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THE POLYENDOCRINE SYNDROMES

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Physicians are often too content after diagnosing hyperfunction of a single endocrine organ. Such a diagnosis may be lacking in completeness. Evidence is increasing that hyperfunction of one endocrine gland may be accompanied by other endocrine hyperplasia and adenomas. Table I lists some of these polyendocrine syndromes that have received recent attention. Several are undoubtedly related, while others are separate and distinct entities.

Table I

1. Multiple endocrine adenoma-peptic ulcer complex (MEA)
2. Zollinger-Ellison syndrome
3. Familial hyperparathyroidism
4. Hyperparathyroidism, hyperthyroidism and thyroid cancer
5. Familial pheochromocytoma
6. Cushing's disease and hyperparathyroidism
7. Carcinoid syndrome in noncarcinoid malignancies
8. Multiple hormone production in single nonendocrine malignancies

Multiple Endocrine Adenoma-Peptic Ulcer Complex (MEA)

During the past few years an opportunity was afforded to study a Negro family with multiple endocrine adenomas and a high incidence of peptic ulcer.[1] Since peptic ulcer and its complications were usually the presenting complaint and also the main cause of death, peptic ulcer is considered an integral part of the denomination. Forty-two members of a family over six generations were studied. Eleven members were proved to have the syndrome while five were highly suspect. The study was carried out with some difficulty since the family members live in widely separated

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areas of Detroit, Philadelphia and New York. The help of Dr. Harold Ballard of New York City in this study and investigation is duly appreciated. Most of the family was cooperative and wanted to know about any evidence of the condition. Some members, however, were fearful that the syndrome might be present and did not wish to know. The anxiety and concern in a family where such a serious hereditary condition exists can be understood. All varieties of response can be seen from complete denial to that of volunteering for medical research.

In addition to the afflicted family members, 74 additional cases of MEA were found recorded in the literature, making a total of 85 patients for analysis.[1] In 65% of the cases, pituitary involvement was present. Chromophobe adenoma occurred most commonly and usually resulted in symptoms of pituitary insufficiency. Acromegaly occurred in several instances in its classic form.

In 82% of the cases reviewed, pancreatic islet cell adenomas or malignancies were found. These tumors ranged from a single large adenoma to multiple small adenomas, both alpha and beta cell type. In the beta cell tumors, features of hypoglycemia were usually present. Despite local or distant metastases in 21 instances, metastatic spread of islet-cell tumor was responsible for death in only one patient. Pancreatic islet cell carcinoma, when occurring with MEA, appears relatively benign compared to the isolated acinar or single beta cell pancreatic carcinoma.

The parathyroid glands were involved in 88% of the cases. Fewer renal and skeletal complications were observed than is usual in primary hyperparathyroidism. The occurrence of renal lithiasis and nephrocalcinosis was 33% compared to an incidence of 75 to 80% in most series of patients with primary hyperparathyroidism. Skeletal involvement due to osteitis fibrosa is rarely seen in MEA. The incidence of primary chief cell hyperplasia and multiple parathyroid adenomas was also much higher than in primary hyperparathyroidism.

In 38% of the cases, adrenocortical involvement was proved at either operation or necropsy and included general hyperplasia, nodular hyperplasia and cortical adenomas. Despite this pathologic evidence of endocrine hyperplasia, there was little clinical or laboratory evidence of adrenocortical hyperfunction except in one patient who had simultaneous aldosteronism and hyperparathyroidism.

The thyroid gland was involved in 19% of the cases, a higher incidence than previously reported. Two patients showed symptoms and signs of thyrotoxicosis, and one patient had a thyroid carcinoma. The remainder had one or more nonfunctioning thyroid adenomas.

Peptic ulcer occurred in 49 of the 85 patients studied. More than half the ulcers were multifocal in origin and often atypical in location. In the majority one or more complications of ulcer such as hemorrhage, obstruction and perforation had occurred. In 15 cases, gastric hypersecretion or gastric rugar hypertrophy could be demonstrated.

Of theoretic interest is the relationship of the endocrine involvement to the ulcer diathesis. Current evidence suggests that the gastrin-like material which has been isolated from the pancreatic, non-beta cell tumors in a number of instances in MEA is the most likely cause for the gastric hypersecretion and the peptic ulcer diathesis. There is no substantial evidence of gastric hypersecretion occurring in hyperfunctioning parathyroid states. If hyperparathyroidism does increase the incidence of peptic ulcer disease, it perhaps does so by altering the gastric mucosal barrier, although proof is lacking. Parathyroid hormone has been shown to depolymerize the mucopolysaccharides in gastric mucin as well as in connective tissue throughout the body.

Serious diarrhea occurred in 11 of the 85 patients with MEA. Typically, the stools in these patients were loose and watery and often were associated with evidence of electrolyte depletion. In several instances, frank steatorrhea proved to be present. The mechanisms of the diarrhea may be explained in several ways. The gastric hyperacidity probably inactivates pancreatic lipase in the duodenal lumen and thereby interferes with proper digestion of fats. Not all patients with diarrhea have had gastric hypersecretion, however, and in at least one instance diarrhea has been relieved by removal of a pancreatic islet cell tumor. Also, extracts of pancreatic islet cell tumors in such patients have been shown to contain a substance which promotes bowel activity in isolated guinea pig ileum. Since both intestinal and bronchial carcinoid tumors may occur in MEA, and since the histology of islet cell tumors and carcinoid tumors may be difficult to differentiate, it is possible that serotonin may be present in sufficient amounts in some cases of MEA to promote peristaltic activity. Recent work from this hospital has demonstrated elevated blood serotonin and histamine levels in patients with Zollinger-Ellison and MEA syndromes, but diarrhea in these patients was thought not due to the increased levels of serotonin.[2] Other patients in the future, however, may demonstrate such a relationship.

For some strange and unexplained reason, there seems to be an increased incidence of lipomas in MEA. Eleven patients in the current review had lipomas, often multicentric and found in unusual locations such as the lung and retroperitoneal space.

It is of interest that a multiendocrine syndrome has been reported to occur spontaneously in animals. Also, after exposure to large doses of Xrays, rats of various ages may develop numerous multiendocrine tumors. The basic defect causing adenomatosis of the endocrine glands is not known, but the high familial incidence suggests a mutant gene that is readily transmittable. Hereditary studies available at present indicate that transmission is along the lines of autosomal dominance with a high degree of penetrance. Chromosomal studies performed on several members of the family reported revealed normal karyotypes.

Zollinger-Ellison Syndrome

It has been ten years since the Zollinger-Ellison syndrome was first described.[3,4] By definition this syndrome is characterized by gastric hyperacidity, severe peptic ulceration with or without diarrhea and one or more non-beta islet cell tumors of the pancreas. Long-term study of these patients indicates that many have underlying

multiple endocrine gland involvement. Both MEA and the Zollinger-Ellison syndrome undoubtedly have a common genetic background. With present information, it is reasonable to assume that the Zollinger-Ellison syndrome is a special variant of the more inclusive MEA-peptic ulcer complex. The Zollinger-Ellison tumor represents the gastrin-secreting islet-cell tumor in MEA and very likely accounts for the high incidence of peptic ulcer disease.

Familial Hyperparathyroidism

Several families have been reported with a high incidence of peptic ulcer, kidney stones or pancreatitis in which underlying primary hyperparathyroidism has been present.[5-7] The histology of the parathyroid glands in these families has varied. Where the parathyroids have demonstrated primary chief cell hyperplasia, the probability of associated polyendocrine involvement increased.[8] Endocrine tumors often remain dormant for many years and it is only by following patients through to operation or necropsy that a final opinion regarding the association of multiple endocrine lesions can be given.

Hyperparathyroidism, Hyperthyroidism and Thyroid Cancer

Several instances of simultaneous hyperthyroidism and hyperparathyroidism are recorded.[9,10] Since both conditions may give rise to hypercalcemia, a problem in differential diagnosis can occur. Most recordings of this combined endocrine hyperfunction have included no evidence of other endocrine involvement. It is not known whether these examples of polyendocrine disease have occurred by chance or are in some way related. Experimental evidence shows that a calcium-rich diet in animals results in increased incidence of thyroid hyperplasia and adenomatous formation.[11] Hellström records an increased number of adenomas and nodular changes in the thyroid gland in patients with primary hyperparathyroidism.[12] Perhaps in some instances such adenomatous changes progress to carcinoma. To support this concept, Ehlenberg and associates reported an unexpectedly high incidence of thyroid carcinoma in patients operated on for parathyroid adenoma.[13] In a series of 93 patients with primary hyperparathyroidism, 7 patients (or 7.5%) were found at operation to have associated thyroid carcinoma. This experience suggests that surgeons operating on patients for parathyroid adenoma should carefully explore the thyroid glands in an attempt to detect areas of early malignancy.

Familial Pheochromocytoma

Approximately 20 families have been reported with familial pheochromocytoma, and in several of these families thyroid carcinoma and even parathyroid adenomas have been found.[14] Pheochromocytomas in these instances are frequently bilateral. This entity is inherited as an autosomal dominant gene with a high penetrance similar to that seen in MEA. Again the question arises as to whether we are dealing with a separate polyendocrine syndrome or a variation of the multiple endocrine-peptic ulcer complex. The fact that patients with familial pheochromocytoma have not had an increased incidence of peptic ulcer suggests this is a separate polyendocrine syndrome.

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Primary Hyperparathyroidism and Cushing's Syndrome

Raker and associates have documented two patients with simultaneous occurrence of primary hyperparathyroidism and Cushing's syndrome.[15] Neither had a family history to suggest hereditary tendency, peptic ulcer disease or other endocrine disorder. Both hyperparathyroidism and Cushing's disease may cause bone disease, nephrocalcinosis and renal stones. There is little supporting evidence that hyperfunction of the adrenal cortex can produce an elevation of the serum calcium; in fact, adrenocortical hypofunction is more likely to be associated with hypercalcemia. Of special interest is the 15-year-old girl who had biochemical evidence of simultaneous hyperparathyroidism and aldosteronism.[1] This is thought to be the only report of this endocrine combination.

Carcinoid Syndrome in Noncarcinoid Malignancies

Intestinal and bronchial carcinoids, as mentioned previously, have been described in association with the multiple endocrine adenoma-peptic ulcer complex.[1] Recent evidence suggests that noncarcinoid tumors found in such organs as the pancreas, lung and thyroid may be associated with the characteristic clinical and laboratory features of the carcinoid syndrome.[16] Of importance to the current discussion of polyendocrine disease is the fact that 3 of 8 patients so described have had evidence of other endocrine hyperfunction. In one patient, simultaneous Cushing's syndrome was present, in another, hyperinsulinism and in a third, hyperparathyroidism. The entire area of carcinoid syndrome and associated multiple endocrine hyperfunction needs further investigation.

Multiple Hormone Production in Single Nonendocrine Malignancies

In recent years there have been numerous reports that malignant tumors from a variety of nonendocrine sources may produce hormone-like substances such as insulin, gastrin, parathyroid hormone, antidiuretic hormone, ACTH, TSH and chorionic gonadotropin. In several cases, two separate hormone-like materials have been isolated from a single tumor. Recently a patient with a malignant islet cell tumor of the pancreas that produced three separate substances similar to ACTH, melanocyte-stimulating hormone and gastrin, was reported.[17] This illustrates another form of polyendocrine disease where multiple hormones are synthesized and released from the cells of a single malignant tumor. Other examples of this unusual polyhormonal syndrome will undoubtedly be uncovered. The ability of a cancerous cell to produce a variety of hormonal substances is intriguing and may hold a clue to the nature and control of certain malignancies.

Delineation of the various polyendocrine syndromes is in its infancy. Exciting advances in this area are awaited as assay methods for various hormones improve. The number of possible combinations occurring as the result of hyperplasia and adenomas in the endocrine glands, as well as those arising in malignant tumors of nonendocrine tissue, staggers the imagination. It is again emphasized that the physician should not be content with diagnosis of hyperfunction in a single endocrine gland, but should be continually on the alert for evidence of polyendocrine involvement.

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