**Pathology week 18 – Pancreas**

- endocrine and exocrine functions

**Anatomy**
- main pancreatic duct most commonly drains into duodenum at papilla of Vater
- accessory pancreatic duct often drains into duodenum through minor papilla proximal to major papilla of Vater
- main pancreatic duct merges with CBD proximal to papilla of Vater, creating ampulla of Vater
- exocrine portion – acinar cells - produce digestive enzymes - 80% of the pancreas
- endocrine portion - islets of Langerhans - secrete insulin, glucagon, somatostatin – 1%

**Function**
- secretes 2 - 2.5 liters/day of bicarbonate-rich fluid containing digestive enzymes/proenzymes
- regulation by both neural stimulation by vagal nerves (acetylcholine) and humoral factors
  - secretin stimulates water and bicarbonate secretion by duct cells
  - released in response to acid load from stomach and fatty acids
  - cholecystokinin promotes discharge of digestive proenzymes by acinar cells
  - released in response to fatty acids and amino acids
- exocrine products secreted as proenzymes (prevent self-digestion)
  - trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase, kallikreinogen, prophospholipase A/B
  - brush border enzyme in lumen of duodenum, enteropeptidase, cleaves trypsinogen into active trypsin
  - which catalyzes cleavage of other proenzymes
  - amylase and lipase do not require trypsin activation - secreted in active form

The self-digestion of the pancreas is prevented by:
- most enzymes secreted as proenzymes
- enzymes sequestered in membrane-bound zymogen granules in acinar cells
- activation proenzymes requires conversion inactive trypsinogen to active trypsin by duodenal enteropeptidase (enterokinase)
- trypsin inhibitors are present in acinar and ducal secretions
- trypsin can inactivate itself
- lysosomal hydrolases can degrade zymogen granules when normal acinar secretion is impaired
- acinar cells are resistant to action of enzymes

**Pathology**
- most significant disorders of endocrine pancreas: diabetes and neoplasms
- most significant disorders of exocrine pancreas: CF, congenital, pancreatitis, neoplasms

**Congenital Anomalies**

**Agenesis** - pancreas totally absent – incompatible with life

**Pancreas Divisum**
- most common significant congenital anomaly of the pancreas: 3-10%
- bulk of pancreas drains through dorsal pancreatic duct and small minor papilla predisposes to chronic pancreatitis

**Annular Pancreas**
- bandlike ring of pancreas surrounds second portion of duodenum
- may cause duodenal obstruction with gastric distention and vomiting

**Ectopic Pancreas**
- in stomach, duodenum, jejunum, Meckel diverticula, and ileum
- may cause pain from localized inflammation, or, rarely, may incite mucosal bleeding
- islet cell tumors arise in ectopic pancreatic tissue

**Pancreatitis**
- group of disorders characterized by inflammation of the pancreas
- range in severity from mild, self-limited disease to a lifethreatening acute inflammatory process
- duration of can range from a transient attack to an irreversible loss of function
- gland can return to normal if underlying cause removed
- chronic pancreatitis defined by presence of irreversible destruction of exocrine pancreas

**Acute Pancreatitis**
- reversible lesions characterized by inflammation of the pancreas ranging in severity from oedema and fat necrosis to parenchymal necrosis with severe hemorrhage
- relatively common, annual incidence rate 10 to 20 cases per 100,000 people
- 80% associated with biliary tract disease or alcoholism
- 5% of patients with gallstones develop pancreatitis
- M:F 1:3 in the group with biliary tract disease and 6:1 in those with alcoholism
- other causes:
  - obstruction of pancreatic duct system periampullary tumors, pancreas divisum, parasites
  - drugs: thiazides, azathioprine, sulfonamides, frusemide, methyldopa
  - infections: mumps, coxsackie viruses, Mycoplasma pneumoniae
  - metabolic: hypertriglycerideremia, hyperparathyroidism, hypercalcemia
  - acute ischaemia: thrombosis, embolism, vasculitis (polyarteritis nodosa, SLE), shock
  - trauma: blunt, surgery, ERCP
  - idiopathic
  - genetic

**Morphology**
(1) microvascular leakage causing oedema
(2) fat necrosis by lipolytic enzymes (released fatty acids combine with calcium to form insoluble salts)
(3) an acute inflammatory reaction
(4) proteolytic destruction of pancreatic parenchyma
(5) destruction of blood vessels with subsequent interstitial hemorrhage

**Pathogenesis**
- autodigestion of pancreatic substance by inappropriately activated pancreatic enzymes
- activation of trypsinogen is an important triggering event in acute pancreatitis
  - activates other proenzymes
  - converts prekallikrein to its activated form, thus bringing into play the kinin system and, by activation of Hageman factor, the clotting and complement systems as well
- 3 possible ways pancreatic enzymes are activated:
  - pancreatic duct obstruction
    - raise intrapancreatic ductal P, accumulation of enzyme-rich interstitial fluid
    - lipase (secreted in an active form) can cause local fat necrosis
    - injured tissues, periacinar myofibroblasts, and leukocytes then release proinflammatory cytokines including IL-1β, IL-6, TNF, PAF, and substance P, initiating local inflammation and promoting development of interstitial oedema through a leaky microvasculature
    - oedema may further compromise local blood flow → ischemic injury to acinar cells
- primary acinar cell injury
  - in pancreatitis due to infections, drugs, trauma and ischaemia/shock
- defective intracellular transport of proenzymes within acinar cells
  - in either pancreatic duct obstruction or exposure to alcohol
- how alcohol causes pancreatitis is unknown
  - transient increases in pancreatic exocrine secretion, contraction of sphincter of Oddi, or direct toxic effects on acinar cells

**Clinical Features**
- "acute abdomen" – constant, intense, referred to upper back
- features due to systemic inflammatory response with leukocytosis, DIC, ARDS, shock, ATN
- due to release of cytokines, bradykinin, prostaglandins, NO, PAF
- elevated amylase and lipase and the exclusion of other causes of abdominal pain
- management: NBM, fluids, supportive therapy
Ransom's Criteria
- for predicting the severity of acute pancreatitis
- alternatively use APACHE II ("Acute Physiology and Chronic Health Evaluation II")
- On admission
  - Age > 55 yrs
  - WCC > 16,000
  - LDH > 600 U/l
  - AST > 120 U/l
  - Glucose > 10 mmol/l
- Within 48 hours
  - Haematocrit fall > 10%
  - Urea rise > 0.9 mmol/l
  - Calcium < 2 mmol
  - pO2 < 60 mmHg
  - Base deficit > 4
  - Fluid sequestration > 6L
Chronic Pancreatitis

- inflammation of pancreas with destruction of exocrine parenchyma, fibrosis, and destruction of endocrine parenchyma
- most common cause: long-term alcohol abuse, usually middle-aged males
- less common causes:
  - long-standing obstruction of pancreatic duct by pseudocysts, calculi, trauma, neoplasms, or pancreas divisum
  - tropical pancreatitis, seen in Africa and Asia, attributed to malnutrition
  - hereditary pancreatitis, caused by germ line mutations in the PRSS1 or SPINK1 genes
  - idiopathic chronic pancreatitis

Pathogenesis

- not well defined, four hypotheses:
  - ductal obstruction by concretions (alcohol believed to increase protein concentrations in the pancreatic juice, form ductal plugs, can calcify)
  - toxins, including alcohol and its metabolites, can exert a direct toxic effect on acinar cells, may lead to accumulation of lipids in acinar cells, acinar cell loss, and parenchymal fibrosis
  - alcohol-induced oxidative stress may generate free radicals in acinar cells, leading to membrane lipid oxidation and activation of transcription factors, including AP1 and NFκB, which in turn induce expression of chemokines that attract mononuclear cells; oxidative stress thereby promotes the fusion of lysosomes andzymogen granules, acinar cell necrosis, inflammation, and fibrosis
  - necrosis-fibrosis - acute pancreatitis initiates a sequence of perilobular fibrosis, duct distortion, and altered pancreatic secretions; with multiple episodes, this can lead to loss of pancreatic parenchyma and fibrosis.

Morphology

- parenchymal fibrosis, reduced number and size of acini with relative sparing of islets of Langerhans, and variable dilation of pancreatic ducts, chronic inflammatory infiltrate around lobules and ducts
- interlobular and intralobular ducts dilated and contain protein plugs

Clinical Features

- different presentations
- repeated attacks abdo pain, or persistent abdominal and back pain
- may be entirely silent until pancreatic insufficiency and diabetes mellitus develop
- recurrent attacks of jaundice or vague attacks of indigestion
- may be precipitated by alcohol abuse, overeating (increases demand on pancreas), or use of opiates and other drugs that increase tone of sphincter of Oddi
- may be mild fever and mild-to-moderate elevations of serum amylase
- calcifications within pancreas on CT and USS
- weight loss and hypoalbuminemic oedema from malabsorption
- 20 to 25 year mortality rate of 50%
- pseudocysts in 10%
- hereditary pancreatitis - 40% lifetime risk of pancreatic cancer

Non-Neoplastic Cysts

- most are pseudocysts but congenital cysts and neoplastic cystic tumors also occur
- unilocular cysts mainly benign, multilocular cysts more often neoplastic and possibly malignant

Congenital Cysts

- anomalous development of pancreatic ducts
- cysts in kidney, liver, and pancreas frequently coexist in polycystic disease
- von hippel-lindau disease - vascular neoplasms in the retina and cerebellum or brain stem in association with congenital cysts (and also neoplasms) in the pancreas, liver, and kidney

Pseudocysts

- localized collections of necrotic-hemorrhagic material rich in pancreatic enzymes
- cysts lack epithelial lining
- account for approximately 75% of cysts in the pancreas
- usually arise after acute pancreatitis, often in setting of chronic alcoholic pancreatitis
- many spontaneously resolve, may be infected, larger pseudocysts may compress/perforate
Neoplasms
- cystic or solid, benign or malignant
- 5% to 15% pancreatic cysts are neoplastic
- make up fewer than 5% of all pancreatic neoplasms
- benign, borderline malignant or malignant
- may present with pain or masses

Pancreatic Carcinoma
- infiltrating ductal adenocarcinoma of pancreas
- fourth leading cause of cancer death
- one of the highest mortality rates of any cancer
- 5-year survival rate less than 5%
- precursors to pancreatic cancer: "pancreatic intraepithelial neoplasias" (PanINs)

Molecular Carcinogenesis
Fundamentally a genetic disease—a disease of inherited and acquired mutations in cancer-associated genes

Epidemiology, aetiology, and pathogenesis
- little known cause of pancreatic cancer
- primarily a disease in elderly, ages 60 to 80
- more common in blacks than in whites
- strongest environmental influence is smoking - double the risk of pancreatic cancer
- chronic pancreatitis and diabetes mellitus both associated with increased risk
- some familial syndrome predispose to pancreatic cancer:
  - HNPCC, BRCA2, hereditary pancreatitis, Peutz-Jeghers syndrome

Morphology
- 60% arise in the head of the gland, 15% in the body, and 5% in the tail
- most are ductal adenocarcinomas, highly invasive
- elicits intense host reaction of fibroblasts, lymphocytes, and ECM ("desmoplastic response")
- most in the head obstruct the CBD – distension of biliary tree, painless jaundice
- mets to liver, lung, bone, omentum

Clinical Features
- usually remain silent until their extension impinges on some other structure
- pain usually first symptom
- obstructive jaundice, weight loss, anorexia, and generalized malaise and weakness
- migratory thrombophlebitis, (Trousseau sign), in 10% of patients
- CEA and CA19-9 antigen elevated

Diabetes
- endocrine pancreas, insulin produced by β cells, Islets of Langerhans
- group of metabolic disorders sharing common underlying feature of hyperglycemia
- results from defects in insulin secretion, insulin action, or both
- most common noncommunicable disease
- diagnosed by elevated random glucose with signs/sx, elevated fasting glucose, abnormal GTT

Classification
- two broad classes:
  - type 1: absolute deficiency of insulin caused by pancreatic β-cell destruction
  - type 2: peripheral resistance to insulin and relative insulin deficiency
- other causes:
  - genetic defects of β-cell function (MODY)
  - genetic defects in insulin processing or action
  - exocrine pancreatic defects (chronic pancreatitis, pancreatectomy, neoplasia, CF)
  - endocrinopathies (acromegaly, Cushings, hyperthyroidism)
  - infections (CMV, coxsackie virus B)
  - drugs (steroids, thyroid hormone, interferon, protease inhibitors, beta agonists, thiazides)
- genetic syndromes (Downs, Kleinfelter, Turner)
- gestational diabetes

**Insulin Action**

- glucagon has opposite effects
- glucose uptake in other peripheral tissues, most notably brain, is insulin-independent

**Pathogenesis of Type 1 DM**
- severe lack of insulin caused by immunologically mediated destruction of β cells by T lymphocytes
- commonly develops in childhood
- rare form of "idiopathic" type 1 diabetes without autoimmunity

**Mechanisms of β Cell Destruction**
- chronic autoimmune attack on β cells
- several mechanisms contribute to β cell destruction:
  - CD4+ TH1 cells react against β-cell antigens and cause cell damage by activating macrophages
  - CD8+ cytotoxic T lymphocytes directly kill β cells and also secrete cytokines that activate macrophages
- locally produced cytokines damage β cells, incl IFN-γ, produced by T cells, and TNF and IL-1, produced by macrophages that are activated during the immune reaction
- all these cytokines induce β-cell apoptosis
- autoantibodies against islet cells and insulin are detected in blood of 70% - 80% of patients

**Factors that predispose to autoimmunity**

**Genetic Susceptibility**
- many genes implicated
- most important class II MHC (HLA) locus
- 95% with type 1 diabetes have HLA-DR3, DR4, or both
- but most individuals who inherit these alleles do not develop the disease

**Environmental Factors**
- some viruses implicated in triggering autoimmunity in type 1 diabetes: coxsackieviruses B, mumps, measles, CMV, rubella, and infectious mononucleosis
- two mechanisms proposed to explain how infections can trigger autoimmunity:
  - infections induce tissue damage and inflammation, leading to release of β-cell antigens and recruitment and activation of lymphocytes and other inflammatory leukocytes
  - viruses produce proteins that mimic self-antigens and immune response to viral protein cross-reacts with self tissue
- infections may be protective - increased incidence reflects reduction in common infections

**Pathogenesis of Type 2 DM**
- role of environmental factors: sedentary life style and dietary habits
- genetic factors even more important than in type 1 diabetes
- identical twins concordance rate 50% to 90%
- no evidence to suggest autoimmune basis
- two metabolic defects characterize type 2 diabetes:
  - decreased ability of peripheral tissues to respond to insulin (insulin resistance)
  - β-cell dysfunction that is manifested as inadequate insulin secretion in face of insulin resistance and hyperglycemia
  - insulin resistance is primary event, followed by increasing degrees of β-cell dysfunction

**Insulin Resistance**

- insulin resistance = resistance to effects of insulin on glucose uptake, metabolism, or storage
- insulin resistance in type 2 diabetes is a complex and multifactorial phenomenon
- almost universal finding in diabetic - obesity
- insulin resistance often 10 to 20 years before onset of diabetes in predisposed individuals
- insulin resistance leads to decreased uptake of glucose in muscle and adipose tissues and an inability of the hormone to suppress hepatic gluconeogenesis
- down-regulation of insulin receptor; decreased insulin receptor phosphorylation and tyrosine kinase activity; reduced levels of active intermediates in insulin signaling pathway
- insulin resistance can be related to defects in insulin receptor or obesity

**β-Cell Dysfunction**

- β-cell dysfunction in type 2 diabetes reflects inability of these cells to adapt themselves to long-term demands of peripheral insulin resistance and increased insulin secretion
- eventually β-cell compensation becomes inadequate, and there is progression to overt diabetes

**Maturity-Onset Diabetes of the Young (MODY)**

- 2-5% diabetics
- primary defect β-cell function that occurs without β-cell loss, affecting either β-cell mass and/or insulin production
- heterogeneous group of genetic defects characterized by
  - (1) autosomal-dominant inheritance as a monogenic defect, with high penetrance
  - (2) early onset, usually before age 25
  - (3) absence of obesity
  - (4) lack of islet cell autoantibodies and insulin resistance syndrome

**Mitochondrial Diabetes**

- inherited maternally, encodes several genes in oxidative phosphor pathway, ribosomal RNAs, transfer RNAs
- impairment of mitochondrial ATP synthesis results in decreased insulin secretion

**Pathogenesis of Complications of Diabetes**

- macrovascular disease (large- and medium-sized muscular arteries) and capillary dysfunction in target organs (microvascular disease)
- macrovascular disease causes accelerated atherosclerosis - increased risk of myocardial infarction, stroke, and lower-extremity gangrene
- microvascular disease - resulting in diabetic retinopathy, nephropathy, and neuropathy

At least three distinct metabolic pathways involved in pathogenesis of long-term diabetic complications:
- formation of advanced glycation end (AGE) products. Effects of these:
  - (1) release of cytokines and growth factors from macrophages and mesangial cells (insulin-like growth factor-1, TGF-β, platelet-derived growth factor, VEGF)
  - (2) increased endothelial permeability
  - (3) increased procoagulant activity on endothelial cells and macrophages (induction of thrombomodulin and tissue factor)
  - (4) enhanced synthesis of ECM by fibroblasts and smooth muscle cells
  - (5) trapping of nonglycated proteins (eg LDL)
  - central role in development atherosclerosis
- activation of intracellular protein kinase C (PKCs). Effects of this:
  - production proangiogenic molecule VEGF – neovascularization in retinopathy
  - increased vasoconstrictor, decreased vasodilator (eNOS) activity
  - production profibrogenic molecules (TGF-β) – incr deposition ECM
  - production procoagulants – plasminogen activator inhibitor, risk thrombosis
  - production pro-inflammatory cytokines
- intracellular hyperglycaemia with disturbances in polyol pathways
  - in tissues that don’t need insulin for glucose transport (nerves, lens, kidney, vessels)

Morphology:
- reduction number and size of islets
- leukocytic infiltration of islets (insulitis) principally composed of T lymphocytes
- β-cell degranulation
- amyloid replacement of islets in type 2 diabetes
- advanced stages - islets may be virtually obliterated +/- fibrosis

Diabetic Macrovascular Disease
- accelerated atherosclerosis involving the aorta and large- and medium-sized arteries
- gangrene of lower extremities, as a result of advanced vascular disease
- larger renal arteries are also subject to severe atherosclerosis
- hyaline arteriolosclerosis, vascular lesion assoc with hypertension more prevalent, more severe

Diabetic Microangiopathy
- diffuse thickening of basement membranes
- most evident in capillaries of skin, skeletal muscle, retina, renal glomeruli, and renal medulla
- also in nonvascular structures renal tubules, Bowman capsule, peripheral nerves, and placenta
- microangiopathy underlies development of diabetic nephropathy, retinopathy, and some forms of neuropathy

Diabetic Nephropathy
- renal failure second to myocardial infarction as cause of death
- three lesions:
  - (1) glomerular lesions
  - (2) renal vascular lesions, principally arteriolosclerosis
  - (3) pyelonephritis, including necrotizing papillitis
- most important glomerular lesions are capillary BM thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis

Diabetic Ocular Complications
- retinopathy, cataract formation, or glaucoma

Diabetic Neuropathy

Clinical Features of Diabetes
- transition from impaired glucose tolerance to overt diabetes may be abrupt, heralded by an event with increased insulin requirements, such as infection
- polyuria, polydipsia, polyphagia, ketoacidosis
- deficiency of insulin causes catabolic state, affects glucose but also fat/protein metabolism
- hyperglycemia exceeds renal threshold for reabsorption, causing glycosuria
- glycosuria induces an osmotic diuresis and polyuria
- tends to deplete intracellular water, triggering osmoreceptors of thirst centers of brain
- negative energy balance, leads to increasing appetite (polyphagia)
- catabolic effects prevail, resulting in weight loss and muscle weakness

**DKA**
- complication of type 1 but may also occur in type 2
- release of the catecholamine hormone epinephrine blocks any residual insulin action and stimulates the release of glucagon
- insulin deficiency coupled with glucagon excess decreases peripheral utilization of glucose while increasing gluconeogenesis, severely exacerbating hyperglycemia
- hyperglycemia causes an osmotic diuresis and dehydration
- insulin deficiency stimulates lipoprotein lipase, with resultant excessive breakdown of adipose stores, and an increase in levels of free fatty acids
- fatty acids reach the liver, esterified to fatty acyl CoA; oxidation of fatty acyl CoA molecules within hepatic mitochondria produces ketone bodies (acetoacetic acid and β-hydroxybutyric acid)
- if urinary excretion of ketones is compromised by dehydration, plasma hydrogen ion concentration increases, and systemic metabolic ketoacidosis results
- release of ketogenic amino acids by protein catabolism aggravates the ketotic state

Sequence of metabolic derangements leading to diabetic coma in type 1 diabetes mellitus. An absolute insulin deficiency leads to a catabolic state, eventuating in ketoacidosis and severe volume depletion.

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<th>Type 1 Versus Type 2 Diabetes Mellitus (DM)</th>
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<td><strong>Type 1 DM</strong></td>
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moderate decreased insulin (late)

Anti-islet cell antibodies | No anti-islet cell antibodies
Ketoacidosis common | Ketoacidosis rare; nonketotic hyperosmolar coma

Genetics |
30-70% concordance in twins | 50-90% concordance in twins

Pathogenesis | Linkage to MHC Class II HLA genes | No HLA linkage
Autoimmune destruction of β-cells mediated by T cells and humoral mediators (TNF, IL-1, NO) | Insulin resistance in skeletal muscle, adipose tissue and liver β-cell dysfunction and relative insulin deficiency

Islet cells | Absolute insulin deficiency | No insulitis
Marked atrophy and fibrosis | Focal atrophy and amyloid deposition
β-cell depletion | Mild β-cell depletion

- hyperosmolar nonketotic coma, a syndrome engendered by severe dehydration resulting from sustained osmotic diuresis in patients who do not drink enough water to compensate for urinary losses from chronic hyperglycemia
- MI, renal vascular insufficiency, and CVAs most common causes of mortality
- hallmark of CVS disease accelerated atherosclerosis of large and medium-sized arteries
- other risk factors for atherosclerosis: obesity, hypertension, dyslipidemia, platelet dysfunction
- all are more common in diabetics
- earliest manifestation of diabetic nephropathy is microalbuminuria (>30 mg/day)
- microalbuminuria is also a marker for greatly increased cardiovascular morbidity and mortality
- increased risk infections of skin and tuberculosis, pneumonia, and pyelonephritis

Pancreatic Endocrine Neoplasms

**Insulinoma**
- β-cell tumors (insulinomas) most common of pancreatic endocrine neoplasms
- clinical triad: (1) attacks of hypoglycemia (2) attacks consist principally of such central nervous system manifestations as confusion, stupor, and loss of consciousness (3) attacks are precipitated by fasting or exercise and are promptly relieved by administration of glucose
- generally benign
- other causes of hypoglycaemia: abnormal insulin sensitivity, diffuse liver disease, inherited glycogenoses, and ectopic production of insulin by certain retroperitoneal fibromas