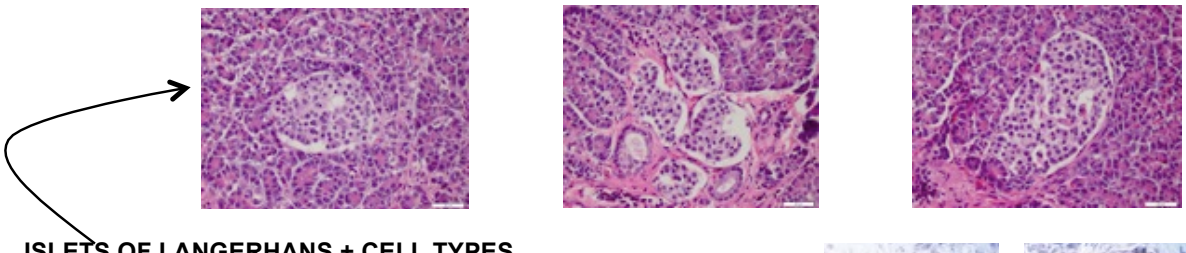
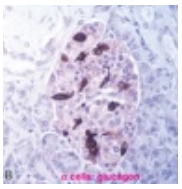
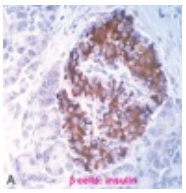
ENDOCRINE PANCREAS: Islets of Langerhans

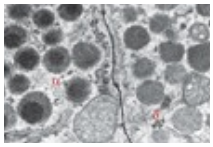
Diabetes Mellitus Type 1 & 2, Pancreatic Neuroendocrine Tumors: Insulinoma, Gastrinoma, Other Rare Tumors



ISLETS OF LANGERHANS + CELL TYPES







- Endocrine cells are clustered in the ***islets of Langerhans***
- 4 MAIN CELL TYPES: *SECRETION*
  - **Alpha (α) Cells: *Glucagon*** (20%)
  - **Beta (β) Cells** (center of islet)**: *Insulin* (68%)**
  - **Delta (δ) Cells: *Somatostatin*** (10%)
  - **PP cells: *Pancreatic polypeptide***
- 2 Rare Cell Types: *Secretion*
  - D1 Cells: *Vasoactive Intenstinal Peptide (VIP)*
  - Enterochromaffin Cells: *Serotonin*

GLUCOSE HOMEOSTASIS

- Normal glycemia: **70-120 mg/dL**
- 3 Processes Crucial to Maintaining Glucose Homeostasis
  - Glucose production in the Liver
  - Glucose uptake & utilization in Peripheral Tissues (Skeletal muscle & Adipose tissue)
  - Regulatory influences of Insulin & Glucagon
    - Insulin & Glucagon have opposing actions
    - **Fasting:** Insulin↓, Glucagon ↑
      - **Liver:** ↑ gluconeogenesis, ↑ glycogenolysis, ↓ glycogen synthesis
    - **After Meal:** Insulin ↑, Glucagon ↓
      - **Muscle:** ↑ glucose uptake & utilization, ↑ glycogen synthesis, ↑ protein synthesis
  - *In addition, other hormones influcening glycemia are glucocorticoids & growth hormone*

INSULIN: Anabolic Hormone

- Key Metabolic Action: ↑ glucose uptake & utilization in striated muscle + fat
- Glucose uptake is NOT insulin-dependent in other tissues (i.e. Nervous System)
- **INCRETIN EFFECT**: Insulin secretion is greater in response to oral glucose vs. IV glucose

INCRETIN

- Hormones synthesized by enteroendocrine cells in the gut
- **GIP** (Glucose-dependent Insulinotropic Peptide *aka Gastic Inhibitory Peptide*) & **GLP-1** (Glucagon-like Peptide 1)
- **Following food ingestion, Incretins:**
  - ↑Glucose-dependent insulin from β cells (GLP-1, GIP) → ↑Glucose uptake by muscles → ↓Blood glucose
  - ↓ Glucose-dependent glucagon from α cells (GLP-1) → ↓ Glucose production by liver → ↓ Blood glucose
  - Delay gastric emptying + promote satiety
- Circulating **incretins are degraded** by enzymes known as dipeptidyl peptidases (DPPs), i.e. ***DPP-4***

INCRETIN EFFECT IN DM TYPE 2

- Incretin efficient is DEFICIENT in patients with Type 2 DM, which contributes to *obesity & hyperglycemia*
- New drugs: GLP-1 Receptor Agonists, DPP-4 Inhibitors

DIABETES MELLITUS (DM)

DIAGNOSTIC CRITERIA FOR DIABETES & PRE-DIABETIC STATES		
	DIABETES	**PRE-DIABETES**
Fasting plasma glucose	≥ 126 mg/dl	100-125 mg/dl
24-hr plasma glucose	≥ 200 mg/dl	140-199 mg/dl
Casual/random plasma glucose *In pt w/ classic hyperglycemic symptoms*	≥ 200 mg/dl	
Glycated hemoglobin	≥ 6.5%	5.7-6.4%

- *A group of diseases in which blood glucose levels are elevated (hyperglycemia)* because of deficiency insulin secretion and/or abnormal insulin action. *Results in ↓ insulin secretion by β cells +/- defects in insulin receptors leading to insulin resistance.*
- *One of the most common diseases in North America, affecting 5% of US population*
  - Most cases are diagnosed
- Diabetes remains the 7th leading cause of death in the US
- **American Indians/Alaskan Natives** (15.9%), Non-Hispanic Blacks (13.2%), Hispanics (12.8%), Asian American (9%), Non-Hispanic Whites (7.6%)

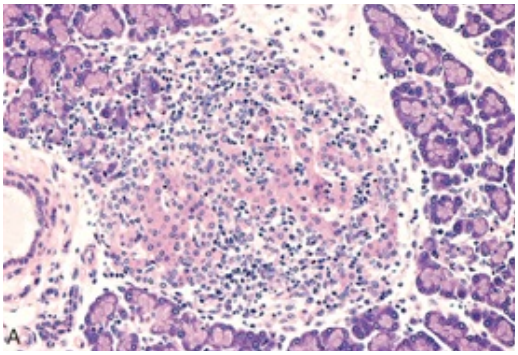
COMPLICATIONS OF DIABETES MELLITUS

- Hypoglycemia
- Hypertension
- Dyslipidemia *(Hypercholesterolemia – LDL cholesterol > 100mg/dl)*
- CV disease death & MI rates 1.7x higher in adults w/ DM
- Stroke rates 1.5x higher in adults w/ DM
- Blindness/Eye problems, *especially in DM patients 40 y/o or older*
- Kidney disease/failure – *DM was primary cause of kidney failure in 44% of all new cases in 2011*
- Amputations *(non-traumatic lower-limb amputations)*

	TYPE 1 **No insulin production**	**TYPE 2** **Resistance to insulin action**
Onset	Sudden	Gradual
Age of Onset	*Juvenile*, **Kids/Young Adults < 30 y/o** (May be at any age though)	*Adult form*, **> 40 y/o** (May develop in young patients)
Body Habitus	Thin or normal	Often obese
Ketoacidosis	**Common**, in severe cases	Rare
Autoantibodies	Usually present (Autoimmune)	Absent (Obesity & Familial Influence)
Endogenous Insulin	Low or absent	Normal, Decreased, or Increased
Concordance in Identical Twins	50%	***90%** 1st degree relatives 5-10x ↑risk
Prevalence	Less prevalent 5% of all DM cases	More prevalent 95% of DM cases
Clinical Presentation	**3 Ps – Polyuria, Polydipsia, Polyphagia** *Progressive **weight loss** & **fatigue***	**Asymptomatic pts: Hyperglycemia** Pts present w/ **Complications**: *Repeated infections, Renal disease, Retinopathy, Peripheral neuropathy* *Fatigue, dizziness, blurred vision*
Treatment	Life-long Insulin	Diet & weight loss are 1st line therapy; Oral hypoglycemic Insulin in late stages

TYPE 1 DM: PATHOGENESIS

- Autoimmune destruction of **insulin-producing β cells** in the Islets of Langerhans (AutoAb)
  - Higher titers of AutoAb associated w/ more accelerated islet cell destruction
  - *Confirmed targets of AutoAb in Type 1 DM: insulin, glutamic acid decarboxylase, insulinoma associated antigens 2 (α & β), ZnT9 (zinc transporter)*
- Occurs in **genetically** susceptible hosts
  - Lifelong risk is markedly increased in relatives of a patient w/ type 1 DM
  - Genome-wide association studies have identified more than 30 susceptibility loci for type 1 DM
  - HLA gene cluster on Chromosome 6p21 contains the locus that accounts for up to 50% of susceptibility
    - This region contains genes coding for MHC Class II molecules expressed on the surface of APC
  - MHC II molecules consists of α & β chains that form a groove containing the peptide presented to APCs
    - Ability of MHC II molecules to present Ags depends on their primary structure
    - Changes in AA composition can ↑/↓ability to bind AutoAg & change susceptibility to type 1 DM
  - More than 90% of patients have either HLA-DR3-DQ2 or HLA-DR3-DQ8 *(general population, only 40%)*
  - HLA allele **DQB1*0602 confers Protection**: Present in 1% of patients w/ DM vs. 20% general population
  - Non-MHC genes are less important contributors to genetic susceptibility
    - Polymorphisms in promoter region of insulin gene
    - Both CTLA-4 & PTPN22 are implicated in susceptibility to type 1 DM, as well as thyroid autoimmune disorders
      - Polymorphisms in **CTLA-4** gene coding for TCR, which switches off T cell attack
      - ***PTPN22*** gene coding for a tyrosine phosphatase that plays role in T cell function
    - AIRE gene, coding for autoimmune regulator, a TF expressed in thymic medulla controls mechanism that prevents immune system from attacking the body itself
- Triggered by 1+ **environmental** factors
  - **PERINATAL**: **Maternal age >25**, pre-eclampsia, neonatal respiratory disease, jaundice due to ABO blood group incompatibility
    - Protective Factors: Low birth weight, short birth length
  - **VIRUSES**: Viral-induced autoimmunity or molecular mimicry
    - *Child immunization of genetically predisposed infants w/ viral or bacterial vaccines is NOT associated w/ ↑ risk of developing type 1 DM*
  - **DIET**: Exposure to cereal products before 3 months or after 7 months associated w/ ↑risk
    - **Vitamin D, Omega-3 fatty acids may be protective**
- Progresses over months or years (latent period) before onset of *symptomatic hyperglycemia*
  - Clinically evident Type 1 DM does not occur until there has been a great loss of functioning β cells



TYPE 1 DM: PATHOLOGY OF ISLETS
Early stage "Insulitis" – Inflammatory cells mostly T-lymphocytes
Late stage – Islets are smaller & fewer than normal

TYPE 2 DM: PATHOGENESIS

- Caused by a combination of **insulin resistance** in target organs & relative **insulin deficiency**
- **No Autoimmune mechanism!**
- Interplay of **genetic + environmental** factors
- **OBESITY*** is the most important Risk Factor – *Obesity decreases insulin sensitivity in susceptible subjects*
  - **Central Obesity** (visceral, abdominal) >>> peripheral obesity
  - >80% of type 2 DM patients are obese
- **SEDENTARY LIFESTYLE** is an independent Risk Factor
- **METABOLIC DERANGEMENTS**
  - ↓ Response to insulin action in skeletal muscle, liver, & adipose tissue *due to ↓# insulin receptors*
  - Inadequate insulin secretion in response to increasing *insulin resistance & hyperglycemia*

Type 2 DM: INSULIN RESISTANCE

- LIVER: Failure to inhibit gluconeogenesis → *fasting hyperglycemia*
- MUSCLE: Failure to stimulate glucose uptake & glycogen synthesis → *postprandial hyperglycemia*
- FAT: Failure to inhibit lipolysis → *↑free fattys acids*

Type 2 DM: OBESITY & INSULIN RESISTANCE – FFAs

- Fasting FFAs are correlated with ↑ insulin resistance
- "Central" adipose tissue undergoes lipolysis more easily than peripheral adipose tissue
- Excess FFAs overwhelm FA oxidation → accumulation of toxic metabolites (i.e. DAG)
- DAG + other toxic metabolites interfere w/ insulin receptor signaling → reduced response to insulin

Type 2 DM: OBESITY & INSULIN RESISTANCE – ADIPOKINES

- Variety of hormones produced by adipocytes
- **LEPTIN**: "Informs" the hypothalamus about the amount of fat
  - *Leptin Deficiency or Resistance is associated w/ obesity & insulin resistance*
- **ADIPONECTIN**: Reduces circulating FFAs & inflammation
  - *Adiponectin levels are reduced in obesity*
- Others: TNF-α, chemokines, plasminogen activator inhibitor, resistin, retinol binding protein 4, IL-1β, uncoupling protein, obestatin...

Type 2 DM: OBESITY & INSULIN RESISTANCE – INFLAMMATION

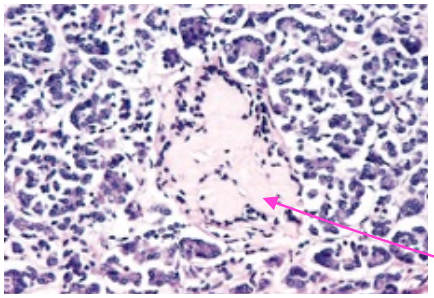
- Inflammatory response (NOT autoimmune) triggered by excess nutrients, FFAs & glucose
- Activation of ***inflammasome*** in macrophages → release of IL-1β → synthesis/release of other cytokines that contribute to insulin resistance

Type 2 DM: OBESITY & INSULIN RESISTANCE – β CELL DYSFUNCTION

- Adipokines + FFAs + Inflammation → Insulin Resistance → β cells hypersecrete insulin → β cell failure → DM
- Pancreatic β cells compensate for insulin resistance by hypersecretion of insulin
- **However, at some point, β cell compensation is followed by β cell failure & diabetes ensues**

Type 2 DM: β CELL DYSFUNCTION MECHANISMS

- Excess FFAs cause ***lipotoxicity*** on β cells
- Chronic hyperglycemia causes ***glucotoxicity***
- ***Incretin*** effect
- ***AMYLOID*** deposition
- *Genetic* factors: polymorphisms in genes regulating insulin secretion



TYPE 2 DM: PATHOLOGY OF ISLETS
Late Stage: AMYLOID Deposition in the islets of Langerhans

ACUTE COMPLICATIONS OF DM

Diabetic Ketoacidosis, Hyperosmolar Hyperosmotic Coma, Hypoglycemic Coma

1. DIABETIC KETOACIDOSIS (DKA)

- Acute complication of DM that can lead to **diabetic coma**
- **More frequent & severe in Type 1 DM**
- Due to insulin deficiency resulting from:
  - Failure to take insulin
  - ↑ Demand for insulin: *stress, infections, illness, pregnancy, cocaine use, trauma* – All conditions leading to release of epinephrine → ↑ glucagon
- Blood glucose: 250-600 mg/dl
- **PATHOPHYSIOLOGY**
  - Insulin Deficiency + Increased Glucagon → ↑Gluconeogenesis + ↑ Lipolysis
  - Worsening hyperglycemia & massive release of FFAs in the blood
  - FFAs are metabolized by the liver to **Ketone Bodies**: Acetoacetic Acid & β-hydroxybutiric acid
  - *Ketonemia & Ketonuria ensue*
  - If urinary excretion is compromised, ***anion-gap metabolic acidosis*** develops
- **PRESENTATION**
  - GRADUAL ONSET W/ PROGRESSION
  - **Early Phase:** thirst + dry mouth, frequent urination, high levels of ketones in urine
  - **Advanced Phase:** profound fatigue, dry/flushed skin, NV + abdominal pain, ***Fruity Odor on Breath*** *(acetate)*, inability to focus, confusion, ***Kussmaul Breathing*** (deep, labored breathing – respiratory compensation)
  - **Late Phase:** Coma
- **TREATMENT**: Fluids, Insulin, Electrolytes (especially K^+)
  - *Patients will be excreting almost all of their excess K^+ so there is an overall net loss of K^+ in the body*

2. HYPEROSMOLAR HYPEROSMOTIC SYNDROME

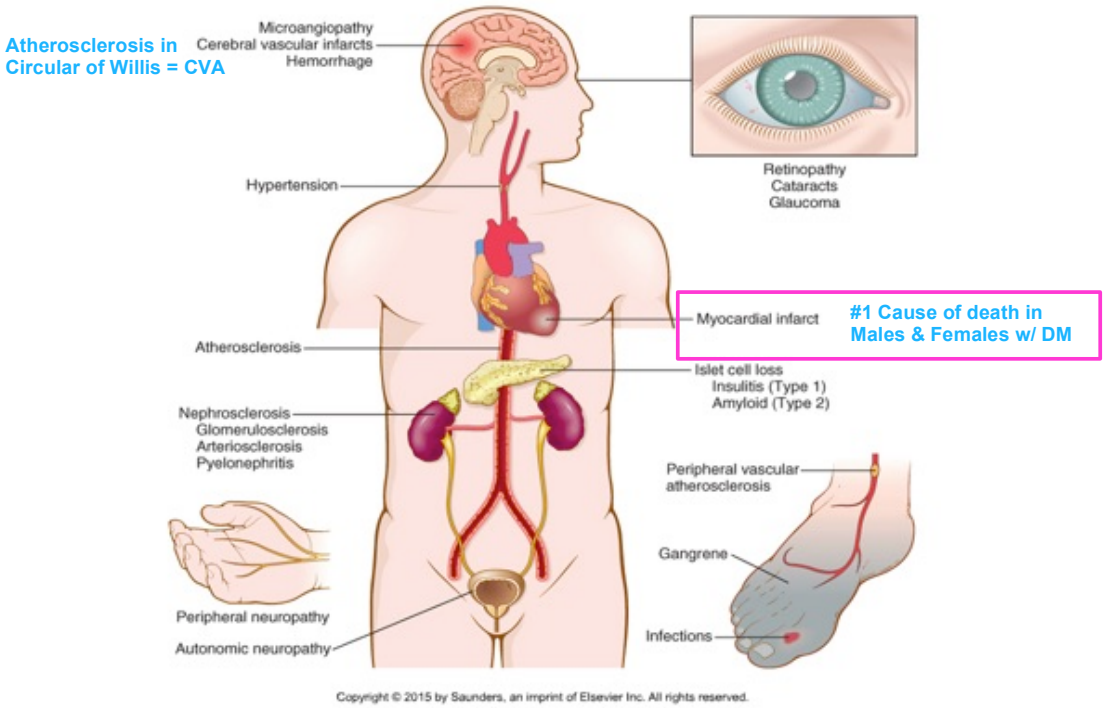
- Acute complication of **Type 2 DM**
- Caused by extreme **dehydration** due to persistent *polyuria*
- Typically affects **Elderly People w/ neurological deficits** (stroke) or **infectious illness** & unable to drink adequate amounts of ater
- **Hyperglycemia** in the range of 600-1200 mg/dl → leading to life-threatening diuresis
- *Hypotension & coma* ensue **w/out ketoacidosis**

3. HYPOGLYCEMIC COMA

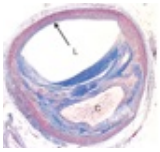
- **Most Common Acute Complication of DM**
- **Causes:** missing meals, excess insulin administration, physical exercise, dose finding during initial phase of tx
- **PRESENTATION:** dizziness, confusion, palpitations, tachy, weakness, tremor, progressing to LOC + coma

LONG-TERM COMPLICATIONS OF DM

Myocardial Infarctions, Cerebral Infarctions, Amputations, Renal Insufficiency, Diabetic Nephropathy/Retinopathy/Neuropathy, Susceptibiliy to Infections (Skin, Tb, pyelonephritis, pneumonia)

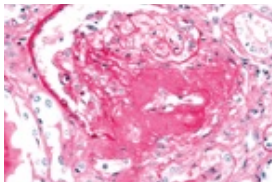


- Underlying Pathogenic Factor: PERSISTENT HYPERGLYCEMIA (*glucotoxicity*)
- **GLYCATED HEMOGLOBIN (Hb_{A1C})** is a marker of glycemic control over the lifespan of an erythrocyte
  - *Recommended **Hb_{A1C}** should be maintained below 7%*
- Mechanisms of Glucotoxicity:
  - Formation of **Advanced Glycation End Products (AGE);** Activation of PKC; Oxidative stress due to NADPH depletion caused by excess aldose reductase activity; Generation of excess fructose-6-phosphate → glycosylation of proteins (proteoglycans)
- Mediated by damage to:
  - Large/Medium Arteries – **MACROVASCULAR Disease**
    - *Hallmark is **Atherosclerosis** → *Cerebral Infarct, Myocardial Infarction, Limb Ischemia (Gangrene → Limb amputation)*

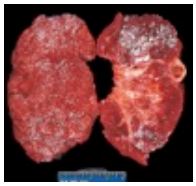


  - Small Vessels – **MICROVASCULAR Disease**
    - *Hallmark is **Hyaline Arteriolosclerosis***
    - *Diabetic Nephropathy (40%)* – Renal Failure requiring Dialysis; Earliest Sign - Microalbuminemia
    - *Diabetic Retinopathy (60-80%),* Most Common Cause of **Blindness** in Developed Countries
    - *Diabetic Neuropathy (50-80%) – Distal symmetric polyneuropathy of LE (motor + sensory)*

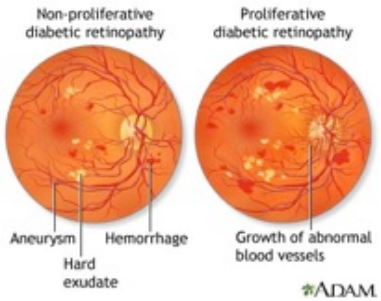
MICROVASCULAR DISEASE

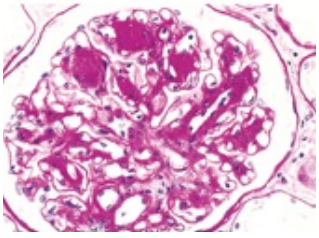


Arteriolosclerosis



Arteriolonephrosclerosis
Scarring on surface→ chronic renal failure





DIABETIC NEPHROPATHY – glomerular lesions, renal vascular lesions (arteriolosclerosis), & pyelonephritis (necrotizing papillitis)
Diffuse Glomerulosclerosis
Nodular Diabetic Glomerulosclerosis (*Kimmelstiel-Wilson Nodules*) → NEPHROTIC SYNDROME

MONOGENIC FORMS OF DM

- Genetic Defects in β cell Function
  - Heterogenous conditions caused by genetic mutations leading to primary defect in β-cell function
  - MODY (Maturity-Onset Diabetes of the Young): Most cases due to germ line mutations of glucokinase
- Genetic Defects that impair tissue response to insulin: *Insulin receptor mutations* that affect receptor synthesis, insulin binding, or RTK activity

PREGNANCY & DIABETES

- **Pre-Gestational Diabetes:** Women w/ pre-existing diabetes become pregnant
  - *Leads to increased risk of still birth & congenital malformations in the fetus*
- Pregnancy is a "diabetogenic" state favoring the emergence of insulin resistance
- **Gestational Diabetes:** Women previously euglycemic develop impaired glucose tolerance & diabetes for the 1st time during pregnancy; resolves following delivery
  - *Due to increased placental size, anti-insulin effect of human placental lactogen*
  - Majority of women w/ gestational diabetes develop overt diabetes over next 10-20 years
- **Risk of Poorly Controlled DM in Pregnancy:** fetal macrosomia (excessive birth weight), obesity & diabetes later in life

SECONDARY DIABETES

- Broad category of diseases that lead to diabetes by different mechanisms
- Destruction of the pancreas: Chronic pancreatitis, hemochromatosis, cystic fibrosis, cancer
- Insulin resistance: Polycystic ovarian syndrome
- ↑ Production of Hyperglycemic Hormones: Cushing syndrome, Acromegaly, Pheochromocytoma
- Drugs: *Vacor, Pentamidine, Glucocorticoids, Calcineurininhibitors, Atypical antipsychotics, Protease inhibitors, Thiazides, Beta blockers, Niacin, Phenytoin*

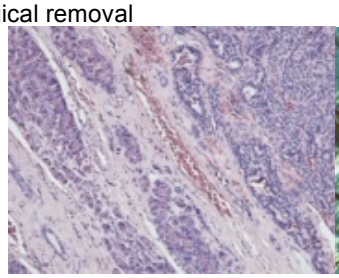
PANCREATIC NEUROENDOCRINE TUMORS

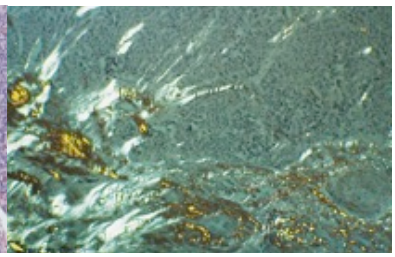
Insulinoma, Gastrinoma, Other: Somatostatinoma, VIPoma, Carcinoid tumors

1. INSULINOMA: Insulin-producing Neuroendocrine Tumor

- **Most Common Pancreatic Neuroendocrine Tumor**
- *Asymptomatic, mild hypoglycemia*
- **CLASSIC WHIPPLE TRIAD in 20%:**
  - Signs & symptoms of hypoglycemia: confusion, stupor, LOC (mental status changes)
  - Glycemia < 50mg/100mL
  - Symptoms relieved by glucose & precipitated by fasting & exercise
- 10-15% associated w/ **MEN1**
- **DIAGNOSIS:** High insulin levels, High insulin:glucagon ratio, imaging localization of tumor
- **TREATMENT:** surgical removal

Insulinoma (Upper R corner) compressing adjacent pancreatic parenchyma

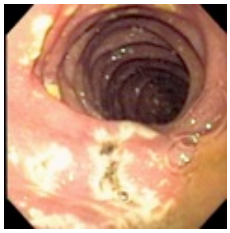




Congo red staining demonstrating **AMYLOID DEPOSITION**, a frequent phenomenon in insulinoma

2. GASTRINOMA: Gastrin-producing Neuroendocrine Tumor

- Locally invasive or metastatic to liver: 50%
- **Zollinger-Ellison Syndrome** in 90%
  - Hypersecretion of gastrin
  - Multiple duodenal, jejunal, & gastric ulcers
  - Treatment resistant peptic ulcers
- Diarrhea: 50%
- Associated w/ MEN1: 25%



3. OTHER PANCREATIC NEUROENDOCRINE TUMORS

- **Somatostatinoma**: Diabetes, cholelithiasis, steatorrhea, hypochlorhydria
- **VIPoma**: Secretory diarrhea
- **Carcinoid tumors**: exceedingly rare