Diagnosis of the Multiglandular Endocrine Neoplasias

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Multiglandular endocrine neoplasms are disorders characterized by autosomal dominant inheritance patterns and by the striking patterns of clinical presentation of these endocrine tumors, which are often hormonally active. Not every patient with adenomas of more than one endocrine gland has one of these classical familial syndromes. This paper will deal with the specific diseases known as multiglandular endocrine neoplasia Types 1, 2A, and 2B. Types 2A and 2B are also known as Types II and III.

The evaluation of patients for the multiglandular endocrine neoplasms (MEN) is especially dependent on laboratory diagnosis because the tumors produce assembled hormone products in very characteristic patterns, but are in most other respects occult. Currently, rapid progress in the area of genetic diagnosis promises to take diagnosis of this group of disorders to a level at which the affected individual can be identified before any clinical manifestation.

Multiglandular Endocrine Neoplasia Type 1

MEN1, also known as Wermer's syndrome and by several other names, is characterized by the presence within an affected kindred, and often within affected individuals, of hyperparathyroidism, pituitary adenomas, and islet cell tumors of the pancreas. The most common islet cell tumors are insulinomas and gastrinomas, the latter causing the Zollinger–Ellison syndrome. Other elements that may be associated with this syndrome, especially in particular kindreds, are multiple lipomas, carcinoid and bronchial adenoma, adrenal cortical adenomas, and thyroid adenomas. The adrenal and thyroid tumors are not specifically associated with the syndrome and are nondiagnostic. The major features of MEN1 may not be manifested in each affected patient. Thus, it is important to consider the phenotype of the kindred as a whole.

The association of endocrine tumors was first recognized by Erdheim in autopsy studies published early in this century (1). Subsequently, Cushing and Davidoff (2) reported a series of autopsy studies in acromegalic patients in which other elements of MEN1, such as parathyroid tumors, were found. Premortem diagnosis of what we would now recognize as MEN1 was first made by Rossi and Dressler (3), who reported a family in which peptic ulcer disease and multiglandular endocrine disorders were found within the kindred. The specific pattern of association of endocrine disorders, which we now recognize as multiglandular endocrine neoplasia Type 1, was appreciated by Underdahl et al. (4) and Moldawer et al. (5) in the early 1950s. The perception that this pattern of association was inherited in an autosomal dominant pattern, and the definition of the syndrome as we understand it today, are attributed to Wermer (6), who called it multiple endocrine adenomatosis. He also recognized the association with peptic ulcer disease. Shortly afterwards, Zollinger and Ellison (7) described the syndrome characterized by severe peptic ulcer disease and nonsulin-producing pancreatic islet cell tumors that bear their names. It is now clear that this gastrinoma syndrome can occur as a component of the MEN1 complex. The term multiple endocrine neoplasia was proposed by Steiner et al. (8) to emphasize the malignant features of some of the tumors.

Hyperparathyroidism

Hyperparathyroidism appears to be the most common feature of the MEN1 syndrome, with at least 80% of reported cases manifesting this problem. In some studies, the presence of primary hyperparathyroidism at the time of diagnosis of affected individuals was nearly universal (9–11). It seems likely that in earlier studies, because access to serum calcium measurement was somewhat more restricted, hyperparathyroidism may have been somewhat underdiagnosed. This high proportion of primary hyperparathyroidism, together with the convenience and low cost of serum calcium measurements, makes measurement of serum calcium a good screening test in potentially affected individuals (12, 13). With increasing experience it should become clear whether this high prevalence of hyperparathyroidism is characteristic of all kindreds.

In some cases, when the patient's neck is surgically explored, enlargement of only one gland may be apparent. However, years of clinical experience indicate that all parathyroid glands in affected individuals have the potential to develop adenomatous or hyperplastic changes.

Clinical manifestations. It is not uncommon for the index case in a kindred to present because of complications of hyperparathyroidism, including kidney stones, skeletal fractures, peptic ulcer disease, or neurophysiologic findings. Hyperparathyroidism produces an exaggerated resorption of bone at the same time as it produces increased conservation of calcium by the kidneys. When the resulting hypercalcemia presents such a large filtered load of calcium to the tubules of the kidney that the calcium-conserving effect is overwhelmed, hypercalciuria results, with a propensity to form stones. The hyperresorption of bone under the influence of parathyrin (PTH) is responsible for significant bone disease in patients in whom this condition becomes advanced. Postmenopausal women are notoriously vulnerable to the effects of PTH on their skeletons, often

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out of proportion to the concentration of their serum calcium.

Hypercalcemia is a well-known stimulant for gastric secretion. This accounts for the tendency of patients with primary hyperparathyroidism to develop peptic ulcer disease. The increase of gastrin and hydrochloric acid secretion caused by hypercalcemia may in some cases overlap the concentrations produced in Zollinger–Ellison syndrome (14, 15). This potential source of confusion and misdiagnosis must be considered in the evaluation of both individuals and families.

Pathogenesis. Recent information about the pathogenesis of the hyperparathyroidism is extremely interesting. There has been a report that a circulating substance in the plasma of patients affected by MEN1 is capable of stimulating parathyroid cells with respect to both growth and secretion (16). This substance resembles basic fibroblast growth factor (16a). If these reports are corroborated, this material may be extremely important from the standpoints of understanding the pathogenesis of MEN1 and providing the potential for early diagnosis. The presence of such a substance would imply that the pathophysiological process is one of diffuse hyperplasia, albeit asymmetrical in many cases. This is in contrast to a recent study that suggests the clonal origin of parathyroid tumors of the sporadic type (17). From the point of view of the management of individual patients and families, the main point is that every patient should be regarded as having either apparent or occult multiglandular parathyroid disease. Very little weight should be placed on the histology of resected parathyroid glands except for the confirmation that the tissue is of parathyroid origin. The parathyroid tumors of multiglandular endocrine neoplasia are rarely malignant.

Diagnosis. The finding of an elevated or inappropriately high PTH concentration in the presence of hypercalcemia constitutes the basis for a diagnosis of hyperparathyroidism. The serum phosphate is typically low or low-normal. With modern assays for PTH, the diagnosis of primary hyperparathyroidism has been greatly improved. The newer immunoassays, which are based on measurement of specific regions of the molecule, constitute a significant diagnostic advance. The detection of asymptomatic hypercalcemia has become a common means of discovery of this condition in patients in whom the risk of MEN1 is already appreciated because of another affected family member. It is critical to exclude the diagnosis of familial hypercalcemic hyperparathyroidism, a distinctly different heritable disorder, in which the ratio of renal calcium clearance to creatinine clearance is much lower, although the serum calcium concentration is high and the PTH concentration is variable (18).

Assay of parathyron. It is not the purpose of this article to discuss exhaustively the immunoassay of PTH. It should be sufficient to say that for many years this has been one of the more difficult hormone assays from the standpoint of diagnostic utility. In the evaluation of data generated by many of the assays that have been used for some years, we must take into account the serum calcium concentration when interpreting the PTH value. Thus a "high-normal" PTH found in the presence of hypercalcemia would be regarded as indicative of hyperparathyroidism, because other causes of hypercalcemia should suppress the concentration of PTH. Distinguishing PTH levels of patients with primary hyperparathyroidism from those with other conditions and from normal individuals has been improved with recent assays. The midmolecule PTH assays have become widely available and constitute a very useful diagnostic test (19). More recently, the intact PTH assay by a two-site radioimmunometric technique has become available; it appears to be an excellent diagnostic test that is not materially affected by retention of inactive fragments, such as may occur in renal failure (20). It is rarely, if ever, necessary to carry out calcium infusion/suppression tests or other such diagnostic maneuvers for hyperparathyroidism. Occasionally, patients with borderline results and increased fractional calcium excretion are placed on a thiazide diuretic under careful observation to determine whether serum calcium will increase without suppression of PTH secretion. Such testing is usually not required in MEN1.
Pituitary Adenomas

The prevalence of pituitary tumors in affected patients is probably about 70% to 80% (21). There is a clinical impression that these may become apparent somewhat later in the course of the disease than the parathyroid tumors, although this impression may in part be influenced by the convenience and frequency with which the appropriate tests are performed as well as by the sensitivity of the tests. The pituitary adenomas of MEN1 comprise a variety of types. In most early studies, the majority of tumors were described as nonfunctioning chromophobe adenomas (22–24). This probably reflects an underdiagnosis of functioning adenomas because prolactin assays were not available when the studies were done. About 15% had eosinophilic tumors and were often described as acromegalic. Acromegaly may have been more readily ascertained than other conditions in early studies because of its strikingly apparent clinical features. Cushing's disease and basophilic tumors were described in about 5% (25). It is extremely difficult to estimate the prevalence of prolactinoma from published reports, since the ability to diagnose this tumor is comparatively recent. However, based on more recent studies, 15% is probably a reasonable estimate.

For each of the hormone-producing pituitary tumors that have been described, the specific hormone produced is measurable. The diagnosis is based on clinical assessment guided by a high index of suspicion and correlated laboratory testing.

Chromophobe adenomas. As noted above, many of the pituitary adenomas are described as nonfunctioning. Such tumors may cause endocrine deficits by a mass effect and thus be endocrinologically significant even though they are nonsecreting.

Prolactinomas. Prolactinomas are now being reported with considerable frequency, and undoubtedly quite a few of the patients said to have nonfunctioning chromophobe adenomas actually had prolactinomas (26–29). For example, some members of the original kindred reported by Wermer have been restudied and found to have prolactinomas (21). While amenorrhea and galactorrhea are the classical clinical findings in patients with prolactinomas, it is now well recognized that the presentation may be more subtle, such as amenorrhea without galactorrhea in women or impotence in men. Prolactinomas are diagnosed by the presence of elevated prolactin concentration, especially in combination with symptoms such as amenorrhea, galactorrhea, or male impotence.

Acromegaly. Of the functioning adenomas, the type most often described in the older literature (2,23) is the eosinophilic adenoma producing acromegaly. These growth hormone-producing tumors have been noted throughout the literature in this field. This is undoubtedly in part because of the overt clinical manifestations of acromegaly. The clinical findings are similar to those of sporadic acromegaly and include hyperglycemia and acral enlargement. Gigantism is rare, since the tumor usually develops after growth is complete. The diagnosis is made by the demonstration of excessive growth hormone secretion, as documented by the measurement of elevated or nonsuppressible concentrations of growth hormone and somatomedin C, whether or not the patient has overt acromegaly.

Cushing's disease. Cushing's disease has also been reported as a component of MEN1, with basophilic adenomas producing corticotropin (adrenocorticotropic hormone, ACTH) (26). The clinical manifestations are similar to those of sporadic Cushing's syndrome, including centripetal obesity, striae, weakness, etc. Cushing's disease is diagnosed by hypercortisolism that is associated with a nonsuppressed corticotropin just as in sporadic cases.

Pancreatic Tumors

Pancreatic tumors occur in about three-fourths of patients affected by MEN1, and most of those that are diagnosed appear to be functional. Gastrinoma is found in about half the patients affected (14,15,23). There is a significant malignant potential for these tumors, with perhaps half or more demonstrating malignant characteristics in addition to the tendency for the gastrinomas of multiple endocrine neoplasia Type 1 to be multifocal (30). Insulinoma is found in perhaps one-fourth of patients with MEN1 (31) and is similar in clinical presentation to sporadic insulinoma. While malignant insulinomas are well described and multiple foci are common (23), a majority of the beta cell tumors are apparently benign from the standpoint of cellular behavior.

The clinical danger to the patient is much greater from the pancreatic tumors than from the other tumors of the MEN1 syndrome. First, the gastrinomas and insulinomas often cause life-threatening emergencies, such as gastrointestinal hemorrhage or hypoglycemic coma. Second, the pancreatic tumors have a malignant potential that is not seen in the tumors of other glands. Metastasis and invasion have been observed in nearly half of the patients in certain series (22,23,32).

Insulinoma. The clinical manifestations of insulinoma in the multiglandular endocrine neoplasia syndrome are similar to those seen in sporadic insulinoma. Patients may suffer from symptoms of neuroglucopenia or from the side effects of the adrenergic defense mechanisms. Patients may report weight gain as a result of hyperphagia or they may report nightmares caused by nocturnal hypoglycemia, symptoms of nervousness or irritability, headaches, or even seizures. The diagnosis is extremely important and should be strongly suspected in patients with family histories of MEN1. Patients who present as sporadic cases are sometimes initially regarded with somewhat greater skepticism because of the controversial aspects of hypoglycemia syndromes, but appropriate evaluation generally clarifies the diagnosis. Hypoglycemia is extremely difficult to manage in these patients if they are not successfully treated surgically. Therefore, because of considerations of blood sugar concentration and the desire to remove the tumor with significant malignant potential, there is a strong argument for an aggressive approach by a surgeon experienced in such tumors.

In the case of MEN-related or sporadic insulinoma, the diagnosis is most definitively made by the demonstration of fasting hypoglycemia with increased concentrations of insulin and C-peptide relative to the degree of hypoglycemia.

In patients who are to undergo surgery, computed tomography, magnetic resonance imaging, and (or) angiography may be useful preoperative investigations as a guide to the surgeon and in helping to decide whether the procedure is likely to be beneficial. The insulinoma in MEN1 may be solitary, in which case a limited resection would potentially be curative. However, it is quite commonly multifocal (31), and great difficulty may be encountered in obtaining a surgical cure without subtotal pancreatectomy.

Gastrinoma. Gastrinomas appear to have a somewhat greater malignant potential than does insulinoma. They

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may be discovered because of investigation of dyspepsia in patients with known family histories of MEN1, or in patients who present with persistent or recurrent peptic ulcer disease or with a bleeding diathesis. Diarrhea may be an important feature in certain individuals. Gastrointestinal hemorrhage and malignant metastases both constitute life-threatening consequences of this tumor.

The diagnosis of gastrinoma, or Zollinger–Ellison syndrome, is suspected in light of the clinical presentation of either severe peptic ulcer disease in the sporicardic case, or any peptic ulcer disease in the patient at risk. Patients who have elevated gastrin secretion and gastric acid secretion are typical of the gastrinoma syndrome. Patients who have achlorhydria or retained antrum or other causes of secondary hypergastrinemia, of course, must be distinguished.

Patients with gastrin concentrations >500 ng/L have a high very high probability of gastrinoma. However, some patients with this condition will have intermediate intervals of gastrin of between 150 and 500 ng/L. The secretin test, which produces a rapid rise in gastrin after secretin injection in patients with gastrinoma, is often helpful in clarifying the diagnosis.

A pitfall in the diagnosis of gastrinoma is the hypergastrinemia and hyperchlorhydria associated with hypercalcemia in patients with primary hyperparathyroidism. Cases have been reported in which there was significant overlap between the acid and gastrin concentration seen in hyperparathyroidism and those seen in Zollinger–Ellison syndrome (15). For this reason, it has been recommended that patients with hypercalcemia and hyperparathyroidism undergo parathyroid resection before the definitive diagnosis or any surgical intervention for gastrinoma. This is one example of the clinical importance of recognition of the MEN1 syndrome and the interaction of its components.

The H2 antagonists have improved the feasibility of medical management of gastrinomas. Surgery for gastrinoma is challenging. If a solitary gastrinoma can be found, it can be resected with an excellent clinical result. Unfortunately, this occurs only in a minority of cases and total gastrectomy is often required, since multifocal disease is common.

Glucagonomas and somatostatinomas. Glucagonomas have also been described in MEN1 (33). These tumors, however, seem to be much less common than insulinomas or gastrinomas. The glucagonoma syndrome consists of the association of a distinctive rash with diabetes mellitus, anemia, and weight loss in several case reports (34–36). There has been a kindred reported with glucagonoma and MEN1 (33). Glucagon concentrations above 500 ng/L are strongly indicative of glucagonoma, and values of 200–500 ng/L are suspicious (36). An immunossay that does not cross-react with intestinal glucagon is essential for reliable diagnostic discrimination.

It is quite possible that a somatostatinoma will eventually be described in association with MEN1, although increased concentrations of somatostatin might suppress certain other manifestations of the syndrome. To date this has not been demonstrated.

Genetics of MEN1

As noted above, MEN1 is an autosomal dominant disorder with variable penetrance. Recent evidence suggests that the gene for MEN1 is located on chromoosone 11 (37). Further research may well lead to a diagnostic test that will identify the abnormal gene in members of affected kindreds, before any phenotypic expression of the abnormality.

Screening

The most important elements in the screening process are the physician’s awareness of the genetics and manifestations of the syndrome, reliable laboratory support, patience, and persistence. All first-degree relatives of affected individuals should be screened, as well as any additional relatives with suggestive symptoms or histories. Laboratory screening should always include a serum calcium determination. Abnormal concentrations of fasting glucose may suggest insulinoma or occult glucagonoma. Tests of pituitary and pancreatic hormonal function should be performed as indicated by the histories of each individual and his or her kindred (e.g., measure prolactin and gonadotropin in amenorrheic women). Radiographic evaluation of the sella turcica should be carried out in patients with indications of pituitary dysfunction. The type of evaluation may depend on the clinical presentation; e.g., hyperprolactinemia and Cushing’s disease are often due to microadenoma and may require more sophisticated studies than are needed for the evaluation for suspected hypopituitarism due to nonfunctioning macroadenoma.

Multiglandular Endocrine Neoplasia Types 2A and 2B

Multiple endocrine neoplasia Types 2A and 2B are two very well-described syndromes. The recognition of these syndromes has developed over the past 30 years or so. Elements including medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism, and mucosal neuroma as well as a Marfanoid habitus have been described (5, 38–41). These features can be clearly circumscribed into two distinct syndromes.

Multiple Endocrine Neoplasia Type 2A

In MEN2A, also known as Sipple’s syndrome, there is an association between medullary thyroid carcinoma and pheochromocytoma (39, 40). The first of these disorders to appear is usually medullary thyroid carcinoma. This is typically followed by pheochromocytoma, which may present several years to a decade later. Hyperparathyroidism is found fairly late in the course of the disease and is extremely rare in patients who have undergone successful surgery for the medullary thyroid carcinoma (42). This observation strongly suggests that the hyperparathyroidism may not be a primary feature of the disease as previously thought (43), but may be a reaction to chronic exposure to high concentrations of calcitonin or other tumor products from the medullary thyroid carcinoma.

Medullary thyroid carcinoma. Medullary thyroid carcinoma is a distinctive and relatively uncommon tumor that typically produces calcitonin. It constitutes approximately 5% of thyroid carcinomas. This carcinoma is typically asymptomatic until it has metastasized. Occasionally, diarrhea or flushing is associated with medullary thyroid carcinoma. Perhaps 25% of the new cases are familial (44).

Histological diagnosis. The histological appearance of medullary thyroid carcinoma stained by conventional techniques may be somewhat nonspecific. In some cases, there are distinctive streaks of amyloid, but in others the findings may be ambiguous. However, the use of specialized stains for calcitonin solves this problem. If the clinicians or pathologists suspect the presence of medullary thyroid
carcinoma, the tissue can be stained with an immunohis-
tochemical stain based on anti-calcitonin antibodies and
immunoperoxidase (45, 46). This is a highly sensitive
and specific method when properly performed. Laboratories
that do not perform this test routinely should refer speci-
mens to laboratories that do. This stain clearly identifies
the concentrated areas of calcitonin within the cells of the
perifollicular "C cells," which are characteristic of medul-
lar thyroid carcinoma (47).

Preoperative diagnosis. The preoperative diagnosis of
medullary thyroid carcinoma in patients in whom it is
suspected and in relatives of patients known to have
Sipple's syndrome is made by provocative testing and
measurement of the serum or plasma concentration of
calcitonin. To detect this tumor in its early, premalignant
phase, also known as C-cell hyperplasia, a sensitive assay
must be used (48). A provocative agent, such as pentagas-
trin injection or calcium infusion, must also be used
because many patients will have baseline values of calcitonin
that are indistinguishable from those of normals, but
nevertheless have distinct increases after such a stimulus.

Pentagastrin (0.5 µg/kg) is given by rapid intravenous
infusion, with calcitonin measurements at 0, 2, and 5 min
(49). Alternatively, a 10-min 3 mg/kg calcium infusion (50)
has largely replaced the original 4-h infusion. Wells et al.
(51) have described a combination calcium and pentaga-
strin infusion. For all these studies, a sensitive, reliable
assay for human calcitonin is essential.

Gagel et al. (52) found that, in individuals with an initial
50% chance of developing MEN2A, the risk falls to about
10% if the stimulated calcitonin response has remained
normal until age 25.

Pheochromocytoma. The pheochromocytomas associated
with medullary thyroid carcinoma are often more difficult
to diagnose than the typical sporadic pheochromocytoma
(54). The symptoms of pheochromocytoma are similar to
those of sporadic pheochromocytoma, with perhaps a little
more emphasis on epinephrine-related symptoms early in
the course of the disease. Patients may have sweating, tachy-
cardia, tremulousness, "nervousness," and eventually
hypertension, which may be episodic and severe.

Table 2. Multiglandular Endocrine Neoplasia Type 2

<table>
<thead>
<tr>
<th>Type 2A</th>
<th>Presentation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary thyroid carcinoma (MTC)</td>
<td>Thyroid nodule or asymptomatic (found on screening)</td>
<td>(Biopsy) stains + MTC multifocal sites</td>
</tr>
<tr>
<td>C-cell hyperplasia</td>
<td>Found on screening</td>
<td>Elevated plasma calcitonin (basal or post-stimulation)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Early</td>
<td>Elevated post-stimulation calcitonin</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>Elevated urinary epinephrine, epinephrine/norepinephrine ratio</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Hyperparathyroidism</td>
<td>Elevated total/normetanephrine ratio</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Normal</td>
<td>Hypercalcemia with elevated PTH</td>
</tr>
<tr>
<td>Type 2B</td>
<td>mucosal neuromas</td>
<td>Clinical observation</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Abnormal optic nerve</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>Occurs at younger age than in MEN2A, otherwise similar</td>
<td>See 2A</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>May occur earlier than in MEN2A, but otherwise similar</td>
<td>See 2A</td>
</tr>
</tbody>
</table>

Diagnostic tests. Although measurement of urinary met-
aneprines or other catecholamine metabolites is usually
adequate for the diagnosis of pheochromocytoma, this is
frequently not the case in the MEN2 syndrome. Patients
with obvious symptoms of pheochromocytoma may never-
threat have total urinary metanephrines that are within
the normal reference range. Some investigators have used
such measures as the epinephrine-to-norepinephrine ratio,
etc., but these are not uniformly reliable. Gagel (54) has
found urinary epinephrine excretion to be the most useful
test. Imaging with radioisotopes has had some good results,
but it is not yet a standard procedure (56–59).

Pheochromocytomas in the MEN2 syndrome are usually
bilateral, although they may appear sequentially. Al-
though selective angiography or other invasive diagnostic
and localization techniques may be useful in sporadic
pheochromocytoma, the fact that the tumors are more
predictable in Sipple's syndrome is very helpful and prob-
obly obviates this measure in most cases. Computerized
abdominal tomography or magnetic resonance image scans
are likely to be useful in such patients.

The "preneoplastic" stages, C-cell hyperplasia and adre-
nal medullary hyperplasia, can be detected by systematic
testing (55).

Clinical manifestation. The diagnosis of pheochromocyt-
toma should be strongly suspected whenever a patient has
hypertension, tachycardia, sweating, or other suggestive
symptoms in the setting of a family history of MEN2. The
fact that medullary thyroid carcinoma almost always ap-
pears some years before the pheochromocytoma can be a
great help to diagnosis. A patient with pheochromocytoma
who is discovered to have medullary thyroid carcinoma
would ordinarily have the pheochromocytoma resected first
because of the potential of the pheochromocytoma to cause
a crisis during surgery, and the operative plan would be
markedly affected by the knowledge that the patient would
probably have bilateral pheochromocytomas (53).

Some authorities have recommended that when only one
pheochromocytoma is grossly apparent, a unilateral resec-
tion should be performed (54). This is understandable in
view of the desire to preserve adrenal function. However, a
very active pheochromocytoma may be only a few millimeters in diameter and be undetectable even by sensitive radiographic methods. There is a high incidence of contralateral hyperplasia and eventual recurrence. Thus, in a number of leading centers, bilateral resection is undertaken at the first operation (54).

Hyperparathyroidism. The hyperparathyroidism that has been noted in association with Sipple’s syndrome was originally thought to be an essential feature of the disease. This was based in part on a report that found hypercalcemia in patients before the development of hypercalcitoni

mia (43, 80). It now appears that the major reason for this finding was the relative insensitivity of the calcitonin assay available when those studies were carried out. Now that patients with medullary thyroid carcinoma are diagnosed relatively early in the course of the disease, before the development of hypercalcemia, we have an opportunity to observe the natural course of the parathyroid glands absent the constant exposure to calcitonin and perhaps other tumor products. In this setting, the hyperparathyroidism is extremely uncommon (42). This implies that the hyperparathyroidism may occur in response to the hormonal environment created by the other tumor. In addition, it has been shown that parathyroid hormone concentrations can be high-normal to moderately elevated in normocalcemic patients with medullary thyroid carcinoma or C-cell hyperplasia, and that resection of the thyroid gland results in a fall in parathyroid hormone levels (61).

Multiple Endocrine Neoplasia Type 2B

Multiple endocrine neoplasia Type 2B has features in common with multiple endocrine neoplasia Type 2A, but is a distinctly separate genetic syndrome (41). Patients with multiple endocrine neoplasia Type 2B have medullary thyroid carcinoma and pheochromocytoma, but they also have characteristic mucosal neuromas that are apparent early in life and that provide a strong clinical diagnostic clue. These patients have a Marfanoid habitus and also often have characteristic changes in the retina. Medullary thyroid carcinomas in patients with multiple endocrine neoplasia Type 2B may tend to be more aggressive than is usually seen in the Type 2A syndrome. Hyperparathyroidism is not regarded as a characteristic feature of MEN2B.

The diagnostic evaluation of patients with the Type 2B syndrome is essentially similar to that of the patients of MEN type 2A, except for the fact that the physical findings are much more important than in other multiglandular endocrine neoplasias.

In both types of multiple endocrine neoplasia Type 2, the only definitive treatment for the thyroid carcinoma is total thyroidectomy. The recurrence rate for less extensive thyroidectomy is appreciable because this is a multifocal tumor in the hereditary disorders.

Variant Syndromes

Syndromes of familial pheochromocytoma and familial medullary thyroid carcinoma have also been described. In some cases, these may be examples of multiple endocrine neoplasia Type 2 with incomplete penetrance for the (apparently absent) tumor. Alternatively, there may well be a completely separate syndrome in these families.

Genetic Diagnosis

Recent evidence indicating that the location of the MEN2A gene is near the centromere on chromosome 10A (62–64) suggests the possibility that a genetic diagnostic test may be feasible in the foreseeable future. This would, of course, be an enormous advance from the standpoint of early diagnosis. It would permit prophylactic thyroidectomy and would unambiguously identify the patients who require careful monitoring for development of pheochromocytoma. This would also raise important ethical questions with respect to diagnosis in utero.

The "two-hit" hypothesis of pathogenesis developed by Knudsen (65, 66) is widely believed to apply to the MEN syndromes. According to this concept, sporadic tumors occur as a result of consecutive allelic somatic mutations. In MEN, as in other hereditary neoplastic diseases (e.g., retinoblastoma), the affected individual is thought to inherit the heterozygous state, greatly increasing the probability of the occurrence of a pair of allelic mutations.

Summary

The multiple endocrine neoplasias are interesting endocrine disorders that are clinically significant in their own right and potentially very important from the standpoint of the information we can obtain from their study. Patients may come to attention because of clinical manifestations of previously undiagnosed disease, or as a result of screening families known to have the syndromes described above. Current endocrine diagnostic methods are adequate to detect the biologically active tumors at an early stage. In MEN1, the signal "tumor" is usually parathyroid hyperplasia or polyadenomatosis indicated by hypercalcemia. In MEN2A, the signal tumor is usually medullary thyroid carcinoma, which is detected by provocative testing for hypercalcitoni

nia. MEN2B is also marked by medullary thyroid carcinoma, as well as a characteristic physical appearance. In all syndromes, first-order relatives of affected individuals should be investigated with serial testing of the appropriate type. Localization of the genes for these diseases may lead to tests for early definitive diagnosis of affected individuals. However, surgical intervention will probably depend on endocrine testing for most of the manifestations of these syndromes, at least for the foreseeable future.

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