

# Neuroendocrine tumours

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# Case 1

- Woman aged 65 years
- Laparotomy for small bowel obstruction
- Appendiceal tumour
- Histology: carcinoid

# Case 1

- Diarrhoea and flushing for 2 years
- Opening bowels up to 6 times daily, watery, high volume,
- flatus++, helped slightly by loperamide
- Flushing at any time of the day - no obvious precipitating,
- aggravating or relieving features

- Investigations:
- Urinary HIAA 200  $\mu\text{mol/day}$
- Chromogranin A and B raised, other gut hormones normal
- Abdominal scan showed lymph node and liver metastases

## Case 2

- Man aged 40 years, aunt had MEN1 and died from metastatic pancreatic tumour
- Mutation found in MEN1 gene
- Has dyspepsia controlled by proton pump inhibitor

- Investigations:
- Calcium 2.7 mmol/L
- PTH 10 pmol/L (<8)
- Prolactin raised
- Abdominal MRI: 2 -cm tumour in tail of pancreas
- Gut hormones: normal chromogranins, gastrin slightly high

## Case 3

- 19-year old man with pheochromocytoma
- SDHD-B mutation
- Sister and mother affected

# NETs

- NET cells first described by Paul Langerhans in 1869
- Previously named APUD cells – Amine Precursor Uptake and Decarboxylation (take up amine precursors and decarboxylase them to produce peptide hormones and biogenic amines)
- APUD cells found in gut, pancreas and nervous system – Neuroendocrine tumours

# NETs

- Criteria for NETs
  - Produce neurotransmitter, neuromodulator or neuropeptide hormone
  - Have dense core granules from which hormones are secreted by exocytosis under external stimuli
  - Absence of axons and synapses

# NETs

- Heterogeneous group of tumours
  - ✓ Gastrointestinal carcinoids
  - ✓ Islet cell pancreatic cells
  - ✓ Chromophobe adenomas of the pituitary
  - ✓ Medullary Carcinoma of thyroid
  - ✓ Pheochromocytoma and paragangliomas

# Epidemiology

- Increasing incidence due to improvements in diagnostic technique
- 0.5% of all malignancies
- 2-3 per 100000 per year
- GI NETs account for majority

# Classification

- Initially called carcinoids
- But did not include all types of NETs
- Classified according to the
  - ✓ Site of origin
  - ✓ Histopathological characteristics
  - ✓ Biological behaviour (secreting or not)

# Inherited tumour syndromes

- MEN 1 - Parathyroid, pancreas, pituitary
- MEN 2 - Medullary thyroid carcinoma, phaeochromocytoma, hyperparathyroidism, mucosal neuromas (2B)

- Neurofibromatosis
- von Hippel-Lindau – cerebellar haemangioma
- Succinyl dehydrogenase mutations (SDH A & B)

# Hormone secretion products

- Pancreas, gut: Insulin, pancreatic polypeptide (PP), vasoactive intestinal polypeptide (VIP), gastrin, glucagon
- Pituitary - Growth hormone, prolactin, adrenocorticotrophin (ACTH)
- Carcinoid - Serotonin (5-hydroxytryptamine, 5HT)

# Morphology

- Staining
- Chromogranin A, synaptophysin, CD57
- Malignancy indices
- Mitoses, Ki67

# Sites

- Foregut
- Midgut
- Hindgut

# Fore gut

- Lung, stomach, duodenum, pancreas
- Gastric
- Type 1 - associated with atrophic gastritis
- Type 2 - Zollinger-Ellison, MEN1
- Type 3 - metastasise

# Fore gut

- Pancreatic
- Gastrinoma, VIP, insulin, PP
- Duodenum
- MEN1 gastrinomas

# Midgut and hindgut

- Small gut, appendix, (caecum)
- Hindgut - colon and rectum

# Effects

- Tumour bulk - primary or secondary
- Local effects - gut and mesentary
- Hormonal

# Hormonal effects

- Flushing, diarrhoea (5HT, VIP)
- Peptic ulcer disease (gastrin)
- Cardiac (5HT) - right heart disease
- Hypoglycaemia (insulin)
- Hypogonadism (prolactin)
- Acromegaly (GH)
- Cushing's syndrome (ACTH)

# Diagnosis and monitoring

- Genetics
- Biochemistry
- Imaging
- Friday,

# Genetics

- Family tree
- Mutation testing (SDH)
- Proband
- First degree relatives

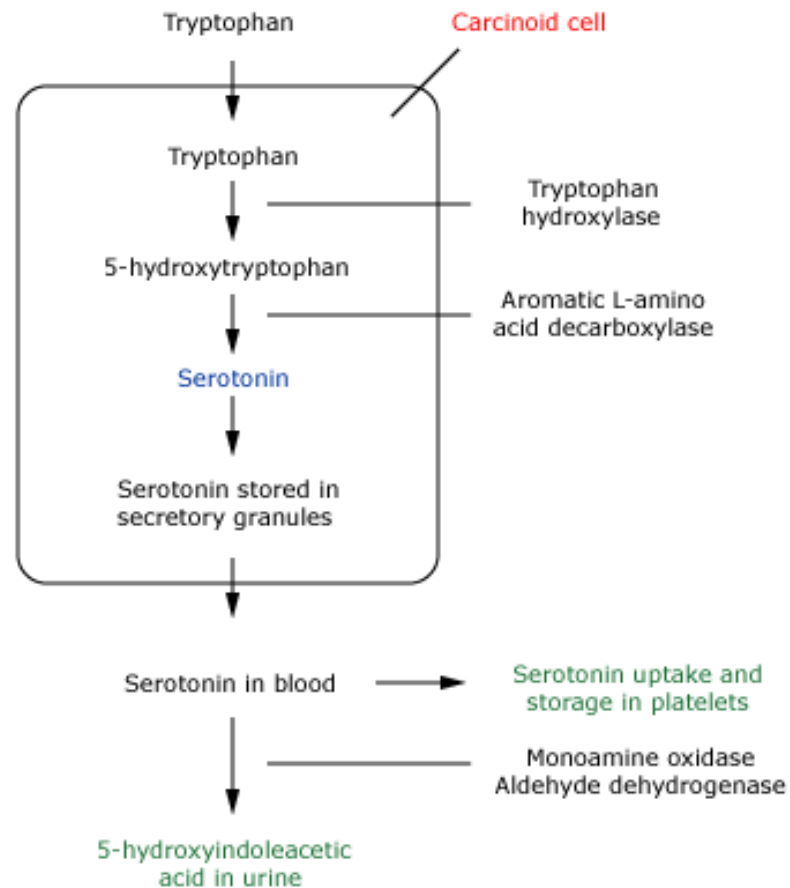
# Biochemistry

- Indoles (5-hydroxy-indoleacetic acid - HIAA)
- Chromogranins A and B
- Gut hormones
- Pituitary hormones
- PTH, Calcium

# Indole metabolism

## Tryptophan and serotonin metabolism

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# Serotonin

- Produced from tryptophan (about 2% of tryptophan metabolism)
- Main sites enterochromaffin cells, serotonergic neurones, pineal
- Can be measured in plasma, platelets or urine
- Liver removes ~30% of portal 5HT
- Lung >90% removal
- Both convert 5HT to 5HIAA

# 5HIA

- Secretion by midgut tumours > foregut
- tumours >> hindgut tumours
- Measurement in plasma and urine possible

# Urine 5HIAA

- Urine testing traditionally used
- Levels usually only elevated with metastases
- Correlates with carcinoid symptoms (usually >2x ULN)
- Specificity ~100%, sensitivity ~70% for diagnosis
- Low predictive value for slightly raised 5-HIAA

# Urine 5HIAA

- False positives
- Dietary - bananas, avocados, tomatoes, walnuts, pineapple
- Drugs

# Plasma 5HIAA

- Correlates well with urine levels
- Obviates 24-h collection
- Needs to be fasting specimen

# Chromogranin A

- Member of chromogranin-secretogranin family
- Main members CgA, CgB, SgII (CgC)
- Produced throughout neuroendocrine system

# Clinical uses

- Secreted by carcinoid and other
- neuroendocrine tumours
- Stable in vitro
- Useful in diagnosis and monitoring
- Sensitivity ~100% but low specificity because
- also secreted by other tumours

# Other hormones

- Gut hormones
- Gastrin, PP, VIP, glucagon, neuropeptide Y
- Insulin
- ACTH

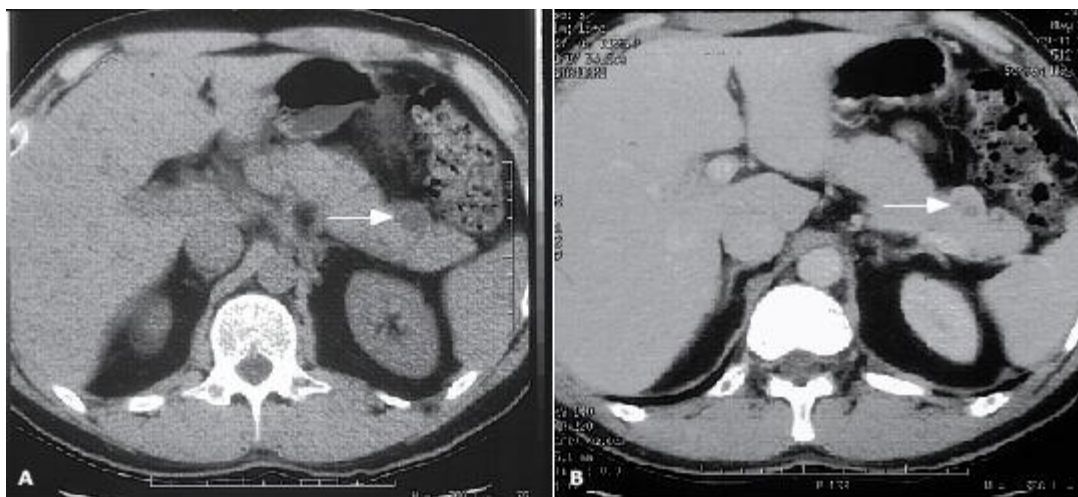
# Imaging

- Ultrasound - transabdominal, endoscopic
- CT/MRI
- Isotopic: meta-iodobenzylguanidine (MIBG),
- octreotide
- Molecular imaging

# Carcinoid syndrome

- Carcinoids – 10% of small bowel tumours
- Most common site appendix, terminal ileum, rectum, bronchus, thymus
- Due to serotonin, bradikinin, histamine, tachykinin – flushing, bronchospasm, diarrhoea, abdominal pain, fibrosis of r heart valves, mesenteric fibrosis
- Almost always when liver mets
- Sometimes co-secrete other hormones – eg.ACTH

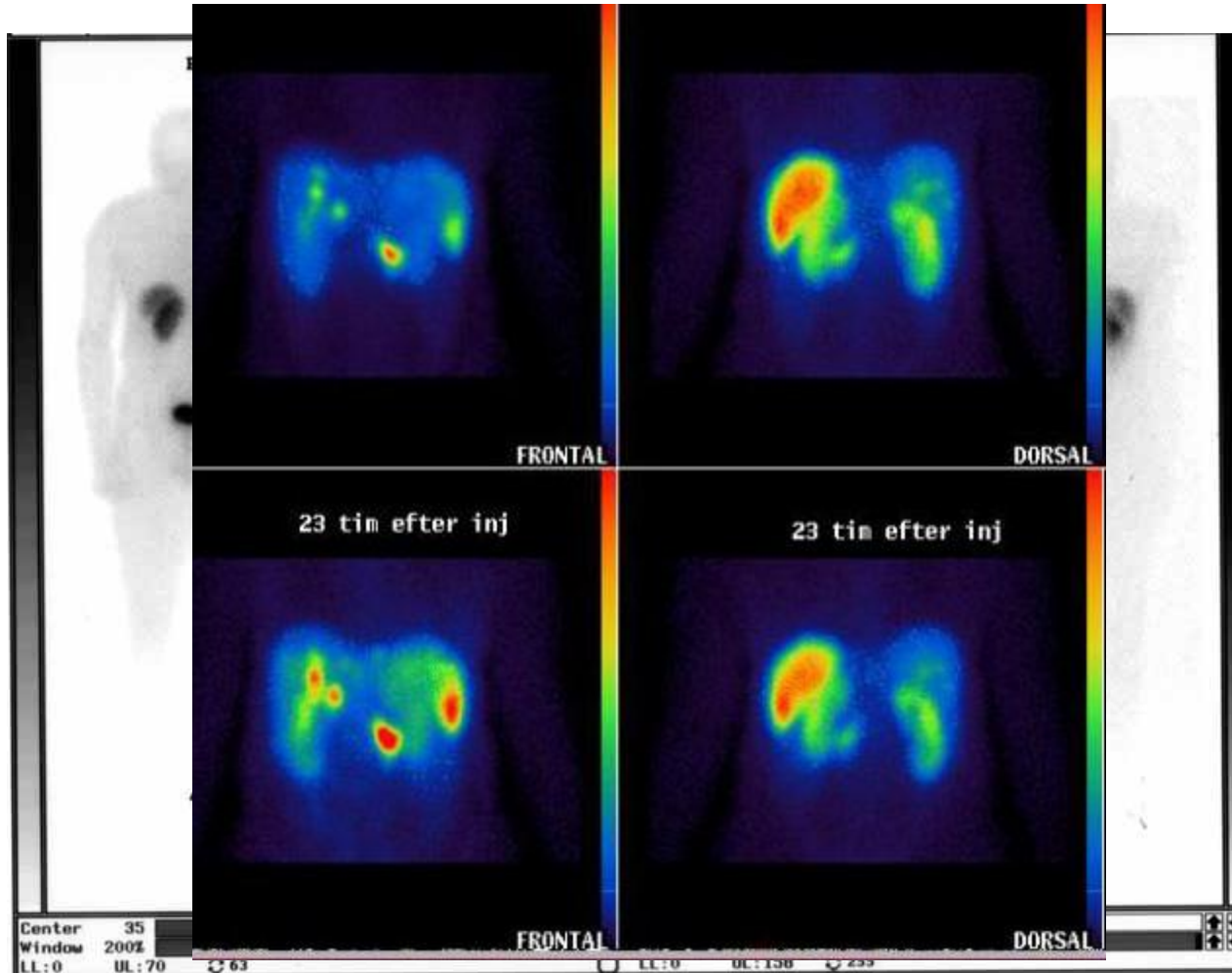
# CT abdomen



Noncontrast CT scan (panel A) reveals a hypodense lesion in pancreas (arrow). The tumor enhances with the administrated contrast material (panel B). This patient did not have abnormally high tumor marker levels. The lesion was resected and found to be a nonfunctional endocrine (islet-cell) tumor.

*Courtesy of Edward Palmer, MD of the Massachusetts General Hospital department.*

# Octreoscan



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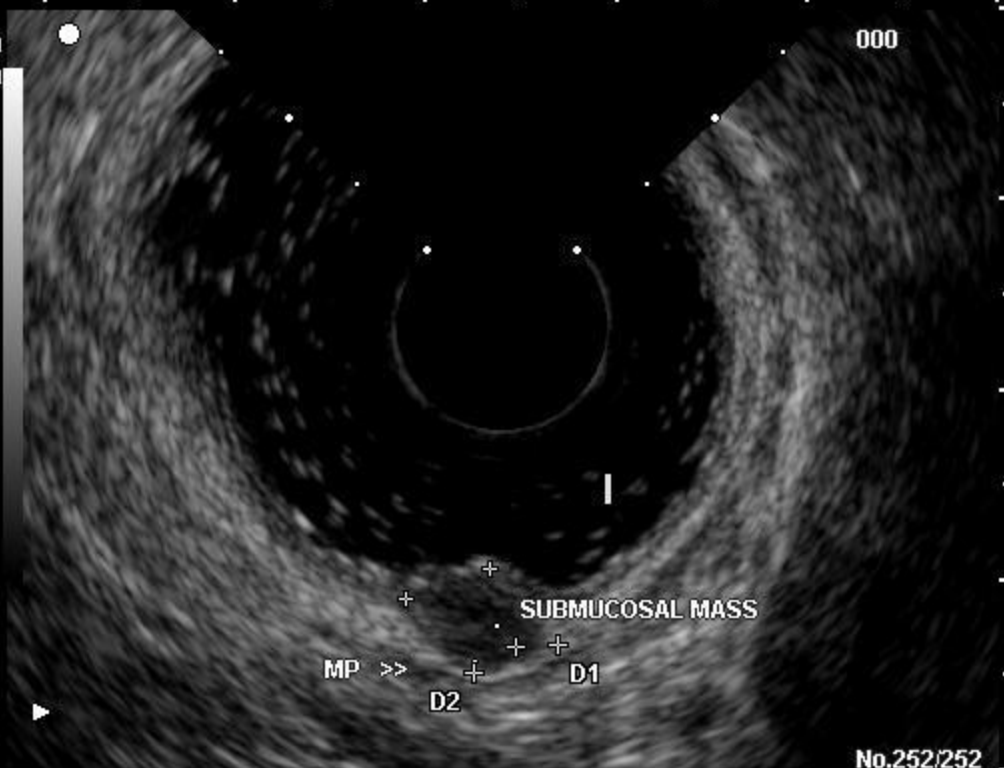
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# Somatostatin (SST)

- Named for growth hormone release inhibition
- Cyclic 14-aa peptide,  $t_{1/2}$  2 minutes
- Many cells have SST receptors - 5 types

# Octreotide

- SST analogue with longer half-life
- Used in treatment of acromegaly,
- neuroendocrine tumours
- Good control of symptoms
- Claimed tumour reduction

# Medical management

- Regular evaluation:
- Imaging
- CT/MRI - abdomen, pituitary
- Echocardiography in carcinoid
- Biochemistry

# Drugs

- Chemotherapy
- Streptozotocin, 5-Fluorouracil (5FU), Doxorubicin
- Cisplatin, etoposide
- Capecitabine
- Somatostatin analogues
- Interferon

# Somatostatin analogues

- Longer-acting formulations allow injection every 28 days
- Good control of symptoms
- No evidence of tumour reduction - big trial
- should report in 2011

# Radiotherapy

- External beam radiotherapy ineffective
- Octreotide
- MIBG
- New isotopes and compounds

# Surgery

- Primary tumour
- Secondary
- Resection
- Embolisation
- Radio Frequency ablation
- Ultrasound ablation

# Prognosis

- Carcinoid
- Often undetected - e.g. symptoms present for median of 9 years before diagnosis
- 5-year survival 94% with localised disease, 64% with local
- metastases, 18% with distant metastases, <20% with
- carcinoid heart disease

# Management

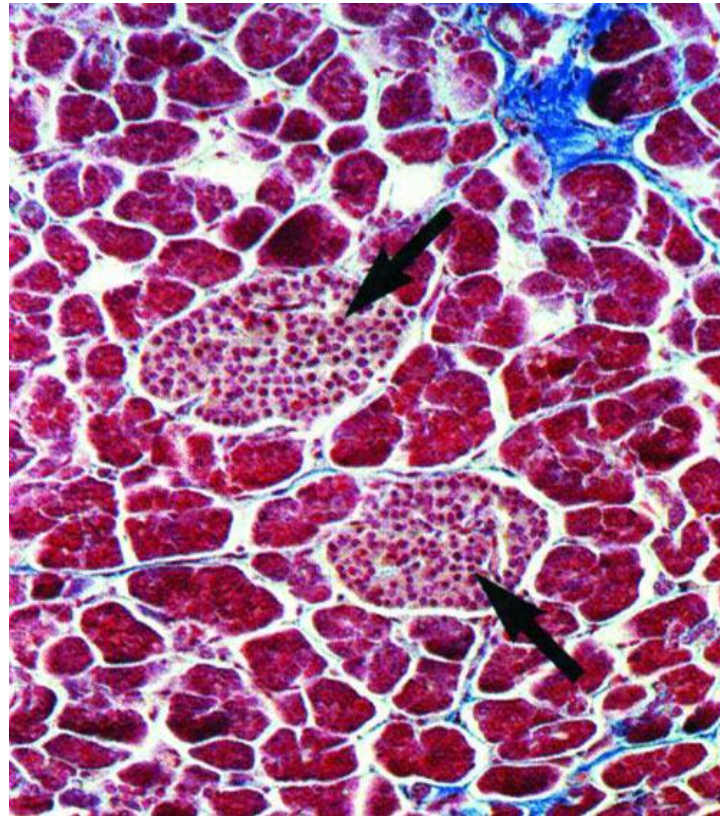
- Multidisciplinary team
- Radiologist
- Medical
- Medical and Clinical Oncologists
- Surgery

# Endocrine tumours of the pancreas

- Endocrine pancreas – islets of Langerhans

Several cell types

- ✓ Alpha
- ✓ Beta
- ✓ Delta
- ✓ Other



# Endocrine tumours of the pancreas

- Endocrine pancreas – islets of Langerhans
- Insulinoma            70%            Hypoglycaemia
- Gastrinoma           25%            Peptic ulcers (ZE)
- VIPoma                5%              Scretory Diarrhoea (VM)
- Glucagonoma        1%              NME, DM
- PPoma                 Abd pain, diarrhoea
- Stomatostatinoma    Abd pain, DM, GS
- Carcinoid             Carcinoid syndrome

# Insulinoma

- Commonest hormone secreting tumor
- Usually benign and solitary (10% malignant)
- Small (<2cm) tumours usually benign
- Leads to hyperinsulinaemia hypoglycaemia
- Whipple's triad (hypoglycaemic symptoms when blood glucose <50mg/dl and corrected by glucose)
- DD – Nesidioblastosis/ insulin autoantibodies

# Insulinoma

- Spontaneous hypoglycaemia
- Fasting hypos
- Early morning seizures

# Diagnosis

**Confirmation of hyperinsulinaemic hypoglycaemia**  
(BG <45mg/dl, insulin >3 $\mu$ U/ml, C-peptide >200pmol/l  
Negative sulphonylurea screening)

**Tumour localization by appropriate imaging**

# Biochemical confirmation

- Demonstration of Whipple's triad
- 72 – hr supervised fasting (Classic diagnostic test)
  - 12 hr – 35%
  - 24 hr - 75%
  - 48 hr – 92%
- Hypoglycaemia in the presence of elevated serum insulin and C-peptide with negative sulphonylurea screening confirms the diagnosis of hyperinsulinaemic hypoglycaemia

# Tumour localisation

- Transabdominal US – less sensitive (obscured by bowel loops)
- Endoscopic US – sensitive esp for tumours of the head
- Spiral CT scan of Abd – not operator dependant – sensitivity 60 – 90% (also helpful to screen for mets)
- Arteriography with or without selective intrarterial calcium stimulation
- Itraoperative US by trained operator – very sensitive
- Abdominal exploration and palpation

# CT abdomen



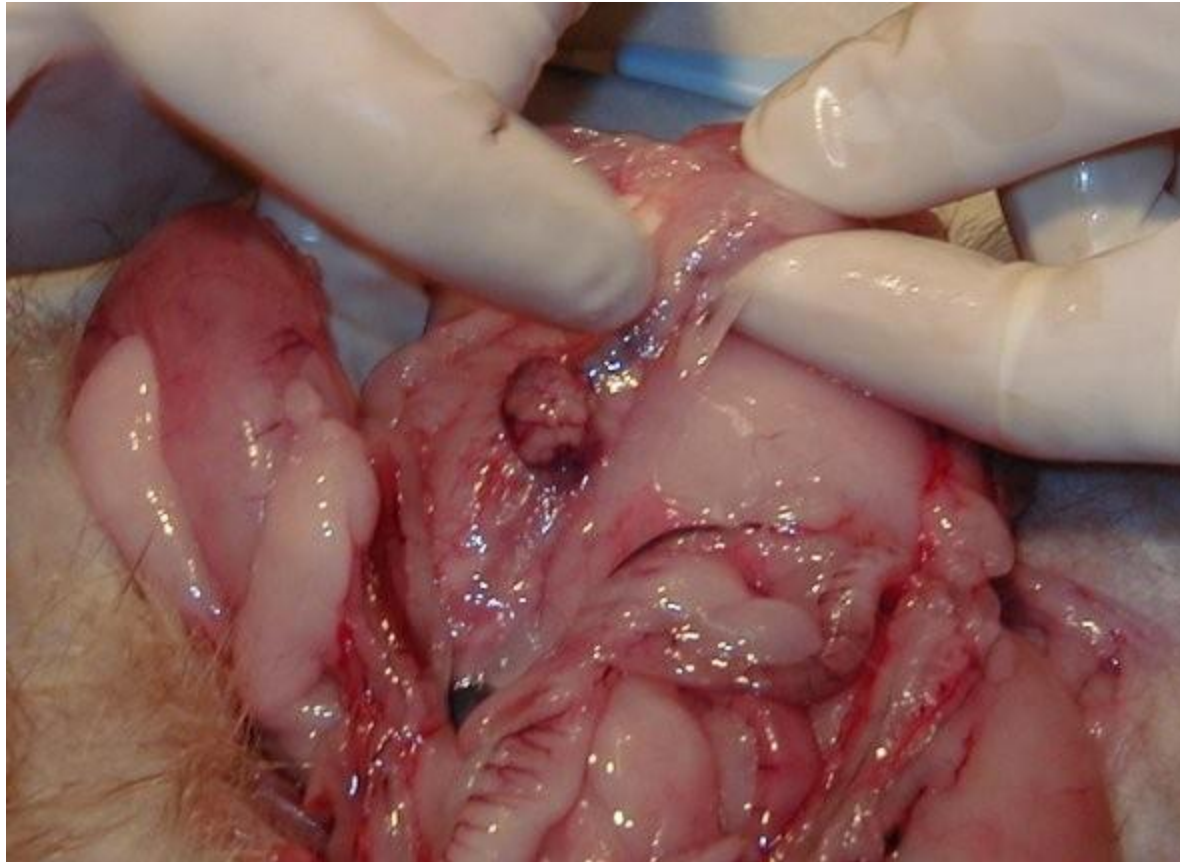
# Endoscopic ultrasound



# Arteriography



# Palpation



# Treatment

- Surgical resection
- Medical treatment
  - ✓ Diazoxide (malignant/old frail and mild hypos)
  - ✓ Somatostatin analogues

# Glucagonoma

- A rare alpha cell tumour
- Usually malignant
- Leads to a skin manifestation – necrolytic migratory erythema
- Other effects – diabetes, DVT, hypoalbuminaemia, anaemia
- Mets common at diagnosis
- If resectable – can be curative

# Necrolytic migratory erythema



# Gastrinoma

- 1/1000 peptic ulcer disease
- Zollinger – Ellison syndrome
- Multiple peptic ulcers with poor response to acid suppression
- Elevated serum gastrin
- 60% malignant
- Can be treated with high dose PPI

# When to suspect gastrinoma..

- Multiple peptic ulcers, atypical sites (distal to duodenal bulb)
- Recurrent or refractory to PPIs
- Associated with diarrhoea
- Associated with hyperparathyroidism (MEN1)
- Family history

# Diagnosis and treatment

- Biochemical confirmation (hypergastrinaemic hyperacidity)
- Fasting gastrin levels (exclude other causes/off acid suppression for 2 weeks)
- Provocative tests (standard meal/ca/pentagastrin)
- Scretin stimulation test – standard (paradoxical rise)

# Tumour localisation

- Similar lines to insulinoma
- Somatostatin Receptor Scintigraphy (SRS) with indium labelled octreotide
- Selective arterial secretin injection and sampling

# Treatment

- Surgical exploration – curative and allows met screening
- Medical – if unoperable or tumour not identified
- High dose PPI/Long acting Somatostatin analogues
- Lifetime tumour surveillance/screen for other MEN tumours

# VIPoma

- Verner – Morrison/WDHHA syndrome, 'pancreatic cholera'
- Watery diarrhoea, hypochlorhydria, hypokalaemia, hyperchloeraemic metabolic acidosis
- VIP activation of cAMP mediated secretion and motility of bowel

# VIPoma

- Rare, commonly malignant and associated with co-secretion of other hormones (gastrin etc)
- Raise VIP levels
- Tumor imaging – usual techniques
- Supportive therapy
- Tumor resection (even if mets for palliation), Octrotide