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Invited Lecture
Familial Multiple Endocrine Neoplasia Type I
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Familial multiple endocrine neoplasia type I (FMENI) is a familial form of hyperparathyroidism encompassing tumors and hyperfunction of other endocrine glands as well. The first suggestion of multiple endocrine organ involvement as a syndrome probably was in the report by Erdheim (1) in 1904 of a subject he examined at postmortem who exhibited a pituitary adenoma as well as hyperplasia of the parathyroid glands. Occasional clinical reports appeared of multiple endocrine hyperfunction throughout the early part of this century. In 1954 Wermer (2) called attention to the familial nature of this syndrome. In 1968 Steiner et al (3) differentiated MEN I from MEN II and in 1975 Chong et al (4) further differentiated type IIA from type IIB multiple endocrine neoplasia.

In familial multiple endocrine neoplasia type I one finds parathyroid hyperplasia and hyperparathyroidism, associated with pancreatic or pituitary tumors which can lead to hypersecretion of gastrin, insulin, glucagon, VIP, prolactin growth hormone, ACTH. Multiple lipomas as well as carcinoid tumors may also be associated with FMENI. FMENII is differentiated from FMENI in that parathyroid hyperplasia is associated not with pancreatic or pituitary tumors but rather with medullary carcinoma of the thyroid and pheochromocytomas. In FMENIIB parathyroid hyperplasia is not expressed but multiple neuromas and ganglioneuromas are.

Characteristically, hyperparathyroidism is the most commonly expressed endocrinopathy in FMENI and appears in up to 95% of affected cases. Less common are gastrinomas (37% of affected cases) and prolactinoma (23%). Insulinoma, acromegaly, ACTH-producing pituitary tumors, VIPomas, and carcinoid are found much less frequently, approximately in 5% of affected members. Also characteristic of hyperparathyroidism in FMENI is the pathology, four-gland hyperplasia rather then single adenoma as found in sporadic hyperparathyroidism. Another feature is the high rate of recurrence of hyperparathyroidism after initial parathyroid resection or transplantation in FMENI (5, 6).

The observations that hyperparathyroidism 1) is the most common endocrinopathy in FMENI, 2) is usually the first manifestation of the disease, 3) involves hyperplasia of all four parathyroid glands and 4) shows a high rate of recurrence suggested the possibility that an intrinsic or extrinsic factor may be driving hyperplasia of the parathyroid glands in FMENI. The development, several years ago, of a rapidly replicating parathyroid cell culture system (7) provided the opportunity to test for extrinsic factors in FMENI. With this system
it was found that plasma taken from subjects with FMENI contains a factor stimulating parathyroid cell growth in vitro (8). The mitogenic response obtained with FMENI plasma exceeded considerably that found with samples taken from normal subjects or those with sporadic hyperparathyroidism, MENII, or sporadic cases of Zollinger-Ellinger syndrome, sporadic pituitary tumors or chronic renal failure (Fig. 1).

The original rapidly-replicating parathyroid cell culture system represented a mixed cell population of endothelial and epithelial hormone-synthesizing cells. Recently, cloned cell systems have been developed from rat (9) and bovine parathyroid glands. With these cloned cell populations it has been possible to test independently, epithelial and endothelial cell responses to the EMENI factor. Assays are based on either $^3$H-thymidine uptake or cell growth determined by a microfluorimetric assay. We found (Zimering et al, to be submitted) that in the parathyroids it is the endothelial cell that is the target for the FMENI factor. The plasma factor from FMENI added to parathyroid endothelial cell cultures, causes a progressive increase in rate of cell growth in proportion to the amount of FMENI plasma factor added (Fig. 2).

Fig. 1. Parathyroid mitogenic activity in plasma taken from normal subjects and those with endocrine-related disorders. $^3$H-thymidine uptake (expressed as percent of basal) determined in a 24-hr test after adding plasma (1:20 dilution) to mixed-cell population of bovine parathyroid cells in culture. N — normal subjects; HPT — sporadic primary hyperparathyroidism; FAM. MEN 1 — multiple endocrine neoplasia type I; MEN 2 — multiple endocrine neoplasia type II; ZE — sporadic cases of Zollinger-Ellison syndrome; PIT. TUM. — sporadic pituitary tumors; CRF — chronic renal failure. From ref (8).
Fig. 2. Nuclear dye (Hoechst 33342) uptake in cultured parathyroid endothelial cells as a function of concentration of added FMENI plasma. Uptake of dye is a function of number of nuclei and hence a measure of cell number.

Fig. 3. Effect of antibodies to albumin or bFGF (1–24) on activity of FMENI factor added to parathyroid endothelial cells.
The response in the parathyroid endothelial cell culture system has allowed further characterization of the factor in FMENI plasma. The effect of the factor is partially neutralized by antibody developed against the synthetic amino-terminal 24-amino acid fragment of basic FGF itself (Fig. 3). Its activity is also partially blocked by preincubation of cells with basic FGF itself. Other observations indicated that the factor can be adsorbed to and eluted from heparin-Sepharose.

The above characteristics: 1) identification of target cell for FMENI plasma factor as the endothelial cell; 2) affinity of the factor for heparin; 3) inhibition of activity by basic FGF, as well as antibody developed against the synthetic fragment of basic FGF, suggest that the circulating factor in FMENI plasma may indeed be related to basic fibroblast growth factor (bFGF).

Basic FGF is part of a family of highly homologous proteins that stimulate the growth of endothelial cells (10); the family includes several recently discovered oncogene products (10, 11). Such reports plus our observations of similarities of the FMENI plasma factor to basic FGF led us to test for possible genetic linkage of FMENI using probes related to bFGF-related oncogenes. In collaboration with S. Bale et al (1988, submitted) linkage was established with a probe for the int-2 oncogene (probe kindly supplied by Dr. Clive Dickson, London). Hst, another proto-oncogene member of the FGF family, is tightly linked to int-2 (12) and could also be implicated in FMENI. Polymorphisms were established using DNA fragments produced by three different restriction enzymes. Products of the TaqI enzyme were particularly informative and showed highly significant linkage in one family to one of the TaqI alleles. The int-2 and hst oncogene products show about 50% homology with bFGF and both are located on the long arm of chromosome 11. Earlier this year Larsson et al (12) showed linkage in FMENI with the PYGM probe. This is a probe for the glycogen phosphorylase enzyme, the gene for which is located in the same region as int-2 (11q13). Larsson et al also found that pancreatic tumors taken from subjects with FMENI showed a deletion of a major segment of the chromosome 11 copy from the unaffected parent. It is presumed, then, that in FMENI there is a genetic mutation near the centromeric region of chromosome 11, and this defect is inherited in an autosomal dominant fashion through the germ line. Postnatally a second mutation (“second hit”) in the normal allele leads to clonal formation in the pancreas and presumably in the pituitary as well. We presume that the inherited gene defect leads also to hypersecretion of the bFGF-like factor circulating in FMENI. It is the circulating growth factor that contributes to parathyroid hyperplasia and perhaps also to tumor production in the pancreas and pituitary. How a heterozygous mutation in chromosome 11 produces hypersecretion of the growth factor is a question of great interest. How the bi-ballelic defect in the pancreatic neoplasm facilitates tumor growth is also a challenging question. Determining the precise genetic defect in FMENI presumably will lead to answers for these questions.
References