Endocrine Tumors of the Gastrointestinal System

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Gastroenteropancreatic Endocrine System

- Clear cells of endodermal origin found in the pancreas, stomach, small and large intestine
- Secrete over 30 polypeptide hormones

Tumors of the GES

- Rare; 1 per 100,000 per population year
  - Insulinomas—1 per 250,000
  - Gastrinomas—1 per 1-2 million
  - VIPomas—1 per 10 million
  - Glucagonomas—1 per 20 million
  - Somatostatinomas—1 per 40 million
  - Pancreatic polypeptide secreting tumors

Tumors of the GES

- May be difficult to diagnose and localize
- Serum panel: gastrin, VIP, glucagon, calcitonin, somatostatin, PP, GIP, neurotensin, insulin, PHM
- Imaging: Somatostatin receptor scintography (SRS), CT, MRI, endoscopic or intraoperative ultrasound, angiography

Imaging

- Recent advances in imaging of pancreatic endocrine tumors include:
- MRI with gadolinium shows 85% sensitivity and 100% specificity, 50% of tumors between 1-2 cm and 100% > 3 cm are detectable
- MRI with Mangan enhancement has been reported to detect insulinomas as small as 10 mm
- Somatostatin receptor scintigraphy is at least 80% for all PETs excluding insulinomas, for which it is closer to 50%

Prognostic Factors

- Poor prognosis has been linked to
  - anaplastic or poorly differentiated tumor
  - lack of Chromogranin A staining
  - loss of function
  - tumor size > 4 cm
  - ectopic hormone production
  - negative octreotide scan

Prognostic Factors

- Poor prognosis has been linked to
  - > 2 % Ki-67 positive cells
  - > 2 mitoses/ 10 hpf
  - p53 over-expression
  - angio or perineural invasion
  - presence of liver metastases

Multiple Endocrine Neoplasia Type 1

- The association of parathyroid, pancreatic islet and pituitary hyperplasia or neoplasia
- Hyperparathyroidism is the most common manifestation
- Neoplasia of the pancreatic islet cells is the second most common manifestation (80%); gastrinoma, insulinoma, glucagonoma, VIPoma, PPoma
- Abnormal growth is characterized by expansion of multiple cell clones

MEN Type 1

- Pituitary tumors occur in over 50% of patients
  - Two mechanisms: (1) clonal expansion of neoplastic pituitary cells and (2) stimulation by ectopic hypothalamic releasing hormones, e.g. CRH, GHRH
- May cause galactorrhea or amenorrhea (prolactin), acromegaly (GH) or Cushing's syndrome (ACTH)
- Ectopic production of ACTH, PTHRP

MEN 1--Screening

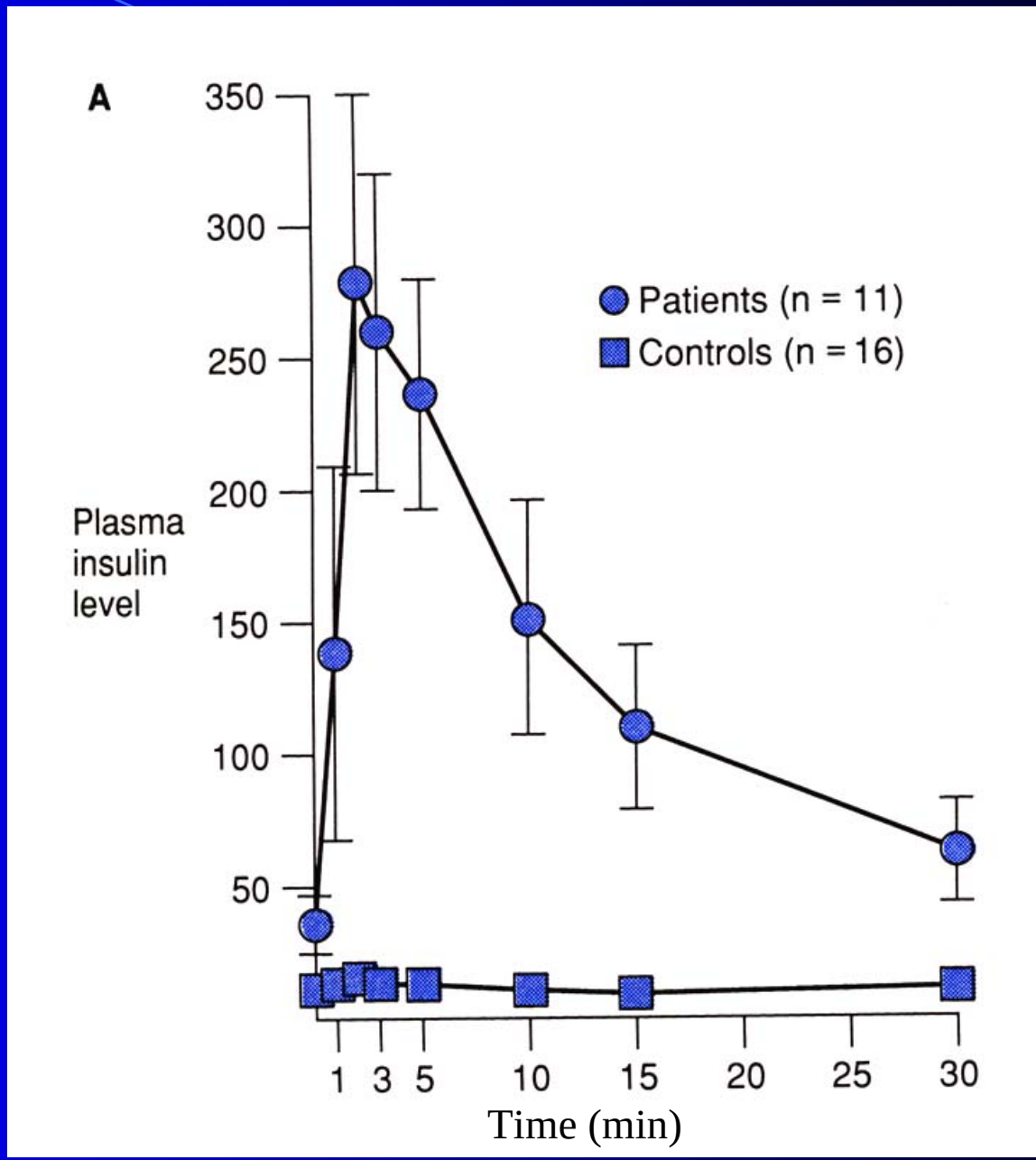
- Serum ionized calcium, q 3-5 yrs, age 15-50
- Serum prolactin, q 3-5 yrs, age > 15
- Serum gastrin, q 3-5 yrs, age > 25
- Genetic testing—mutational analysis of the MEN 1 gene
- If positive, add imaging of pituitary every 5-10 years until age 60

Insulinoma

- Insulinoma is the most common type of functioning pancreatic endocrine tumor (PET)
- Most common in males age 30-60
- 70% solitary, benign, localized to pancreas
- Whipple's Triad: 1) neuroglycopenic and adrenergic symptoms of hypoglycemia, 2) documented low blood sugars, 3) rapid relief of symptoms after eating
- Dx: 48 hour fast; fasting hypoglycemia with inappropriately elevated serum insulin, C-peptide or proinsulin

Provocative Testing for Insulinoma by Rapid Infusion of Calcium

(2 mg/kg over 1 minute)

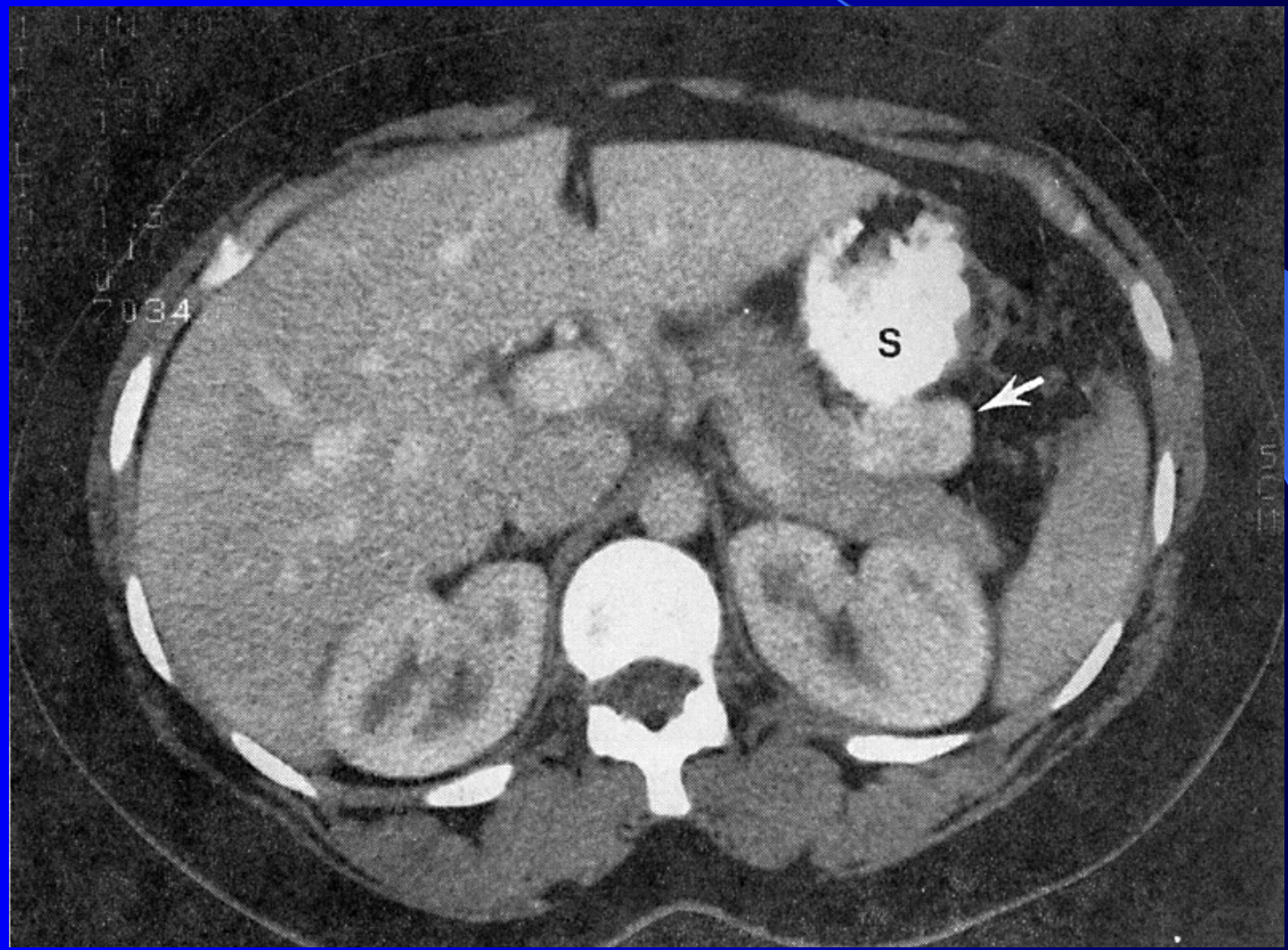


Insulinoma

- Localization: CT, selective injection of calcium, intraoperative ultrasound plus pancreatic palpation can identify nearly all tumors

- Rx: surgery, frequent small meals, diazoxide which decreases beta cell secretion of insulin, continuous infusion of glucose or glucagon; no good long term medical therapy

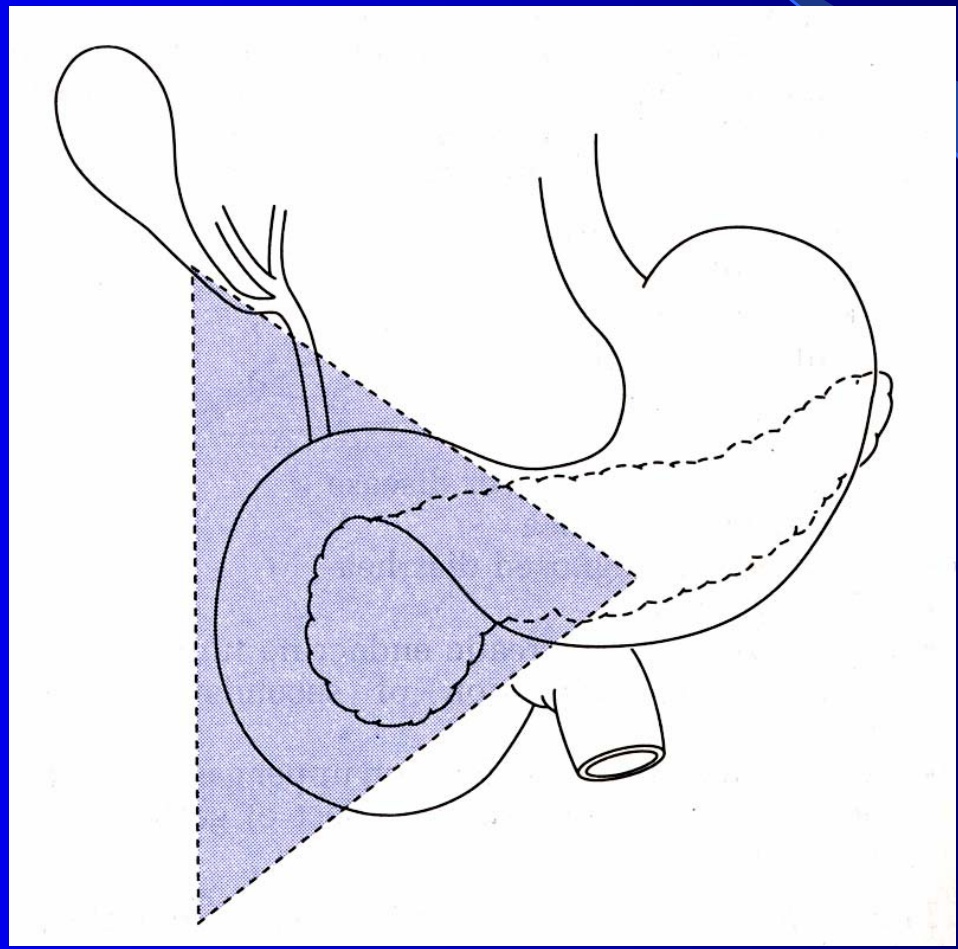
Insulinoma



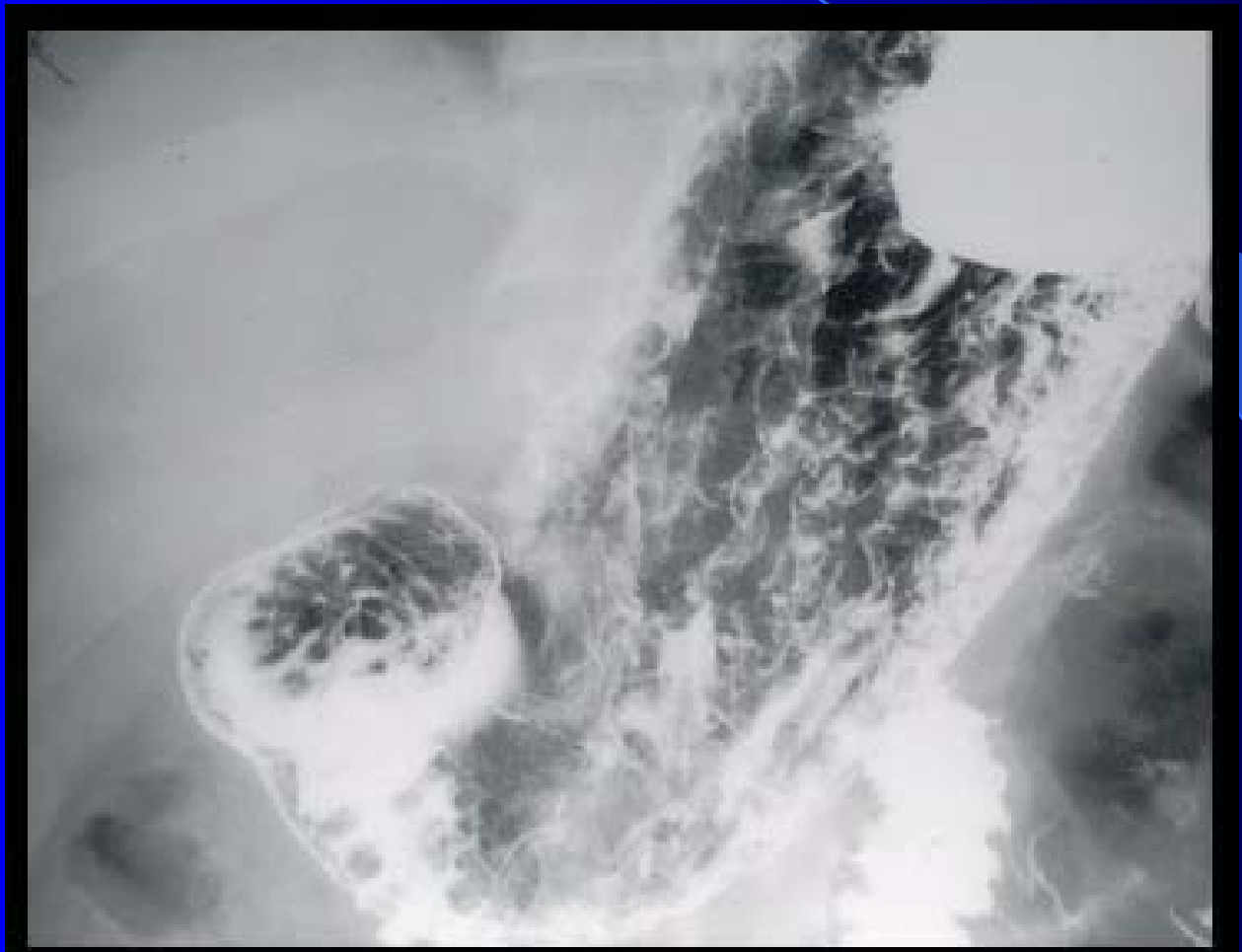
Gastrinoma

- Gastrinoma is the second most common type of functioning PET
- 2/3 sporadic, 1/3 MEN 1
- Sporadic: solitary, 60% malignant, 80% found in gastrinoma triangle; over 40% have hepatic metastases at time of diagnosis
- MEN 1: small, multiple, benign or malignant
- ZES: recurrent severe peptic ulcer disease, gastric hypersecretion, pancreatic tumor

Gastrinoma Triangle



Zollinger-Ellison

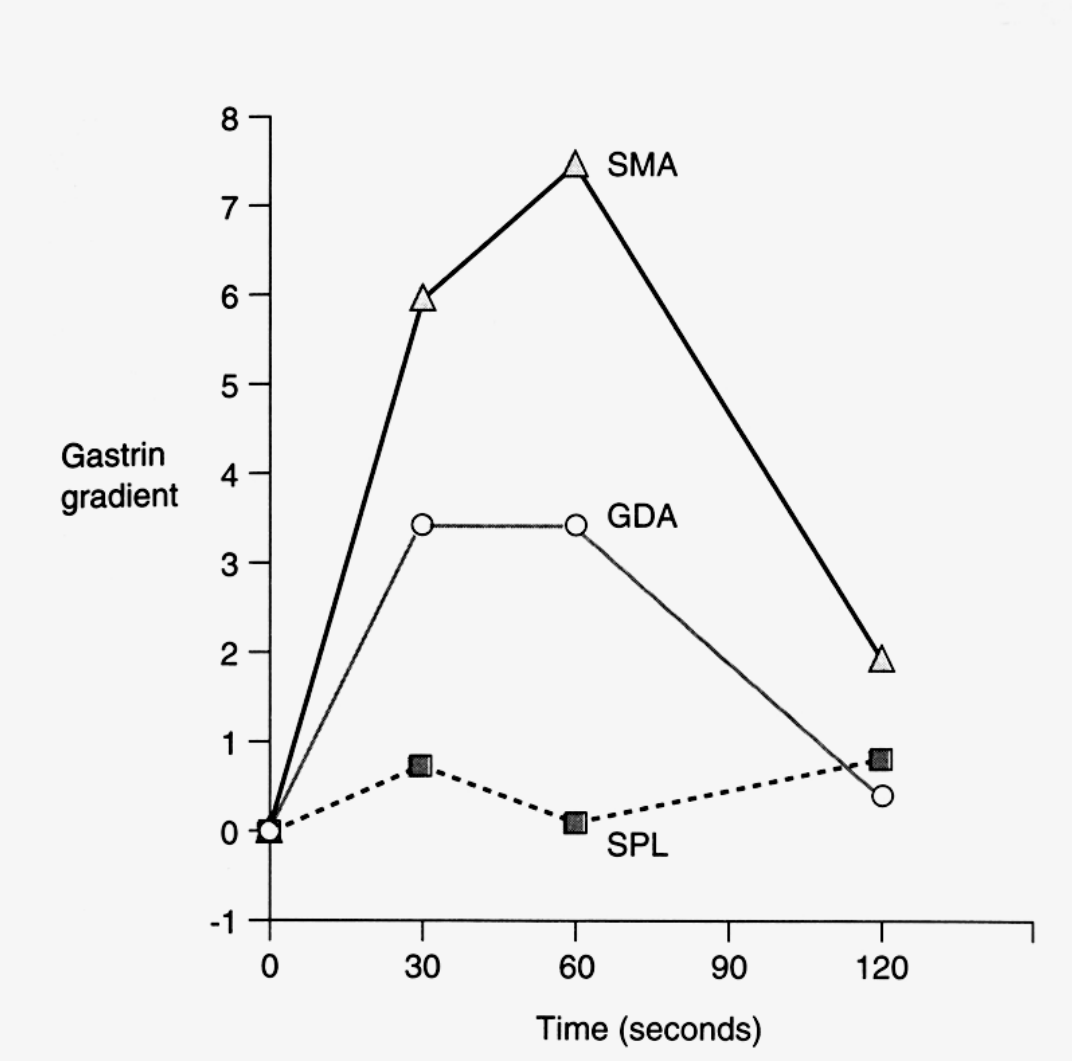


Double contrast upper GI showing thickened rugal folds in the stomach and duodenal C-loop - classic findings of Zollinger Ellison syndrome.

Zollinger-Ellison Syndrome

- Gastric acid hypersecretion caused by excessive production of gastrin
- Gastrin levels and gastric acid hypersecretion are stimulated by calcium infusion and by intrinsic hypercalcemia
- Peptic ulcers are present in > 90%, diarrhea, steatorrhea, esophagitis
- Dx: Serum gastrin: basal > 300 pg/ml, secretin stimulated increase > 200 pg/ml; gastric pH < 2.5

Secretin Stimulation Test



SPL-splenic artery

GDA-gastroduodenal artery

SMA-superior mesenteric artery

ZES--Pharmacotherapy

- Proton pump (H^+, K^+ ATPase) inhibitors
  - omeprazole
- H_2 receptor antagonists
  - ranitidine
  - cimetidine
- Somatostatin analogs
  - Octreotide

ZES-Therapy

- Pharmacotherapy may be combined with surgery
  - Enucleation can result in improved survival in sporadic cases
  - For patients with MEN 1, a more aggressive surgical approach is recommended

Gastrinoma—Genetic Alterations

- MEN 1 gene (menin) at chromosomal locus 11q13 is a tumor suppressor gene
  - As part of MEN 1 syndrome
  - In 27-37% of sporadic gastrinomas
- *p16/MTS 1* tumor suppressor gene
- HER-2/*neu* proto-oncogene
- Amplification of chromosome 9q
- Deletions of chromosome 1

Watery Diarrhea Syndrome

- Syndrome of watery diarrhea, hypokalemia, hypochlorhydria, acidosis
- Pancreatic islet cell tumors and carcinoid
- Vasoactive intestinal polypeptide (VIP) inhibits absorption and stimulates secretion of sodium. chloride, potassium and water in the small intestine and stimulates bowel motility
- Rx: surgical removal, octreotide

VIPoma

- Syndrome of islet cell tumor, severe watery diarrhea which is isotonic with plasma, hypokalemia, acidosis and dehydration, achlorhydria or hypochlorhydria, hypercalcemia, hypotension secondary to peripheral dilatation, and glucose intolerance
- These tumors may also secrete neurotensin, PP, calcitonin, peptide histidine methionine (PHM) which shares a common precursor with VIP, and an inhibitor of gastric acid secretion

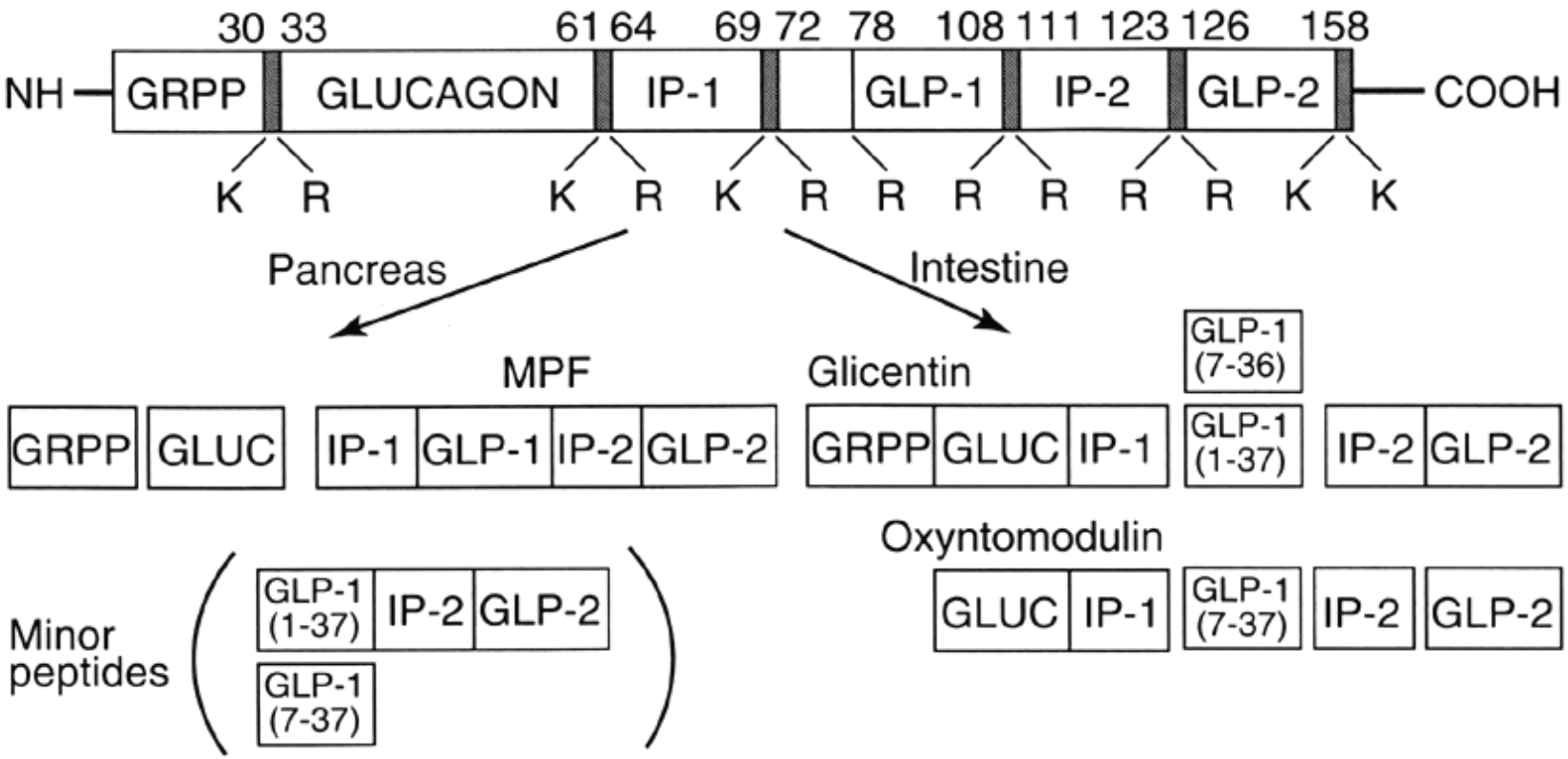
VIPoma

- Occur in adults 30-50 years of age and children 2-4 years of age
- 50% are metastatic at time of diagnosis
- Death occurs from renal failure or cardiac arrest secondary to acidosis and dehydration
- Treatment includes supportive therapy, surgery, chemotherapy (streptozotocin), antisecretory drugs, octreotide, and interferon

Glucagonoma

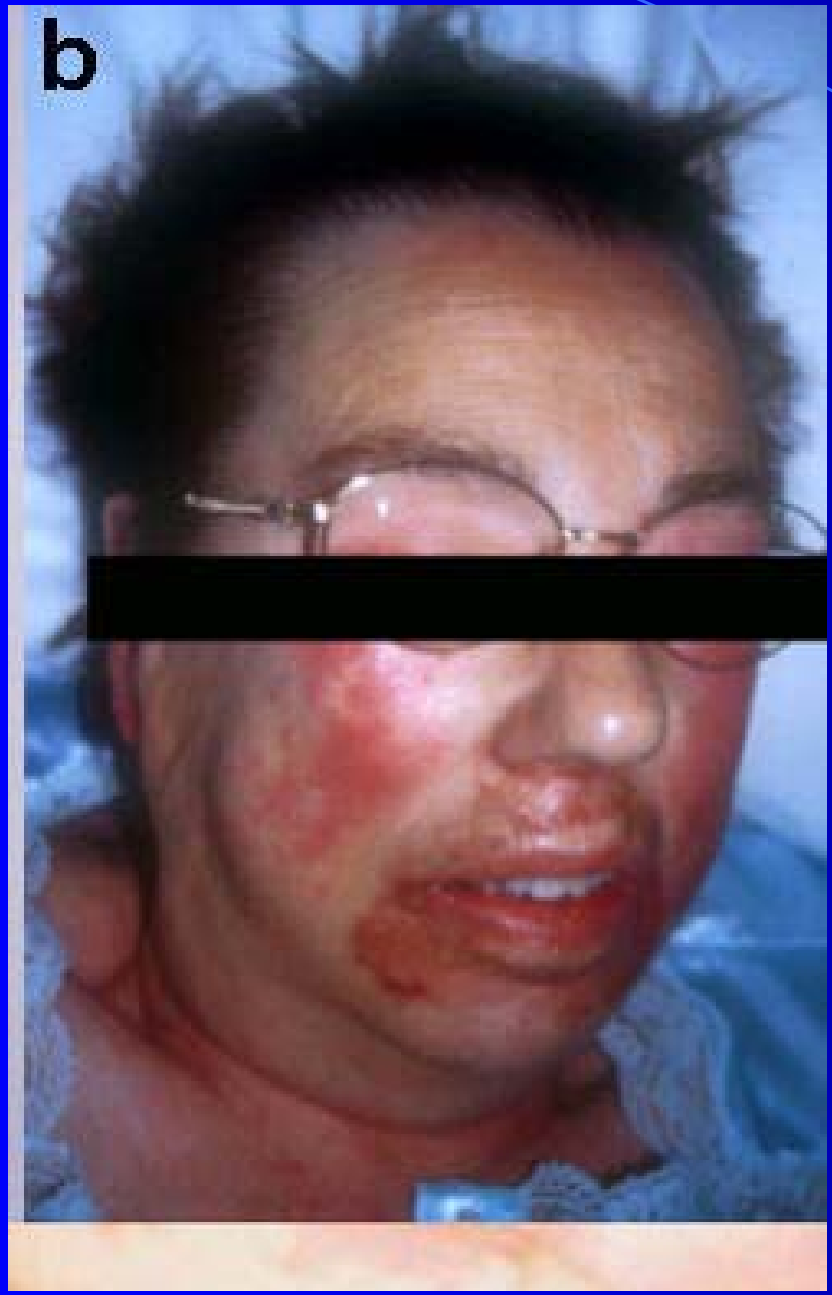
- > 4 cm, found in body and tail of pancreas, >50% of patients have hepatic metastases at diagnosis
- Pre-proglucagon
- Pancreas—glucagon, a major hyperglycemic hormone, counterregulatory to insulin
- Intestine—GLP-1, a potent stimulator of insulin secretion, glycentin (stimulates growth of intestinal mucosa), oxyntomodulin (role in gastric acid secretion)

Alternative Processing of Glucagon



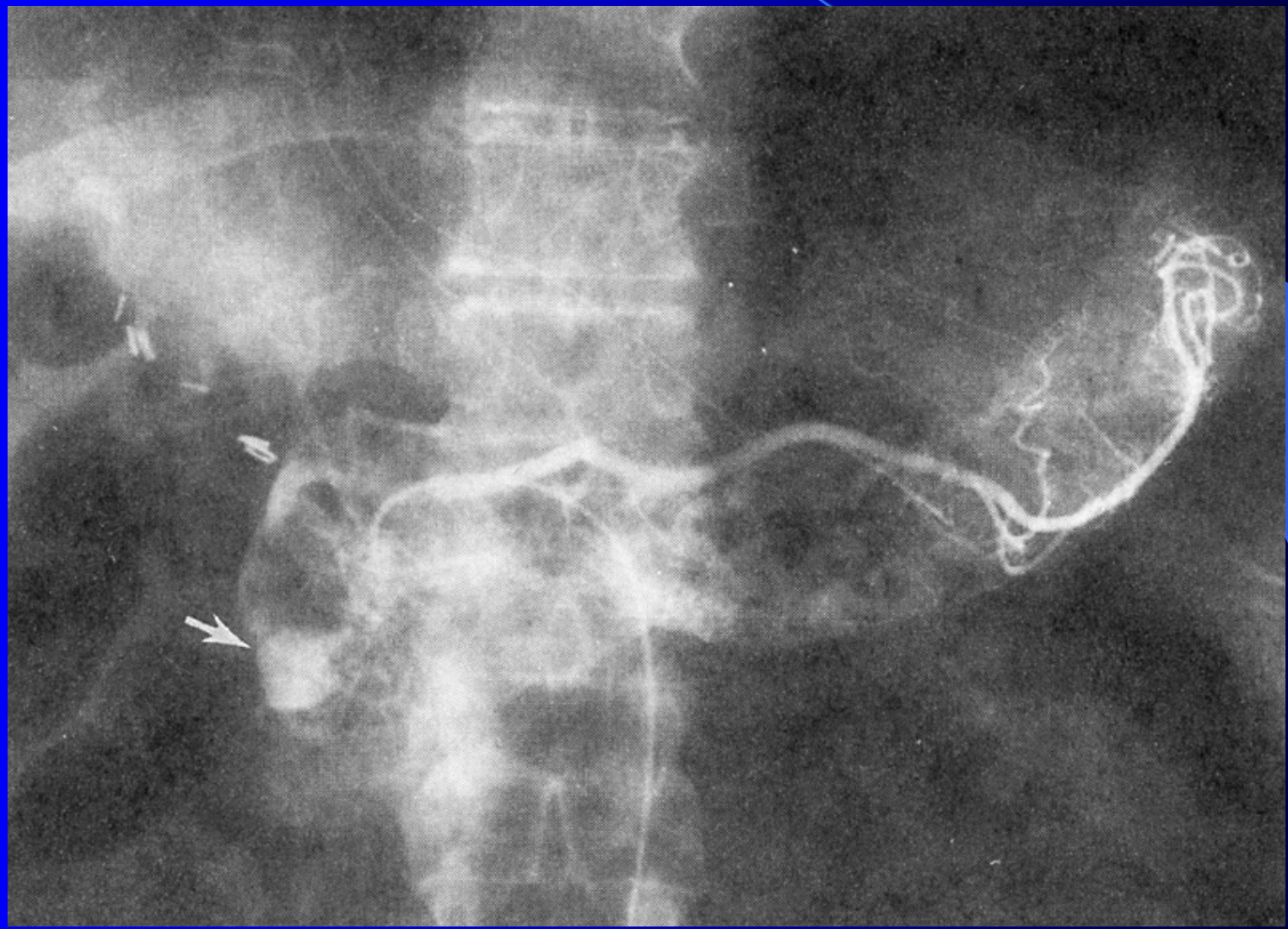
Pancreatic Glucagonoma

- Syndrome of hyperglycemia, necrolytic migratory erythema (↑glucagon,↓amino acids, ↓zinc), anorexia, glossitis, normochromic normocytic anemia, diarrhea, weight loss, depression and venous thrombosis
- Hyperglycemia is a result of increased hepatic glycogenolysis and gluconeogenesis; plasma glucagon > 1000 pg/ml. Diabetes occurs in 75-95% of patients
- Rx: surgical removal; octreotide



Necrolytic migratory erythema

Glucagonoma



Pancreatic Glucagonoma

- Rx: surgical removal, but metastases are common (90% liver, 30% lymph nodes)
- Octreotide
- Topical or oral zinc
- Aspirin to prevent thrombo-embolic disease

Somatostatinoma

- Somatostatin inhibits pancreatic and GI functions
- Pancreatic tumors (43% of cases) cause mild diabetes, cholelithiasis, steatorrhea, indigestion and hypochlorhydria
- Intestinal tumors (57% of cases) found in duodenal wall and ampulla of Vater, often manifest with local symptoms as well

Somatostatinoma

- Diagnosis is made by demonstration of elevated plasma somatostatin levels
- Stimulatory tests with secretin or calcium-pentagastrin may be helpful in cases of pancreatic tumor with normal basal somatostatin.

Table 34-9. RARE FUNCTIONAL PANCREATIC ENDOCRINE NEOPLASMS

Tumor	Hormone/Candidate	Features
Calcitoninoma	Calcitonin	Secretory diarrhea
Parathyrinoma	PTH-related protein	Hypercalcemia Bone pain Normal serum PTH
GRFoma	Growth hormone releasing factor	Acromegaly
ACTHoma	Adrenocorticotropic hormone	Cushing syndrome
Neurotensinoma	Neurotensin	Tachycardia Hypotension Malabsorption

PTH, parathyroid hormone.

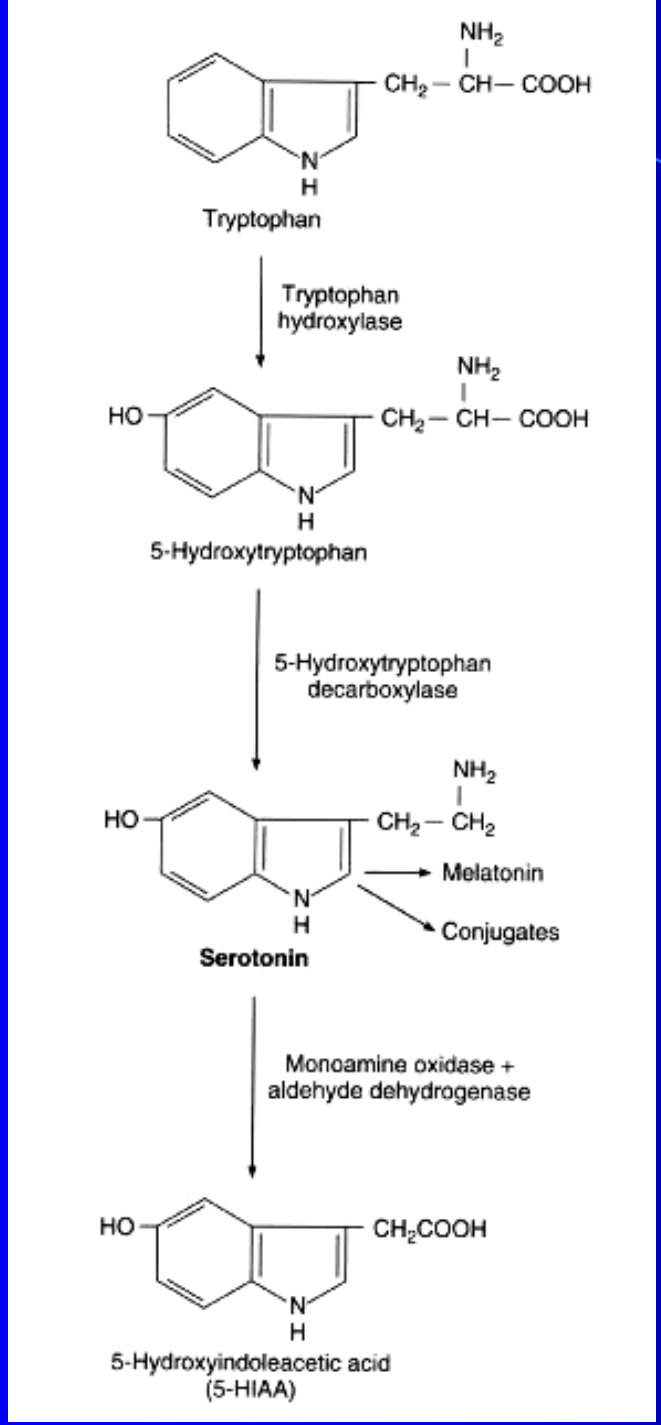
Carcinoid Tumors

- Carcinoid tumors are common and account for 55% of all endocrine tumors, 1 in 150 small intestines at autopsy, 1 in 300 appendectomies, 1 in 2500 proctoscopies. They are rarely malignant.
- Other sites as lung bronchus, thymus, stomach, pancreas exhibit a higher degree of local invasion, lymph node metastases and distant metastases, usually liver.
- Carcinoid syndrome occurs in <10%
- *Patients with the full blown carcinoid syndrome usually have hepatic metastases. Why?*

Carcinoid

- Syndrome of flushing, wheezing, gastrointestinal hypermotility and cardiac disease is most common. Atypical syndrome (5%) consists of flush, headache and bronchoconstriction. Local symptoms may occur first.
- Foregut and midgut tumors produce large amount of serotonin (5-hydroxytryptamine) or 5-hydroxytryptophan and patients excrete increased levels of 5-hydroxyindoleacetic acid (5-HIAA).
- Gastric carcinoids (9% of all GI carcinoid tumors) produce histamine. Can occur in MEN I patients with ZES (~1 in 3).

Serotonin Metabolism



- Foregut tumors may have absent or reduced levels of L-amino acid decarboxylase.
- Secreted 5-hydroxytryptophan is converted to serotonin in other tissues.
- Tryptophan and niacin deficiencies can occur.

Carcinoid Tumors

- Diagnosis
  - Symptoms, endocrine or local
  - Intestinal: Urinary 5-HIAA >150 μmol/d; note interfering factors
  - Plasma chromogranin A
  - Gastric: Serum gastrin, secretin stimulation test, histopathological diagnosis

Carcinoid Tumors

- Treatment
  - Surgery: debulking, percutaneous embolization of the hepatic artery; tricuspid valve replacement
  - Chemotherapy: antimetabolites such as streptozotocin and 5-FU, octreotide, interferon, [^{111}In]pentreotide
  - Pharmacologic Therapy
    - Antiserotonin agents: methysergide, cyproheptadine
    - H1 and H2 receptor blockers (gastric tumors-histamine)
    - Octreotide (midgut-tachykinins)
  - Supplemental niacin *Why not just give tryptophan?*
  - ***What is a serious side effect of methysergide?***

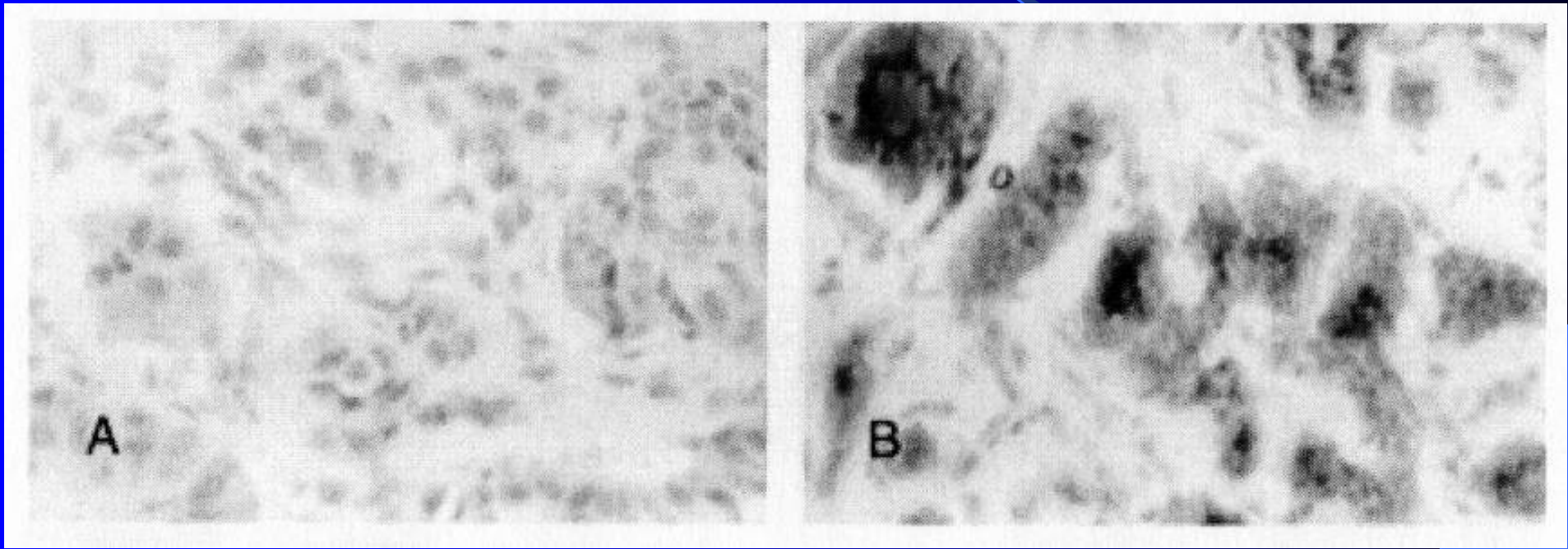
Interferon Therapy

- Used for metastatic PETs
- Interferon-α (IFN-α) stimulates natural killer cells, increases class I antigen on tumor cells and controls hormonal symptoms

Interferon Therapy

- Interferon-α (IFN-α) binds to a membrane receptor and up-regulates intracellular mediators such as Jaks and Stats.
- Jaks and Stats transduce the signal to the nucleus resulting in up-regulation of target genes, including the interferon regulatory factors, IRF-1 and IRF-2.
- IRF-1 is a tumor suppressor transcription factor; up-regulation correlates with tumor response to IFN- α. IRF-1 is also an apoptotic factor and may act in part through p68, an inhibitor of protein synthesis.

Carcinoid IRF-1



Midgut carcinoid before and after treatment with IFN-α.

44% biochemical response with interferon-α and 11% tumor shrinkage in tumors with < 2% Ki 67 positive cells

Peptide receptor targeted radiotherapy

- Somatostatin receptor mediated endocytosis
- therapy of somatostatin receptor subtype sst_2 and sst_5 positive metastatic carcinoids and PET
- couple α- or β-emitting radionuclides or chemotherapeuticals to somatostatin analogues

Peptide receptor targeted therapy

- new therapeutic sst analogues that interact with additional receptor subtypes, e.g. SOM230
- transfer of genes encoding sst receptors to receptor negative tumors
- somatostatin immunotherapy?
- anti-angiogenesis agents