**INTRODUCTION**

Multilocular radiolucencies are produced by multiple, often, frequently coalescing, and overlapping pathologic compartments in bone. They may occur in the maxilla but are found more commonly in the mandible.

The true multilocular lesion contains two or more pathologic chambers partially separated by septa of bone, which are usually discernible on radiographic examination. On occasion, the septa may be so thin and their images so indistinct as to cause the multilocular lesion to appear unilocular on radiographic examination.

**COMMONLY SEEN APPEARANCE OF MULTILUCULAR RADIOLUCENCY**

- Soap Bubble
- Honeycomb
- Tennis Racket

**CLASSIFICATION BASED ON SITE**

- Anterior to first and second molar
- Central giant cell granuloma
- Aneurysmal bone cyst
- Simple bone cyst
- Brown tumour
- Posteriorly to involving ramus
- Ameloblastoma
- Odontogenic myxoma
- Cherubism

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**CONTENT**

- Classification of multilocular radiolucencies of jaw
- Some normal anatomic radiolucencies
- Ameloblastoma
- Central giant cell tumour
- Odontogenic myxoma
- Cherubism
- Keratocystic odontogenic tumour
- Aneurysmal bone cyst
- Other rare entities
CLASSIFICATION BASED ON ORIGIN

Cysts
- Keratocystic odontogenic tumour
- Glandular odontogenic Cyst
- Botryoid Odontogenic Cyst

Benign Tumours
1. Odontogenic epithelial tumours without ectomesenchyme
   - Ameloblastoma
2. Ectomesenchymal tumours
   - odontogenic Myxoma
   - central odontogenic Fibroma
3. Ectomesenchymal with or without hard tissue
   - ameloblastic fibroma
4. Mesodermal tumour
   - Central hemangioma
   - A-v malformations
   - Desmoelastic fibroma of bone
   - intra-osseous angiophlebitis

GIANT CELL LESIONS

Giant Cell Granuloma
Aneurysmal Bone Cyst
Cherubism

SYNDROMES

Basal cell nevus syndrome

MALIGNANT DISEASE

Central mucoepidermoid carcinoma
Malignant Ameloblastoma
Ameloblastic carcinoma

RARETIES

Pseudo tumour of hemophillia
Mesangiopericytoma
Neurilemmoma
Giant cell lesion due to hyperparathyroidism
SOME ANATOMIC RADIOLUCENCIES OF INTEREST

Mandibular canal
Largest of nutrient canal appears as thin radioluent channel bounded by definite/thin radiopaque line.

Mental fossa
Due to relative thinness of bone in this area, it may be seen as a radiolucency over incisor roots which may be mistaken for an periapical pathology.

MAXILLARY SINUS
Shows multilocular radiolucency pattern with well defined cortical borders in adults. It usually extend from the canine to the maxillary tuberosity region. In older individual, it can extend into the alveolar ridge.

Submandibular gland fossa
Radioluent area with sparse trabeculae with ovoid round or rectangular shape. Separated superiorly by mylohyoid ridge and inferiorly by inferior border of mandible.

Airway shadow
Bilateral relatively radiolucent area seen on panoramic radiograph results from lack of soft tissue between posterolateral surface of tongue and region of soft palate and posterior pharynx.

AMEOBLASTOMA
Represents 11-13% of all odontogenic tumour. The lesion exhibits unilocular and multilocular pattern. Multi locular image may exhibit soap bubble or honeycomb appearance. It is a locally invasive tumour causing erosion, resorption and mobility of teeth and can also cause pain and swelling of the surrounding structure.

At advanced stage the lesion can cause expansion of cortical plate and erosion of bone and soft tissue.

Lesion comprises of solid cystic area or both.
The majority (83.3% to 88%) occur in the mandible, where 61% of total tumors involve the third molar region and ascending ramus. Incidence peaks between 20 and 50 years, with an average age of 40 years. Radiographically, these multilocular lesions may appear in a soap-bubble or honeycomb pattern.

The maxilla lacks the thick compact cortical plate and the porous nature of bone tends to osseous spread of ameloblastomas. Maxillary tumors are also close to the nasal cavity with its sinuses and perinasal structures at the base of the skull. These factors contribute to wide invasion and makes complete resection of the tumor more difficult.

Recently, it has been shown that the desmoplastic ameloblastoma has a greater tendency to occur in the anterior regions of the jaws and characteristically shows a mixed radiolucent-radiopaque pattern. One study reports that this variant had a predilection for the maxilla. Extraosseous ameloblastomas are rare lesions that occur mostly on the gingiva. They are found in older individuals and follow a nonaggressive course.

**RADIOGRAPHIC FEATURES**

Periphery: Well defined and frequently delineated by cortical border.

Internal Structure: Totally radiolucent with bony septa creating internal compartment. Since the septa is closely associated with cystic components they are often remodelled into curved shape providing honey comb or soap bubble appearance. The localizations are generally larger in posterior mandible and are smaller in anterior mandible.

- **Unicystic type:** This appears as a unicocelular radiolucency resembling a cyst. However, unlike cyst, it causes a break or discontinuity in the peripheral cortex and may even show trabeculae within the lumen.

- **Spider-web pattern:** This is the most common appearance, where the lesion is seen as a large radiolucency with scalloped borders. From the center of the lumen coarse strands of trabeculae radiate peripherally, giving rise to a gross caricature of a spider.

- **Soap-bubble pattern** This lesion is seen as a multilocular radiolucency with large compartments of varying sizes, giving rise to the soap-bubble appearance, or a multi-chambered or multi-cystic 'bunch of grapes' appearance.

- **Honeycomb or solid pattern** This is also called a beehive pattern. These are tumors that have not undergone cystic degeneration. Hence, multiple small radiolucent areas are seen surrounded by hexagonal or polygonal thick-walled bony cortices, giving rise to a honeycomb appearance.
ADDITIONAL IMAGING

Multidetector CT is useful to confirm diagnosis and to demonstrate the anatomic extend. It can also detect the soft tissue algorithm and detect perforation of outer cortex, therefor it has a better advantage over CBCT.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

- Dentigerous cyst: mostly dentigerous cyst will be having site of attachment at CEJ and ameloblastomas will be having internal septa
- Odontogenic keratocyst: Curved septa is present but the keratocyst tend to grow along the bone without marked expansion.
- Giant Cell Granuloma: Shows granular or wispy well defined septa
- Odontogenic myxoma: similar appearance but the septa will be straight and shows tennis racket appearance.

MANAGEMENT

- Radical Surgical excision
- Wide Block Resection with placement of bone graft
- Resection of tumour with 1-2cm margin of normal bone as detected by frozen section.
- Life Time Follow Up is required
GIANT CELL GRANULOMA

Central giant cell granuloma (CGCG) is a benign intraosseous lesion first described by Jaffe in 1953. It is the most common jaw lesion, with painless swelling being the common symptom. The incidence of CGCG is estimated to be 0.0001% with 60% of cases occurring before the age of 30. Gender predilection reports are variable, but the majority of these occur in females with a female:male ratio of 2:1. It has been noted that the development of CGCG occasionally coincides with the onset of pregnancy or menarche. CGCG is more prevalent in the anterior than the posterior jaws, often crossing the midline (50%), and the mandible is more commonly affected than the maxilla and confined to the tooth-bearing areas of the jaws.

IMAGING

In the maxilla, CGCG usually presents at the maxillary sinus. The radiographic appearance in the mandible is twice as common as in the maxilla. The epicenter is usually anterior to the first molar. The periphery may be a well-defined radiolucent margin with no cortication. In the maxilla, it is ill defined and resembles malignancy. Margin may be thin or poorly opacified.

INTERNAL STRUCTURE

Some may show a subtle granular pattern of calcification which may require bright light source behind the film for identification. Occasionally, granular bone is arranged into wispy ill-defined septa and specially they emanate at right angles at from the periphery. In some instances the septa are brighter defined and divide the internal aspects into compartments creating a multilocular appearance. Triangular crenations are often observed at the margin.

The radiological features of central giant cell granuloma are divided into three stages:

- Stage 1: lesion less than 2cm mostly unilocular or multilocular with no internal septa
- Stage 2: radiolucent or granular with thin ill-defined septa
- Stage 3: lesion displaces erupted and unerupted teeth; crenations are also seen at the margin.
PATHOLOGICAL DILEMMA??

According to Miles central giant cell granuloma may be resulting from trauma or vascular insult. If the bone supply is cut off no giant cell reaction occurs and it results in traumatic bone cyst. If the blood supply is maintained aneurysmal bone cyst or CGCG develops. CGCG is believed to be due to confluence of two or more adjacent resorption lacunae with triangular or V shaped crenations at the periphery.

PANORAMIC RADIOGRAPH SHOWING ILL DEFINED SEPTAE

Radiovisiographic Differential Diagnosis

- Odontogenic Myxoma: older age group and seen as sharp tennis racket appearance of granular internal structure is present.
- ABC: causes marked expansion of jaw and usually seen in posterior aspect.
- Ameloblastoma: course curved and well defined septe and usually seen in posterior mandible.
- Hyperparathyroidism: the radiological and histological differential diagnosis is similar to brown tumour.
- Central Hemangioma: more seen in ramus symphysis region.
- Management:
  - Enucleation, curetage or resection of jaw.
  - Hyperparathyroidism must be considered if the lesion is occurring after second decade of life.

CHERUBISM

- Autosomal dominant disease/ familial intra osseous swelling of the jaw.
- Penetrance is 100% pronounced in males usually seen in ages between 2 to 6 years.
- Location: bilateral mandibular ramus, maxillary sinus wall, orbital floor and tuberosity region.
- Prognosis: cherub like appearance by tilting the eye ball superiorly the lesion usually does not perforate the cortex; perforation of submandibular lymph node may occur. It regresses by puberty and bony architecture comes to normal at about 30 years of age.

IMAGING

- Periphery: well defined and in some instance is corticated.
- Internal structure: fine granular bone and wispy trabecula forming prominent multi locular pattern.
- Effect on surrounding structure: maxillary lesions can cause enlargement of maxillary sinus, teeth are sometimes displaced anteriorly on postero anterior view, teeth associated with the lesion will be seen hanging in air.

MANAGEMENT

- Enucleation, curetage or resection of jaw.
- Hyperparathyroidism must be considered if the lesion is occurring after second decade of life.
PANORAMIC RADIOGRAPH SHOWS EXPANSIVE MULTiloculated CYSTIC LESIONS DISTRIBUTED IN THE MAXILLARY AND MANDIBLE WITH LOSS AND MEDIAL DISPLACEMENT OF THE DESEDENT TEETH.

Case courtesy of Dr Hani Salam, Radiopaedia.org, rID: 14110

RADIGRAPHIC DIFFERENTIAL DIAGNOSIS

Central Giant cell granuloma: cherubism is usually bilateral with epicenter of the lesion situated in the posterior mandibular region.

Multiple odontogenic keratocyst: in basal cell nevus syndrome bilateral symmetry and anterior displacement of teeth is a characteristic feature of cherubism which can differentiate it from fibrous dysplasia.

MANAGEMENT

- Periodic radiographic evaluation
- Surgical recontouring
- Orthodontic correction of teeth

ODONTOGENIC MYXOMA

Develops only in the bones of facial region
- Aims from the odontogenic mesenchyme, not encapsulated and tend to infiltrate the surrounding bone but don't metastasize
- They have a loose gelatinous or myxoid-like consistency and extend into the trabecular spaces. Also the lack of encapsulation will lead to high chance of recurrence
- The lesion has slight female tendency and the swelling grows eventually larger if untreated.
Location: mostly affect mandible, occurs most commonly in premolar and molar area and very rarely in the ramus and condyle region. Myxomas in maxilla usually involve premolar and molar region and the zygomatic process.

Internal structure: Residual bone trapped in the tumour will show curved and straight course and fine septa which gives multilocular appearance with thin etched septa. The septa are usually straight and show tennis racket or step ladder pattern.

Effects on adjacent structure: The lesion usually scallops between the roots of adjacent teeth similar to simple bone cyst.

According to Barros and colleagues, the odontogenic myxoma consist of one of the two patterns:

Stage 1: Osteoporetic appearance with more prevalent medullary space separated by thin septa of bone giving the classic radiographic pattern with well-defined locules and trabeculae intersecting at right angles. The internal configuration of bony septa resembled lichen planus of jaw bone. These lesion resemble strings of tennis racket.

Stage 2: The second stage is characterised by breakdown or destructive phase characterised by loss of internal locules the septa appear beyond the peripheral margin giving hair on end or sunburst appearance.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

- Ameloblastoma
- Central giant cell granuloma
- Central hemangiona

The thin septa with less expected bone expansion will help in making a differential diagnosis.

Additional imaging:
- MRI helps in assessing the intraosseous extent.
KERATOCYSTIC ODONTOGENIC TUMOUR

One tenth of the cystic lesion of jaw, seen commonly between second and third decade of life, with slight male predilection.

The cyst is sometimes seen around unerupted teeth.

KOT usually have no symptom, although mild pain may occur with secondary infection

Aspiration may reveal thick yellow cheesy material/keratin

Location: posterior body of mandible and coronal region, the epicenter is located superior to the inferior alveolar canal

Periphery and Shape: Shows evidence of cortical border (A thick sclerotic margin is usually present), the border may be smooth, round or oval shape identical to other cyst and may have scalloped outline.

Internal Structure: Most commonly Radiolucent curved internal septa may be present giving the lesion a multilocular appearance.

Effect on surrounding structure: KOT grows along the internal aspect of jaws causing minimum expansion of the cortical plate. The relatively slight expansion probably contribute to their late detection. Perforation is commonly seen

KOT occasionally displace or resorb teeth and inferior alveolar canal may be displaced Inferiorly. In some cases lumen of KOT is usually variable and is termed as milky way lumen. Park and Kim coined the term luminal haze

TREATMENT

resection with generous amount of surrounding bone to prevent recurrence
AXIAL CT SECTION OF KOT MANDIBLE WITH MINIMUM BONE EXPANSION

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

Dentigerous cyst: can be differentiated only if the point of attachment is apical to cemento-enamel junction or if no expansion of cortical plates occur.
Ameloblastoma: has a greater propensity to expand.
Lateral Periodontal Cyst: usually seen in maxillo-

MANAGEMENT

Since there is high tendency to recur, CT imaging is advised to know exact extension.
Treatment includes surgical resection, enucleation, and marsupialization.

BOTRYOID ODONTOGENIC CYST

Botryoid or grape-like odontogenic cyst was first described by Weathers and Waldon in 1973. It is a multicystic variant of lateral periodontal cyst.
Most often, it presents as an asymptomatic multicystic radiolucency lateral to the root of a vital mandibular cuspid or premolar tooth and rarely in the anterior maxillary region.

IMAGING

Periphery: continues corticated well-defined borders / scalloped outline
Internal structure: multilocular and bilocular appearance
Effect on surrounding structure: the lesion appears to invade the lamina dura of adjacent teeth and also seen high on the alveolar crest.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

Lateral periodontal cyst: mostly unilocular in appearance
Keratocystic odontogenic tumour: mostly seen posteriorly and does not cause much expansion
Glandular odontogenic cyst
Ameloblastoma
TREATMENT

Enucleation and follow-up

Occlusal mandibular view showing multilocular pattern and expansion in botryoid odontogenic cyst

IMAGING

Location: more commonly on anterior mandible and globulomaxillary region of maxilla.
Periphery and shapes: smooth and scalloped
Internal structure: unilocular and multilocular
Effect on surrounding structure: outer cortical plate expansion and perforation is also seen

ODONTOGENIC SIALOCYST / GLANDULAR ODONTOGENIC CYST

Rare cyst developing from odontogenic epithelium with a spectrum of characteristics including salivary gland features such as mucus producing cells.
Slight female predilection and tendency to recur after surgery.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

Ameloblastoma
Botryoid odontogenic cyst

CASE COURTESY OF DR BRENDAH FRIESE, RADIOPOEDIA.ORG, R12660

AFTER 10 MONTH FOLLOW UP
ANEURYSMAL BONE CYST

In diagnostic imaging, these lesions behave aggressively benign tumors with proliferation of vascular spaces, fibroblast, osteoclast-like cells poorly calcified woven bone.

more than 90% is reported in individuals below 30 years of age, with slight female predilection. There will be fair bone expansion with pain and tenderness on palpation.

IMAGING FEATURES

Location: The mandible is involved more often than the maxilla in the ratio 3:2 and the molar ramus region is more involved.

periphery: It is usually well defined with circular or hydraulic shape.

Internal Structure: wispy ill-defined septa showing multi-locular appearance.

Effect on surrounding tissue: extreme expansion of outer cortical plate.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

Central Giant cell Granuloma: However, ABC causes more expansion and is usually seen in the posterior region.

Ameloblastoma: Usually occurs in an older age group.

Cherubism has bilateral presentation.

Diagnosis is usually confirmed by hemorrhagic aspirate and a CT scan is recommended.
MANAGEMENT

Surgical curettage and primary resection.
- Rescure rate is 19% to 50%.

CENTRAL HEMANGIOMA

Although hemangiomas are most commonly seen in soft tissue, it occurs less frequently in central bone lesions.
- Shafers et al. described capillary hemangiomas as the most common histologic type.
- 85% were evident in the first year of life and 73% were present at birth, whereas AVM is most commonly seen in teenagers.
- Female patients were affected more commonly than males.

CLINICAL FINDINGS

- Facial asymmetry, especially over the mandibular region.
- The overlying skin may be 2 degrees F more warmer.
- Palpable or paresthesia.
- Pulsatile or whistling noise, tinnitus, epistaxis, blurred vision, etc. are commonly seen.
- Oozing of blood from the gingival sulcus.
- Tooth may be loose or exhibit a pumping movement.
- Expansion of alveolar process may be observed.
- Blood aspiration where an AVM may cause syringe to fill without aspiration of plunger.

IMAGING

Location: mandible twice as common as in maxilla. Most common site is posterior body and ramus within the inferior alveolar canal.
- Periphery: well-defined and corticated formation of linear spicules of bone emanating from the surface in a sunray appearance when the hemangioma breaks through the outer cortex and displaces the periosteum.
- Internal structure: coarse dense and well-defined trabeculae may produce a honeycomb appearance.
- When inferior alveolar canal is involved, the whole canal increases in width and often normal path of canal is altered into serpiginous shape sometimes creating a multi-locular radiolucency.

EFFECT ON SURROUNDING TISSUE

- The roots of the teeth in the vicinity of lesion is resorbed or displaced.
- Calvarial hemangioma often have a sunburst appearance with septa in the radiograph perpendicular to margin, differentiating it from osteosarcoma.
- Internal calcifications are also seen in Sturge-Weber syndrome.
- There is convolutional calcification of masses of vessel on the surface of brain described as tram line calcification because of parallel calcified vessel walls.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

- Osteosarcoma
- Chondrosarcoma
- A-V malformations
- Ameloblastoma differentiated by involvement of inferior alveolar canal and clinical findings.
ORTHOPANTOMOGRAPH OF THE PATIENT SHOWING SUNBURST PATTERN OF THE TRABECULAE IN RELATION TO THE RIGHT SIDE OF THE MANDIBLE

POSTERIOR ANTERIOR VIEW SHOWING WELL DEFINED EXPANSILE LESION IN RELATION TO THE RIGHT SIDE OF THE MANDIBLE WITH RADIATING TRABECULAE WITH CHARACTERISTIC SUNBURST PATTERN

ARTERIOVENOUS MALFORMATIONS

A-V fistula is the direct communication between an artery and a vein. It is usually followed by trauma but in rare cases it may be seen as developmental anomaly. The head and neck region is the most common site. There is slight female predilection.

IMAGING

LOCATION: Ramus and retromolar area and involving the mandibular canine
Periphery: margins are usually well defined and corticated
Internal structure: enlarged lesion with multilocular appearance
Effect on surrounding structure and can erode adjacent bone and teeth

ADDITIONAL IMAGING

MDCT with contrast CT
Angiography by injecting a radiopaque contrast dye
**RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS**

- Hemangioma
- Ameloblastoma

Association of inferior alveolar canal is an important differentiating aid

**TREATMENT**

- Cryosurgery with injection of sclerosing agent
- Embolisation or occlusion of feeder artery
- Cyanoacrylate injection directly into the feeder vessel using a microballoon catheter
- Ligation of feeder vessel

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**DESMOPLASTIC FIBROMA**

Locally aggressive lytic benign tumour of bone, the cause of the tumour is unknown but trauma may play an important role in development

Mostly seen in second decade of life

Painless swelling and pain in extragnathic site, deviation of mandible

Malocclusion, trismus, hypoplasia of mandible are also noted

**IMAGING**

- **Location**: most commonly on mandible posterior to molar in the angle-ramus region
- **Periphery**: there is no well defined border
- **Internal structure**: a multilocular lesion is produced by pseudo trabeculae which results from uneven destruction in bone the trabeculae may be in a lace like pattern
- **Effect on surrounding structure**: expansion of cortical plate and perforation is also present.
  - In maxilla it is seen extending to sinus and also into the nasal cavity.

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**TREATMENT**

- Segmental Resection of bone
Multilocular Radiolucenties associated with malignancies

Central Mucoepidermoid Carcinoma

Epithelial tumour arising from bone likely originating from pleuripotent epithelial lining or from cyst
It mimics a benign tumour with most common complaint of painless swelling causing facial asymmetry, paraesthesia when inferior alveolar canal is involved.
More commonly seen in females

Imaging

Location: mandible more commonly involved than in maxilla in the premolar molar region and very rarely in the anterior mandible
Periphery and shape: unilocular or multilocular expansile mass border is often well corticated and often grooved, the peripheral cortication may be impressively thin which belies its malignant nature
Internal structure: multilocular with soap bubble or honey comb pattern. Regions of amorphous sclerotic bone formed by the remodelling of residual bone
Effect on surrounding structure: the lesion may cause expansion of cortical plate with teeth rarely involved and lamina dura often involved

Radiographic Differential Diagnosis

Recurrent Ameloblastoma
Odontogenic myxoma
Diagnosis usually confirmed by histologic features

Treatment

Enbloc resection with post operative radiation therapy may be required to control spread to lymph nodes
MALIGNANT AMELOBLASTOMA AND AMELOBLASTIC CARCINOMA

Malignant ameloblastoma is defined as ameloblastoma with typical benign histologic features that is deemed malignant because of biologic behaviour - metastasis.

Ameloblastic Carcinoma - there is typical histologic findings of neoplasm

Clinical features - other than the features of benign lesion it shows metastasis to cervical lymph node, viscera, spine, local extension may occur to adjacent bone, connective tissue or salivary gland.

IMAGING

Location - more commonly in mandible in the premolar molar area.

Periphery and shape - well defined shape occurs with crenations or scalloping. It may also breach the cortical boundary and invades the surrounding tissue.

Internal structure - unilocular or multilocular with thick or robust septa giving a soap bubble or honeycomb appearance.

Effect on surrounding structure - the mandibular canal may be displaced or eroded.

RADIOGRAPHIC DIFFERENTIAL DIAGNOSIS

Central mucoepidermoid carcinoma
Ameloblastoma
Odontogenic myxoma
Diagnosis is confirmed by histology.

MANAGEMENT

Enbloc resection and followup

Rare multilocular radiolucency of jaw
Ameloblastic fibromas are rare and comprise approximately 2% of odontogenic tumors. The tumors are considered a tumor of childhood and adolescence and occur almost exclusively in the first and second decades of life. A slight male predominance has been noted. The most common location for the tumor is the posterior mandible, followed by the posterior maxilla. Patients often present with painless swelling of the jaw and the lesion may affect the normal eruption of teeth in the area. An impacted tooth may be associated with the tumor in approximately three quarters of the cases. Some lesions are asymptomatic, with up to 20% of cases initially detected upon review of routine dental radiographs.

Radiographically, ameloblastic fibromas are unilocular lesions, occasionally multilocular when larger, with smooth well-demarcated borders. Cortical expansion may or may not be discernable on plain film. Because lesions are frequently associated with unerupted teeth, they may initially be interpreted as dentigerous cysts.

**Basal Cell Nevus Syndrome**

**Reference**

- White and Pharoah textbook of oral radiology first South Asian edition
- Wood & Goaz differential diagnosis of oral and maxillofacial region 5th edition
- Langlais and Langland Diagnostic Imaging of the Jaws
THANK YOU
NORMAL ANATOMIC LANDMARKS IN INTRA ORAL RADIOGRAHS

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INTRODUCTION :

The radiographic recognition of disease requires a sound knowledge of the radiographic appearance of normal structures. Intelligent diagnosis mandates an appreciation of the wide range of variation in the appearance of normal anatomic structures. Similarly, most patients demonstrate many of the normal radiographic landmarks, but it is a rare patient who shows them all. Accordingly, the absence of one or even several such landmarks in any individual should not necessarily be considered abnormal.

THE RADIOGRAPHIC APPEARANCE OF VARIOUS STRUCTURES WHICH CAN BE VISUALIZED IN IOPA CAN BE CLASSIFIED AS :

- TEETH
- SUPPORTING STRUCTURES
- MAXILLA
- MANDIBLE
- OTHER RESTORATIVE MATERIALS

RADIOPAQUE :

- TEETH
- SUPPORTING STRUCTURES
- MAXILLA
- MANDIBLE
- OTHER RESTORATIVE MATERIALS

- ENAMEL
- DENTIN
- CEMENTUM
- LAMINAR DURA
- ALVEOLAR CREST
- CANCELLOUS BONE
- NASAL SEPTUM
- ANS
- FLOOR OF NASAL CAVITY
- MAXILLARY SINUS
- INFERIOR NASAL CONCHAE
- NASOLABIAL FOLD
- INFERIOR BORDER OF MANDIBLE
CERVICAL BURNOUT:

Radiographs sometimes show diffuse radiolucent areas with ill-defined borders present on mesial & distal aspects of teeth in cervical region.

These regions appear between the edge of the enamel cap and the crest of the alveolar ridge. It should not be confused with root caries.

Artifact – less x-ray absorption in area.
PDL SPACE:
- Periodontal ligament space (PDL) space is primarily composed of collagen.
- So appears as radiolucent space between tooth root and lamina dura
- Thin in middle, wider in crest and root apex area (function related).

CANCELLOUS BONE:
- It lies between the cortical plates in both the jaws.
- It is composed of thin radiopaque plates/lines and rods surrounding many small radiolucent marrow spaces.
- Anterior-thin & dense trabeculae.
- Posteriorly—thicker & numerous spaces.

MAXILLA:
- INCISIVE FORAMEN:
  - NASOPALATINE/ANTERIOR PALATINE FORAMEN
  - Opening located in the midline of anterior portion of hard palate directly posterior to central incisors
  - On radiograph small ovoid or round radiolucent area located between roots of maxillary central incisors.

NASOPALTINE CANAL
- SUPERIOR FORAMINA OF INCISIVE CANAL
  - The superior foramina are the openings of two small canals.
  - These two small canals extend downward and medially from the floor of the nasal cavity, and join together to form the incisive canal and share a common exit, the incisive foramen.
  - Two small radiolucencies located superior to the apices of the maxillary central incisors, in the floor of the nasal cavity, and in the inferior border on both sides of the septum.

INCISIVE FORAMEN:
- NASOPALATINE/ANTERIOR PALATINE FORAMEN
  - Opening located in the midline of anterior portion of hard palate directly posterior to central incisors.
  - On radiograph small ovoid or round radiolucent area located between roots of maxillary central incisors.

MEDIAN PALATINE SUTURE:
- INTER MAXILLARY SUTURE
  - A thin radiolucent line between the maxillary central incisors. This is bounded on both sides by dense cortical bone that appear radiopaque.
  - The suture may terminate at the alveolar crest in a small rounded or V-shaped enlargement.
  - As this suture fuses with age, it may appear less distinct radiographically.
LATERAL FOSSA:
- INCISIVE FOSSA, CANINE FOSSA
- A radiolucent area between the canine and the lateral incisors

NASAL FOSSA:
- NASAL CAVITY
- A large radiolucent area above the maxillary incisors.

NASAL SEPTUM:
- A vertical radiopaque partition that divides the nasal cavity.
- The nasal septum may be superimposed over the median palatal suture.

FLOOR OF NASAL CAVITY:
- A dense radiopaque band above the maxillary incisors.

ANTERIOR NASAL SPINE:
- A V-shaped radiopaque area located at the intersection of the floor of the nasal cavity and nasal septum.

INFERIOR NASAL CONCHAE:
- A diffuse radiopaque mass or projection within the nasal cavity.
**NASO LACRIMAL CANAL:**
- A well-defined slightly ovoid radiolucency, just above the apex of the maxillary canine, when a steep vertical angulation is used.
- It is seen more routinely on the maxillary occlusal projections.

**NOSE:**
- Soft tissue of the nose is frequently seen in the projections of the maxillary central and lateral incisors, superimposed on the roots of these teeth.
- The image of the nose has a uniform, slightly opaque appearance, with a sharp border. Sometimes, the radiolucent nares may be identified.

**NASOLABIAL FOLD:**
- This is an oblique line demarcating a region that appears to be covered by slight radiopacity frequently seen in the premolar region.
- The line of contrast is sharp, and the area of increased radiopacity is posterior to the line. The image of the fold becomes more prominent with age.

**MAXILLARY SINUS:**
- A radiolucent area located above the apices of the maxillary molars. The borders of the maxillary sinus are composed of dense cortical bone and appear as a radiopaque line.
- Septa within the maxillary sinus: Radiopaque lines within the sinus.
- Nutrient canals within the maxillary sinus: A narrow, radiolucent band bounded by two thin radiopaque lines.

**INVERTED “Y”**
- This refers to the intersection of the maxillary sinus and the nasal cavity as seen on the radiograph.
- A radiopaque upside down “Y” formed by the intersection of the floor of the nasal fossa and the anterior border of the maxillary sinus, usually located above the maxillary canine.

**MAXILLARY TUBEROSITY:**
- A radiopaque bulge posterior to the third molar region.
PTERYGOID PLATES:
- A single radiopaque homogeneous shadow without any evidence of trabeculation.
- It may not be seen on all radiographs.

HAMULAR PROCESS:
- A radiopaque hook-like projection posterior to the maxillary tuberosity area.
- The length, shape, and density is variable.

ZYGOMA AND ZYGOMATIC PROCESS:
- A diffuse radiopaque band extending posteriorly from the zygomatic process of the maxilla.
- A "J" or "U" shaped radiopacity located superior to the maxillary first molar region.

MANDIBLE:

GENIAL TUBERCLES:
- Ring shaped radiopacities below the apices of the mandibular incisors.

LINGUAL FORAMEN:
- A small radiolucent dot inferior to the apexes of the mandibular incisors.
NUTRIENT CANALS:
- Vertical radiolucent lines
- These are more prominent in the anterior region and in the edentulous mandible.

MENTAL RIDGE:
- A thick radiopaque band that extends from the premolar to the incisor region.
- It may appear superimposed on the mandibular anterior teeth.

MENTAL FOSSA:
- A radiolucent area above the mental ridge.
- The appearance varies and is determined by the thickness of the bone in the anterior region.

MENTAL FORAMEN:
- A small ovoid or round radiolucent area located in the apical region of the premolars.
- It is frequently misdiagnosed as a periapical lesion because of its apical location.

SYMPHYSIS:
- A radiolucent line through the midline of the jaw

MYLOHYOID RIDGE:
- A dense radiopaque band that extends downwards and forward from the molar region.
- It usually appears more prominent in the molar region and may be superimposed over the roots of the mandibular teeth.
- It may appear continuous with the internal oblique ridge.
INTERNAL OBLIQUE RIDGE:
- A radiopaque band that extends downwards and forward from the ramus.
- Depending on the technique used, the internal and external oblique ridge may appear superimposed on one another.
- When the ridges appear separate, then the superior radiopaque band is the external oblique ridge and the inferior radiopaque band is the internal oblique ridge.

EXTERNAL OBLIQUE RIDGE:
- A radiopaque band extending downwards and forwards from the anterior border of the ramus of the mandible.
- It typically ends in the mandibular third molar region.

MANDIBULAR CANAL:
- A radiolucent band, outlined by two thin radiopaque lines that represent the cortical walls of the canal.
- It may appear below or superimposed on the mandibular molar teeth.

INFERIOR BORDER OF MANDIBLE:
- A dense radiopaque band of bone.

CORONOID PROCESS OF MANDIBLE:
- A triangular radiopacity superimposed over or inferior to the maxillary tuberosity region.
- It is seen on the maxillary molar periapical radiograph, and not a mandibular periapical radiograph.

SUBMANDIBULAR FOSSA:
- A radiolucent area in the molar region below the mylohyoid ridge.
- Few bony trabeculae are seen in this region.
RESTORATIVE MATERIALS:

QUESTIONS?

- WHAT IS INVERTED "Y" LINE?
- RESTORATIVE MATERIALS AND THEIR RADIOGRAPHIC APPEARANCE?
- WHAT IS PRIMARY LANDMARK IN MANDIBULAR PREMOLAR AREA?
- WHAT STRUCTURE REPRESENTS THE DEPRESSION IN BONE IN LABIAL ASPECT OF MAXILLA?
- RADIOGRAPHIC APPEARANCE OF NUTRIENT CANALS?
OROFACIAL PAIN

Definition

Classification of Orofacial pain

Types & nature of pain

Theories of Pain

Neurophysiology of Pain & Pain pathway.

Dental conditions that cause head & neck pain

Introduction.

Pain is derived from Greek – ‘Poin’ and Latin – ‘Poema’

The words “pain” and “suffering” have often been used synonymously, but the experience of suffering has been differentiated from pain.

Purpose of Pain

Though unpleasant, pain serves important adaptive purposes:

- Identifies and localizes noxious stimuli
- Protective – withdrawal reflex response - limits injury
- Experience of pain – avoids potentially harmful injuries
- Immobility due to pain – assists in healing

DEFINITION OF PAIN

An unpleasant, sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

(*International Association for the Study of Pain)
Classification of Pain Based on Pathophysiologic mechanisms:
- Physiologic
- Nociceptive / Inflammatory
- Neuropathic

Physiologic pain defines rapidly perceived nontraumatic discomfort of very short duration.

Nociceptive pain is defined as noxious perception resulting from cellular damage following surgical, traumatic, or disease-related injuries. Inflammation and inflammatory mediators play a major role.

Nociceptive Pain
- Somatic nociceptive pain is well localized and generally follows a dermatomal pattern. It is usually described as sharp, crushing, or tearing in character.
- Visceral nociceptive pain defines discomfort associated with peritoneal irritation as well as dilation of smooth muscle surrounding visceral or tubular passages.

Neuropathic pain is defined by the International Association for the Study of Pain as “Pain initiated or caused by a pathologic lesion or dysfunction” in peripheral nerves and CNS.

Disease states associated with classic neuropathic symptoms include infection (eg, herpes zoster), metabolic derangements (eg, diabetic neuropathy), toxicity (eg, chemotherapy).

Terms related to pain
- Nociceptor: A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.
- Hyperalgesia: Increased pain from a stimulus that normally provokes pain.
- Allodynia: Pain due to a stimulus that does not normally provoke pain.

Sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.

Hyperpathia: Increased or exaggerated pain intensity with minor stimulation.

Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.

Paresthesia: Unpleasant often shock-like or electrical sensation precipitated by touch or pressure.
Axis I (Physical conditions)

Somatic Pain

A- Superficial somatic pain
- Cutaneous pain, mucogingival pain.

B- Deep somatic pain
- Musculoskeletal pain
- Visceral pain
- Neuralgic pain
- Vascular pain

Neuropathic Pain

1) Continuous neuropathic pain
2) Episodic neuropathic pain

a) Centrally mediated pain
   - Atypical odontalgia
   - Postherpetic neuralgia
   - Causalgia

b) Peripherally mediated pain
   - Neuritic pain
   - Peripheral neuritis, deafferentation, BMS.

B) AXIS II Categories (Psychologic conditions)

(I) Mood disorders
   a) Depressive disorders
   b) Bipolar disorders
   c) Mood disorders resulting from a medical condition

(II) Anxiety disorders
   a) Generalized anxiety disorders
   b) Post-traumatic stress disorders
   c) Anxiety disorders resulting from a medical condition

(III) Somatoform disorders
   a) Undifferentiated somatoform disorders
   b) Conversion disorders
   c) Pain disorders

(IV) Other conditions
   a) Psychological factors affecting a medical condition
      - Personality traits
      - Maladaptive health behavior
      - Stress-related physiologic response
   b) Any other mental disorders

Types and Nature of Pain

- According to duration:
  i) Acute pain
  ii) Chronic pain

- According to intensity:
  i) Mild pain
  ii) Moderate pain
  iii) Severe pain

- According to origin:
  i) Somatic pain
     - Superficial somatic pain: Cutaneous & mucogingival
     - Deep somatic pain: Musculoskeletal & visceral

  ii) Neuropathic pain:
     - Paroxysmal
     - Continuous

- According to temporal relationship & duration:
  - Intermittent
  - Continuous
  - Recurrent
  - Remissive
  - Periodic
According to onset:
- Spontaneous
- Induced
- Triggered

According to pain localization:
- Localized
- Diffuse
- Radiating
- Lancinating
- Spreading
- Migrating

According to qualities of pain:
- Steady
- Paroxysmal
- Sharp
- Dull
- Pricking
- Stinging
- Burning
- Throbbing
- Aching

Theories of Pain perception

- The four most influential theories of pain perception include the
  - Specificity (or Labeled Line) Theory
  - Intensity Theory
  - Pattern Theory
  - Gate Control Theory

Specificity Theory of Pain.

- One of the earliest ideas, termed the Specificity theory, was proposed by Descartes.
- The theory suggested that specific pain fibers carry specific coding that discriminates between different forms of noxious and non-noxious sensations.
- The fundamental tenet of the Specificity Theory is that each modality has a specific receptor and associated sensory fiber (primary afferent) that is sensitive to one specific stimulus (Dubner et al. 1978)

Intensity Theory of Pain.

- The intensity theory, proposed by Sydenham, suggested that the intensity of the peripheral stimulus determines which sensation is perceived.
- The theory defines pain, not as a unique sensory experience but rather, as an emotion that occurs when a stimulus is stronger than usual.

Pattern Theory of Pain.

- J. P. Nafe postulated this “quantitative theory of feeling” in 1929.
- This theory ignored findings of specialized nerve endings and many of the observations supporting the specificity and intensive theories of pain.
- The theory stated that any somaesthetic sensation occurred by a specific and particular pattern of neural firing and that the spatial and temporal profile of firing of the peripheral nerves encoded the stimulus type and intensity.
Gate Control Theory of Pain.

› In 1965, Ronald Melzack and Charles Patrick Wall (Melzack and Wall 1965) proposed a theory that would revolutionize pain research

› Melzack and Wall accepted that there are Nociceptors (pain fibers) and touch fibers and proposed that these fibers synapse in two different regions within the dorsal horn of the spinal cord: cells in the Substantia Gelatinosa and the “transmission” cells.

Gate Control Theory of Pain.

› The model proposed that signals produced in primary afferents from stimulation of the skin were transmitted to three regions within the spinal cord:

1) the Substantia Gelatinosa,
2) the Dorsal column, and
3) a group of cells that they called ‘Transmission cells’.

Gate Control Theory of Pain.

› They proposed that the gate in the spinal cord is the substantia gelatinosa in the dorsal horn, which modulates the transmission of sensory information from the primary afferent neurons to transmission cells in the spinal cord.

› This gating mechanism is controlled by the activity in the large and small fibers.

Gate Control Theory of Pain.

› Large-fiber activity inhibits (or closes) the gate, whereas small-fiber activity facilitates (or opens) the gate.

› When nociceptive information reaches a threshold that exceeds the inhibition elicited, it “opens the gate” and activates pathways that lead to the experience of pain and its related behaviors.

› Therefore, the Gate Control Theory of Pain provided on a neural basis.

Neurophysiology of Pain.

› The structure of a peripheral neuron.
Peripheral Receptors

- The propagation of pain is initiated with the activation of physiological receptors, called **Nociceptors**
- Present on skin, mucosa, membranes, deep fascias, connective tissues of visceral organs, ligaments and articular capsules, periosteum, muscles, tendons, and arterial vessels

Nociception is by

- **Transduction**: It is defined as responses of peripheral nociceptors to traumatic or potentially damaging chemical, thermal, or mechanical stimulation.
- **Conduction**: It refers to the propagation of action potentials from peripheral nociceptive endings via myelinated and unmyelinated nerve fibers.
- **Transmission**: Transmission refers to the transfer of noxious impulses from primary nociceptors to cells in the spinal cord dorsal horn.

General classification of neurons

<table>
<thead>
<tr>
<th>Nerve fiber Type</th>
<th>Diameter</th>
<th>Velocity</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>A fibers</td>
<td>13 to 20 μm</td>
<td>70 to 120 m/s</td>
<td>Alpha fibers</td>
</tr>
<tr>
<td></td>
<td>6 to 13 μm</td>
<td>40 to 70 m/s</td>
<td>Beta fibers</td>
</tr>
<tr>
<td></td>
<td>3 to 8 μm</td>
<td>15 to 40 m/s</td>
<td>Gamma fibers</td>
</tr>
<tr>
<td></td>
<td>1 to 5 μm</td>
<td>5 to 15 m/s</td>
<td>Delta fibers</td>
</tr>
<tr>
<td>Type C fibers</td>
<td>0.5 to 1 μm</td>
<td>0.5 to 2 m/s</td>
<td></td>
</tr>
</tbody>
</table>

Pain Pathways – Neurophysiology of Pain

- The portions of the nervous system responsible for the sensation and perception of pain may be divided into three areas:
  1. Afferent pathways
  2. CNS
  3. Efferent pathways
Afferent Pathway of Pain.

The afferent portion is composed of:

a) Nociceptors (pain receptors)
b) Afferent nerve fibres
c) Spinal cord network

Afferent pathways terminate in the dorsal horn of the spinal cord (1st afferent neuron). The 2nd afferent neuron forms spinal part of afferent system.

Efferent Pathway of Pain.

The efferent pathways, composed of the fibers connecting the reticular formation, midbrain, and substantia gelatinosa, are responsible for modulating pain sensation.

Peripheral Nerve input into the Spinal Cord

Nociceptive Reflex on biting a hard object.

Dental Conditions causing Acute and Chronic Orofacial Pain.
Acute Facial Pain

- Dental and Oral causes
- Maxillary sinusitis
- Salivary gland disorders
- Temperomandibular disorders

Salivary gland tumours

- Salivary stones – submandibular salivary gland
- Pain is intermittent – occurs just before eating
- Associated tenderness
- Bimanual palpation
- Occlusal radiographs, Ultrasound
- Oral and Maxillofacial Surgeons – surgical removal

Temperomandibular disorders

- 5-12% population
- 20-40yrs
- Depression, psychological factors.
- Common—acute onset pain—prolonged opening
- Pain of muscles of mastication and neck.
- Management—Reassurance, soft diet, analgesics.

Masticatory form

- Muscles of mastication, around and in ear – radiates to temple
- In arthralgia the pain – around the joint
- Continuous—day & night
- Aching, deep pain

Investigations

- Questionnaires
- Panoramic radiographs
- Ultrasound
- MRI
- CT

- Disc problems—clenching habit
- Tenderness—temporalis & masseter
- In arthralgia—tenderness around the joint
History and Examination

- Listen to the history and allow time for the patient to complete their statement
- Timing: onset, duration, and periodicity.
- Location and radiation
- Quality and severity.
- Relieving and aggravating factors
- Associated factors
- Other pain conditions
- Impact of life

Extraoral examination

- Visual inspection
  - Colour changes
  - Swelling
  - Skin lesions
- Palpation of lumps & Salivary glands
- Muscles of mastication
- Movement of TMJ

Non-Dental Conditions That Cause Head & Neck Pain

- Psychogenic Pain
- Causalgia
- Phantom limb pain
- Vascular syndrome
  - Migraine
  - Atypical facial neuralgia

Oral Conditions That Cause Head & Neck Pain

- Craniofacial neuralgias
  - Trigeminal neuralgia
  - Glossopharyngeal neuralgia
  - Postherpetic neuralgia
- Sinus & paranasal sinus tumours
- Chronic systemic diseases
- Bone diseases

- Pain in TMJ disturbances & associated musculature
  - Hyperplasia of condyle
  - Injuries to articular disc
  - Fractures of condyle
  - Inflammatory disturbances
  - Myofascial Pain Dysfunction Syndrome
- Pain from jaw cysts & tumours
- Osteitis & osteomyelitis

Psychological assessment
- Family history
- Social history
- Life events
- Complete Drug history
- Past & Present Medical history
• Pain from lesions of oral mucosa
  - Infections
  - Anemia
  - Hormonal disturbances
  - Dermatological diseases
  - Connective tissue diseases
  - Allergic stomatitis

• Pain in salivary gland diseases

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**Neuropathic pain**

- Defined as: Pain initiated or caused by a primary lesion or dysfunction in the nervous system
- Etiologies: Infections, trauma, metabolic abnormalities, radiation, neurotoxins, nerve compression, inflammation & tumour infiltration
- Described as: electric shock, burning, cold, pricking, tingling, itching
- Episodic neuropathic pains have periods of complete remission between episodes whereas continuous neuropathic pains present with periods of high & low intensity but no periods of remission

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**TRIGEMINAL NEURALGIA**
(Tic douloureux or Trigeminal neuralgia or Fothergill’s disease)

Trigeminal neuralgia - ‘Sudden, Usually unilateral, severe, brief, stabbing, recurrent pains in the distribution of one or more branches of the fifth cranial nerve’.

**Clinical features:**
- **Age**: Onset between 5th and 7th decades
- **Gender**: F:M = 3:2

---

**MEASUREMENT OF PAIN & DISABILITY**

Pain intensity is measured by using ratings such as **Visual Analog Scale (VAS)**

VAS consists of a 10 cm line on which 0cm is “no pain” 10cm is “pain as bad as it could be”

<table>
<thead>
<tr>
<th>No pain</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Worst pain</th>
</tr>
</thead>
</table>

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**Wong-Baker FACES Pain Rating Scale**

- **Neuritis**:
  - An inflammatory process associated with a nerve or group of nerves & pain is felt in the peripheral distribution of affected nerves
  - Pain is unremitting & may have a burning character
  - May be associated with paresthesia.

- **Neuralgia**:
  - A highly intense, paroxysmal & painful condition in the distribution area of a peripheral sensory nerve

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Three characteristic symptoms:-
- Unilateral paroxysmal, electrical shock-like intense pain of short duration lasting few seconds to few minutes
- Pain restricted to somatic region supplied by the affected branch
- Presence of trigger zone on mucosa or skin
- **Trigger zones**
  - Vermillion border of the lips, the ala of nose, the cheeks, around the eyes, supraorbital foramina, infraorbital foramina, inner canthus of eye, lateral to the ala & mental foramen
  - Trigger: Touch, movement, wind exposure, chewing, brushing the teeth, shaving, talking, swallowing or exposure to temperature change

- **Duration of pain:**
  A pain duration between 1 second and 2 minutes for each attack

- **Periodicity of pain:**
  Paroxysm is followed by a refractory phase, relative or absolute, the duration of which is a function of the duration as well as the severity of the preceding attack

---

**GLOSSOPHARYNGEAL NEURALGIA**

- Characterized by severe pain in the region of tonsil & ear
- Location of trigger zone & pain sensation follows distribution of glossopharyngeal nerve: pharynx, post. tongue, ear & infrauricular retromandibular area
- Pain is triggered by talking, yawning, chewing & swallowing or contact of food with pharyngeal mucosa

**Pathophysiology:**
Intracranial or extracranial tumors & vascular abnormalities that compress CN IX

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**NERVIS INTERMEDIUS NEURALGIA**
*(Geniculate neuralgia or Seventh nerve neuralgia)*

- Is uncommon paroxysmal neuralgia of facial nerve, characterized by pain in ear & anterior tongue or soft palate

**Pathophysiology:**
Involvement of facial nerve by neural or vascular malformation

**Clinical features:**
- Age: Old age
- Pain is felt in tympanic membrane, walls of external auditory meatus & external structures of ear
- Occasionally, felt in palate, tongue & deeply in facial musculature
- Triggered by touching ear

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**CAUSALGIA**
*(Complex Regional Pain Syndrome or Reflex Sympathetic Dystrophy)*

- Represents a group of clinical symptoms that are associated with neuropathic pain condition related to a nerve injury

**Etiopathogenesis:**
Triad of conditions: An injury, an abnormal sympathetic response & a predisposing personality

**Precipitating Factor:**
Trauma associated with nerve injury

**Clinical features:**
- Spontaneous burning pain & tenderness
Motor dysfunction, sweating & cutaneous atrophy
- Involved skin may become edematous & erythematous
- Thin glossy skin, ↑ or ↓ hair growth & fibrosis
- Underlying bone is demineralized
- Weakness of all muscles of affected distal extremity

Diagnostic consideration:
a) The syndrome usually, but not always develops in wake of an initiating noxious event
b) Continuing pain & allodynia &/or hyperalgesia, disproportionate to initiating event, this precipitating event at times can appear trivial & heal quickly

Clinical features:
Age: At any age, increasing age is a risk factor
Symptoms:
- History of lesions months before
- Persistent pain, paresthesia, hyperesthesia, allodynia months to years after zoster lesions have healed
Signs:
- Sensory deficit

Diagnostic consideration of Neurovascular Pain
<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>Duration</th>
<th>Type</th>
<th>Trigger</th>
<th>Signs</th>
<th>Symptom</th>
<th>Investigation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigeminal neuralgia</td>
<td>Occipital area</td>
<td>Continuous</td>
<td>Burning, shooting pain</td>
<td>Time of day, travel</td>
<td>Headache, morning headache, light touch, shaking head</td>
<td>Alcohol, hypoglycemia</td>
<td>MRI</td>
<td>Neurectomy</td>
</tr>
<tr>
<td>Facial neuralgia</td>
<td>Facial area</td>
<td>Continuous</td>
<td>Burning, cold, burning</td>
<td>Time of day, travel</td>
<td>Headache, morning headache, light touch, shaking head</td>
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</tbody>
</table>

ATYPICAL FACIAL PAIN
- Atypical facial pain is persistent idiopathic facial pain which lacks clear diagnostic criteria and standard treatment
Association between stress and orofacial pain

Atypical odontogenic pain
- Atypical odontogenic pain is a chronic form of dental pain without signs of pathology.
- Pathophysiology has been proposed to be psychogenic, vascular, neuropathic or idiopathic.

PHANTOM PAIN
- In the oral cavity, phantom tooth pain is usually associated with tooth extraction.

BURNING MOUTH SYNDROME
- Burning mouth syndrome (BMS) is a disorder presenting with an intraoral burning sensation for which no medical or dental cause can be found.
- Poor quality of life, depression, anxiety are also often associated with this disorder.

Conclusion.
From perception of pain as 'stimulus-response relationship', the concept of pain has evolved to be a consequence of complex interactions between sensory, emotional, and behavioral factors.

All pain management should begin with educating the patient on his or her pain condition.

- The following suggestions emphasize the inhibitory pain-modulating factors.

- Provide a definitive diagnosis - Whenever possible, the patient should be given a definitive diagnosis of the pain condition. There is nothing more unsettling to the patient than fear of the unknown.
- Do not deny the patient's pain
Too often in the past when the clinician could not find somatic evidence to explain the pain, the patient was thought to have a psychologic problem. Because the clinician assumed the problem was only in the mind, the pain was believed to be not real but instead merely fabricated.
• **Provide realistic expectations**

Unfortunately, not all pain conditions can be completely resolved. Pain that has its origin in diseased structures that cannot be healed will likely continue, even in the presence of the best medical therapy.

• There are certain neuropathic pain conditions that are also resistant to therapy.

• It is important that patients be informed of the likely outcome of their disorder. Many disorders have a natural course that represents a specific time frame with increase of pain and then resolution.

• When these conditions exist, the patient should be informed of the normal time required for healing and likely outcome.

• Perhaps the most important instructions for the clinician to remember when managing pain are: listen carefully, consider all possibilities, cure if you can and manage if you cannot cure, but always console.’

Jeffrey P. Okeson

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• Thanks.
INTRODUCTION

- Healthy oral soft tissues present a typical pink to red hue with slight topographical variations of color.
- The chromatic range is due to the interaction of a number of tissues that compose the mucosal lining:
  1. Presence or absence of keratin on the surface epithelium
  2. Quantity, superficial or deep location of blood vessels in the subjacent stroma
  3. Existence of lobules of adipocytes, and
  4. Absence of melanin pigmentation in the basal cell layer of the epithelium

Oral mucous membrane

The oral cavity is lined by a mucous membrane, consisting of a stratified squamous epithelium, which may or may not be keratinized, and an underlying connective tissue layer, the lamina propria.

Oral pigmentation

Pigmentation is defined as the process of deposition of pigments in tissues. Various diseases can lead to varied colorations in the mucosa. Pigmented lesions of oral cavity are due to:

- Augmentation of melanin production
- Increased number of melanocytes (melanocytosis)
- Deposition of accidentally introduced exogenous materials
Melanin

- Melanin is found universally in nature, the pigment derivative of tyrosine and is synthesized by melanocytes, which typically reside in the basal cell layer of the epithelium.
- Melanin is synthesized within specialized structures known as melanosomes.
- Becker in 1927 first identified melanocytes in the oral epithelium.
- During early stages of intrauterine life, precursors of melanocytes, i.e., melanoblasts, differentiate into the dendritic cells and migrate to the epidermis from the neural crest.
- Keratinocytes actually control melanocytic growth.
- Their presence in the skin is thought to protect against the damaging effects of actinic irradiation.
- They also act as scavengers in protecting against various cytotoxic intermediates.

Types of melanin

- Eumelanin - brown-black
- Pheomelanin - red-yellow
- Mixed type melanin
- Neuromelanin
- Oxymelanin

- Overproduction of melanin may be caused by a variety of mechanisms, the most common of which is related to increased sun exposure.
- Intraorally hyperpigmentation is more commonly a consequence of physiologic or idiopathic sources.
- Neoplasia
- Medication or oral contraceptive use
- High serum concentrations of pituitary adrenocorticotropic hormone
- Genetic factors
- Autoimmune disease

The function of oral melanocytes

- Melanin determines the color of skin, hair and eyes.
- Protection from stresses such as UV radiation, reactive oxygen species (ROS) and free radicals in the environment - melanin.
- Sequester bacteria-derived enzymes and toxins.
- Act as antigen presenting cells, can stimulate T-cell proliferation, and can phagocytose microorganisms.

The keratinocyte-melanocyte unit

- Mature melanocytes contain all the proteins required for melanin biosynthesis and for the structural maturation of melanosomes, including tyrosinase (TYR), tyrosinase-related proteins-1 (TRP-1) and TRP-2, gp 100, and melanoma antigen recognizable by T lymphocytes.
- Melanosomes are packed in globules enclosed by the melanocyte plasma membrane, released into the extracellular space from various areas of the melanocyte dendrites, phagocytosed by keratinocytes, and are then dispersed around the perinuclear area.

Production of melanin by melanosomes

CLASSIFICATION


MISCELLANOUS LESIONS THAT MAY BE ASSOCIATED WITH ORAL MUCOSAL DISCOLORATION

Investigations
- Biopsy
- Diascopy
- Radiography
- Blood tests
- Dermoscopy/epiluminiscence microscopy
- Binocular stereomicroscopes

Primary lesions

Classification

According to Color:
1. BROWN: Erythematous, Papular, Venules, Superficial, Muscular, Hypochromic
2. BLACK: Melanotic, Melanoma, Nevus, Melanoma, Bluish melanoma
3. GRAY: Faintly Blue Toned
4. BLUE/PURPLE: Kaposis Sarcoma, Angiokeratoma, Angiography
5. RED: Hemorrhagic telangiectasia

According to Shape & Size:
1. SMALL: Introverted, Oral Malignant Melanoma, Melanoma, Nevus, Papilloma
2. MEDIUM: Melanoma, Telangiectasia, Leukoplakia
3. LARGE: Melanoma, Post-inflammatory Pigmentation

According to Location & Site:
1. Oral:
   1. Oral: Hemangioma, Melanotic Mucosa, Nevus, Angiokeratoma
   2. Oral: Koilocytic, Benign Oral Hemorrhagic telangiectasia, Physiologic pigmentation, Neurofibromatosis, Leukoplakia
2. Oral: Hemangioma, Telangiectasia, Bluish melanoma

According to Syndrome Associated:
2. Localized: Pigmentary Syndrome, Lentigo-Hemangiomatous Syndrome

Primary lesions

Diagnosis
- Biopsy
- Diascopy
- Radiography
- Blood tests
- Dermoscopy/epiluminiscence microscopy
- Binocular stereomicroscopes

Mischellaneous lesions that may be associated with oral mucosal discoloration

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmented granuloma</td>
<td>Red, Bluish</td>
</tr>
<tr>
<td>Neoplastic budding</td>
<td>Red, Blue</td>
</tr>
<tr>
<td>Neoplastic papillary</td>
<td>Red, Blue</td>
</tr>
<tr>
<td>Neoplastic melanoma</td>
<td>Bluish</td>
</tr>
<tr>
<td>Macrophotometric carcinoma</td>
<td>Blue</td>
</tr>
<tr>
<td>Acute cutaneous</td>
<td>Red, Blue</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Bluish, Yellow</td>
</tr>
<tr>
<td>Vascular kaposia</td>
<td>Red, Bluish</td>
</tr>
<tr>
<td>Vascular papilloma</td>
<td>Red, Bluish</td>
</tr>
<tr>
<td>Vascular granuloma</td>
<td>Bluish, Yellow</td>
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<tr>
<td>Vascular spindle</td>
<td>Bluish, Yellow</td>
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<tr>
<td>Vascular cell tumor</td>
<td>Bluish, Yellow</td>
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</tbody>
</table>
ENDOGENOUS PIGMENTATION

• Hemoglobin, hemosiderin, and melanin represent the most common endogenous source of mucosal color change.
• A submucosal collection of hemoglobin or hemosiderin, produced by extravasation or lysis of red blood cells, may impart a red, blue, or brown ephemeral appearance to the oral mucosa.
• Melanin, which is synthesized by melanocytes and nerve cells, may appear brown, blue, or black, depending on the amount of melanin and its spatial location within the tissue (i.e., superficial vs. deep).

Common Causes of Endogenous Oral and Perioral Discoloration

<table>
<thead>
<tr>
<th>Cause</th>
<th>Biology</th>
<th>Examples of Associated Lesions, Conditions, or Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascul</td>
<td>Development, hematoma, embolism, genetics, anatomic</td>
<td>Varieties, hemangiomas, angiodysplasia, Kaposi’s sarcoma, Bunting syndrome, stomatitis, angiomyolipoma, CRST syndrome</td>
</tr>
<tr>
<td>Ectasia/Hereditary Hemorrhagic Telangiectasia</td>
<td>Trauma, ulcers, purpura, inflammation, edema</td>
<td>Kaposi sarcoma, ectodermal dysplasia, telangiectasia, hereditary hemorrhagic telangiectasia, CRST syndrome</td>
</tr>
<tr>
<td>Melanin</td>
<td>Physiologic, developmental, uveitis, embolism, infection, skin, genetics, carcinomas, stellate</td>
<td>Melanosis mucosae, oculodermal melanocytosis, lentiginous naevus, malignant melanoma, dysplastic nevi, nevus spilus, Lisch nodules, xanthomatosis, albinism, melasma, albinism, melasma, Rest. Kinns’ disease, abnormal melanocytes, Carney’s syndrome, EVAN syndrome</td>
</tr>
<tr>
<td>Bile</td>
<td>Trauma, alcohol, infection, embolism, genetics, carcinomas, stellate</td>
<td>Juvenile</td>
</tr>
</tbody>
</table>

FOCAL MELANOCYTIC PIGMENTATION

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freckle/Ephelis</td>
<td>Melanocytic macule, Oral melanocytic lesions, Melanocytic naevus, Melanocytic nevus</td>
</tr>
</tbody>
</table>

Freckle/Ephelis

- Common, asymptomatic, small (1–3 mm), well-circumscribed, tan- or brown-colored macule
- Seen on the sun-exposed regions of the facial and perioral skin
- Commonly observed in light-skinned individuals and are quite prevalent in those of light to intermediate skin type
- Developmental in origin
- Polymorphisms in the MC1R gene are strongly associated with the development of childhood freckles
- Another putative freckles-predisposition gene has also been mapped to chromosome 4q23–q34
- More abundant in number and darker in intensity during childhood and adolescence
- Become darker during periods of prolonged sun exposure (spring, summer) and less intense during the autumn and winter months
- With increasing age, the number of ephelides and color intensity tends to diminish
- No therapeutic intervention is required.
Oral/Labial Melanotic Macule

- The melanotic macule is a unique, benign, pigmented lesion that has no known dermal counterpart.
- Melanotic macules are the most common oral lesions of melanocytic origin.
- Although the etiology remains elusive, trauma has been postulated to play a role.
- Sun exposure is not a precipitating factor.

Clinical Features

- More frequently in females, usually in the lower lip (labial melanotic macule) and gingiva.
- Any mucosal site may be affected.
- Congenital melanotic macules occur primarily in the tongue.
- Small (<1 cm), well-circumscribed, oval or irregular in outline, and often uniformly pigmented.
- Unlike an ephelis, a melanotic macule does not become darker with continued sun exposure.
- Differential diagnosis – melanocytic nevus, malignant melanoma, amalgam tattoo, focal ecchymosis.

Oral Melanoacanthoma

- Unusual, benign, melanocytic lesion that is unique to the mucosal tissues.
- Innocuous melanocytic lesion that may spontaneously resolve, with or without surgical intervention.
- Rapid onset and acute trauma or a history of chronic irritation usually precede the development of the lesion.
- The biopsy procedure itself may lead to spontaneous regression of the lesion.
- The underlying source of the irritation should be eliminated to minimize recurrence.

Clinical Features

- Oral melanoacanthoma usually presents as a rapidly enlarging, ill-defined, darkly pigmented macular or plaque-like lesion, and mostly develop in black females.
- Occur between the third and fourth decades of life.
- Typically, a solitary lesion, may be bilateral and multifocal lesions.
- Generally asymptomatic, may be associated with pain.
- Although any mucosal surface may be involved, close to 50% of melanoacanthomas arise on the buccal mucosa.
- The size of the lesion is variable, ranging from small and localized to large, diffuse areas of involvement, measuring several centimeters in diameter.
- The borders are typically irregular in appearance, and the pigmentation may or may not be uniform.

Diagnosis

- Because oral melanoacanthoma may resemble other melanocytic lesions, such as pigmented nevus, melanotic macule, and melanoma, a biopsy is warranted to obtain a definitive diagnosis.
Oral Nevi (Oral melanocytic nevus, nevocellular nevus, mole, mucosal melanocytic nevus)

- Categorized as hamartomas, developmental malformations, the nevi are benign proliferations of nevus cells in either epithelium or connective tissue.
- In 1943, Ackermann and Field have reported the first case of an oral nevus.
- King et al., adopted the less anatomically specific term, intramucosal nevus.
- Adult whites harbor this lesion rather commonly but intraoral lesions are much less common.

Clinical, a pigmented nevus is an asymptomatic, well-circumscribed, round or oval, flat or slightly elevated papule or plaque, and of size usually ranging between 0.1 cm and 3 cm. The color varies from brown to blue, dusky gray to black.
- The hard palate, buccal mucosa, and gingiva are the most commonly affected intraoral sites.
- They can be seen in persons of all ages with the mean age group affected being 3rd-4th decade. Women are affected more commonly than men.

Nevus cells

- Nevus cells are a variant of melanocytes.
- They are larger than typical melanocytes, do not have dendrites, and have more abundant cytoplasm with coarse granules.
- Multinucleated cell variants are also seen.
- They are usually located at the dermoepidermal junction or in the dermis of the skin.
- Most nevic cells tend to be round, ovoid, or spindle shaped.
- Nevus cells have tendency to closely approximate one another if not aggregate in clusters, and have ability to migrate into and/or within the submucosal tissues.

Nevus Classification

- Nevus may also be classified as congenital or acquired (Buchner and Hansen).
- On the basis of the histologic location of the nevus cells, cutaneous acquired nevi can be classified into three categories:
  1. Junctional nevus — when nevus cells are limited to the basal cell layer of the epithelium.
  2. Compound nevus — nevus cells are in the epidermis and dermis.
  3. Intradermal nevus (common mole) — nests of nevus cells are entirely in the dermis.

Etiology and Pathogenesis

- Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise as a consequence of melanocytic growth and proliferation.
- Genetic and environmental factors, sun exposure, play a role in nevogenesis.
- Familial atypical multiple mole melanoma syndrome.
- Epithelioid blue nevus may be associated with the Carney complex.
- Turner’s syndrome and Noonan’s syndrome; and congenital nevi are typical of neurocutaneous melanosis.
- A recent study by Pollock et al. demonstrated that up to 90% of dermal melanocytic nevi exhibit somatic, activating mutations in the BRAF oncogene. Mutations in the HRAS and NRAS oncogenes have also been identified. This lends further credence to the notion that melanocytic nevus are neoplastic.
In the evolutionary stage of an intramucosal (or intradermal) nevus, the nevus cells as a single mass may detach from the basal layer, wedging at the junction of the epithelium and the basement membrane.

These junctional masses usually small (<5 mm), macular or palpable, and tan to brown in appearance.

Later, intramucosal nevi are thought to undergo the following changes:
- The nevus cells and some melanocytes become dispersed throughout the connective tissue, and some intramucosal nevi can even reach the submucosa.
- These changes lead to a decrease in the amount of pigmentation; intramucosal melanomas can show a marked decrease in marking of the mucosa.
- Once the lesion reaches a given size, its growth tends to cease and may remain static indefinitely. In rare cases, multifocal lesions have been described.

Clinical Features

- Cutaneous nevi are a common occurrence.
- The average Caucasian adult patient may have several nevi; some individuals may have dozens.
- Higher in males than females.
- Oral melanocytic nevi are rare, typically present as solitary lesions, and may be more common in females.
- Lesions are usually asymptomatic and often present as a small (≤1 cm), solitary, brown or blue, well-circumscribed nodule or macule.
- Once the lesion reaches a given size, its growth tends to cease and may remain static indefinitely. In rare cases, multifocal lesions have been described.

Pathology

- Junctional nevi are usually small (<5 mm), macular or palpable, and tan to brown in appearance.
- Intramucosal nevi are thought to undergo the following changes:
  - The nevus cells and some melanocytes become dispersed throughout the connective tissue, and some intramucosal nevi can even reach the submucosa.
  - These changes lead to a decrease in the amount of pigmentation; intramucosal melanomas can show a marked decrease in marking of the mucosa.
  - Once the lesion reaches a given size, its growth tends to cease and may remain static indefinitely. In rare cases, multifocal lesions have been described.

Blue nevus

- The common blue nevus is the second most common type found in the oral cavity. The blue nevus is common in the mouth and in the skin, which account for 25–36% of all oral nevi, according to different studies.
- Junctional and compound nevi account for only 3–6% of all oral nevi.
- Rare reports of congenital nevus, Spitz nevus, balloon cell nevus, and the cellular, epithelioid, and plaque-type variants of blue nevus have also been described.
- The blue nevus is described as such because the melanocytes may reside deep in the connective tissue and the overlying blood vessels often dampen the brown coloration of melanin, which may yield a blue tint.

Blue nevi are characterized by a variety of microscopic appearances.
- Common blue nevus: Intramucosal proliferation of pigment laden, spindle-shaped melanocytes, most common.
- Cellular blue nevus: Submucosal proliferation of both spindle-shaped and larger, round- or ovoid-shaped melanocytes, less frequently occurring, more aggressive, and has a greater rate of recurrence. Rare reports of malignant transformation have also been associated with the cellular cutaneous variant.

Malignant Melanoma

- Oral melanomas are uncommon, and, similar to their cutaneous counterparts, are thought to arise primarily from melanocytes in the basal layer of the squamous mucosa. Melanocytic density is higher in these regions than in other sites of internal organs, leading to the belief that most cutaneous melanomas are derived from cells of the mucosa.
- Oral melanomas may involve the entire oral cavity, and lesions have been reported in the tongue, floor of the mouth, lips, and nasal cavity. Oral melanomas are more aggressive than cutaneous melanomas.
- Malignant melanomas are associated with increased risk of malignant transformation, and patients with melanomas are at increased risk of developing additional primary and secondary malignancies.
- Oral melanomas are more aggressive than cutaneous melanomas, and patients with oral melanomas are at increased risk of developing additional primary and secondary malignancies.
- Other recurrent molecular findings, including BRAF, NRAS, and HRAS proto-oncogenes, have also been described.
Clinical Features

- Cutaneous melanoma is most common among white populations that live in the sunbelt regions of the world.
- Males older than 45 years.
- Has a male predilection, but melanoma is one of the most commonly occurring cancers in women of child-bearing age.
- Melanomas may develop either de novo or, much less commonly, arise from an existing melanocytic nevus.
- On the facial skin, the malar region is a common site.
- In general, the clinical characteristics of cutaneous melanoma are best described by the ABCDE criteria.
- These criteria are very useful (although not absolute) in differentiating cutaneous melanoma from other locally pigmented melanocytic lesions.

Criteria for clinical diagnosis of melanoma - ABCDE-rule

1. Symmetry: Is when one-half of the lesion does not match the other half of lesion.
2. Border irregularity: Is when the edges are notched, ragged or blurred.
3. Color irregularity: Colored pigmentation is seen ranging from black, brown, tan, red, blue and white.
4. Diameter: More than 6 mm.
5. Elevation: A rise in the surface is also sign.

Types of melanoma

- Superficial spreading
- Nodular melanoma
- Lentigo maligna melanoma
- Acral lentiginous melanoma
- Mucosal lentiginous melanoma
- Ameloblastic malignant melanoma

The Clark scale has five levels:

- Level 1: Melanoma is confined to the epidermis (the outer layer of the skin).
- Level 2: Melanoma has invaded the papillary dermis (the outermost layer of the dermis, the next layer of skin).
- Level 3: Melanoma has invaded throughout the papillary dermis and is touching on the next, deeper layer of the dermis.
- Level 4: Melanoma has invaded this next deeper layer, the reticular dermis.
- Level 5: Melanoma has now invaded the fat under the dermis.

Diagnosis

One of the main clinical and microscopic challenges in diagnosing oral melanoma is determining whether the lesion is a primary neoplasm or a metastasis from a distant site.

This is not a semantic distinction since confirming the primary site will dictate the patient's clinical stage and the type of therapy he or she will undergo.

A history of a previous melanoma, sparing of the palate and gingiva, amelanosis, and microscopic features, such as a lack of junctional activity and pagetoid spread, are findings that may be more suggestive of a metastatic tumor.

[B] Malignant melanoma presenting as a mass on the maxillary gingiva.
For primary oral melanomas, ablative surgery with wide margins remains the treatment of choice. Adjuvant radiation therapy may also be necessary. A variety of chemotherapeutic and immunotherapeutic strategies are often used if metastases are identified or for palliation.

### Management

#### Physiologic Pigmentation

- Multifocal/diffuse pigmentation
- Most common multifocal or generalized melanosis
- Dark-complexioned individuals, including blacks, Asians, and Latinos, frequently show patchy to generalized hyperpigmentation of the oral mucosa.
- Although in many patients, the pigment is restricted to the gingiva, melanosis of other mucosal surfaces is not uncommon.
- The pigment is typically first observed during childhood and does not develop de novo in adulthood.

#### Differential Diagnosis

- Idiopathic
- Drug-induced
- Smoking-induced melanosis
- Hypopigmentation associated with endocrinopathies and other systemic diseases.
Microscopically, physiologic pigmentation is characterized by the presence of increased amounts of melanin pigment within the basal cell layer. This pigmentation is considered a variation of normal.

Gingivectomy and laser therapy have been used to remove pigmented oral mucosa. Cryosurgery has also been reported to effectively remove oral pigmentation.

Drug-Induced Melanosis

**Etiology and Pathogenesis**

Medications may induce a variety of different forms of mucocutaneous pigmentation, including melanosis. The chief drugs implicated in drug-induced melanosis are the antimalarials, including chloroquine, hydroxychloroquine, and quinacrine. In the Western World, these medications are typically used in the treatment of autoimmune diseases.

Other common classes of medications that induce melanosis include the phenothiazines, oral contraceptives, and cytotoxic medications such as cyclophosphamide and busulfan.

**Clinical Features**

It has been estimated that 10%-20% of all cases of acquired melanocytic pigmentation may be drug-induced.

Intraorally, the pigment can be diffuse yet localized to one mucosal surface, often the hard palate, or it can be multifocal and involve multiple surfaces. Some drugs may even be associated with a specific pattern of pigmentation.

Much like other forms of diffuse pigmentation, the lesions are flat and without any evidence of nodularity or swelling.

Sun exposure may exacerbate cutaneous drug-induced pigmentation.

**Drugs causing oral perioral pigmentation**

- Amiodarone
- Amodioquine
- Azidothymidine
- Bleomycin
- Chloroquine
- Chlorpromazine
- Cyclophosphamide
- Gold
- Hydroxychloroquine
- Hydroxyurea
- Imipramine
- Ketoconazole
- Mepacrin


**Pathology**

Microscopically, there is usually evidence of basilar hyperpigmentation and melanin incontinence without a concomitant increase in the number of melanocytes.

Although the mechanisms by which melanin synthesis is increased remain unknown, one theory is that the drugs or drug metabolites stimulate melanogenesis.

Alternatively, some drugs, including chloroquine and chlorpromazine, have been shown to physically bind melanin. This complexation of melanin and drugs within melanocytes may contribute to the adverse mucocutaneous effects.

Drug-induced pigmentation of the palate in a patient who was taking quinacrine for the treatment of discoid lupus erythematosus.
Tetracycline-induced melanosis of the palate

Chemo therapy-induced pigmentation of the right dorsal tongue


**Diagnosis**

If the onset of the melanosis can be chronologically and accurately associated with the use of a specific medication (frequently within several weeks or months before development of the pigmentation), then no further intervention is warranted.

In most cases, the discoloration tends to fade within a few months after the drug is discontinued.

However, pigmentation associated with hormone therapy may tend to persist for longer periods of time, despite discontinuation of the medications. A differential diagnosis includes other causes of diffuse mucosal pigmentation. Laboratory tests may be necessary to rule out an underlying endocrinopathy.

**Smoker’s Melanosis**

- Diffuse melanosis of the anterior vestibular maxillary and mandibular gingivae, buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers.
- Most smokers (including heavy smokers) usually fail to show such changes; however, in certain individuals, melanin synthesis may be stimulated by tobacco smoke products.
- Indeed, among dark-skinned individuals who normally exhibit physiologic pigmentation, smoking stimulates a further increase in oral pigmentation.
- The pigmented areas are brown, flat, and irregular; some are even geographic or map-like in configuration.
- Smoking tobacco (cigarette) does not appear to be associated with an increase in oral melanosis.

**Postinflammatory (Inflammatory) Hyperpigmentation**

- Most commonly in dark-complexioned individuals.
- Most cases present as diffuse or diffuse pigmentation in areas that were subjected to prior local or inflammatory.
- In rare cases, the mucosa overlying a nonmelanocytic malignancy may become pigmented.
- Characterization has also been described in planus (lichen planus pigmentosus).

**Melasma (Chloasma)**

- Melasma is a relatively common, acquired symmetric melanosis that typically develops on sun-exposed areas of the skin and frequently on the face.
- The forehead, cheeks, upper lips, and chin are the most commonly affected areas.
- There is a distinct female predilection, and most cases arise in darker-skinned individuals less common in males.
- Evolves rather rapidly over a period of a few weeks.
- Pigmentary changes associated with sun exposure and hormonal factors, including pregnancy and contraceptive hormones.
In various thyroid abnormalities, including hypothyroidism, may also play a role in the pathogenesis of pregnancy- and non-pregnancy-associated melasma.

A biopsy typically reveals basilar melanosis with no increase in the number of melanocytes. However, the melanocytes that are present may be larger than those in the adjacent normally pigmented areas.

Spontaneously resolve after parturition, cessation of the exogenous hormones, or regulation of endogenous sex hormone levels.

A successful therapeutic approach for the treatment of melasma consists in the topical administration of a triple combination product (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone)

**Hypoadrenocorticism (Adrenal Insufficiency or Addison’s Disease)**

**Etiology and Pathogenesis**

- In adults, autoimmune disease represents one of the most common causes where the majority of patients show the presence of circulating autoantibodies to steroidogenic enzyme 21-hydroxylase.
- However, infectious agents, neoplasia, trauma, certain medications, and iatrogenic causes may lead to adrenal destruction or impairment of endogenous steroid production. In rare cases, adrenal insufficiency may also be a consequence of genetic disease.
- As a result, a decrease in endogenous corticosteroid levels occurs.
- As steroid levels decrease, there is a compensatory activation of ACTH secretion from the anterior pituitary gland. ACTH then acts on the adrenal cortex to stimulate steroid production and ACTH secretion stops.
- If low steroid levels persist, there is a loss of feedback inhibition, resulting in persistent secretion of ACTH into the serum.
- Concurrently, the serum levels of α-melanocyte-stimulating hormone (α-MSH) also increase.
- At the molecular level, this is explained by the fact that the precursor proopiomelanocortin gene contains the sequences of both the ACTH and α-MSH genes.
- During processing of the progenitor hormone, the ACTH and α-MSH genes may be cleaved independently of one another, thus creating two distinct hormones.
- Apart from the wide array of tissues and organs that these hormones act upon, both α-MSH and ACTH are also thought to have stimulatory effects on melanocytes. However, the exact mechanism by which melanin synthesis increases remains unclear.

**Clinical Features**

- Weakness, poorly defined fatigue, and depression are some of the typical presenting signs of the illness.
- The first sign of disease may be mucocutaneous hyperpigmentation.
- Generalized bronzing of the skin and diffuse but patchy hyperpigmentation are hallmarks of hypoadrenocorticism.
- Any oral surface may be affected. In some patients, oral melanosis may be the first manifestation of their disease.
- Diffuse hyperpigmentation is more commonly associated with chronic rather than acute-onset disease.

**Diagnosis**

- Endocrinopathic disease should be suspected whenever oral melanosis is accompanied by cutaneous bronzing.
- An oral biopsy typically shows increased melanin in the basal cell layer with melanin incontinence.
- Differential diagnosis - photosensitization and drug-induced pigmentation.
- Laboratory data: serum cortisol and electrolyte levels. Serum cortisol levels less than 100 nmol/L at 9:00 am is diagnostic of adrenal insufficiency. Hyponatremia and hyperkalemia are frequently associated with adrenal insufficiency.
- Treatment: exogenous steroid replacement therapy with glucocorticoids and mineralocorticoids. There is evidence supporting the use of adrenal androgens such as dehydroepiandrosterone to improve the quality of life of patients with Addison’s disease.
Cushing's Syndrome/Cushing's Disease

**Etiology and Pathogenesis**
- Cushing's syndrome develops as a consequence of prolonged exposure to relatively high concentrations of endogenous or exogenous corticosteroids.
- Most cases are iatrogenic in origin and associated with poorly controlled or unmonitored use of topical or systemic steroids.
- Pituitary tumor
- Hyperadrenocorticism
- Ectopic secretion of corticosteroids, ACTH, or corticotropin-releasing hormone by various neoplasms, including small cell carcinoma of the lung.
- Germ line mutations in ACTH receptor

**Clinical Features**
- More prevalent in female patients.
- Prepubertal onset is more commonly seen in boys.
- Apart from the wide array of systemic complications, including weight gain and the characteristic "moon faces," diffuse mucocutaneous pigmentation may be seen in a subset of patients, specifically those whose pathology is associated with increased ACTH secretion.

**Diagnosis and management**
- Three main tests are used for the diagnosis of Cushing's syndrome: a low-dose dexamethasone suppression test, midnight plasma cortisol, 24-hour urinary free cortisol.

**Hyperthyroidism (Graves' Disease)**
- Melanosis is a common consequence of hyperthyroidism (Graves' disease), especially in dark-skinned individuals.
- Studies suggest that at least 40% of black patients with thyroid disease present with mucocutaneous hyperpigmentation.
- In contrast, melanosis is very rarely observed in Caucasian patients with this disease. The pigmentation tends to resolve following treatment of the thyroid abnormality.

**Primary Biliary Cirrhosis**
- Diffuse mucocutaneous hyperpigmentation may be one of the earliest manifestations of primary biliary cirrhosis.
- Up to 47% of patients with this condition develop diffuse melanosis.
- Primary biliary cirrhosis may also be a source of generalized nonmelanocytic discoloration.
- Hyperbilirubinemia often induces a yellowish discoloration of the skin, eyes, and mucous membranes.
- Treatment of the underlying disease will lead to resolution of jaundice.
- The mechanism by which excessive thyroid activity stimulates melanin synthesis remains unclear.
Vitamin B12 (Cobalamin) Deficiency

- Diffuse mucocutaneous hyperpigmentation is rare, and poorly recognized, complication of vitamin B12 deficiency.
- This hyperpigmentation is reminiscent of Addison’s disease.
- The pigmentation resolves following restoration of vitamin B12 levels.
- The predominant mechanism of hyperpigmentation is hypothesized as 1) Deficiency of vitamin B12 decreases the level of reduced glutathione, which activate tyrosinase and thus leads to transfer to melanosomes.
- 2) Defect in the melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence. The dominant mechanism of hyperpigmentation is not a defect in melanin transport but is rather an increase in melanin synthesis.

Peutz-Jeghers Syndrome

- An autosomal dominant disease that is associated with mutations in the STK11/LKB1 tumor suppressor gene.
- Clinical manifestations include intestinal polyposis, cancer susceptibility, and multiple, small, pigmented macules of the lips, perioral skin, hands, and feet.
- The macules may resemble ephelides, usually measuring <0.5 cm in diameter. However, the intensity of the macular pigment is not influenced by sun exposure.
- Although uncommon, similar appearing lesions may also develop on the anterior tongue and buccal and labial mucosae.

Typical pattern of pigmentation representative of Peutz-Jeghers syndrome

- Histologically, these lesions show increased basilar melanin without an increase in the number of melanocytes.
- The medical management for Peutz-Jeghers syndrome consists of surveillance and treatment of hamartomatous polyps.
- Other genetic diseases associated with a triad of gastrointestinal disease, cancer susceptibility, and mucocutaneous pigmented macules among other findings include Cowden syndrome (and the allelic Bannayan-Riley-Ruvalcaba and Lesch-Nyhan syndromes) and Cronkhite-Canada syndrome.

Café au Lait Pigmentation

- Café au lait (“coffee with milk”) spots are occasionally observed in the general population. Multiple café au lait spots are often indicative of an underlying genetic disorder.
- Tan- or brown-colored, irregularly shaped macules of varying size.
- They may occur anywhere on the skin.
- Café au lait pigmentation may be identified in a number of different genetic disorders, including neurofibromatosis type 1, McCune-Albright syndrome, and Noonan syndrome.
Diseases Commonly Associated With Café au Lait Pigmentation

- Neurofibromatosis type I
  - Autosomal dominant disease caused by a mutation or a deletion of the NF1 gene localized in chromosome 17.
  - Associated with the development of multiple neurofibromas of various histologic subtypes.
  - Size, number, and age at onset of the cutaneous café au lait spots are of diagnostic importance for this disease.
  - Axillary and/or inguinal freckling (Crowe's sign) and pigmented lesions of the iris (Lisch nodules) are also highly characteristic of neurofibromatosis type I.

- McCune-Albright syndrome
  - Extremely rare disorder that classically affects the bones, skin, and endocrine system.
  - Fibrous dysplasia of bone, patches of abnormal skin, and multiple endocrine dysfunctions.
  - McCune-Albright syndrome and the genetically and phenotypically similar Mazabraud disease are sporadically occurring diseases that are characterized by polyostotic fibrous dysplasia, various endocrinopathies (McCune-Albright), and soft tissue myxomas (Mazabraud disease).
  - In some patients, Addison's disease or Cushing's syndrome may be a potential consequence of McCune-Albright syndrome.
  - Café au lait spots in McCune-Albright syndrome appear distinct from those associated with neurofibromatosis; the borders are irregularly outlined, whereas in neurofibromatosis, the borders are typically smooth.

- Noonan's syndrome and the allelic LEOPARD syndrome (multiple lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness) are autosomal dominant disorders that, among other findings, are also associated with pigmented mucocutaneous macules and multiple melanocytic nevi.
  - Noonan's phenotype is typically associated with numerous, small, freckle-like macules often involving the facial skin.

- The LEOPARD phenotype is associated with multiple lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness.

- HIV/AIDS-Associated Melanosis
  - Diffuse or multifocal mucocutaneous pigmentation has been frequently described in HIV seropositive patients.
  - The pigmentation may be related to intake of various medications, including antifungal and antiretroviral drugs, or as a result of adenocortical destruction by virulent infectious organisms.
  - Recent studies suggest that melanosis may be an early, potentially late-stage, clinical manifestation of HIV/AIDS.
  - Goldman et al. demonstrated a significant correlation between mucocutaneous pigment loss and CD4 lymphocyte count.
  - Studies have also shown that immune dysfunction associated with HIV/AIDS leads to increased secretion of α-MSH from the anterior pituitary gland, which may also stimulate increased melanin synthesis.

- Progressive hyperpigmentation of the skin, nails, and mucous membranes.
  - The buccal mucosa is the most frequently affected site, but the gingiva, palate, and tongue may also be involved.
  - Unlike diffuse melanoses, HIV-associated pigmentation is microscopically characterized by basilar melanin pigment, with incontinence into the underlying submucosa.
IDIOPATHIC PIGMENTATION

Laugier–Hunziker Pigmentation

Etiology and Pathogenesis

Laugier–Hunziker pigmentation (also known as Laugier–Hunziker syndrome) was initially described as an acquired, idiopathic, macular hyperpigmentation of the oral mucosal tissues, specifically involving the lips and buccal mucosa.

- Pigmentation of the esophagus, genital, and conjunctival mucosa and the acral surfaces is seen.
- Up to 60% of affected patients also may have nail involvement, usually in the form of longitudinal melanotic streaks and without any evidence of dystrophic change. The fingernails are more commonly affected than the toenails.
- Rare condition in adult patients with equal sex predilection.
- Caucasian or light-skinned individuals.
- Possible genetic predisposition.

Clinical and Microscopic Features

- Patients typically present with multiple, discrete, irregularly shaped brown or dark brown macules.
- Individual macules are usually no more than 5 mm in diameter.
- In rare instances, the lesions may coalesce to produce a diffuse area of involvement.
- Increased melanin pigmentation in the basal cell layer without an increase in the number of melanocytes and melanin incontinence in the superficial lamina propria are characteristic of this syndrome.

Differential Diagnosis

- Physiologic pigmentation
- Drug or heavy metal–induced pigmentation
- Endocrinopathic disease
- Peutz–Jeghers syndrome.

Management

- Generally not indicated
- Laser and cryotherapy

DEPIGMENTATION
Vitiligo

• Vitiligo is a relatively common, acquired, autoimmune disease that is associated with hypomelanosis.
• Vitiligo affects 0.5%–2.0% of the world population with no gender or racial preference.

Etiology and Pathogenesis

• Autoimmunity, cytotoxicity, genetics, and alterations from metabolic or oxidative stress have been implicated in this condition where the end result is a destruction of the melanocytes.
• The pathogenesis of vitiligo is multifactorial, with both genetic and environmental factors playing a role in the development of this disease.

Clinical Features

• classification - non-segmental vitiligo, segmental vitiligo, and unclassified/undetermined vitiligo.
• Multiple achromatic patches with remitting-relapsing course are seen in non-segmental vitiligo.
• Segmental vitiligo shows characteristic dermatomeric distribution of the achromatic patches with a rapid onset that is usually not progressive.

• The onset of vitiligo—any age but mostly second and third decade of life.
• The depigmentation is more apparent in patients who have a darker skin tone. Yet the disease actually occurs in all races.

• Vitiligo may also arise in patients undergoing immunotherapy for the treatment of malignant melanomas.
• Vitiligo rarely affects the intraoral mucosal tissues. However, hypomelanosis of the inner and outer surfaces of the lips and perioral skin may be seen in up to 20% of patients.

Management

• Objective is to stimulate repigmentation.
• Topical corticosteroids, topical calcineurin inhibitors, ultraviolet B narrow band, and psoralen and ultraviolet A exposure.
• From the standpoint of therapy, labial vitiligo is more resistant to the typical treatments used for cutaneous vitiligo. Collagen lack of hair follicles, the lips do not have reservoir of melanocytes that can be stimulated to produce pigment. Thus, surgical intervention may be the only option to achieve an esthetic result. Autologous epithelial grafts have been used successfully, with patients often reporting a more acceptable cosmetic appearance.
• Split-thickness skin grafts have been reported as having the highest repigmentation success rate.
• Punch grafting and micropigmentation (whereby an exogenous brown pigment is injected into the lip, much like a tattoo).
• For some instances, surgical intervention may stimulate spontaneous repigmentation of vitiligenous lesions elsewhere on the body.

Hemoglobin and Iron Associated Pigmentation

Ecchymosis

Ecchymosis is common on the lips and face due to the close proximity to the fascia but is unusual in cases needed to blunt force trauma and anticoagulation.

• Immediately following the traumatic event, extravasation of the corpuscular blood elements into the connective tissue will appear as a bright red macule or as a swelling if a hematoma forms. The lesion will assume a brown discoloration within a few days, after the hemoglobin is degraded to hemosiderin.

• Patients taking anticoagulants may present with oral ecchymosis, particularly on the buccal mucosa or tongue, either of which can be traumatic while chewing.

Ecchymosis of the oral mucosa may also be encountered in patients with autoimmune hemolytic anemia and those with disorders such as leprosy or amyloidosis.

Purpura/Petechiae

• Capillary hemorrhages will appear initially and turn brown in a few days once the extravasated cells have lysed and have been degraded to hemosiderin.

• The distinction between purpura and petechiae is essentially semantic, based solely on the size of the focal hemorrhage.

• Petechiae are typically characterized as being pinpoint or slightly larger than pinpoint and purpura as multiple, small 2–4 mm collections of extravasated blood. The same precipitating events can elicit either clinical presentation.

• Oral purpura/petechiae may develop as a consequence of trauma, viral, or systemic disease.
Viral disease is more commonly associated with oral rather than cutaneous petechiae. In most cases, the petechiae are identified on the soft palate, although any mucosal site may be affected. Within two weeks, the lesions should resolve. Failure to do so should arouse suspicion of a hemorrhagic diathesis, a persistent infectious disease, or other systemic disease, and appropriate laboratory investigations must be undertaken.

Causes of Oral Purpura/Petechiae

- Amyloidosis
- Aplastic anemia
- Bulimia
- Chronic renal failure
- Forceful coughing
- Hemophilia
- Henoch–Schönlein purpura
- Hereditary angioedema
- Idiopathic mononucleosis
- Leukemia
- Lupus erythematosus
- Oral intubation
- Oral submucous fibrosis
- Papular-purpuric “gloves and socks” syndrome
- Perioral acne
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Thrombocytopenia
- Von Willebrand disease
- Hemochromatosis

Hemochromatosis

- Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition (usually in the form of hemosiderin) in the liver and other organs and tissues.
- Idiopathic, neonatal, blood transfusion, and heritable forms of this disease are recognized.
- Complications of hemochromatosis may include liver cirrhosis, diabetes, anemia, heart failure, hypertension, and bronzing of the skin.
- Studies also suggest an increased incidence of cancer in patients with hemochromatosis. The cutaneous pigmentation is seen in over 90% of affected patients, regardless of the etiology of the disease.
- The primary oral manifestation of hemochromatosis is a blue-gray to brown pigmentation affecting mainly the palate and gingiva.
- Early on in the course of disease, the pigmentation may be more commonly a result of basilar melanosis rather than iron-associated pigment.
- Iron deposition within the adrenal cortex may lead to hypoadrenocorticism and ACTH hypersecretion, with the associated addisonian-type changes. In the later stages of hemochromatosis, the pigmentation is usually a result of hemosiderosis and melanosis.
- A lower labial gland biopsy has been shown to be an easy and effective method for the diagnosis of hemochromatosis.

Sources of Exogenous Oral and Perioral Pigmentation

- Metal
- Nutrients, medications, environment
- Chemicals, essential, oral cavity
- Bacteria
- Drug components
- Poisonous drug
- Plant derivatives, tooth, oral cavity

Example of associated lesion, condition, or disease

- Anagalestis, erythema, black tongue, heavy metal pigmentation
- Gouge's stain
- Fungi, mycotoxicosis, pigmentation
- Hairy tongue
- Monocystic dilation pigmentation
- Oral erosions, ulcerations, oral cavity

EXOGENOUS PIGMENTATION
Amalgam Tattoo

**Etiology and Pathogenesis**
- The most common pigmented lesion in the oral mucosa is amalgam tattoo.
- By definition, these are iatrogenic in origin and typically a consequence of the inadvertent deposition of amalgam restorative material into the submucosal tissue.

**Clinical Features**
- Found in 1%-3% of the general population.
- Small, asymptomatic, macular, and bluish gray or even black lesions.
- The gingiva, alveolar mucosa, buccal mucosa, and floor of the mouth represent the most common sites.
- The lesions are often found in the vicinity of teeth with large amalgam restorations, crowned teeth that probably had amalgams, around the apical region of endodontically treated teeth with retrograde restorations or obturated with silver points, and in areas in and around healed extraction sites.
- Amalgam tattoo of the head and neck skin may occur in dentists and represents an occupational hazard resulting from failure to use facial protective barriers.

Graphite Tattoos

- Graphite tattoos are an unusual source of focal exogenous pigmentation.
- They are most commonly seen on the palate and gingiva and represent traumatic implantation of graphite particles from a pencil.
- Solitary gray or black macule.
- When the graphite tattoo involves areas of cosmetic concern, removal of the lesion and a subsequent autogenous connective tissue graft provide a highly esthetic outcome.

Ornamental Tattoos

- Mucosal tattoos in the form of lettering or intricate artwork are becoming increasingly common phenomena.
- Amateur tattoo inks are permanent and consist of simple, carbon particles originating from a variety of sources, including burnt wood, plastic, or paper, and from a variety of inks, such as India ink, pen ink, and plant-derived matter.
- Q-Switched laser therapy has been used successfully to remove tattoos of the oral mucosa.
- In certain tribal cultures, esthetically pleasing pigment is plant derived. An unusual South African female tribal custom includes brushing the teeth and gums with a chewed root of the tree Euclea natalensis, with the belief that it promotes oral health. This plant root contains naphthoquinones and other organic substances that have putative antibacterial properties. Naphthoquinones are pigmented, and the mouths of root users are typically bright orange. Unlike ornamental tattoos, this form of pigmentation is usually transient and reversible.

Medicinal Metal-Induced Pigmentation

- Gold therapy.
- Colloidal silver: "complementary and alternative medicine therapies.
- Gold and colloidal silver have both been associated with diffuse cutaneous pigmentation.
- Silver may cause a generalized blue-gray discoloration (argyria), whereas gold-induced pigment may appear blue-gray or purple (chrysiasis).
- Chronic use of toothpaste and mouthwash has been associated with focal mucocutaneous pigmentation.
- Generalized black pigmentation of the tongue has been attributed to the chewing of Bismuth subsalicylate tablets, a commonly used antacid.

Heavy Metal Pigmentation

- Diffuse oral pigmentation may be associated with ingestion of heavy metals.
- Occupational and health hazard for some individuals who work in certain industrial plants and for those who live in the environment in and around these types of facilities.
- Other environmental sources - paints, old plumbing, and seafood.
- Lead, mercury, bismuth, and arsenic have all been shown to be deposited in oral tissue if ingested in sufficient quantities over an extended period of time.
- These ingested metal salts tend to extravasate from vessels in areas of chronic inflammation.
• The pigmentation is usually found along the free marginal gingiva, where it often dramatically outlines the gingival cuff.
• This metallic line usually has a gray to black appearance. In some patients, the oral pigmentation may be the first sign of heavy metal toxicity.
• Additional systemic signs and symptoms of heavy metal poisoning may include behavioral changes, neurologic disorders, intestinal pain, and salivary fever.
• Diffuse mucocutaneous melanosis may also be observed in some affected individuals.

**Drug-Induced Pigmentation**

• Minocycline, which is a tetracycline derivative and frequently used in the treatment of acne, is a relatively common cause of drug-induced nonmelanin-associated oral pigmentation.
• Minocycline metabolites may become incorporated into the normal bone. Thus, although the teeth may appear normal in appearance, the surrounding bone may appear green, blue, or even black.
• As a result, the palatal and alveolar mucosa may appear similarly and diffusely discolored. In addition, roots show a green color, whereas developing roots tend to be black.
• Methacycline and Imatinib cause mucosal pigmentation.

**Vascular lesions**

- Infantile hemangioma
  - Flat popular lesion - bright red (superficial), purple, blue, or normal skin color (deep)
- Congenital hemangioma
  - Red-purple color plaques with coarse telangiectasia, or flat, violaceous lesions, or as a grayish tumor surrounded by a pale halo with multiple tiny telangiectasis
- Kaposiform hemangioendothelioma
  - Tiny purple or red spots and blue ulcerative discoloration near or around the lesion
- Pyogenic granuloma
  - Red-purple, pedunculated nodule
- Capillary malformation
  - Flat or small papules, or small vascular malformation
- Arteriovenous malformation
  - Red-violaceous macule

**Sturge-Weber syndrome (encephalotrigeminal angiomatosis)**

• It is a congenital, non-hereditary condition of unknown etiology.
• The disease shows facial port-wine stain, ocular abnormalities (glaucoma and choroidal hemangioma), and leptomeningeal angiomata.
• Most common manifestation is the angiomatous lesion of gingiva that varies from slight vascular hyperplasia to massive hemangiomatous proliferation.
• There is an increase in the vascular component and gingival hemorrhage at minimal trauma.

**Hairy Tongue**

• The change in oral flora associated with chronic antibiotic therapy may be causative in some patients.
• The filiform papillae are elongated, have the appearance of fine hairs. The hyperplastic papillae then become pigmented by the colonization of chromogenic bacteria, which can impart a variety of colors, including white, green, brown, or black.
• Smoking of tobacco or crack cocaine has been associated with black hairy tongue.
• Black hairy tongue has also been associated with other pharmacologic agents such as tetracycline, linezolid, olanzapine, bismuth, and psychotropic medications.
OTHER SYNDROMES ASSOCIATED WITH HYPERPIGMENTATION

- Cowden syndrome
- Cronkhite–Canada syndrome
- De novo–Degos syndrome
- Naegeli–Franceschetti–Jadassohn syndrome
- LEOPARD syndrome
- Nelson's syndrome

TREATMENT OF MUCOCUTANEOUS MELANOSIS

Perioral and facial pigmentation are more challenging to treat since the skin type may dictate the occurrence of postoperative complications including post-inflammatory hyperpigmentation. Experimental forms of phototherapy have also been employed, including intense pulsed light and fractional photothermolysis.

First-line therapy remains the application of topical medications—bleaching creams. Although single agents such as azelaic acid or hydroquinone have been used, more commonly, dual- or triple-combination therapy is recommended. A combination of 4% hydroquinone (0.08%) retinoic acid (0.01%) fluocinolone acetonide has proven to be effective in greater than 90% of patients. However, the majority of patients undergoing such therapy may experience immunologic sensitivity or other treatment-related adverse events, including the development of exogenous ochronosis.

Different thickness flaps, gingivectomy, cryotherapy, electrosurgery, bur abrasion, and scraping with a scalpel have been successfully used to treat gingival pigmentation.

Laser therapy has also proven to be an effective modality for use in the treatment of both oral and pigmentation. Various types of lasers have been used, including super pulsed CO2, Q-switched Nd:YAG, and Q-switched alexandrite lasers.

Conclusion

- Pigmented lesions within the oral cavity may present a diagnostic dilemma for the clinician.
- A differential diagnosis for a pigmented lesion may include traumatic, reactive, neoplastic, and systemic pathologies.
- A clinico-pathologic correlation is often required to ensure accurate diagnosis of systemic causes of diffuse pigmentation.
References

- Textbook of oral pathology: Shafer's 7th edition
Radiation Biology

Study of effects of ionizing radiation on living systems

Sources of Radiation

- Natural radiation (83%) - 3.1 mSv/300 mrem
- Artificial radiation (17%) - 0.6 mSv/60 mrem

SOURCES OF RADIATION:
- Radon 2 mSv (55%)
- Cosmic 0.27 mSv (8%)
- Rocks/soil 0.28 mSv (8%)
- Food/water 0.4 mSv (11%)
- Medical x-rays 0.39 mSv (11%)
- Nuclear medicine 0.14 mSv (4%)
- Consumer products 0.1 mSv (3%)
- Other sources <0.01 mSv (<1%)

Radiation biology

Study of effects of ionizing radiation on living systems

History

First recorded experiment in radiobiology - performed by Becquerel when he intentionally left a radium container in his vest pocket.
2 weeks later - erythema - ulceration - several weeks to heal
Pierre Curie - 1901 - repeated the experiment - radium burn on his forearm

What does radiation do inside the body?

Photons interaction with biological molecules - free radical production

How do X-rays cause damage?

Ionization - is a process where an atom or group of atoms loses one or more electrons

The rate of loss of energy from a particle as it moves along its track through matter is its linear energy transfer (LET). Radiations with high LET have higher tendency for ionization → severe damage.

- The initial interaction between ionizing radiation and matter occurs at the level of the electron within first $10^{-13}$ sec after exposure.
- The generation of free radicals occurs in less than $10^{-10}$ sec after the passage of a photon.

Absorption of x-rays:
1. Compton Effect
2. Photoelectric Effect

The diagrams represent the Compton and Photoelectric Effects.
Interaction of radiation with biological molecules

1. Direct or Target Action Theory (1/3rd)
2. Indirect Action or Poison Chemical Theory (2/3rd)

Interaction of radiation with biological molecules:

- Sparsely ionizing radiations such as x-rays or gamma-rays induce damage mainly through indirect effect while densely ionizing radiations such as neutrons and alpha particles cause damage primarily through direct effect.
- Indirect effects can be altered with use of radioprotectors during radiotherapy while direct not.

Effect on biological molecules:

- Proteins
  - Denaturation
  - Induce inter & intra-molecular cross-linking
  - Disruption of secondary and tertiary structure
- Nucleic acids
  - Primary mechanism of radiation induced cell death
  - Change or loss of base
  - Disruption of hydrogen bonds between DNA strands
  - Breakage of DNA strands
  - Cross-linking of DNA strands

Effects at cellular levels:

- Intracellular
  - Nucleus – most sensitive; inhibition of cell division
  - Cell cytoplasm – increased permeability to Na & K ions, swelling & disorganization of mitochondria, focal cytoplasmic necrosis
  - Telomerase is produced – cell becomes immortal
  - Chromosomes – single or double armed chromosomal aberrations
Aberrations

- **Chromosome aberrations** – irradiated early in interphase, before the chromosome material has duplicated – break in both chromatids strands

- **Chromatid aberrations** – irradiated later in interphase, after DNA material has doubled – break seen in one chromatid strand

**EFFECT ON CELL KINETICS**

**Effects on cell kinetics**

- Mitotic delay
- Bystander effect
- Cell death
- Recovery

**CELL CYCLE CHECK POINTS**

- To prevent progression of defective DNA through cell cycle
  - two check points – G1S and G2M

**CELL CYCLE CHECK POINTS**

<table>
<thead>
<tr>
<th>CHECK POINT</th>
<th>BEFORE A CELL MAKES THE FINAL COMMITMENT TO REPLICATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1-S CHECK</td>
<td>Before a cell makes the final commitment to replicate, the G1/S checkpoint checks for DNA damage;</td>
</tr>
<tr>
<td>POINT</td>
<td>- If damage is present, the DNA-repair machinery and mechanisms that arrest the cell cycle</td>
</tr>
<tr>
<td></td>
<td>- The delay in cell cycle progression provides the time needed for DNA repair;</td>
</tr>
<tr>
<td></td>
<td>- If the damage is not repairable, apoptotic pathways are activated to kill the cell.</td>
</tr>
</tbody>
</table>
The G2/M checkpoint monitors the completion of DNA replication and checks whether the cell can safely initiate mitosis and separate sister chromatids. This checkpoint is particularly important in cells exposed to ionizing radiation. Cells damaged by ionizing radiation activate the G2/M checkpoint and arrest in G2; defects in this checkpoint give rise to chromosomal abnormalities.

**Recovery:**
- Enzymatic repair of single-stranded breaks of DNA
- Damage to both strands: lethal to cell.

**Mitotic delay**
- Radiation affects the expression of both cyclins and cyclin-dependent kinases
- Delay in cellular progression through cell division

**Cell death**
- Cell death can occur by two ways
  1. Mitotic death
  2. Apoptosis
- Mitotic death: Also called reproductive death
  - Dominant mode of cell killing
  - Cell dies when they attempt to divide
  - Double strand breakage in DNA frequent cause of cell death
  - Mean lethal dose for loss of proliferative capacity - 2Gy

**Mitotic delay**
- Low dose: Mild delay in G2 phase
- Moderate dose: G2 block
- Larger doses: Incomplete recovery
2. Apoptosis:
- Typically observe after low radiation dose
- occurs within hours after radiation exposure seen in lymphomas, serous cells of salivary glands
- lead to rapid onset xerostomia after moderate dose of radiations

**RADIosenSITIVITY AND CELL TYPE**

- Different cells from various organs of the same individual may respond to irradiation quite differently
- This variation was recognized as early as 1906 by the French radiobiologists and is called "Law of Bergonie and Tribondeau".

**BOX 2-1 Relative Radiosensitivity of Various Organs**

<table>
<thead>
<tr>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid organs</td>
<td>Fine vasculature</td>
<td>Neurons</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Growing cartilage</td>
<td>Muscle</td>
</tr>
<tr>
<td>Lungs</td>
<td>Salivary glands</td>
<td>Liver</td>
</tr>
</tbody>
</table>

**RADIosenSITIVITY AND CELL TYPE**

- MODIFIED BY ANCEL AND VITEMBERGER
- The appearance of radiation damage is dependent on 2 factors
  - Biologic stress on the cell (most important biologic stress—cell division—rapidly dividing cells express damage earlier; slowly dividing cells express later)
  - Conditions to which the cell is exposed pre and post irradiation
**Rubin and Casarett Classification**

- Classification of cellular populations based on reproductive kinetics into five categories.
- To explain the difference in observed cellular and tissue radiosensitivity based on the reproductive and functional characteristics of various cell lines.

| Vegetative intermitotic cells | Most radiosensitive  
|                              | Primitive in differentiation  
|                              | High mitotic rate  
|                              | E.g. cells of spermatogenic and erythroblastic series, basal cells of oral mucous membrane.  
| Differentiating intermitotic cells | Less radiosensitive than vegetative cells  
|                              | Divide regularly  
|                              | Undergo some differentiation between divisions  
|                              | E.g. inner enamel epithelium of developing teeth, cells of hematopoietic series, spermatocytes and oocytes.  
| Multi potential connective tissue cells | Have intermediate sensitivity  
|                              | Divide when there is demand for more cells  
|                              | E.g. endothelial cells, fibroblasts, mesenchymal cells  
| Reverting post mitotic cells | Radio resistant because they divide infrequently  
|                              | E.g. acinar, ductal, parenchymal cells of glands.  
| Fixed post mitotic cells | Most resistant  
|                              | Highly differentiated cells incapable of division  
|                              | E.g. neurons, striated muscle cells, epithelial cells, erythrocytes.  

**Michalowski Classification**

- **H-Type populations**
  - Tissues with hierarchical organisation: include bone marrow, intestinal epithelium, epidermis and many others.
  - Basal layer of proliferating stem cells and superficial layers of non-proliferating functional cells.
  - Radiation injury appears at a predictable time determined by life span of mature cells, when they are depleted by normal physiological wear and tear.
  - E.g. radiation mucositis appears 2 weeks after onset of RT.

- **F-Type populations**
  - Composed of functional parenchyma.
  - Has very low turnover rate.
  - Flexible: Regain reproductive function in event of tissue loss.
  - E.g. bone, soft tissue, endocrine tissue.
  - Fibrosis of tissues following RT.

**Biologic Effects of Radiation**
Classification of biologic effects of radiation

1. Somatic & Genetic Effects
2. Stochastic & Deterministic Effects
3. Short-term vs. Long-term Effects

1. Somatic vs. Genetic Effects

<table>
<thead>
<tr>
<th>Somatic</th>
<th>Definition</th>
<th>Effects</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acute</td>
<td>leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic</td>
<td>small amount absorbed repeatedly over long time (latent period ≥20 yrs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Definition</th>
<th>Effects</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Radiation to reproductive organs damage the DNA of sperm or eggs</td>
<td>Congenital abnormality</td>
</tr>
</tbody>
</table>

2. Stochastic vs. Deterministic Effects

<table>
<thead>
<tr>
<th>Stochastic</th>
<th>Traits</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No threshold dose</td>
<td>Every exposure to ionizing radiation carries with it the possibility of inducing a stochastic effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation of skin &amp; certain tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deterministic (non stochastic)</th>
<th>Traits</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>certainly effects</td>
<td>Threshold dose</td>
<td>Lethal DNA damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tissue and organ function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Examples</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xeroderma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otosclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cataracts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal development</td>
</tr>
</tbody>
</table>

3. Short-term vs. Long-term Effects

<table>
<thead>
<tr>
<th>Traits</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>effects</td>
<td>sensitivity of its parenchymal cells</td>
</tr>
<tr>
<td></td>
<td>high radiosensitive - mitosis-linked cell death</td>
</tr>
<tr>
<td></td>
<td>Muscle - low radiosensitive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-term effects</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depend primarily on extent of damage to the vasculature</td>
<td>Progressive fibroatrophy of the irradiated tissue</td>
</tr>
</tbody>
</table>

FACTORS MODIFYING EFFECT OF RADIATION
**FACTORS : MODIFY EFFECT OF RADIATION**

**DOSE**

- The severity of deterministic damage seen in irradiated tissues or organs depends on the amount of radiation received.
- All individuals receiving doses above the threshold level show damage in proportion to the dose.

**Dose Rate**

- A high dose rate causes more damage than exposure to the same total dose given at a lower dose rate.
- When organisms are exposed at lower dose rates, a greater opportunity exists for repair of damage, thereby resulting in less net damage.

**Oxygen**

- Presence of oxygen alters how cells process free radicals.
- In presence of oxygen free radicals lead to irreparable lethal changes.

**OXYGEN ENHANCEMENT RATIO:**

- Magnitude of the effect of oxygen on radiosensitivity.
- Ratio of hypoxic to aerated cells to achieve the same biologic effect.
- Sparsely ionizing radiation: 2.5-3

**Cellage in division cycle**

- Cells in late G2 – most radiosensitive.
- S phase – radioresistant.
- Late G1 and early S – intermediate sensitivity.

**Linear Energy Transfer**

- Higher-LET radiations (α particles) are more efficient in damaging biologic systems because their high ionization density is more likely than x rays to induce double strand breakage in DNA.
EFFECTS OF THERAPEUTIC RADIATION ON ORAL TISSUES

Effects of Radiation on the Oral Tissues

- Oral Mucous Membrane
- Salivary Glands
- Taste buds
- Teeth
- Bone

Oral Mucous Membrane - Basal layer - vegetative and differentiating inter-mitotic cells (radiosensitive)

2nd week after therapy - redness and inflammation (Mucositis)

PATHOPHYSIOLOGY OF ORAL MUCOSITIS

Salivary Glands

- Radiation induces fatty degeneration, fibrosis, acinar atrophy and cellular necrosis within the glands
- Serous acini are more radiosensitive
- Reduced saliva, thick and ropy
- Xerostomia

Salivary Glands

- Viscous saliva
- Decrease salivary flow
- pH on unit less = 5.5
- Buffering capacity decreases by 44%
- Irreversible effects occur at a total dose of 6,000 cGy for 5 weeks

Management

- Frequent sips of water, sugarless chewing gum, pilocarpine hydrochloride (5mg – 4 times a day), Bethanechol 25-200mg/day

Management

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Effects on Taste
- Partial or complete loss of taste if taste buds are irradiated
- Irradiation of posterior tongue → loss of bitter and acid flavours
- Irradiation of anterior tongue → loss of sweet and salt flavours
- Generally cells regenerate in 4 months

Management
Dietary consultation - improve quality of food
Zinc sulphate capsules - 220mg twice daily with food, elemental zinc - 100mg

Radiation effect on teeth
- Before calcification: Destroys tooth bud
- After calcification: inhibits cellular differentiation → malformation and arrested growth
- During development: Retards growth
- Eruptive Mechanism: Radioresistant
- In adults: No effect on calcified tissue
- Pulp: Fibroatrophy

Radiation Caries
- Radiation caries is a rampant form of dental decay that may occur in individuals who receive a course of radiotherapy that includes exposure of the salivary glands
- The carious lesions result from changes in the salivary glands and saliva, including reduced flow, decreased pH, reduced buffering capacity, and increased viscosity

- Because of the reduced or absent cleansing action of normal saliva, debris accumulates quickly
- Irradiation of the teeth by itself does not influence the course of radiation caries

Clinically, three types of radiation caries exist
- The most common is widespread superficial lesions attacking buccal, occlusal, incisal, and palatal surfaces
- Another type involves primarily the cementum & dentin in the cervical region
- These lesions may progress around the teeth circumferentially and result in loss of the crown
• A final type appears as a dark pigmentation of the entire crown

• The incisal edges may be markedly worn

Management
Hydrogen peroxide rinses 3% (maintenance of oral hygiene)
Topical fluoride applications

MUSCLES & JOINTS

• Trismus may develop due to tumour invasion of the masticatory muscles and/or the TMJ or

• be the result of radiotherapy if masticatory muscles and/or the TMJ is included in the field of radiation, or a combination of both

• Trismus develops 3-6 mths after radiation treatment is completed and frequently becomes a lifelong problem Ichimura and Tanaka, 1993

• Trismus is attributed to muscle fibrosis and scarring in response to radiation injury as well as to fibrosis of the ligaments around the TMJ and scarring of the pterygomandibular raphes

OSTEORADIONECROSIS

-Also known as post radiation osteonecrosis (PRON)
- first described by - Regaud in 1920
- serious deforming , debilitating complication of radiation therapy

PATHOPHYSIOLOGY:
1. Meyer in 1970:
   - triad of radiation , trauma and infection
   - irradiated bone → traumatic event → ingress of microorganisms → osteoradionecrosis

Failure :
- Failure to demonstrate bacterial invasion in compromised bone
- ORN can occur without any definable traumatic event
- poor response to treatment with antibiotic therapy

   - Cumulative tissue damage induced by radiation rather than trauma or bacterial invasion → hypocellular, hypovascular and hypoxic
3. Fibroatrophic theory:
- Introduced in 2004
- Key event in progression of ORN is activation and dysregulation of fibroblastic activity → atrophic tissue

Three distinct phases:
1. Prefibrotic phase: acute inflammatory response → changes in endothelial cells
2. Constitutive organized phase: abnormal fibroblastic activity → disorganization of ECM
3. Late fibroatrophic phase: attempted tissue remodelling → fragile tissue; carries inherent risk of reactivation of inflammation secondary to local trauma

-In head and neck region commonest site is mandible > maxilla > temporal bone > sphenoid bone > base of skull

Signs and symptoms:
- Pain
- Swelling
- Trismus
- Halitosis
- Exposed bone
- Pathological fracture
- Oro-cutaneous fistula

IMAGING STUDIES:
- Early changes: areas of decalcification
- Late changes: formation of sequestrum and involucrum
PREVENTION OF ORN:
- Recommendations given by Sleeper and Meyer
  1. Mouth should be made as clean as possible with scaling and irrigation
  2. All infections should be eliminated
  3. All infected and non vital teeth should be extracted
  4. All periodontally compromised teeth should be extracted
  5. All teeth in line of irradiation (good or bad)

MANAGEMENT OF OSTEO RADIONECROSIS:
- Control of infection if present
  - remove debris and gentle irrigation
- Supportive treatment with fluids + diet high in protein
  - pain management - narcotic analgesics, nerve blocks, nerve avulsion
  - hyperbaric oxygen therapy

HYPERBARIC OXYGEN THERAPY:
- Consist of exposing a patient to intermittent short term 100% oxygen inhalation at a pressure greater than 1 atmosphere
  - HBO → induce endothelial cell proliferation → neovascularization

Contraindications:
- Untreated pneumothorax
- Pregnancy
- Emphysema
- URTI, optic neuritis, ear problems

DETERMINISTIC EFFECTS OF WHOLE BODY RADIATION

Whole body radiation

- Acute Radiation Syndrome: The acute radiation syndrome is a collection of signs and symptoms experienced by individuals after a brief whole-body exposure to radiation

<table>
<thead>
<tr>
<th>Dose in Gy</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>Prodromal symptoms</td>
</tr>
<tr>
<td>2-4</td>
<td>Mild hematopoietic symptoms</td>
</tr>
<tr>
<td>4-7</td>
<td>Severe hematopoietic symptoms</td>
</tr>
<tr>
<td>7-15</td>
<td>Gastrointestinal symptoms</td>
</tr>
<tr>
<td>&gt;50</td>
<td>Cardiovascular and CNS symptoms</td>
</tr>
</tbody>
</table>

Acute Radiation Syndrome

- Prodromal symptoms
  - Minutes to hours after exposure
  - Anorexia, nausea, vomiting, diarrhea, fatigue and weakness
  - Higher the dose, the more rapid the onset and greater will be severity of symptoms
- Latent period
  - Extends from hours to days
  - Patient is apparently normal
Radiation causes damage to hematopoietic cells of bone marrow & spleen.

Remarkable fall in the number of granulocytes, platelets and erythrocytes.

Clinical signs: Infection, hemorrhage & anemia.

Death may occur 10 to 30 days after radiation.

**GI Syndrome**
- Rapidly proliferating basal epithelial cells of the intestinal villi are damaged.
- Loss of epithelial layer of the intestinal mucosa → loss of plasma & electrolytes.
- Reduced efficiency of intestinal absorption.
- Ulceration and hemorrhage in the intestines.
- Bacteria invade denuded areas → septicemia.
- Diarrhea, dehydration, loss of weight.
- Death occurs within 2 weeks, combination of fluid and electrolyte loss, infection and nutritional impairment.

**CVS and CNS syndrome**
- Irreversible condition.
- > 50 Gy causes death in 1-2 days.
- Circulatory system collapses, drastic fall in BP.
- Incoordination, disorientation, and convulsions.

**Late Effects**
- Growth & development.
- Cataracts.
- Shortened life span.

**General effects of radiation**

**i. Early or acute signs**
- Increased susceptibility to chapping.
- Intolerance to surgical scrub.
- Blunting & leveling of finger ridges.
- Britteness & ridging of finger nails.

**ii. Late or chronic signs**
- Loss of hair.
- Dryness & atrophy of skin – sweat glands destroyed.
- Pigmentations, telangiectasis, keratosis.
- Indolent type of ulcers.
- Possibility of malignant changes in tissue.
Hematopoietic injury – leucopenia, which in some cases may progress to leukemia, anemia, lymphopenia

Eyes
- Epilation of eyelashes
- Inflammation, fibrosis, & decreased flexibility of eyelids
- Dryness
- Ulceration & cataract

Ears
- Edema of mucosa & collection of fluid causing obstruction of Eustachian tube – Radiation Otitis Media
- Deafness due to rupture of ear drum

Testicles
- Suppression of germinal activity
- Alteration in fertility

Oral mucous membrane
- Reddening & inflammation (mucositis)
- Sloughing & pseudomembrane formation
- Secondary infection
- Obliteration of vasculature
- Fibrosis of underlying C/T
- Oral ulcerations

Taste buds – alterations in taste

Salivary glands – parenchymal component affected – fibrosis, adiposis, loss of fine vasculature.
- Xerostomia
- Composition of saliva altered
- Increased Na, Cl, Ca, Mg & proteins
- Loses lubricating property
- PH decreases – decalcification of enamel
- Compensatory gland hypertrophy

Adult teeth are resistant to radiation
- Prior to calcification tooth buds destroy
- During calcification defect in cellular differentiation - ↓sed vascularity, cellularity of pulp & prone to pulpitis
- Radiation caries

Bone
- Loss of vasculature & hematopoietic elements
- Marrow replaced by fatty marrow & fibrous connective tissue
- Lack of osteoblasts & osteoblastic activity
- Osteoradionecrosis following radiation
12. Whole body radiation
   - Acute radiation syndrome – death within one month
   - Late somatic effects – radiation induced cancers

Late Somatic Effects of Radiation

- Radiation leads to modification of biologic molecules
- Molecular changes may lead to alteration in cells and organisms
- If enough cells are killed → injury or death
- If cells are modified → cancer

Susceptibility of different tissues to radiation induced cancer

<table>
<thead>
<tr>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon, Stomach, lung, bone marrow (leukemia)</td>
<td>Breast (women), esophagus</td>
<td>Bladder, liver, thyroid, skin, bone surface, brain, salivary glands</td>
</tr>
</tbody>
</table>

- Radiation induced cancers are indistinguishable from cancers produced by other causes
- Risk is greater in childhood
- Most cancers appear approximately 10 yrs after exposure
- Risk of leukemia is higher than solid tumors; higher rate of cell division and differentiation of hematopoietic stem cells
EFFECT ON GROWTH AND DEVELOPMENT

- Children exposed to radiation → reduced height, weight, skeletal development
- Developing human brain is radiosensitive: in utero exposure → mental retardation (4% chance of mental retardation per 100 mSv at 8 to 15 weeks of gestation)

EFFECTS ON FETUS & UTERUS

- Preimplantation:
  - Dose of 0.2 Gy → death of embryo
- Organogenesis:
  - Congenital anomalies
- The fetal period:
  - Largest degree of growth retardation.

DOUBLING DOSE

- The amount of radiation a population requires to produce in the next generation as many additional mutations as arise spontaneously
- In humans: approx 2 Gy

CLINICAL APPLICATIONS

- Provides greater tumour destruction than is possible with a large single dose
- Increased cellular repair of normal tissue
- Increases the mean oxygen tension in an irradiated tumour

RATIONALE OF FRACTIONATION IN RADIOTHERAPY

- Repair of sublethal damage in normal cells
- Reassortment of cells within the cell cycle
- Repopulation of normal cells
- Reoxygenation of tumour bed

4 R’s of Radiobiology
BIOLOGIC BASIS OF DOSE FRACTIONATION

1. REPAIR OF SUBLETHAL DAMAGE:
   - Reflects the ability of cells to recover from damage that does not cause lethality
   - Repair capacity is greater in late responding tissues
   - Decreasing the dose per fraction will result in greater sparing of late responding tissues

2. REDISTRIBUTION:
   - First radiation dose preferentially kills cells in the sensitive phases
   - Cells surviving the first dose will resume their progression through cell cycle into more radiosensitive phases
   - Resulting in net sensitization to the next dose fraction
   - Redistribution results in net gain in therapeutic ratio

3. REGENERATION:
   - Depletion of cells following radiation or surgery triggers a regenerative response, resulting in net increase in cell production
   - Decrease normal tissue injury

4. REDOXENATION:
   - Hypoxic cells are radioresistant
   - Preferential elimination of more radiosensitive oxygenated cells increases oxygen availability to surviving hypoxic cells
   - Increase tissue sensitivity to radiation

According to standard therapeutic regimen:
Dose of 200cGY is delivered; 5 days a week for 5-6 weeks with total dosage of 50-60 Gy
ALTERED FRACTIONATION SCHEMES

1. HYPERFRACTIONATION:
   - Smaller fraction size (115-120cGy)
   - Two to three times in a day
   - Total dosage is larger (74-80Gy)
   - Treatment duration is same
   Advantages:
   - Improve therapeutic ratio
   - Redistribution of tumor cells into more radiosensitive phases due to multiple fractions
   - Differential sparing of late responding normal tissue

2. ACCELERATED FRACTIONATION:
   - Same fraction size (180-200cGy)
   - Two to three times in a day
   - Total dosage is similar
   - Treatment duration is short
   Advantages:
   - Reduce the opportunity for accelerated repopulation of cells

3. HYPOFRACTIONATION:
   - Larger fraction size (600-800cGy)
   - Fractions delivered with gap of several days
   - Total dosage is lower (2100-3200cGy)
   - Treatment duration is short
   Advantages:
   - Evolved for the treatment of malignant melanoma (conventional fractions allow tumor cells to recover between fraction intervals, high dose per fraction will overcome the reparative capacity of tumor cells)

RADIOSENSITIZATION

Target at:
- Reducing hypoxia
- Concomitant chemotherapy
- Targeted therapy

REDUCING HYPOXIA
- Correction of anemia
- Infusion of erythropoietin
- Hyperbaric oxygen therapy
- CONCOMITANT CHEMOTHERAPY
  - Decrease micrometastasis
  - Kill hypoxic cells (mitomycin active in hypoxic condition)
  - Kills radioresistant cells in S phase of cell cycle

RADIOPROTECTORS

Agents that when present prior to or shortly after radiation exposure alter the response of normal tissues to irradiation.
- Sulfhydryl compounds such as cysteine and cysteamine have long been known to act as radioprotectors via free radical scavenging → Alter the indirect effect of radiation → protection of normal tissue
The toxic biological effects of ionizing radiation, although complex, varied and incompletely understood, form the basis for the use of radiation therapy as a cancer treatment. These biological effects are initiated when packets of energy are deposited in a volume of tissue and remove electrons from constituent atoms through a process called ionization. Accordingly, the physics of radiation oncology is focused on the details of how, where, and how much energy can be deposited in diseased tissue in the hopes of eradicating it, while simultaneously minimizing the energy released in healthy tissue. This process requires an understanding of the nature of the radiation and the matter through which it passes and how that matter is changed as a result of the energy deposition events.

1. Oral radiology, principles & interpretation: White & pharoah
2. Essentials of dental radiography & radiology: Whaites
5. Dental management of the oncologic patient: DCNA 2008

ADVANCES IN RADIOTHERAPY

CONFORMATIONAL RADIOTHERAPY

1. MULTI-LEAF COLLIMATOR:
   - Enables flexible portal shaping
   - Achieve desired dose distribution with in target volume
   - Field-in-field technique

CONFORMATIONAL RADIOTHERAPY

2. 3D CRT / 3 DIMENSIONAL CONFORMATIONAL RADIOTHERAPY
   - Deliver high radiation dose in 3D volumes that conform to the shape of the tumor and involved nodes
   - Reduce dose administered to normal tissues
   - Can be delivered in two ways:
     A) Use of geometric field shaping analogues
     B) Combination of field shaping with modulation of intensity (IMRT)

THANKYOU
CONFORMATIONAL RADIOTHERAPY

- Careful delineation of macroscopic / gross tumor volume (GTV)
- Regions likely to harbor microscopic disease - clinically target volume (CTV)
- Planning target volume:
  : will exclude the normal tissue to be spared from radiations
  : will generate the volume to compensate patient movement or other inaccuracies

Hormesis

- Hormesis is a dose response phenomenon in which small doses of a toxin have the opposite effect of large doses
  - E.g. exposing mice to small doses of radiation shortly before exposing them to very high levels of radiation actually decreases the likelihood of cancer

- The initial low dose of radiation may activate certain repair mechanisms in the body and these mechanisms are efficient enough to not only neutralize the radiation effects but may even repair other defects not caused by the radiation

- There is a lot of debate about hormesis, but the general opinion is that this is not something that can be relied on when discussing the effects of radiation exposure