Extrinsic Glands of the Digestive Tract

- The liver is an extrinsic gland – outside of the GI tract proper
- Brunner's glands – in the wall of the duodenal submucosa
- Other extrinsic glands of digestion, develop from gut but are located outside of it
    - Salivary glands
    - Pancreas

Gland morphology, structure, and content

- Structures
    - Some have ducts and secretory portions
        - Brunner's glands, salivary glands, pancreas
    - Some have secretory portions but lack ducts, secret directly into lumen
        - Glands of GI mucosa
- Morphology
    - Tubular (exocrine)
    - Alveolar (actiniums) – flask-like
    - Tubulo-alveolar – have both morphologies
- Branching
    - With branches – compound gland
    - Without branches – simple gland
- Secretory content
    - Serous – secretory products are predominantly proteins or glycoproteins of sizes 4-100 kDa, more watery and less dense
        - Amylase, lipases, iron=binding protein lactoferrin (antimicrobial protein), immunoglobulin A
    - Mucous – source of lubricant and protection of epithelia, secretory products heavily glycosylated proteins >250 kDa (usually 1-10 million Da)
        - Mucins

Salivary glands – a group of exocrine glands, release products to outside world (lumen of GI tract)

- Three types
    - **Parotid gland** – biggest gland, side of face, accounts for ≈25% of saliva
        - Where mumps virus occurs
        - Serous gland – only glycoproteins, no mucins, similar to pancreas
    - **Submandibular gland** – second largest, underneath jaw, bulk of saliva
        - Both serous and mucous
    - **Sublingual gland** – smallest, underneath tongue, small amount of saliva
        - Some serous , but mostly mucous
- Rabies virus – affects these glands, virus is secreted into ducts which open on side of mouth (the reason for infectious bite)
- Functions
    - Saliva – for mastication and lubrication
        - Beginning of digestion – amylase, a primary product of parotid, and other enzymes (lingual lipase, Dnase, Rnase)
        - Mucins and water form basis for lubrication of food
        - Remineralization of teeth
            - Statherin, proline-rich proteins
        - Microbial control
            - Histatins, sIgA, lysozyme, lactoferrin, salivary peroxidase, fibronectin
        - pH maintenance
            - Bicarbonate, histatins
        - Protection of mucosal lining of mouth
            - Mucins, basic proline-rich glycoprotein, epidermal growth factor
        - Functions can be lost
            - An estimated 4% of US population have dry mouth
                - Sjogren's syndrome – autoimmune inflammatory disease of salivary glands
                - Irradiation of the head and neck
                - Medication side-effects
        - Consequences: tooth decay and demineralization can occur
- Components of saliva
    - Many proteins, some urea, interesting inorganic constituents (low Na^+ and Cl^-, and reabsorbed at level of ducts under normal conditions, whereas K^+ is excreted by the striated ducts)
    - We produce over a liter of saliva a day (≈1200 mL)
- Common construction of salivary glands
    - **Secretory portion** – acinar (alveolar) cells, acinar means grape
        - All polarized, simple, shaped like a pyramid or column

        - Have basement membrane on the outside, but myoepithelial cells before
            - Myoepithelial cells are weakly contractile and able to propel primary saliva out of secretory portion lumen and into the duct
            - Myoepithelial cells extend to the first part of the duct, so there's a direct connection between last secretory and first ductal portion.
                - Continuous epithelium prevents saliva from entering interstitial space, except through transporters
        - Connected by tight junctions, saliva restricted to apical lumen
        - Receptors on basolateral, along with myoepithelia and basal lamina
        - Parotid – mostly serous, but with fat cells (look like mucous cells at low magnification)
            - Amylase the principal product, some lipases
            - In light microscope, one can see nuclei at base but not lumen very often in secretory portions
            - At EM level, can see dark spheres or granules where protein products are stored. Can see nucleus at bottom of cell and tight junctions
                - Clusters of cells all empty into a small, common lumen
            - Secretion is regulated by neural stimuli
            - At very high magnification, can see granule fusing with apical membrane and contents being released into lumen. Little microviili seen projecting from apical surface. Can see important tight junctions protecting cells from proteases
        - Submandibular gland – serous and mucous, with some fat and ducts within the lobule itself
            - Unlike parotid, submandibular has mucous-secreting cells in addition to the serous-secreting cells
                - Serous-secreting cells look exactly like those in parotid gland – have granules in apical cytoplasm with nucleus down in lower half, secrete into lumen
                - Mucous-secreting cells have a different histological appearance and content is very different – contains mucins, nuclei are pushed down against basal layer, but granules can fuse with apical membrane and release their contents into lumen. Tight junctions between adjacent cells prohibit mucins prevent from entering lateral spaces
        - Sublingual gland
            - At high magnification, secretory portion is mostly mucous but there are also serous components in **demilunes**
                - Demilune – mucous-secreting gland that also contains some serous-secreting cells in it that make a glycoprotein product
                    - Have dark protein-rich granules and large nuclei in EM
            - In EM, you can see adjacent cells joined by tight junctions with a central lumen
    - **Myoepithelial cells** – hard to identify, in between the base of the secretory cell and the basement membrane of a group of cells that all empty on a single lumen
        - They are mildly contractile, with smooth muscle myosin along the base of cell groups
        - In scanning EM, they appear to "hug" acinar cells, contractions help push out primary saliva
    - **Duct portion**
        - **Intercalated duct** – in between secretory portion and next part of the duct (striated duct)
            - Cuboidal, smaller profile than striated
        - **Striated duct** – pumping action and many mitochondria
            - Columnar, long, larger cross-sectional profile
            - Intracellular striations are actually aligned mitochondria - Na^+ is being reabsorbed (pumped out with aid of ATP hydrolysis) by cells of striated duct, not in intercalated duct
        - Ducts modify primary saliva and conduct it away from secretory portions
        - After striated ducts in the salivary gland, larger **interlobular ducts** conduct modified saliva to the mouth
            - Columnar cells, located in the connective tissue-rich septa of the salivary gland (present in all three glands), they are not striated
            - Gradually becomes stratified squamous as it approaches the mouth where oral mucosal cells are of this morphology

Pancreas – last extrinsic gland of the digestive tract

- Exocrine – principal source of digestive enzymes in small intestine
- Endocrine – excretes products into blood
- All secretory products are serous
- Structure
    - Head
    - Tail
    - Ducts – collect secretions from all acini within pancreas into a central duct that joins the common bile duct and enters at beginning of duodenum
- Development – both endocrine and exocrine portions develop from the foregut; ventral and dorsal pancreas develop and ultimately fuse
    - Thus, there are two ducts - a major one with the common bile duct and a minor duct that empty pancreatic secretions into the duodenum
- Bile gallstones are an important cause of acute pancreatitis – secretions get backed up because of obstruction to duodenal entrance, extremely painful
- Histology – pancreas superficially resembles that of the salivary glands, with one important difference
    - Endocrine portions of the gland
        - **Islets of Langerhans** – 1 to 2 million in the mature pancreas, organized into groups of cells, they are not present in parotid
        - Blood cells and ducts present, no striated ducts (no reabsorption of primary contents)
    - Exocrine portion of pancreas – stained bright pink, many acinus present facing a common lumen

    - Look similar to other serous glands – pyramidal shape and polarity, an epithelial cell with tight junctions between apical and lateral surfaces
        - Zymogen granules – contain all pancreatic enzymes in a mixture, one cell makes all of the 20-40 pancreatic enzymes secreted into lumen
- Products of exocrine pancreas
    - Zymogens – inactive proteases, inactive precursors later activated by enterokinase in duodenum (trypsinogen, chymotrypsinogen, procarboxypeptidase, prophoplipase A, etc)
        - Stored in the same granule
        - Small sizes – serous
        - May be glycoproteins but carbohydrate moieties are a minor portion
        - **Enteropeptidase** – located on the apical brush border of the duodenal epithelial cells, cleaves trypsinogen to release hexapeptide and form trypsin
            - **Trypsin** activates other pancreatic enzymes
        - In different forms of pancreatitis, there can be inappropriate activation of trypsinogen in the granule itself or the lumen of an acinus – dire consequences
- Granules fuse with apical membrane → release contents into lumen → conducted into intercalated ducts of the pancreas (via **centroacinar cells** – the beginning of intercalated duct) → ducts fuse to form larger ducts of pancreas (not striated because not reabsorbing any primary secretory material)
- Secretions are visible in the exocrine pancreatic ducts, can see individual exocrine cells, zymogen granules, centro-acinar cells (present at the exit sites of acinus that connects to intercalated ducts)
    - Centroacinar and intercalated duct cells – small cuboidal cells, secrete bicarbonate to neutralize the HCl secreted by gastric mucosa
    - Centroacinar cells – the first dells of the pancreatic duct system
        - Form tight junction with acinar cells
        - There is complete continuity and sealing so that contents cannot make it to basolateral environment and into the blood
    - Secretions are primary here,
    - Centroacinar "duct" cells → Intercalated duct cells → intralobular duct cells → interlobular duct cells
        - Intralobular ducts don't secrete bicarbonate, columnar epithelia
        - Interlobular ducts conduct secretions out into duodenum, within connective tissue septa, conducts pancreatic secretions towards duodenum, much larger
        - Arteries, veins, capillaries also present in exocrine pancreas; everything continuous and well-sealed to prevent release of enzymes into bloodstream
- Exocrine pancreas function controlled at the neural and hormonal levels
    - Neural
        - Vagus nerve stimulates enzyme secretion
    - Hormonal
        - Acid of stomach when hits duodenum and also pyloric portion of stomach, secretin is secreted (by an enteroendocrine cell) to stimulate the intercalated duct cells to secret bicarbonate
        - Fat stimulates CCK to stimulate receptors on basal surface of exocrine pancreatic cells which stimulates 1) signal transduction and ultimate secretion of contents into lumen and then into duodenum, 2) contraction of gallbladder to release bile into the common bile duct and out into the duodenum
- Islets of Langerhans – contain the endocrine portion of the pancreas
    - Has no central lumen
    - A group of cells that secret all of their protein secretory contents into blood
    - Highly vascularized
        - Abundance of fenestrated capillaries because release of proteins from granules is into basal interstitium and into the blood
    - Three major types of cells – one protein made by a single cell type (unlike exocrine pancreas where all enzymes made by each cell)
        - Insulin-secreting cells (α cells)
        - Glucagon-secreting cells (β cells)
        - Somatastatin-secreting cells (δ cells)
    - Still exist in diabetics, but juvenile diabetes is complete loss of β cells that respond to glucose and secret insulin into the bloodstream
    - Glucagon and insulin are opposing hormones
    - Endocrine cells types in islets have distinct granules, insulin stored in active form in granules until appropriate stimulation that stimulates secretion into surrounding space
        - Cells show polarity – they secret hormones toward fenestrated capillaries
        - No tight junctions between any cells, may have occasional gap junctions
- Features of salivary glands and pancreas – all compound
    - Salivary glands
        - Parotid – serous, there are intercalated ducts that move immediately into striated ducts (presence of mitochondria)
        - Submandibular – more mucous but still some serous, acini and striated ducts
        - Sublingual – exclusively mucous, less abundant striations
        - All salivary glands connect up through larger and larger tubes to the secretory duct that takes secretions to surface of the mouth
        - All eventually have striated squamous epithelia
    - Pancreas – on the surface looks like parotid
        - Islets of Langerhans
        - Intercalated ducts merge into an intralobular duct that is not striated and then into a continuing epithelia that is not stratified and then into duodenum where pancreatic enzymes are the predominant enzymes acting on molecules