Lecture 2 – Bone

- Protection of brain, lungs, other internal organs
- Structural support for heart, lungs, and marrow
- Attachment sites for muscles
- Mineral reservoir for calcium (99% of body's) and phosphorous (85% of body's)
- Trap for dangerous minerals (ex:// lead)
- Transduction of sound
- Endocrine organ (osteocalcin regulates insulin signaling, glucose metabolism, and fat mass)

Structure

- Compact/Cortical
    - Diaphysis of long bone, "envelope" of cuboid bones (vertebrae)
    - 10% porosity, 70-80% calcified (4x mass of trabecular bone)
    - Protective, subject to bending/torsion/compressive forces
    - Has Haversian system structure
- Trabecular/Cancellous
    - Metaphysis and epiphysis of long bone, cuboid bone
    - 3D branching lattice formed along areas of mechanical stress
    - 50-90% porosity, 15-25% calcified (1/4 mass of compact bone)
    - High surface area ➔ high cellular activity (has marrow)
    - Metabolic turnover 8x greater than cortical bone
    - Subject to compressive forces
    - Trabeculae lined with endosteum (contains osteoprogenitors, osteoblasts, osteoclasts)
- Woven Bone
    - Immature/primitive, rapidly growing
        - Normally – embryos, newborns, fracture calluses, metaphyseal region of bone
        - Abnormally – tumors, osteogenesis imperfecta, Pagetic bone
    - Disorganized, no uniform orientation of collagen fibers, coarse fibers, cells randomly arranged, varying mineral content, isotropic mechanical behavior (behavior the same no matter direction of applied force)
- Lamellar Bone
    - Mature bone, remodeling of woven bone
        - Begins 1 month after birth, by 4 years most bones are lamellar
    - Throughout body – cortical and trabecular, intramembranous and endochondral
    - Highly organized collagen fibers, anisotropic mechanical behavior (greatest strength parallel to long axis of collagen fibers)
- Periosteum – dense CT surrounding bone important in bone repair
    - Outer fibrous layer
    - Inner layer with bone cells, precursors, and blood vessels
- Endosteum – thin layer of CT lining inner surface of bone, facing marrow
    - Contains osteoblasts and their precursors

Composition

- <3% lipid, 5-8% water
- 20-40% organic
    - 90% Type I collagen
        - triple helix (2 α1 chains, 1 α2 chain) 1000aa in length
        - post-translationally modified, assembled in fibrils
        - secreted pro-form and enzymatically cleaved
        - binds and orients other proteins that nucleate hydroxyapatite matrix mineralization
    - Type II, II, IV collagen
        - Also present, involved in fiber bundling regulation and overall matrix organization
    - Noncollagenous proteins
        - Proteoglycans and hyaluronan – space fillers, regulate collagen organization
    - Glycosylated proteins
        - Alkaline phosphatase (regulates P_i and Ca^{++} dynamics)
        - Osteonectin (collage-hydroxyapatite bridge)
    - Glycosylated proteins with cell-attachment properties
        - RGD domains bind integrins, influence cell-ECM interactions
    - γ-carboxylated (Gal) containing proteins
        - regulates mineralization, other functions
    - Cytokines, growth factors, hormones
- 60-70% inorganic (hydroxyapatite)
    - Flat crystal (small, imperfect) – reservoir for minerals (Calcium, phosphate, magnesium)

Bone Growth

- Endochondral ossification – within cartilage (long bones, fracture healing is also similar)
    - Zones – reserve cartilage, proliferation, hypertrophy, calcification
    1. Formation of cartilage template
    2. Chondrocyte hypertrophy (area surrounded by a bone collar), then apoptosis
    3. Vascularization, invasion of osteoblast precursors (Starts with intramembranous ossification)
    4. Osteoblasts differentiate, replace cartilage with bone (ossification, bone collar gets longer)
    5. Osteoclasts generate marrow cavity
- Intramembranous ossification (flat bones mainly in the skull)
    - Mesenchymal cells form clusters of osteoprogenitors that differentiate in place

Bone Cells

- Osteoblasts (bone forming)
    - Derived from mesenchymal stem cells (development) and bone marrow stem cells (post-natal)
        - Runx2 (Cbfa1) needed for bone development (present in osteoblasts, odontoblasts, ameloblasts, cementoblasts, some stages of cartilage
        - Upstream regulator of osterix (OSX), a bone phenotype similar to Run2x knockout
            - Lack causes Cleidocranial dysplasia (defects in bone development)
    - Lines osteoid (unmineralized bone surface, mixture of bone matrix proteins), which it secretes
        - Indirectly responsible for mineralization of osteoid
    - Basophilic, lots of RER, produce type I collagen, alkaline phosphatase, etc
    - Regulates differentiation and regulation of osteoclasts
    - Indirectly maintains Ca^{++} balance

- Bone Cell Differentiation
    1. Proliferation and ECM biosynthesis (Cbfa1, histone, collagen, TGFβ1, osteopontin)
    2. ECM development, maturation, and organization (Alkaline phosphate, BSP, collagen)
    3. ECM mineralization (osteocalcin, osteopontin, collagenase)
        - Apoptosis
- Osteocytes (terminally differentiated osteoblasts that support bone structure and metabolic function)
    - Most abundance cell in bone (90%), form from osteoblasts embedded in lacunae (matrix gaps)
    - Extend many filopodial processes through canniliculi
        - Cell viability – nutrient and gas exchange
        - Mechanosensation
        - Transducing stress signals (Stretch, bend) to osteoblasts – regulate biological activity
            - Deformation of canniliculi enhances osteoblast activity
- Osteoclasts (bone resorption)
    - Large, multinucleated, derived from pluripotent hematopoetic cells in bone marrow (they also give rise to monocytes and macrophages) via M-CSF and RANKL
    - Produce TRAP (tartrate-resistant acid phosphatase) within cytoplasmic vesicles and vacuoles
    - Found inside Howship's lacunae along bone surface

Bone Remodeling

- Localized degradation of bone mineral and organics followed by synthesis of new bone
    - Occurs in local microenvironment, usually activated by systemic factors
        - Damage repair, facilitate tissue growth, systemics (low calcium, lactation, etc)
    - Sealing zone – integrins bind RDG-containing proteins in bone matrix sealing off area under the osteoclast, allowing for bone resportion factors to be concentrated in this rea
    - Ruffled border – adjacent to resorbing bone surface are osteoclast deep folds by bone, increased surface area for release of resportion factors
- Occurs on bone surfaces (periosteal, endosteal, Haversian canals, trabecular surfaces)
- Cycle takes 3-4 months (2-5% cortical bone remodeled per year, 50% trabecular bone remodeled per year)
    - People older than 35 have an imbalanced cycle – greater resportion
- 5 phases
    1. Activation of osteoclast
    2. Resportion of bone
    3. Reversal of phase
    4. Formation of bone (activation of osteoblast, mineralization)
    5. Resting

Lecture 3 – Tooth Development

- Initiation begins at 37 days of development, formation of primary epithelial band (horseshoe-band of thickened epithelium in location of upper and lower jaws), with each band have 2 subdivisions
    - Dental lamina – thickening of oral epithelium adjacent to condensation of ectomesenchyme
        - 20 areas of enlargement, or knobs, appear (primary tooth buds)
        - Buds in anterior mandibular region appears first (not all appear at same time)
        - Buds have already determined crown morphology
        - Successional lamina – lamina from which permanent teeth develop
        - Begins function 6th week prenatal to 15th year after birth (3rd molar)
    - Vestibular lamina

Tooth Development process has 3 stages

1. Bud stage – characterized by rounded, localized growth of epithelium surrounded by proliferating mesenchymal cells packed closely beneath and around epithelial band
    - Enamel organ = peripherally located low columnar cells, centrally located polygonal cells
2. Cap stage – condensation of ectomesechyme immediately subjacent to tooth bud caused by lack of ECM secretion by cells, thus preventing separation. Histodifferentiation begins at this stage
    - Epithelial outgrowth now called enamel organ (it will eventually form the enamel)
    - Enamel knot – densely packed non-dividing accumulation of cells projecting from inner enamel epithelium into dental papillae, thought to determine cusp number. First noted by p21 gene expression.
        - Enamel cord – pattern of enamel knot extending between inner and outer dental epithelium
    - Dental papillae – ball of condensed ectomesenchymal cells (will form dentin and pulp). Peripheral cells adjacent to inner dental epithelium will enlarge and later differentiate into odontoblasts
    - Dental follicle/sac – condensed ectomesenchymal tissue surrounding enamel organ and dental papillae, gives rise to cementum and periodontal ligament
    - Lateral lamina – extension from the dental lamina that is connect to the enamel organ. Remnant can cause cysts
    - Enamel niche – artefact from histological preparation
    - Dental organ – term used to constitute structure that has enamel organ, dental papillae, and dental follicle
3. Bell stage – Histo and morphodifferentiation (ameloblasts/odontoblasts defined, tooth crown assumes final shape)
    - Outer dental epithelium – cuboidal cells covering enamel organ, organize a network of capillaries that bring nutrients to ameloblasts.
        - At end of bell stage, formerly smooth surface of outer dental epithelium is laid in folds, with adjacent mesenchyme of the dental sac between them that form papillae that contain capillary loops providing nutrients for intense metabolic activity of avascular enamel organ
    - Stellate reticulum – star-shaped cells with processes present between outer and inner dental epithelium.
        - Secrete GAGs (hydrophilic), swelling cells and pushing them apart (maintain contact = star shaped)
        - Cushion-like to support delicate enamel organ, absent in portion that outlines root portions.
    - stratum intermedium – cell layer between inner dental epithelium and stellate reticulum which have high alkaline phosphatase activity, assist inner dental epithelium (ameloblasts) in enamel formation.
    - Inner dental epithelium – short columnar cells bordering dental papilla, eventually become ameloblasts that form enamel via differentiation into tall columnar cells
        - Exert an organizing influence on underlying mesenchymal cells in dental papillae
        - Folding of inner dental epithelium causes future crown patterning. Cessation of mitotic activity within inner dental epithelium determines shape of tooth.

- Dental papilla – before inner dental epithelium begins producing enamel, peripheral cells of mesechymal dental papillae differentiate into odontoblasts under organizing influence of epithelium.
    - First cuboidal, then columnar and acquire specific potential to produce dentin
    - Basement membrane separating enamel organ and dental papilla just before dentin formation called "membrane preformative", and becomes the dento-enamel junction
- Cervical loop – where inner and outer dental epithelium meet. Ameloblasts and odontoblasts differentiate here.
    - Where cells will continue to divide until tooth crown attains full size
    - Gives rise to epithelium for root formation after crown formation complete
    - Also called "Zone of Reflexion"

Vascular Supply

- Clusters of blood vessels in dental follicle and papilla
- Clustering of vessels in papilla coincide with position of root formation
- Enamel organ is avascular, vessels seen is close association with it supply it

Nerve Supply

- Initially noted in dental follicle during bud to cap stage
- Seen in dental papilla at start of dentinogenesis
- Nerve fibers don't enter enamel organ

Clinical Correlation

- Ameloblastoma – tumours of odontogenic epithelium that arise from cell rests of enamel organ or from developing enamel organ among other things
    - Histology resembles enamel organ epithelium with peripheral columnar ameloblast-like cells surrounding loosely arranged stellate-reticulum-like cells
- Odontogenic myxoma – tumour of the jaw that arises from odontogenic ectomesenchyme.
    - Histology resembles mesenchymal portion of developing tooth (dental papilla)

Permanent Dentition

    - Primary dentition initiates 6-8 weeks in utero
    - Successional permanent teeth initiates 20 week in utero to 10 months after birth
    - Permanent molars between 20^{th} week in utero and 5^{th} year of life
- Tooth germs for anteriors and premolars form from further proliferative activity within dental lamina lingual to deciduous tooth germ
- Permanent molars have no predecessors; tooth germ originates from dental lamina that extends posteriorly beneath oral epithelium after jaws have grown

Hard tissue formation starts at the late portion of bell stage (deposition called apposition)

- After crown attains its final shape during bell stage, inner dental epithelial cells stop to proliferate (except cervical loop cells)
- First layer of dentin appears at cusp tips and progresses cervically, columnar cells of inner dental epithelium become elongated and show reverse polarization (unique to ameloblasts, and to some degree odontoblasts) with nuclei adjacent to stratum intermediate
- Boundary between odontoblasts and inner dental epithelium defines future dento-enamel junction
- At the same time (or soon after) first layer of dentin is formed (aka mantle dentin), inner dental epithelial cells differentiate into ameloblasts and secrete enamel proteins (amelogenesis).

- Proteins further help in terminal differentiation of odontoblasts
- Ameloblasts will start laying down organic matrix of enamel against new formed dentinal surface
- Enamel matrix will mineralize immediately to form first layer of enamel

- At the same time inner dental epithelium differentiates, undifferentiated ectomesenchymal cells increase rapidly in size and ultimately differentiate into odontoblasts
  - The increase in size of the papillary cells leads to elimination of the acellular zone between dental papilla and inner dental epithelium
  - Differentiation of odontoblasts from ectomesemchymal cells are induced by influence from the inner dental epithelium (no inner dental epithelium, no dentin formed)
- Dentinogenesis – formation of dentin by odontoblasts (highly polarized with nuclei away from inner dental epithelial) that differentiate from ectomesechymal cells of dental papilla with expression of signalling molecules and growth factors from inner dental epithelium
  - First layer of dentin characterized by large-diameter collagen Type III (von Korff's fibers), followed by collagen type I, to form Mantle Dentin
  - Odontoblasts develop stubby processes at side close to inner dental epithelium extending into forming ECM (Tomes' fibers)
  - As odontoblasts move pulpward, Tomes' Fibers elongate and become active in dentine matrix formation
    - Odontoblast movement to center of dental papilla as it lays down predentin gives the tubular structure of dentin (unlike enamel)
    - Predentin, then mineralized to become dentin (similar to osteoid in bone)
      1. Formation of collagen matrix (mostly type I, except Mantle Dentin which has type III
      2. Deposition of calcium and hydroxyapatite (phosphate) crystals into matrix
- Amelogenesis – begins after a few µm of dentin apposition

1. Morphogenic stage – crown shape determined
2. Histodifferentiation – inner dental epithelium differentiates into ameloblasts
   - Acquire phenotype, change polarity (reverse polarized), develop extensive protein secretory machinery, prepare to secrete organic matrix
3. Secretory stage – elaborate and organize entire enamel thickness. Short, conical processes (Tomes' processes) develop at apical end. Main protein is amelogenin.
4. Maturation stage – ameloblasts modulate and transport specific ions required for concurrent accretion of minerals.
   - Are active in absorption of organic matrix and water to allow mineralization
   - After mineralization, secrete organic cuticle on surface of enamel (developmental/primary cuticle) for protection
5. Ameloblasts are shorter, contact stratum intermedium and outer dental epithelium and fuse to form reduced dental (enamel) epithelium
   - Reduced enamel epithelium remains until eruption, where cervical portion is not destroyed as it interacts with oral epithelium to become junctional epithelium

1. Production of partially mineralized matrix (30% mineralization)
2. Influx of additional mineral coincident with removal of organic material and water (96% mineralization)
   - Proteins: amelogenin, amelobastin, enamilin

Amelogenesis Imperfecta

Hypomaturation, hypoplastic (at the time matrix is laid down), hypocalcified

Review

4 stages: 1. Elongation of inner dental epithlium 2. Differentiation of odontoblasts 3. Formation of dentin 4. Formation of enamel	3 things to remember - Differentiation of cells into odonto and ameloblasts - Dentin formed before enamel - Dentin initiates enamel formation

1. Epithelium separate from dental papilla by acellular zone
2. Inner dental epithelial cells elongated, acellular zone lost by differentiation of odontoblasts
3. Odontoblasts retreat toward center of pulp, leaving behind dentin
4. Amelobasts begin migrating outward, leaving behind enamel
-

Timeline

- 42-48 days – dental lamina formation
- 55-56 days – bud stage, deciduous incisors; canines, molars
- 14 weeks – bell stage for deciduous teeth, bud stage for permanent teeth
- 18 weeks – dentin and functional ameloblasts in deciduous teeth
- 32 weeks – dentin and functional ameloblasts in permanent first molars

Root Formation

- Begins after enamel and dentin formation has reached future CEJ
- Epithelial cells of inner and outer dental epithelium proliferate from cervical loop of enamel organ to form Hertwig's epithelial root seath
    - Root sheath determines if tooth has single/multiple roots and if it is short/long, curve/straight
    - Eventually fragments to form several discrete clusters of epithelial cells known as cell rests of malassez
        - Persist in adults within periodontal ligament adjacent to surface of cementum
- Epithelial diaphragm – proliferating end of root sheath bends at near 45^{o} angle. Epithelial diaphragm will encircle the apical opening of dental pulp during root development
    - Secondary apical foramen a result of 2 or 3 tongues of epithelium growing inwards towards each other
- Root formation happens right before tooth eruption
- Supporting structures (periodontal ligament, cementum) form at same time root is forming
- As root sheath fragments, dental follicle cells penetrate between epithelial cells and lie close to newly formed root dentin, where they develop into cementoblasts
- Fibers of periodontal ligament, also from cells of dental follicle, get anchored in organic matrix of cementum, which is later mineralized

Lecture 4 – Oral Mucosa

- Protection – barrier for mechanical trauma and microb insults
- Sensation – temperature, touch, pain, taste, thirst, reflexes (swallowing, etching, gagging, salivating)
- Secretion – saliva
- Thermal regulation in dogs

Types of Oral Mucosa

- Masticatory (25%) – gingiva and hard palate, in contact with food during mastication, keratinized, attached to bone
- Lining (60%) – covers floor, ventral tongue, alveolar mucosa, cheeks, lips, soft palate. Minimal attrition, not keratinized, free moving
- Specialized (15%) – covers dorsal tongue and composed of cornified epithelial papillae (irregular surface)

General Features

- Separated from skin by vermillion zone of lips which is more deeply coloured than rest of oral mucosa
- Factors affecting colour:
    - Concentration and state of dilation of blood vessels in underlying CT
    - Thickness of epithelium
    - Degree of keratinization
    - Amount of melanin pigmentation
    - Hyperkeratinisation – thickening of keratin layers, looks white in the mouth

Differentiating Features

- Colour, moist surface
- Absence of adnexal skin structures (hair follicles, sweat glands, sebaceous glands)
- Fordyce's disease – sebaceous glands in oral cavity predominantly in upper lip, buccal and alveolar mucosa
    - Pale yellow spots is part of normal variation
- Minor salivary glands in oral mucosa
- Texture of surface – smoother than skin (with a few exceptions)
- Oral mucosa varies in firmness

Structure

- Overlying oral epithelium
    - Keratinized or non-keratinized stratified squamous
    - Interface between epithelium and CT comprised of structureless layer called basement membrane
        - Interface is irregular, downward projections of eithelium called rete ridges, upward projections of CT called CT papillae
- Underlying CT (lamina propria and submucosa) – salivary glands, sebaceous glands, lymphoid tissue
- Junction between oral epithelium and lamina propria MORE evident than between lamina propria and submucosa
- No muscularis mucosae layer in oral mucosa (unlike in GI tract) – muscle in oral cavity is unnamed
- Submucosa (loose fat/glandular tissue with blood vessels and nerves) under oral mucosa provides flexibility
- Oral mucoperiosteum (gingiva and hard palate) – no submucosa, lamina propria directly attached to periosteum for firm, inelastic attachment

Oral Epithelium

- Progenitor population – divide and provide new cells
- Maturing population – undergo differentiation/maturation
- Turnover times – estimated times necessary to replace all cells in epithelium
    - Nonkeratinized epithelium faster turnover
    - Oral ulcers during cancer chemotherapy – side effect seen on buccal and labial mucosa
        - Skin – 8-10 weeks
        - Gut – 1-2 weeks
        - Gingiva – 6-8 weeks
        - Cheek – 3.5 weeks
- Types:
    - Orthokeratinized – no nucleus in keratin layer
    - Parakeratinized – has nucleus in keratin layer
    - Nonkeratinized
- Lining Mucosa:
    - Stratum basale – basal cell layer comprised of cuboidal cells. Progenitor cells divide and provide new cells via mitotic division to replace dead surface cells which are shed
    - Stratum spinosum/intermedium – cells are oval, represent bulk of epithelium
    - Stratum superficiale – cells are flat, contain small oval nuclei that are continuously shed

Lip Histology

- Skin – keratinized with adnexal skin structures
- Oral mucosa – moist, nonkeratinized associated with small round seromucous glands in lamina propria
    - No adnexal skin structures, submucosa fibers of orbicularis oris present
- Vermillion zone – very think keratinization (not referred to as a keratinized tissue) with no adnexal skin structures, does contain sebaceous glands
    - Red colour because of thinness, contains eleidin (transparent substance present in stratum lucidum of skin epithelium), blood vessels near surface

Soft Palate

- Nonkeratinized, highly vasuclarized (more pink than hard palate)
- Lamina propria and submucosa present (unlike hard palate with only lamina propria – mucoperiosteum),
- Submucosa contains salivary glands and muscle of soft palate

Cheeks

- Similar to lips and soft palate – nonkeratinized, lamina propria, and submucosa
    - Submucosa of cheeks has fat cells and lobules of minor salivary glands and muscle fibers

Ventral Tongue

- Nonkeratinized, lamina propria, submucosa
- Extremely dense muscle fibers interlacing CT fibers in submucosa

Mouth Floor

- Nonkeratinized, lamina propria, submucosa
- Epithelium loosely attached to lamina propria
- No muscle, lots of salivary glands

Masticatory Mucosa

- covers gingiva and hard palate, thicker than nonkeratinized
- stratum basale and spinosum same as nonkeratinized epithelium
- stratum granulosum – cells contain keratohyaline granules
- stratum corneum – contains thin, flat nonnucleated (pyknotic nucleus) cells filled with keratin. Unlike hard keratin in nails and hair, keratin overlying masticatory oral mucosa is soft.
    - Keratin = tough, nonliving material resistant to friction and impervious to bacterial invasion
    - Rete pegs are long and slender in keratinized epithelium

Gingiva

    - Attached gingiva attaches with the neck of the tooth via junctional epithelium
    - Stippling seen (small pits in epithelium) due to deep rete pegs. Lamina propria composed of long narrow papillae NOT highly vascularized. No distinct submucosa because of direct attachment to periosteum and cememtum by collagen fibers
- Free Gingiva – keratinized, not stippled, bound on inner margin by gingival sulcus (which separates it from tooth), bound on outer margin by oral cavity, bound apically by free gingival groove
- Attached Gingiva – keratinized, stippled, separated from alveolar mucosa via mucogingival junction/groove, attached to tooth via junctional epithelium

Junctions

- Dentogingival junction – where oral mucosa meets surface of tooth
    - Weak area (attachment loss) in oral mucosa, which is otherwise continuous
    - Bacteria on tooth surface produce toxins – can inflame and damage if it enters into mucosal tissues
    - Healthy gingival sulcus – 0.5-3mm (mild inflammation is normal, 1.8mm average)
    - Floor of sulcus and epithelium cervical to it is junctional epithelium (in contact with tooth surface – enamel, sometimes cementum)
    - Wall of gingival sulcus lined by nonkeratinized derived from and continuous with rest of oral mucosa (aka oral sulcular epithelium)
- Junctional epithelium – floor of sulcus and epithelium cervical to is, attached to tooth (enamel, sometimes cementum) and surface continuous with sulcular epithelium, origin from apical reduced enamel epithelium
    - Derived from reduced enamel epithelium
    - Consists of flat cells aligned parallel to tooth surface, inceasing in thickness from apex to crown
    - Attached to enamel via internal basal lamina, to CT via external basal lamina (hemidesmosomes in both basal lamina)

Turnover

- High rate of division, migrate 2-3 cell layers from tooth surface, then join main migratory route in coronal direction parallel to tooth surface to be desquamated into gingival sulcus
- Junctional epithelium readily regenerates from sulcular epithelium or oral epithelium if it is damaged
- CT normally contains plenty of neutrophils (different from normal oral mucosa)
    - Minor inflammation normal for gingiva, but not for other oral mucosa

Col

- Depressinos in interdental (embrasure) area. Similar to outline of depression with buccal and lingual peaks
- Epithelium identical to junctional epithelium and has same origin (dental epithelium)
- Incidences of gingivitis greater interdentally at Col – may be more vulnerable to inflammation

Blood Supply (tables 12-4 and 12-5)

- To gingiva – derived from periosteal vessels to periosteum and alveolar process
- To dentogingival junction – continuation of interalveolar arteries
- Nerve supply to gingiva – terminal branches of periodontal nerve fivers and branches of infraorbital and palatine, or lingual, mental, and buccal nerves

Hard Palate

- Orthokeratinized (parakeratinized in some areas) showing ridges (rugae)
- Lamina propria shows long papillae with thick, dense CT
- Submucosa is mucoperiosteum with dense collagenous CT attaching directly to periosteum. Contains fat and salivary glands

Papilla

- Filiform papilla – majority of papillae, covers anterior part of tongue
    - Appear as slender, threadlike keratinized projections (2-3mm) of surface epithelial cells
    - Facilitate mastication by compressing and breaking food when tongue apposed to hard palate
    - Directed towards throat, assist in movement of food towards throat
    - No taste buds
    - Hairy tongue – overgrowth of filiform papilla
- Fungiform papilla – interspersed between filiform
    - More numerous near tip of tongue
    - Smooth, round, appear red because of highly vascular CT core
    - Seen through thin, nonkeratinized epithelium
    - Taste buds seen within epithelium
- Foliate papilla – present on lateral margins of posterior tongue, appear leaf-like
    - Consist of 4-11 parallel ridges that alternate with deep grooves in mucosa
    - A few taste buds present on epithelium
    - Contain serous glands underlying taste buds which cleanse grooves
- Circumvallate papilla – on V-shaped sulcus
    - 10-14 in number between base and body of tongue
    - Large (3mm diameter) with deep surrounding groove
    - Ducts of von Ebner glands (serous salivary glands) open into grooves
    - Taste buds seen lining walls of papillae

Taste Buds

- Barrel-shaped, found in oral epithelium, on tongue, soft palate, epiglottis, larynx, pharynx
- Neuroepithelial structures – epithelial cells closely associated with clib-shaped sensory nerve endings
    - Nerves arise from chorda tympani (anterior tongue), glossopharyngeal (posterior tongue), vagus (epiglottis and larynx) and lie among taste cells
- Each bud has 10-14 cells, majority are taste with elongated microvilli projecting into taste pore
    - Type 1 (60%) – dark cells
    - Type 2 (30%) – light cells
    - Type 3 (7%)
    - Type 4 (3%) – basal cells

- Tastes:
    - Sweet – anterior
    - Salt – lateral anterior
    - Sour – lateral
    - Bitter – circumvallate papilla
    - Umani (meat taste)

Epithelial Maturation

- Nonkeratinized tissue – has no granular layer
- Basal lamina – membrane separating epithelium and lamina propria
    - Basal cells attach here via hemidesmosomes
    - Epithelial cell-cell contact via desmosomes, anchored intracellularly by tonofibrils
- Nonkeratinocytes in Oral Epithelium
    - 10% of epithelial population
    - 3 major categories, all clear cells with halo around nuclei
        - Langerhan's cells (suprabasal) – found on stratum spinosum, antigen trapping and presentation. Dendritic cells, no desmosomes or tonofilaments
        - Merkel cells (basal cell layer) – found in gingiva, touch receptors. Nondendritic cells, sparse desmosomes and tonofilaments
        - Melanocytes (basal cell layer) – found in gingiva, melanin producing cells. Dendritic cells, have melanin granules (melanosome)
        - Lymphocytes and leukocytes – inflammatory cells that are not clear cells.
- Lamina Propria – contains various cells, vessels, nerves, and fibers (collagen and elastic) embedded in amorphous ground substance
    - Superficial papillary layer – associated with rete ridges
        - Thin, loose collagen fibers with many capillary loops
    - Deep reticular layer – between papillary layer and deeper structures
        - Reticular – netlike arrangement of collagen fibers
        - Thick collagen bundles parallel to surface
    - Cells present in Lamina Propria
        - Fibroblasts (stellate/elongated with lots of rER) – secretion of fibers and ground substance, located throughout lamina propria
        - Histiocyte (spindle shaped/stellate, many lysosomes) – macrophage precursor, located throughout lamina propria
        - Macrophage (round, many lysosomes and vesicles) – phagocytosis, antigen presentation, located areas of chronic inflammation
        - Mast cell (round/oval, basophilic granules) – secretion of inflammatory mediators (histamine, heparin, serotonin), located throughout lamina propria (often subepithelial)
        - Neutrophil (round, lobed nucleus, many lysosomes) – phagocytosis and cell killing, located areas of acute inflammation (may be in epithelium)
        - Lymphocyte (round, scant cytoplasm) – humoral immune response, located areas of acute and chronic inflammation
        - Plasma cell (cartwheel nucleus, lots of rER) – immunoglobulin synthesis, located areas of chronic inflammation (often perivascular)
        - Endothelial cell (lots of pinocytotic vesicles, associated with basal lamina) – lining of blood and lymph channels, located lining vascular channels throughout lamina propria

Lecture 15 – Periodontium

- Composed of cementum, PDL, alveolar bone, and gingiva facing the tooth
- Forms a specialized joint called Gomphosis

Cementum

- Covers/protects root dentin
  - Thickest in apex/interradicular area – 50-200µm (can exceed 600µm)
  - Thinnest in cervical area – 10-15µm
- Provides attachment for PDL
- Compensates for tooth resorption

Cementum vs Bone

- Similar to Bone
  - Organic fibrous network, ground substance, crystal type, and development
  - Lacunae with cementocytes
  - Canaliculi
  - Cellular component
  - Incremental lines (resting lines) from continuous but phasic cementum deposition
- Differences from Bone
  - Not vascularized (resistant to resorption, minor ability to remodel)
  - No neural component
  - Less mineralized (45-50% vs 70%), more permeable than other dental tissues
  - Two unique cementum molecules – cementum attachment protein and IFG

Development (root dentin → granular layer of Tomes → intermediate cementum → acellular cementum)

- Hertwig's Epithelial Sheath inductive signaling to ectomesenchymal cells to differentiate into osteoblasts and secrete dentin → interrupts HERS
  - Ectomesenchymal cells from inner portion of dental follicle come in contact with dentin by differentiating into cementoblasts
- Three Theories of cementoblast activation
  - Infiltrating dental follicle receives reciprocal signal from dentin or surrounding HERS and differentiate into cementoblasts (epithelial cell transformation)
  - HERS cells directly differentiate into cementoblasts
  - Epithelial cell rests of Malassez
- Cementogenesis associated proteins
  - Growth factors – TGF, PDGF, FGF
  - Adhesion molecules – bone sialoprotein, osteopontin
  - Epithelial/enamel like factors
  - Collagens
  - Gla proteins (matrix, bone)
  - Transcription factors – Cbfa1, RunX2, osterix
  - Alkaline phosphatase
- Intermediate Cementum (Hyaline layer of Hopewell-Smith)
  - First layer of cementum, formed by inner cells of HERS before HERS disintegrates
  - 10µm thick, mineralizes more than adjacent dentin or secondary cementum, seals dentinal tubules
  - Between granular dentin layer of Tomes and secondary cementum

Cementum Classification

- Acellular (primary) cementum – covers root adjacent to dentin
    - Thin cervical area requires no cells for viability as fluids bathe surface
    - Border with dentin not clearly demarcated, precementum layer absent
    - Slow development/deposition, incremental lines close together
- Cellular (secondary) cementum – apical and interradicular areas and overlaying acellular cementum
    - More cellular as thickness increases to maintain viability
    - Border with dentin clearly demarcated, precementum layer present
    - Fast development, incremental lines far apart, lacunae with cementocytes with processes in canaliculi
- Extrinsic fibers (PDL derived) – same orientation as PDL principle fibers (perpendicular/oblique to root surface)
- Intrinsic fibers (cementoblast derived) – parallel to root surface, perpendicular to extrinsic fibers
- Mixed fiber cementum – area with both extrinsic and intrinsic fibers

- Acellular afibrillar cementum
    - Enamel surface only, close to CE junction
    - No collagen, no role in attachment
    - Unsure whether it is a developmental anomaly or a true product of epithelial cells
- Acellular extrinsic cementum (primary cementum)
    - Covers 2/3 of the root, mainly cervical half, increases in thickness towards apical end (50µm → 200µm)
    - Collagen fibers derived from sharpey's fibers
    - Ground substance derived from cementoblasts
    - Principle tissue of attachment, function for anchoring tooth
    - Well mineralized fibers
- Cellular intrinsic cementum (secondary cementum)
    - Forms after tooth is in occlusion
    - Middle to apical third and interradicular area
    - Cells have same phenotype as osteoblasts
    - Majority of cells parallel to root surface
    - Major function in adaptation and repair, minor role in attachment
- Secondary mixed fiber cementum
    - Both intrinsic (1-2µm, uniformly mineralized) and extrinsic (5-7µm, variably mineralized) fibers
    - Bulk of secondary cementum
    - Has cementocytes, laminated structure, cementoid on surface
    - Apical and interradicular areas
    - Major function in adaptation

- OMG rule for CE Junction – 60% overlaps, 30% meets, 10% has a gap

Cementum Aging

- Ligament bundles attaching to cementum calcify – surface changes from smooth to rough over time
- Continuous deposition of cementum in apical area – maintains tooth length, but obstructs foramen
- Cementum resorption – active for a period, then stops for cementum deposition (creates reversal lines)
- Resorption of dentin over time covered by cemental repair
- Cementicles – calcified nodules in PDL, single or multiple near cemental surface, common with aging/at trauma sites, free in the ligament but attached/embedded in cementum
    - Origin – Nidus of epithelial cells composed of calcium phosphate and collagen to 45-50% mineralization

Cemental Repair

- Protective function of cementoblasts after resorption of dentin or cementum
- Resorption of dentin and cementum due to trauma
- Loss of cementum accompanied by loss of attachment
    - Following reparative cementum deposition, attachment is regained

Alveolar Process

- 2nd month of fetal development, mandible and maxillar form a groove open towards surface of oral cavity
    - As tooth germ develops, bony septa form gradually. Alveolar process starts developing strictly during tooth eruption
- Alveolar process composed of outer cortical plates, central spongiosa, and bone lining alveolus (bundle bone) where Sharpey's fibers attach
- Tooth root → PDL → bundle bone → alveolar bone with incremental lines → supporting bone → bone marrow

Alveolar Bone Proper (Bundle Bone)

- Also called bundle bone because often perforated by collagen fiber bundles
    - Contains either perforating fibers from PDL (Sharpey's fibers) or just compact/dense bone
- Perpendicular/oblique to surface of alveolar bone and along root surface
- Perforated by foramina that transmit nerves and vessels (cribriform plate)
- Radiographically is the lamina dura, radiodense because of high mineralization of fiber bundles
    - Living of alveolus fairly smooth, but gets rough with age
- Similar in structure to compact bone elsewhere (has both Haversian and Volkman's canals for nutrient channels
- Extends on both lingual and buccal sides
- Alveolar crest 1.5-2.0mm below level of CEJ
    - Line connecting CEJ's of adjacent teeth should be parallel to alveolar crest
- Resorption and Regeneration – resorbed on side with pressure, regenerated on side with tension
    - Decreased bone (osteopenia) of alveolar process noted with inactivity of teeth due to loss of antagonists

Periodontal Ligament

- Forms from dental follicle shortly after root development begins
- Soft specialized CT between cementum and bundle bone
- 0.15-0.38µm thick, thinnest in middle portion of root
- High turnover rate, width decreases with age
- Nerve supply from inferior and superior alveolar nerves, fibers enter pockets from apical regions and lateral socket walls. Apical region contains more nerve endings (except in case of upper incisors)
- Fed by perforating arteries (from cribriform plate in bundle bone). Small capillaries derive from superior and inferior alveolar arteries, rich supply for high cell turnover
    - Posterior supply more prominent than anterior, mandibular supply more prominent than maxillary
- Functions of periodontium
    - Tooth support/shock absorber to withstand masticatory forces
    - Sensory receptors needed for proper jaw positioning
    - Blood vessels provide essential nutrients to PDL

- Intercellular substances
    - Interstitial space – present between each bundle of ligament fibers, contains nerves and vessels, designed to withstand masticatory forces.
    - Ground substance – amorphous background material, binds tissue and fluids, similar to CT ground substance
        - Major constituent of PDL
        - Major GAG = dermatan sulfate, 70% water (critical to withstand forces)
        - Increased function → ↑ PDL size, ↑ fiber thickness, bone trabeculae ↑ in # and thickness
            - Opposite with reduced function, due to increased cementum deposition
- Cells – osteoblasts, osteoclasts, fibroblasts (most abundant), epithelial cells (cells rests of Malassez), macrophages, undifferentiated cells (perivascular region), cementoblasts, cementoclasts (pathological)
- Fibers
    - Principle Fibers – Collagen I, III, XII
        - Bundles of PDL, continually remodeled, smaller average diameter than elsewhere in body
            - Shorter halflife = less time for fibrillar assembly
        - Located between tooth and bone, two groups:
            - Dentoalveolar (Sharpey's fibers at each end, embedded in bone and cementum)
                - Alveolar crest – below CEJ, oriented down and out
                - Horizontal – apical to ACG, perpendicular to rooth surface
                - Oblique – most numerous, oblique orientation, attached coronally to bone
                - Apical group – around apex (base of socket)
                - Interradicular – multirooted teeth, from cementum and bone forming crest of interradicular septum
            - Gingival ligament fibers
                - Dentogingival group – most numerous, cervical cementum → F/A gingiva
                - Alveologingival – alveolar crest bone → F/A gingiva
                - Circular – around neck of teeth → F gingiva
                - Dentoperiosteal – apically from cementum over outer cortical plate → alveolar process, vestibule, floor of mouth
                - Transseptal – cementum → cementum of adjacent teeth, pass over alveolar crest
        - Oxytalan fibers – elastic fiber variants, perpendicular to teeth, adjacent to capillaries
            - Bundles of microfibrils, run oblique from cementum to vessels, neural element association
            - Most numerous in cervical area, regulate vascular flow in relation to tooth function
        - Eluanin – elastic fiber variant

16 – Tooth Eruption

- Continuous process

Pre Eruptive

- All movements of primary and permanent tooth germs from early initiation and formation to crown completion (ends with initial root formation)
  - 2 types – total bodily movement and tilted/anchored at one point
- Alleviate problems of jaw growth (second molar moves distal, anterior teeth move proximal)
- Response to positional changes in neighboring crowns and changes in maxilla and mandible
- Permanent teeth develop lingual to primary teeth
- Permanent premolars move from occlusal level to position between primary tooth roots
- All movements in pre-eruptive phase occur within crypts of developing crowns

Eruptive

- Initiation of root formation to tooth in functional position in occlusion
- Has intraosseous (1-10µm/day) and extraosseous (75µm/day) eruption phases

- Root formation
  - Required for root formation
  - Proliferation of epithelial root sheath ➔ Initiation of root dentin/pulp
  - Increase fibrous tissue of follicle
- Movement
  - Occurs incisally/occlusally so that roots can form normally
  - Reduced enamel epithelium fuses and contacts oral epithelium
- Penetration
  - Tooth's crown tip passing through layers into oral cavity
- Occlusal contact
  - Intraoral incisal/occlusal movement of erupting teeth continue until occlusal contact

Histological Changes

- Degeneration of CT immediately overlaying erupting teeth
- Eruption pathway – altered tissue area overlying teeth
- Macrophages destroy cells and fibers via hydrolytic enzymes
- Gubernacular cord – CT overlying successional tooth connecting it with lamina propria of oral mucosa via fibrous CT strand that contains remnants of dental lamina
- Gubernacular Canal – holes noted in skull representing openings of gubernacular cords, widen as permanent teeth erupt to allow for eruption
- Surrounding fibers change from parallel to tooth surface to bundles attached to tooth surface extending towards periodontium bone
  - PDL has contractile properties – changes drastically during eruption
  - Collagen fiber formation/turnover is rapid ➔ fibers attach, detach, reattach rapidly ➔ fibers organize and increase in number and density as tooth erupts
- Eruption creates space for root formation
  - Fibroblasts around root apex form collagen, attach to newly formed cementum
  - Bone trabeculae fill in space left behind during eruption in ladder pattern ➔ denser as tooth erupts
  - PDL fibers attach to apical cementum, extend into adjacent alveolar bone as tooth reaches occlusion

Tooth movement

1. Root formation – accommodated during eruption, may not be cause of tooth eruption
    a. Tissue beneath growing root resists apical movement – occlusal movement of crown as root lengthens
2. Bone remodeling – eruptive pathway forms in presence of dental follicle (gubernacular canal)
    a. Bone formation also occurs apical to developing tooth
    b. Dental follicle – reduced dental epithelium initiates cascade of intercellular signals ➔ osteoclast recruitment ➔ move remodeling
        i. Eruption delayed in those with osteoclast differentiation defects
3. PDL – formation/renewal of PDL via traction power of fibroblasts
    a. Presense of PDL doesn't always correlate to tooth eruption
    b. Other factors – vascular pressures within PDL

Post Eruptive

- After teeth are functioning, to maintain occlusion while jaws continue growing and compensate for occlusal and proximal wear
    - Clinical crown – exposed crown to area of gingival attachment
    - Anatomic crown – entire crown from cusp tip to CEJ
- Movement to accommodate growing jaws (14-18 years old) – formation of new bone at alveolar crest and base of socket to keep pace with increasing jaw height
- Movements to compensate for continued occlusal wear – compensation primarily occurs by continuous deposition of cementum at tooth apex only after tooth moves (similar to eruptive tooth movement)
- Mesial drift – movements to compensate for interproximal wear
    - Contraction of transseptal fibers – maintain tooth contact after wear
    - Adaptability of bone tissue – PDL fiber pressure causes bone resorption while PDL fiber tension causes bone formation
    - Anterior compartment of occlusal force – anteriorly directed force generated when teeth clench via mesial inclination of teeth – elimination of opposing tooth decreases mesial drift
    - Soft tissue pressure – buccal mucosa and tongue
- Active eruption – compensates for incisal/occusal wear
- Passive eruption – gradual recession of gingiva and underlying alveolar bone

Tooth Shedding

1. Osteoclast remodeling – 4-20 nuclei, derived from monocyte-macrophage lineage
    a. Resorb hard tissue by separating mineral from collagen matrix via hydrolytic enzymes
    b. Occurs at ruffled border ➔ increased surface area of osteoclast in contact with bone
        i. Extracellular phase
        ii. Intracellular phase
2. Odontoclast (cementoclast, dentinoclast)
3. Soft tissue resorption

- Shed element following shedding of primary incisor
    - Complete resorption of roots
    - Resorption lacunae present
    - Coronal pulp left intact

Six/four rule for primary tooth emergence

- 6 months – 4 teeth – all crowns have started calcification
- 12 months – 8 teeth – all crowns completed
- 18 months – 12 teeth
- 24 months – 16 teeth
- 30 months – 20 teeth – all primary teeth erupted
- 4 years – all primary teeth roots completed

Rule of 4s for permanent teeth

- Birth – 4 1st molars calcification
- 4 years – all crowns initiated calcification
- 8 years – all crowns completed
- 12 years – all crowns emerged
- 16 years – all roots completed

Rule of 6s for dental development

- 6 weeks utero – beginning of dental development
- 6 months old – emergence of first primary teeth
- 6 years old – emergence of first permanent teeth

Primary tooth eruption difficulties

- Natal/neonatal teeth (must be extracted)
- Ankylosed teeth
- Submerged teeth
- Congenitally missing teeth
- Cleidocranial dysplasia – many supernumary teeth, none of which erupt
- Osteopetrosis – osteoclast defect, teeth form but bone does not resorb, so no tooth eruption

17 – Salivary Glands

- Major glands
  - Parotid (serous) – largest, 25% of total saliva, exit at Stenson's duct
    - Rich in amylase, proline rich proteins
  - Sublingual (mucous) – intermediate, 60% of total saliva, exit at Wharton's duct
  - Submandibular (mixed) – small, 5% of total saliva, exit at Bartholin's duct, ducts of Rivinus
- Minor glands
  - Labial/lips (mixed)
  - Buccal/cheeks (mixed)
  - Soft palate (mucous)
  - Lingual
    - Anterior (mixed) – glands of Blandin-Nuhn
    - Middle (serous) – von Ebner glands, below sulci of circumvallate and foliate papillae
    - Posterior (mucous) – Weber glands

Function

- Protection
  - Lubricant (glycoprotein)
  - Barrier against noxious stimuli, microbial toxins, minor traumas
  - Washing non-adherent and acellular debris
  - Formation of salivary pellicle (calcium-binding proteins, tooth protection, plaque, etc)
- Buffering (phosphate ions and bicarbonate)
  - Bacteria require specific pH conditions
  - Neutralization of acids
- Digestion
  - Neutralizes esophageal contents
  - Dilutes gastric chime
  - Forms food bolus
  - Breaks starch
- Antimicrobial
  - Lysozyme hydrolyses cell walls of some bacteria
  - Lactoferrin binds free iron, deprives bacterial of this essential ion
  - IgA agglutinates microorganisms
- Maintenance of tooth integrity
  - Calcium and phosphate ions – ionic exchange with tooth surface
- Tissue repair
  - Bleeding time of oral tissues shorter than others
  - Resulting clot less solid than normal
  - Remineralization
- Taste
  - Solubilizing food substance that can be sensed by receptors
  - Maintenance of tooth buds

Development

- Parotid gland – ectoderm, 4-6 weeks in utero
- Sublingual/submandibular glands – endoderm, foregut
    - Submandibular gland 6 weeks
    - Sublingual and minor glands 8-12 weeks
        - Differentiation of ectomesenchyme
        - Development of fibrous capsule
        - Formation of septa, divide gland into lobes and lobules
- Individual glands arise as proliferation of oral epithelium (parotid), forming focal thickening that grows into underlying ectomesenchyme
    - Continued growth gives a small bud connected to surface via trailing cord of epithelial cells; mesenchymal cells condense around bud
    - Clefts develop in bod, forming 2+ new buds – continuation of process called branching morphogenesis, produces successive generations of buds and hierarchic ramification of gland

Salivary Acinus – functional unit of salivary gland

- Acinus – cluster of pyramidal cells (serious, mucous, or both) that secrete into terminal collecting duct
    - Collecting duct called intercalated ducts
    - All glands are arranged in lobules or lobes composed of many acini
- Serous cells – produce proteins and glycoproteins that are enzymatic, antimicrobial, or calcium binding
    - Usually undergo glycosylation (addition of sugar residue) – N-linked oligosaccharide side chains
    - Have rER – ribosomal sites → cisternae
    - Prominent golgi → carbohydrate moieties added, secretory granules for exocytosis
    - Zygomen granules – precursors to amylase
    - Secretory process continuous by cyclic
    - Complex foldings of cytoplasmic membrane
    - Junctional complex:
        - Tight junctions – fusion of outer cell layer
        - Intermediate junctions – intercellular communication
        - Desmosomes – firm adhesion
- Mucous cells – production, storage, secretion of proteinaceous material
    - More carbohydrates (mucins) → more prominent golgi
        - Mucin mixed with oral fluids ➔ mucous, thick and viscous saliva
        - Mucin appears light/foamy
    - Less prominent rER, mitochondria
    - Less interdigitations

Formation and Secretion

- Primary saliva – isotonic, organic components, water
    - Serous and mucous cells, intercalated duct
- Modified saliva – hypotonic
    - Striated and terminal ducts
    - Reabsorption and secretion of electrolytes

- Macromolecular component
    - Synthesis of proteins (rER and golgi)
        - Ribosomes → rER → posttranslational modification (N-/O- linked oligosaccharides) → golgi apparatus → secretory granules
    - Exocytosis continues until appropriate secretory stimulus is received
        - Sympathetic neurotransmitter norepinephrine effective stimulus for exocytosis
            - Binds to β-adrenergic receptors on cell surface
        - Granule membrane is endocytosed and recycled/degraded
- Secretion via parasympathetic innervation
    - Binding of ACH to muscarinic receptors activates phospholipase → IP_3 → Ca^{++} release → opening of K^+ and Cl^- channels
        - Increased lumen Cl^- and Na^+ creates osmotic gradient ➔ water movement into lumen via aquaporins and HCO_3^- into lumen via apical Cl^- channels
    - Norepinephrine via α-adrenergic receptors and substance P can also set off this cascade

Myoepithelial cells

- From oral epithelium
- Remain outside secretory end pieces and intercalated ducts
    - Supports secretory cells
    - Contract/widen diameter or intercalated ducts
    - Provide signals to acinar cells to maintain cell polarity and structural organization
- Contract/squeeze acinus cells through multiple long extended processes → secretion
    - 1-3 myoepithelial cells per salivary end piece or intercalated duct
        - Those along intercalated ducts are more spindle shaped with fewer processes
        - Each cell has 4-8 processes
        - Desmosomes between myoepithelial cells and secretory cells (adherence)
        - Myofilaments aggregate to form dark bodies along course of process
- Ultrastructurally very similar to smooth muscle

Salivary Duct System

- Secretory potion lies within acinar cells
    - Substances enter/leave cell via ion exchange with adjacent vessels
- Excretory portion lies in CT between septa and lobules
    - Purely saliva collecting tubes
- Smallest diameter in direct contact with salivary acini
- Become larger and merge into collecting ducts
- Acinar cells drain into intercalated ducts (low cuboidal cells) → open into striated ducts (more columnar)
    - Both intercalated and striated ducts are intralobular (present inside lobules)
    - Remaining excretory ducts are extralobular (outside lobules)
- Intercalated ducts – prominent in serous secretion (parotid gland)
    - Small diameter, lined with small cuboidal cells
    - Nucleus centrally located, well developed rER and golgi, few microvilli
    - Myoepithelial cells present

- Striated ducts – largest portion of duct system
    - Columnar cells
    - Nucleus centrally located, eosinophilic cytoplasm, some rER and golgi, short microvilli
    - Prominent striations – indentations of cytoplasmic membrane with lots of mitochondria between folds
    - Modify secretion – low Na^+ and Cl^-, high K^+ (hypotonic)
    - Basal cells
- Terminal excretory ducts – alter electrolyte concentration, add mucoid substance
    - Have same histology as striated ducts near striated ducts
    - Lining becomes stratified as duct reaches oral mucosa
    - Goblet cells, basal cells, clear cells
- Ductal modification – reabsorption and secretion of electrolytes to make solution hypotonic
    - ANS controlled
    - Happens in striated and terminal ducts
    - Affects salivary flow rate
        - $\uparrow[Na^+]$ and $[Cl^-]$, $\downarrow[K^+]$ = high flow rate
        - $\downarrow[Na^+]$ and $[Cl^-]$, $\uparrow[K^+]$ = low flow rate
- CT cells – fibroblasts, inflammatory cells, mast cells, adipose cells, ECM (glycoproteins and proteoglycans), collagen fibers, oxytalan fibers, blood supply and vessels

- Nerve Supply – no direct inhibitory innervation
    - Parasympathetic (more prevalent) and sympathetic impulses
        - Parasympathetic – may occur in isolation, fluid release, exocytosis, vasodilation
        - Both – contraction of myoepithelial cells
    - Two main types of innervation – epilemmal and hypolemmal
    - β-adrenergic receptors induce protein secretion
    - L-adrenergic and cholinergic receptors induce water and electrolyte secretion
- Hormones – modify salivary content, CANNOT initiate salivary flow
- Age increases presence of oncocytes (eosinophilic cells with mitochondria)

Clinical Considerations

- Obstruction
- Drugs
- Systemic disorders
- Infections
- Therapeutic radiation
- Plaque and calculus