test, in which plasma catecholamines are measured before and after an oral dose of clonidine, has not been assessed in patients with MEN II. It has been suggested however that an early biochemical abnormality in patients with pheochromocytoma, also present in those with adrenal medullary hyperplasia, is an increase in the ratio of urinary epinephrine (E) to norepinephrine (NE) (E : NE > 0.15) (137). With currently available adrenal imaging technology, the diagnosis of pheochromocytoma cannot be made without biochemical evidence of increased adrenal medullary activity; imaging must be considered solely as a localization procedure following biochemical diagnosis by conventional measurements of catecholamines, metanephrines, and VMA. Computed tomography of the adrenals (adrenal CT) is the most sensitive imaging technique generally available, detecting lesions as small as 1 cm in diameter (139-141). However, without biochemical confirmation of increased catecholamine secretion, a positive finding on adrenal CT cannot be considered specific for pheochromocytoma. Adrenal venography and arteriography are less sensitive than CT in the diagnosis of pheochromocytoma, but findings suggestive of adrenal medullary hyperplasia have been reported with venography in some patients (142). Specific radionuclide imaging of the adrenal medulla utilizing ^{131}I-metaiodobenzylguanidine has been reported by Valk and coworkers (143). Since this agent is selectively concentrated by catecholamine vesicles in the adrenal medulla, increased uptake by a hyperfunctioning medulla may be a useful parameter of increased medullary activity in addition to providing an adrenal image.

Despite the deceptively mild symptoms in many patients with pheochromocytoma, this tumor is probably the major cause of morbidity and mortality in families with MEN II. In some families symptoms of pheochromocytoma dominate the clinical picture (135). In one kindred from the Netherlands the expression of pheochromocytoma was so characteristic, family members knew that once a relative began having attacks of trembling and shivering he would die within seven years (cited in ref. 135). Persistent surveillance for development of pheochromocytoma in all family members at risk is mandatory. Evaluation must be particularly rigorous in patients prior to any surgical procedure, including thyroidectomy for CCH or MTC.

The recommended treatment of pheochromocytoma in patients with MEN II is bilateral adrenalectomy, even in patients with a tumor demonstrated in only one gland (133, 135, 144). Almost invariably either bilateral tumors or tumor with contralateral adrenal medullary hyperplasia are present. Attempts to autotransplant adrenocortical tissue have not been successful and lifelong glucocorticoid with or without mineralocorticoid replacement is necessary.

Hyperparathyroidism

Parathyroid hyperplasia in MEN II is described in from 40 to 80 percent of patients (91). Although clinically significant hyperparathyroidism in MEN II is a characteristic of some families with the syndrome, clinical evidence of hyperparathyroidism in MEN II is most frequently minimal or absent. In fact as many as 50 to 70 percent of patients are normocalcemic so that parathyroid involvement is frequently not detected until neck exploration at the time of thyroidectomy for MTC.

Conventional preoperative evaluation of parathyroid status in patients with MEN II is frequently unrevealing. Although some normocalcemic patients with parathyroid hyperplasia do have at least intermittently elevated serum PTH levels, most normocalcemic patients with surgically documented hyperplasia have normal preoperative levels of PTH (145). In this latter group, evidence of subclinical hyperparathyroidism has been demonstrated by diminished suppressibility of PTH to calcium infusion (Fig. 14) (146).

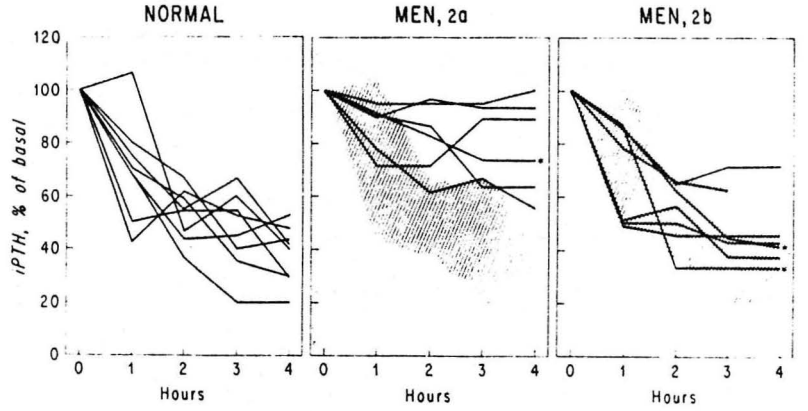

FIG. 14 Effect of four-hour calcium infusion on serum immunoreactive parathyroid hormone (iPTH) concentration in normal subjects and patients with multiple endocrine neoplasia (MEN), types 2a and 2b. iPTH is shown as the per cent of the basal value for each subject. In the middle and right panels, the normal range is shaded. MEN patients who had pheochromocytoma are denoted by an asterisk.

Although parathyroid hyperplasia in MEN II has been postulated to be secondary to excess calcitonin secreted by MTC, a few patients with a family history of MEN II-associated MTC have had parathyroid hyperplasia without evidence of MTC or CCH (147). Furthermore, hyperparathyroidism is not seen in patients with sporadic MTC or MTC associated with MEN III. Parathyroid stimulation has also been attributed to excess catecholamine secretion (148) but no evidence for this could be found in one series of 12 patients with pheochromocytoma (149). Most investigators attribute parathyroid hyperplasia to the underlying MEN II mutation.

Management of hyperparathyroidism in patients with MEN II should take into account the paucity of clinical sequelae of parathyroid involvement in most affected families. Block and coworkers recommend a conservative approach in both normocalcemic and hypercalcemic patients (145). At the time of thyroidectomy for MTC only grossly enlarged parathyroids are excised, even though it is recognized that normal-sized glands are frequently hyperplastic. Subtotal parathyroidectomy is performed if all 4 glands are enlarged. Utilizing this approach no hypercalcemic patient has either had persistent or recurrent hypercalcemia postoperatively or has developed complications of hyperparathyroidism. The risk of hypoparathyroidism is also reduced considerably.

Family Screening in MEN II

Although MTC is an indolent neoplasm in many patients with MEN II, its potential for virulence is well recognized. Since this tumor usually metastasizes

very early in its course, detection and treatment before extrathyroidal metastasis requires that screening of family members at risk be initiated when the MTC is still at a clinically occult stage — preferably CCH or microinvasive carcinoma (Fig. 15). Annual screening with basal and calcium-pentagastrin provoked calcitonin levels should begin at approximately 5 to 8 years of age and be continued through age 50. At each screening, attention should also be directed to symptoms and signs of pheochromocytoma, and urinary catecholamines, VMA and metanephrines should be measured. If symptoms and/or signs suggestive of pheochromocytoma appear but no biochemical evidence of excess catecholamine secretion is present, frequency of screening should be increased to every 3 to 6 months. A serum calcium should also be measured as part of the screening session.

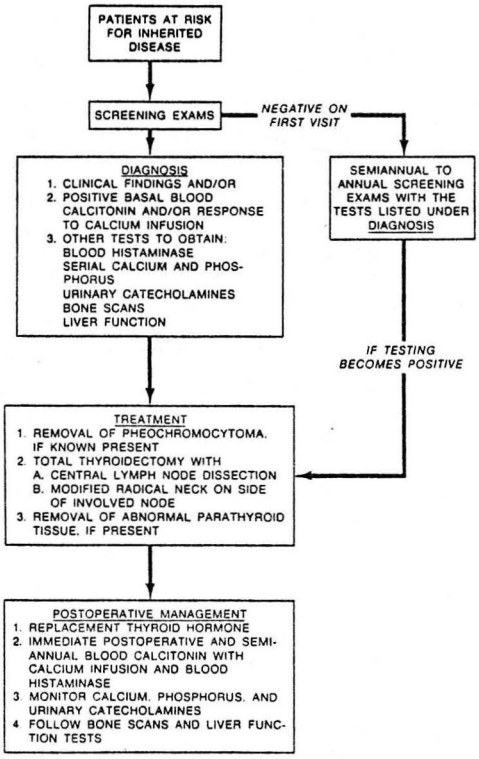

Fig. 15 Screening procedure for MEN II family members.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE III (MULTIPLE MUCOSAL NEUROMA SYNDROME)

MTC and pheochromocytoma are the principal components of both MEN II and MEN III. Differentiation between the two syndromes is made on the basis of the distinctive mucosal neuromas, facial appearance, and skeletal abnormalities present in patients with MEN III. In addition, hyperparathyroidism is only rarely a feature of MEN III (150); however mild chief cell hyperplasia has been observed

without clinical or laboratory evidence of hyperparathyroidism (151). The association of mucosal neuromas with MTC and pheochromocytoma was first made by Williams and Pollock in 1966 (152), and in 1968 Gorlin et al. (153) and Schimke et al. (154) described the characteristic dysmorphic features. Khairi and coworkers proposed the designation MEN III for this syndrome in 1975 to emphasize its distinction from MEN II (150).

Although transmission of MEN III occurs in an autosomal dominant pattern, approximately 50 percent of patients do not have a family history of the disorder. However an apparently sporadic mutation resulting in the MEN III syndrome is likely to be transmitted as an autosomal dominant, and children of individuals with a negative family history must still be considered at high risk of developing the disease. A review by Carney and coworkers in 1979 documented 107 patients with MEN III reported in the literature up to that time (155).

Medullary Thyroid Carcinoma and Pheochromocytoma

MTC associated with MEN III frequently arises during childhood or adolescence and is a much more virulent neoplasm than in MEN II families. Carcinoma has been detected as early as 15 months of age (156) and metastatic disease as early as 3 years (157). In one recent series regional lymph node metastases were present in 76 percent of all patients at the time of initial surgery; mean age of these patients was 20 years (155). The premalignant lesion of CCH without concomitant MTC has been described in only 2 patients with MEN III (121, 158). However because of the aggressiveness of MTC in MEN III Carney et al. suggest that even benign appearing intrafollicular proliferation of C-cells in this syndrome be designated 'in situ MTC' rather than CCH (155).

Diagnosis and treatment of MTC in MEN III are the same as in MEN II. Survival following treatment of MEN III-associated MTC is markedly reduced -- in one series a 5-year survival following thyroidectomy of 80% and a 10-year survival of 50% have been reported (155). Postoperative normalization of serum calcitonin occurred in only a third of patients with MEN III reported by Carney and coworkers, whereas approximately 70 percent of all patients with MEN II-associated MTC had normal calcitonins postoperatively.

Pheochromocytoma occurs with about the same frequency in MEN III as in MEN II -- 30 to 50 percent of patients with MEN III have associated pheochromocytoma -- but because of the aggressiveness of the MTC, pheochromocytoma is a less frequent cause of death in patients with MEN III (155, 159).

Mucosal Neuromas

These lesions consist of unencapsulated tangles of thickened nerve fibers primarily involving the lips and tongue but also occurring in some patients on buccal, gingival, nasal, conjunctival, and laryngeal mucosa. Occasional ganglion cells are present within these lesions. Gastrointestinal tract involvement is characterized by ganglioneuromatosis of myenteric and submucosal plexi in the esophagus, stomach, small intestine and colon; pancreatic, appendiceal, and gallbladder lesions have also been described (160). Clinical manifestations of the neuromas are dependent on their location.

Oral cavity. The lips and anterior third of the tongue are the earliest and most common sites of involvement with mucosal or submucosal neuromas (Fig. 16). These whitish yellow or pink nodules are usually recognized by the age of 3 years (161) and are responsible for the enlarged, everted, patulous lips characteristic of MEN III patients. Similar lesions may be found in the gingiva and buccal mucosa. Oral cavity lesions are asymptomatic and benign and are of concern to some patients only for cosmetic reasons (162, 163).

Fig. A.

Fig. B.

Fig. 16 Patient with MEN III demonstrating
a. thick bumpy lips and eversion of upper eyelids.
b. neuromas on anterior third of the tongue.

Eyes. Thickening, nodularity, and eversion of the eyelids are due to neuromatous involvement of the tarsal plate (Fig. 17). Subconjunctival neuromas may be found in both palpebral and bulbar conjunctivae and are described as yellowish, elevated masses. Other ocular findings include thickened corneal nerves, at times visible without a slit lamp (Fig. 18), and occasionally a punctate keratitis due to decreased tear production. Impaired pupillary dilatation has also been described. Ocular symptoms are usually limited to the keratitis present in some patients, but decreased visual acuity attributed to thickened corneal nerves is an occasional complication (164, 165).

Fig. 17 Appearance of mucosal neuromas on eyelid margins.

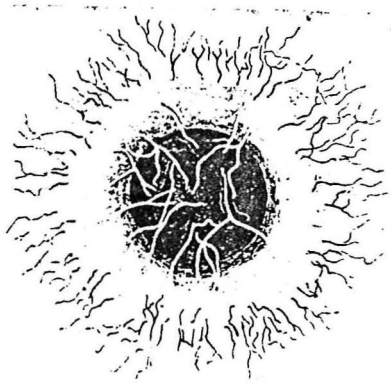

Fig. 18 Drawing of the eye illustrating medullated white nerve fibers traversing the cornea and anastomosing in the pupillary area.

Upper respiratory tract. Neuromas of the nasal vestibule and vocal cords have been reported. Vocal cord involvement may result in hoarseness (165).

Gastrointestinal tract. Lesions histologically resembling oral and ocular neuromas are found in the submucosal and myenteric plexi of the gastrointestinal tract in many patients with MEN III. Ganglion cells are more numerous in these neuromas than in their oral and ocular counterparts, and gastrointestinal involvement is thus usually designated ganglioneuromatosis (or more appropriately, neurogangliomatosis to emphasize the predominance of nerve fiber proliferation) (160, 166-168). The most frequent symptom of gastrointestinal involvement is constipation, usually beginning during the first several years of life. Some patients initially present with toxic megacolon (160). Less commonly dysphagia and vomiting have been reported, attributed to esophageal and gastric involvement, respectively (166, 169). Diarrhea occurs in some patients but is probably related to the MTC in most of these. Radiographic findings in patients with intestinal ganglioneuromatosis include megacolon and colonic diverticula (166, 170). An abnormal haustral pattern as well as abnormal mucosal folds in the colon may be demonstrated on barium enema. Other findings include segmental dilatation and tertiary contractions of the esophagus; gastroesophageal reflux; gastric distention and delayed gastric emptying; and segmental dilatation of the small intestine (166). No symptoms referable to involvement of the pancreas or appendix have been identified.

Other Findings in MEN III

Musculoskeletal abnormalities. A Marfan-like, asthenic habitus with decreased upper to lower body segment ratio, as well as arachnodactyly, joint laxity, high arched palate, increased arm span, pectus excavatum or carinatum, and kyphoscoliosis are found in most patients with MEN III (Fig. 19) (150). Lens subluxation and cardiovascular abnormalities seen in patients with Marfan syndrome are not present in patients with MEN III. Slipped capital femoral epiphysis, pes cavus, and clubfoot are also described in some patients.

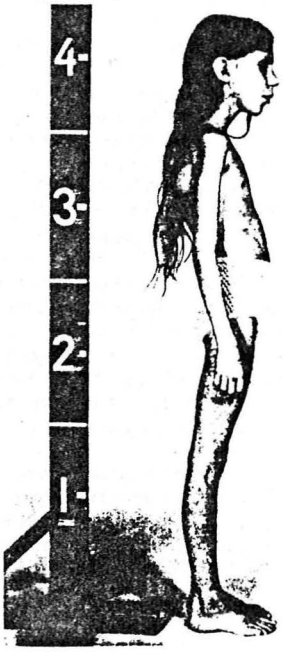

Fig. 19 Patient with MEN III demonstrating Marfanoid habitus, mild kyphosis and poor muscle bulk.

Neonatal feeding difficulties. Feeding difficulties with failure to thrive may be a common early manifestation of MEN III. Poor suck and/or difficulty swallowing associated with generalized hypotonia or delayed neuromuscular development was present in 7 of 9 patients in 1 recent report (157). It is possible these problems are early signs of intestinal ganglioneuromatosis.

Abnormal cutaneous response to intradermal histamine. After intradermal injection of histamine, patients with MEN III develop a wheal but have either a markedly attenuated or absent flare response. This phenomenon is not correlated with elevated serum levels of histaminase. Cutaneous nerves with increased diameter have been found in patients with MEN III; this observation has been cited as anatomic evidence that an impaired axon reflex underlies the deficient flare response (171, 172).

Sensorimotor neuropathy. Neurogenic weakness with atrophy of peroneal and intrinsic foot and hand muscles, absent deep tendon reflexes, and diminished thermal-pressure discrimination have been associated with neuromatous plaques overlying the posterior columns of the spinal cord and with neuromas in the cauda equina and sciatic nerve (173). Neuromuscular symptoms are usually mild but skeletal abnormalities such as pes cavus may be secondary to the neuropathy.

Family Screening in MEN III

A screening program similar to that developed for MEN II families is utilized. However, because of the earlier age of onset of MTC associated with MEN III, it is recommended that screening begin about 1 year of age. It has been suggested that only patients with the characteristic mucosal neuromas and facial features need to be screened for endocrine involvement since MTC and pheochromocytoma have not been described in MEN III family members who do not have these abnormalities (161). It is probably not advisable however to defer screening of young children who are at risk but who lack evidence of neuromatous involvement since neuromas are frequently unrecognized until several years of age; by this time MTC may have already progressed beyond a curable stage in affected individuals.

MULTIPLE ENDOCRINE NEOPLASIA OF MIXED TYPE

Sporadic reports of patients with multiple endocrine tumors suggest that overlap between MEN I and MEN II may occur. The MEN I neoplasm identified in these cases is frequently a carcinoid tumor or adrenocortical adenoma whereas the MEN II component varies from pheochromocytoma to MTC to neurofibroma, the latter of which has only very rarely been associated with the MEN II syndrome (4,5). One subset of patients with pituitary adenoma and pheochromocytoma, usually unilateral, has been culled from the literature by Tateishi et al. (174) and Anderson et al. (175). Acromegaly was reported in most of these patients and hyperparathyroidism was an additional finding in 2 patients. Another patient with acromegaly, hyperparathyroidism and pheochromocytoma (176) and one with a probable prolactinoma and pheochromocytoma (177) have recently been described. The proposal that such patients represent an overlap of MEN syndromes is weakened by 1) the lack of evidence of autosomal dominant transmission and 2) the failure in most instances to demonstrate multicentric tumors. ZES has been reported in 1 patient with MEN II but this is probably a fortuitous occurrence (178).

One syndrome that may be a distinct variant of MEN is an association of pheochromocytoma with pancreatic islet cell tumor. Carney and coworkers have reported 1 family in which pheochromocytoma and an islet cell tumor were present in mother and daughter, and 2 other unrelated families with familial pheochromocytoma in which an islet cell tumor was identified in 1 member of each family (8). A similar family has been reported by Janson et al. (6) and Hull et al. (7).

Nonfamilial occurrence of pheochromocytoma, frequently bilateral, associated with islet cell tumor has also been described (179-182). The islet cell tumors in all cases except one have been clinically nonsecretory; in one patient with a unilateral pheochromocytoma and no family history of endocrine tumors a gastrin-secreting islet cell carcinoma producing ZES was present (181). Familial Von Hippel-Lindau disease was present in the family identified by Hull et al. and has been described in some of the apparently sporadic cases as well; neurofibromatosis was detected in one of the patients reported by Carney et al. (8). Features of MEN common to many of these patients are 1) a familial association in which transmission is consistent with an autosomal dominant mutation, 2) multicentricity of the pheochromocytoma and of the islet cell tumor and 3) early age at diagnosis (8). MEN, Type IV is probably an appropriate designation of this syndrome.

PATHOGENESIS OF MULTIPLE ENDOCRINE NEOPLASIA

It has been proposed by Knudson that dominantly inherited cancer syndromes such as MEN are the result of 2 pathogenetic events (183). The first of these is a germinal mutation that renders all cells of the body highly susceptible to transformation to a neoplastic state. This germinal mutation however is not sufficient by itself to effect transformation, and a second change in the cell is necessary. The second proposed event is a somatic cell change, possibly a second mutation that involves an allele corresponding to the site of the germinal mutation. Alternatively, the somatic cell change may be a chromosomal break or rearrangement. By this model sporadic, that is uninherited, tumors also require these same 2 events but in this situation they both occur in the same somatic cell. This "two-hit model" of carcinogenesis offers great explanatory potential for 2 important characteristics of inherited tumors: (1) These tumors, including the components of the MEN syndromes, are usually multicentric. Since all cells of the body, as a result of the germinal mutation, have an increased susceptibility to tumor formation, common exposure of many cells to the event(s) responsible for the somatic cell change should produce multiple transformed cells. Many of these will subsequently proliferate and form tumors. (2) Inherited tumors develop at an earlier age than sporadic tumors. For a tumor to develop in a patient who congenitally carries one of the mutations requisite for tumor formation, only one additional event is necessary before transformation occurs. On the other hand, for the same tumor to develop sporadically, two rare and random events must take place in the same somatic cell. A delay in tumor function is the expected result.

Even if this model is correct there are still many unanswered questions regarding the pathogenesis of familial tumors and the MEN syndromes. Tumors in patients with MEN occur in specific associations -- what elements do tissues that harbor tumors have in common that predispose to neoplasia? Common embryologic derivation may be important in explaining the association of MTC and pheochromocytoma in MEN II and MEN III — both tumors develop from cells derived from the neural crest. It has been determined by Baylin et al. in studies of G6PD heterozygotes with MEN II that MTC and pheochromocytoma each arises as a clone from a single cell (184, 185). Thus the somatic cell change is a monoclonal event. Furthermore these investigators have found on analysis of multiple tumors from the same patient that some tumors have one G6PD isozyme whereas others have another isozyme (186). It appears then that the somatic cell change is a relatively late event and does not affect a neural crest stem cell. If the latter situation were the case, all tumors would have the same isozyme. However common embryologic origin does not explain the parathyroid involvement in patients with MEN II. The parathyroids are not neural crest derivatives and therefore participation of the parathyroid glands in MEN II cannot be explained on this basis. Similarly, the components of MEN I do not share common embryologic precursors and their

association must also have some other explanation. The finding that many (but not all) MEN tumors have certain biochemical characteristics in common — for example amine precursor uptake and decarboxylation (APUD) -- offers no explanatory mechanism for the occurrence of specific tumor associations (187).

In the MEN syndromes adenomas predominate in some tissues and carcinomas of varying virulence in others. In still other tissues cellular hyperplasia is the only abnormality detected, whereas at times hyperplasia precedes tumor formation. What determines the heterogeneity of this pathologic response to presumably the same stimuli? Could hyperplasia be the result of the putative germinal mutation and tumor formation the consequence of subsequent somatic cell change (147)?

In many patients with MEN, the entire syndrome is not completely expressed — are there secondary modulating factors that influence tumor development in individuals carrying both the germinal mutation and the somatic cell change? Does for example hypercalcemia influence gastrinoma formation in genetically predisposed islet cells of patients with MEN I? Increased levels of nerve growth factor have been demonstrated in one patient with MEN III (188) -- could this have a role in promoting neuroma formation in this disorder?

Activation of cellular oncogenes, in some cases by chromosomal translocation or deletion, has been implicated as the stimulus for tumorigenesis in certain instances in animals and man — does this phenomenon play a role in tumor formation in patients with MEN? What are the specific biochemical and molecular events that result in transformation? To date no (189, 190) or only very subtle (191) chromosomal abnormalities have been identified in patients with MEN.

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