MEDICAL GRAND ROUNDS

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MULTIPLE ENDOCRINE ADENOMA - PEPTIC ULCER SYNDROME

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I Historical Aspects

The Multiple Endocrine Adenoma - Peptic Ulcer Syndrome is characterized by: 1) hyperplasia or neoplasia of one or more endocrine glands, especially the parathyroid, pancreatic islets, and pituitary, and 2) a high incidence of peptic ulcer disease. The occurrence of 2 or more endocrine tumors in the same patient was first documented in autopsy findings by Erdheim in 1903 (1) and by Cushing and Davidoff in 1927 (2).

The first clinical observations of the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome began in 1939 with Rossier and Dressler's description of a family in which 2 sisters manifested evidence of multiple forms of endocrine disease, while the male members of the sibship manifested various types of peptic ulcer disease without endocrine involvement. These authors hypothesized that the disorder in this family was of an hereditary nature in which the ulcer component was expressed in men and the endocrine component expressed in women (3).

The real conceptual breakthrough in the delineation of the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome as we understand it today came in 1954 and is attributed to Wermer, who described the familial aggregation of multiple endocrine adenomas of the pituitary, pancreas, and parathyroid glands (4). Wermer proposed that this was a distinct syndrome inherited as an autosomal dominant trait. Recognizing the frequent occurrence of peptic ulcer disease in these patients, Wermer also suggested the existence of a genetic relationship between the ulcer diathesis and the endocrine adenomas.

One year later, in 1955 Zollinger and Ellison described what was originally thought to be a different syndrome characterized by fulminating peptic ulcer disease and noninsulin producing islet cell tumors of the pancreas (5). It is now generally recognized that the Zollinger-Ellison Syndrome is not in fact a separate and discrete clinical disorder, but represents the gastrin-secreting islet cell tumor component of the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome (6-11).

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II Epidemiological Aspects

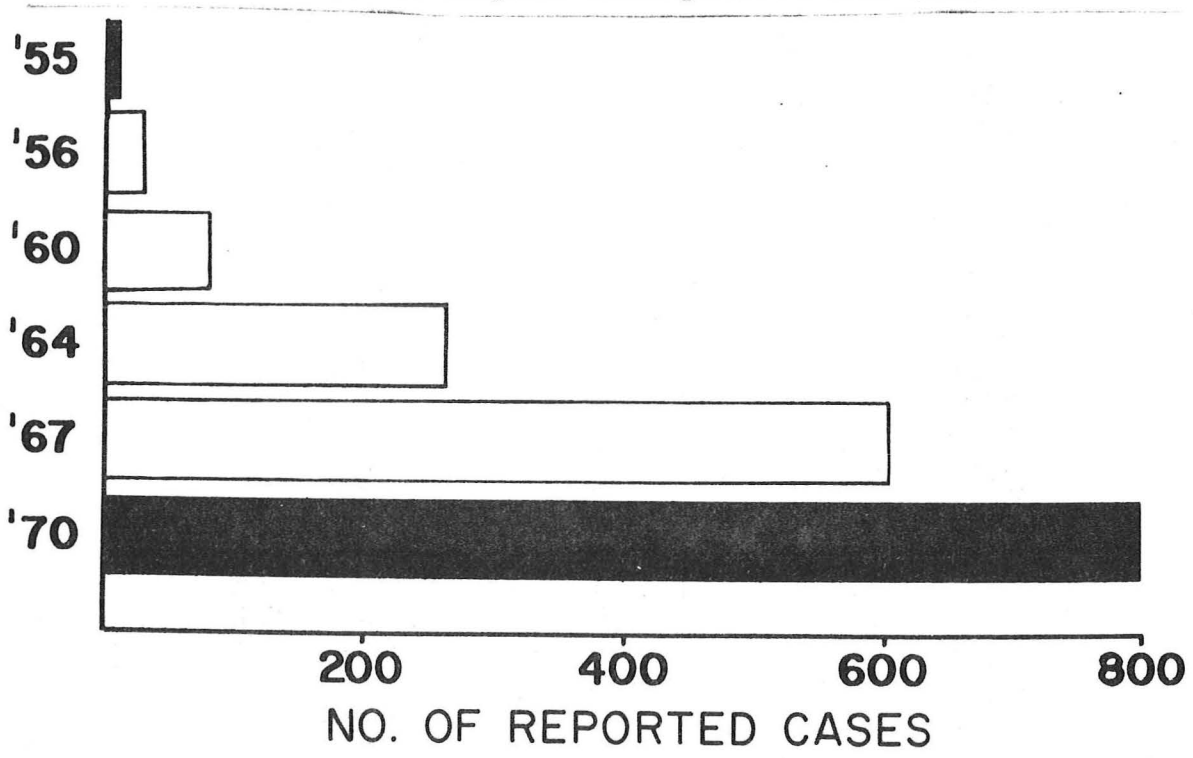
The sexes are affected with about equal frequency (6). The majority of affected women develop clinically manifest disease at about age 35, while the peak for affected men occurs during the fourth decade (6,12). The youngest affected patient described was 15 years of age when clinical signs first became apparent (6). The syndrome has been described to date in Italian, Swiss, Mexican, Puerto Rican, and French families as well as in both white and black American families (13).

The exact population frequency of the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome is not known. At least 42 unrelated families with the classic syndrome involving a total of 171 affected relatives have been described in the literature since Wermer's original description in 1954. In addition, the recent literature contains more than 800 case reports of patients with the Zollinger-Ellison Syndrome (13a) and more than 100 case reports of patients with multiple endocrine adenomas on whom no family data are provided.

Two types of evidence suggest that the Multiple Endocrine Adenoma - Peptic

Ulcer Syndrome is not a rare disorder. First, Snyder, et al. are currently following 38 affected members of 5 unrelated families who live in the Galveston area (14-15). Second, analysis of the cases of the Zollinger-Ellison Syndrome reported between 1955 to 1971 clearly shows that what was considered to be a rare disorder in the early 1960's is increasing in its clinical recognition (Fig. 1). These figures in no way represent the true frequency of the disorder since the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome has become so well identified that individual case reports are nowadays not submitted for publication.

Fig. 1
Number of cases of Z-E syndrome reported
since its original description in 1955 (13a).



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III Genetics

All published family data (reviewed in 6 and 12, 14-19) are consistent with Wermer's original postulation that the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome is inherited as an autosomal dominant trait. Although the gene appears to be fully penetrant by the second decade of life (14,16), it is widely variable in its clinical expression from one affected patient to another in the same family (6). The single most convincing pedigree is that reported by Ballard, et al. (6) in which the gene for the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome was transmitted through 6 generations of a large family. It is not possible from the current literature to determine whether the so-called "nonfamilial" cases of this syndrome represent examples of either new dominant mutations or incompletely studied families.

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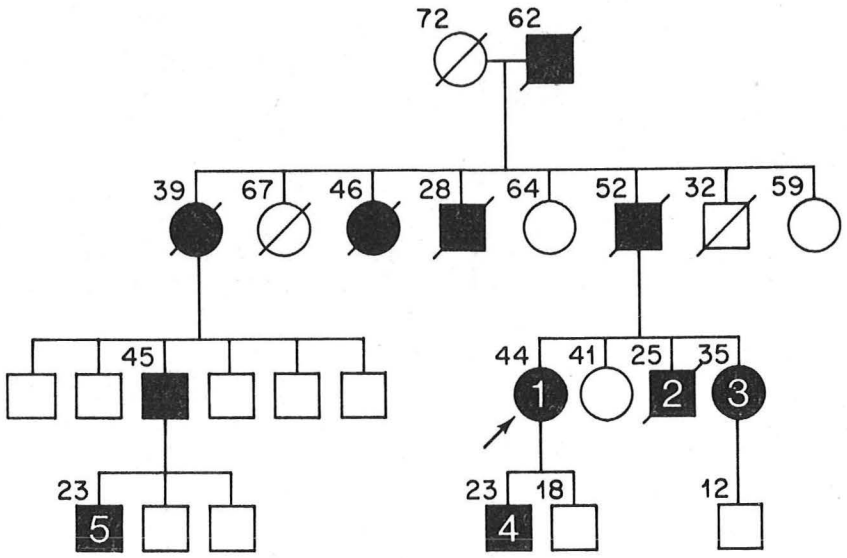
A pedigree of a typical family with the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome is shown in Fig. 2. Several of the affected members of this family, who are patients of Dr. Norman Kaplan, have been admitted to [redacted] on a number of occasions. The Parkland patients are [redacted]. ([redacted]) and [redacted]. ([redacted]).

Figure 2



1 Islet cell adenomas
Parathyroid adenomas
Lipomas

2 Lipomas, kidney stones

3 Islet cell adenomas
Parathyroid adenomas
Pituitary adenoma
Lipomas

4 Peptic ulcer disease

5 Pituitary adenoma

IV Clinical Features

A. Tissues Showing Involvement

The clinical picture is widely variable, depending largely on which glandular tissues are involved and whether or not the involved glands are functional (6,18). The parathyroid, pancreas, and pituitary are the most frequently involved glands, followed in order of decreasing frequency by the adrenal and thyroid (Table 1). Multiple lipomas, bronchial and intestinal carcinoid tumors, schwannomas, and thymomas may also occur. It has recently been demonstrated that the gastrin-secreting G cells of the fundus of the stomach may also display primary tumorous changes in affected subjects (10).

Table 1

FREQUENCY OF INVOLVEMENT OF VARIOUS ENDOCRINE GLANDS

Parathyroids	90%	
Pancreas	87%	
δ cells		49%
β cells		24%
Both		14%
Pituitary	67%	
chromophobe		40%
eosinophilic		27%
Adrenal	38%	
Thyroid	9%	

About 66% of affected subjects show some combination of 2 or more tumors. About 20% manifest a combination of 3 tumors involving the parathyroids, pancreas, and pituitary. The tumors in the involved gland usually demonstrate either simple hyperplasia or benign adenoma formation. However, malignant changes can occur, albeit infrequent (6).

B. Modes of Clinical Presentation

The majority of affected subjects will initially present with one of the following clinical patterns: 1) symptoms of peptic ulcer and its complications, 2) symptoms of hypoglycemia, 3) hypercalcemia and/or nephrocalcinosis, 4) complaints referable to pituitary dysfunction such as headaches, visual field defects, and secondary amenorrhea, and 5) multiple lipomas of the skin.

A minority (probably < 10%) of affected subjects will initially come to medical attention with one of the following clinical patterns: acromegaly, Cushing's syndrome, nonfunctional thyroid adenoma, hyperthyroidism, hepatomegaly due to metastatic liver disease, or flushing.

C. Relation of Multiple Endocrine Adenoma - Peptic Ulcer Syndrome to Zollinger - Ellison Syndrome

The peptic ulcer associated with the Multiple Endocrine Adenoma Syndrome seems identical in all respects to that of the Zollinger-Ellison Syndrome (6,9,20-24). Like in the Zollinger-Ellison Syndrome, the ulcer in the Multiple Endocrine Adenoma Syndrome is related to a non-β (i.e., δ) islet cell tumor that secretes gastrin, which in turn is responsible for the gastric hypersecretion, ulcer formation, diarrhea, and steatorrhea. The peptic ulcer disease is characterized by massive gastric hypersecretion and by ulcers that are usually multifocal and atypical in location. They may be found anywhere from the esophagus to the jejeunum but, as with ordinary peptic ulcers, the most frequent site is the first part of the duodenum. The patients present with all the typical signs and symptoms of peptic ulceration, including perforation, bleeding, and obstruction. The ulcers frequently recur after ordinary surgery, and total gastrectomy may eventually be required. Radiographic findings include giant gastric rugae, duodenal nodularity, ectopic ulcers in the esophagus, lower duodenum, and jejeunum, and intestinal hyperperistalsis (25,26).

The associated endocrine manifestations of the Multiple Endocrine Adenoma Syndrome are present in over 50% of cases of the Zollinger-Ellison Syndrome as well as in 50% of the first degree relatives of such cases (6,11). Thus, most geneticists (8) and most gastroenterologists (9) now regard the Zollinger-Ellison Syndrome as the gastrin-secreting, pancreatic islet cell tumor component of the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome.

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D. Natural History

Enough data are not currently available to assess the natural history of this disorder. However, Ballard, et al., in analyzing the clinical courses of 85 affected subjects who had been reported in the literature up to 1964, found that 32 of these 85 subjects died as a complication of their underlying disorder (6). The causes of death were as follows: 16 subjects died of complications of peptic ulcer, 6 died of complications of hypoglycemia, 3 died of complications of pancreatic surgery, 2 died following craniotomy for extirpation of a pituitary adenoma, 2 died of pituitary insufficiency, 2 died in uremia, and 1 died from disseminated islet cell carcinomatosis.

More recent case reports, published since 1964, show a strikingly lower frequency of deaths attributable to the disorder. This apparent decline in mortality since 1964 undoubtedly reflects a better understanding of the syndrome, especially in regard to management of the ulcer component.

V Diagnosis of the Asymptomatic Relative at Genetic Risk

Since the Multiple Endocrine Adenomata - Peptic Ulcer Syndrome is transmitted in families as an autosomal dominant trait, one-half of the first-degree relatives (i.e., parents, siblings, and children) of affected patients can be expected to carry the same gene and ultimately manifest clinical signs of the syndrome. A reasonable approach for screening relatives at genetic risk is as follows:

1) Review history for possible peptic ulcer disease, hypoglycemia, renal calculi, lipoma, or hypopituitarism

2) Examine patient for multiple lipomas

3) Blood tests - serum calcium and phosphorus; serum gastrin by radioimmunoassay

4) X-rays - lateral skull film

Screening with an upper GI series has not proved of value in diagnosing asymptomatic affected relatives (14).

VI Pathogenesis

A. Development of a Unifying Hypothesis

Any unifying hypothesis that attempts to explain the pathogensis of

the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome must incorporate the following known facts:

1) The syndrome is the result of an inherited mutation transmitted as an autosomal dominant trait.

2) The mutant (abnormal) gene acts in responsive tissues to disrupt the normal processes that regulate cell growth as a result of which stimulation of cell multiplication and adenomatous changes occur.

3) Although the mutant gene is present in all body cells of an affected individual, only cells of the parathyroid, the pancreas, the pituitary, the adrenal, the thyroid, and the adipose tissue are rendered responsive to its abnormal action.

4) Even among affected individuals who presumably inherit the same mutant gene, there is considerable variation in its expression - that is, islet cell tumors and parathyroid tumors may develop in some subjects, whereas only a pituitary tumor will develop in other subjects.

5) Although the mutant gene is present in susceptible body cells from the time of embryologic development, its abnormal action does not become manifest clinically until the second to fourth decades of life.

6) The single gene inheritance of this syndrome implies that its entire pathogenesis, no matter how complex and how variable, is due to a single biochemical abnormality.

B. Mutation Model for Hereditary Tumor Formation

Perhaps the best hypothesis to account for all of the above facts in the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome is Knudson's Mutation Model for tumor formation (27-32). The model proposes that in both hereditary and nonhereditary tumors, 2 mutational steps involving a pair of homologous genes in the same cell are necessary to convert a normal cell into an adenomatous or neoplastic cell. In hereditary cases, the first step is an inherited dominant mutation that is present in all body cells. Since only a small number of tumors is found in affected subjects who inherit the gene, it is apparent that not all of these gene-carrying cells become tumors; rather the gene creates an increased probability that abnormal growth will occur. A second mutational event must ensue, and this is usually somatic and affects one or more tissues in a random manner. (Hence, the small number of tumors and their variable locations in subjects with the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome.) In nonhereditary cases, 2 events involving homologous genes

are also necessary - the first may be considered as a rare and random somatic cell mutation; and the second, the same that occurs in hereditary cases. Thus, there is no fundamental difference between the process in hereditary and nonhereditary tumors. However, hereditary cases, since each cell in the body has inherited the first alteration, have a much greater probability of 2 or more cells becoming tumor cells, in which case the tumors may be multifocal in the same tissue or involve multiple different tissues. In nonhereditary cases, the probability that 2 rare mutational events would both occur in 2 or more different cells in the same individual is immeasurably low. By this model, all nonhereditary tumors are unifocal and usually involve only 1 tissue. Although nonhereditary solitary endocrine tumors are expected when the first mutation is in somatic tissue, it would be a highly improbable event for one person to sustain solitary tumors in more than one endocrine tissue. Therefore, even when individuals with the Multiple Endocrine Adenoma - Peptic Ulcer Syndrome do not have a positive family history, they should be considered as carriers of the gene for the syndrome.

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C. Role of the Cell Surface in the Control of Cell Proliferation

Assuming that the Knudson model applies to Multiple Endocrine Adenoma - Peptic Ulcer Syndrome, then the doubly mutated cell has been rendered defective for some tissue-specific function associated with the regulation of cell proliferation. Stated in biochemical terms, the factor that normally controls and limits the extent of growth of these endocrine and adipose tissue cells has become defective because of genetic alteration. Although the genetic locus whose alteration can produce the adenomatous growth seen in this syndrome has not yet been identified, an excellent candidate for such a locus is one

that determines the cell surface specificity of certain endocrine and adipose tissue cells. Recent studies indicate that tissue-specific receptor sites located on the surface of cells comprise the major mechanisms by which cell proliferation is regulated in mammalian cells. In normally growing cells, at least 3 broad categories of receptors can be shown to participate in the control of cell growth: 1) receptors that regulate the transport of incoming nutrients; 2) receptors that modulate or transmit signals from the external environment to the inside of the cell; and 3) receptor sites that directly control the rate of DNA synthesis and cell division (33).

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