Development of the Respiratory System

- Embryology Overview
  - Doctor's Advice: Visualize Final Anatomy
- **Ectodermal Placodes**: Sensory Organ Development
  - Otic Placode
    - Site of auditory (inner ear) structures development
  - **Nasal Placode (Olfactory Placode)**
    - Thickening of surface **ectoderm**
    - Invaginates to form **nasal pit**
    - **Forms nostrils (nares)**
    - **Forms vestibules**
- **Facial Prominences**: Mesenchymal Centers of Growth
  - General Function
    - Mesenchymal origin
    - Shape skeletal structure of the face
  - **Frontonasal Prominence**
    - Develops in frontal bone region
    - Extends downwards
    - Gives rise to:
    - **Nasal septum (Superior Part)**
    - **Medial nasal prominences**
    - **Lateral nasal prominences**

Q13.The medial nasal prominence participate in all of the following except?

a) Tip of the nose
b) Palatine shelves
c) Nasal crest
d) Philtrum of upper lip
e) Upper jaw

  - **Lateral Nasal Prominences**
    - Form alae of the nose
    - **Form lateral wall of the nasal cavity**
  - **Medial Nasal Prominences**
    - Inter-Maxillary Segment Derivatives
      - **Philtrum of the upper lip**
      - **Medial one-third of the upper lip**
      - **Primary palate**
      - Alveolar part of the maxilla (upper four incisor teeth)

9. With development of the nose, the philtrum of the upper lip is developed from which of the following?
A) Frontonasal prominence
B) Maxillary prominence
C) Lateral nasal prominence
D) Medial nasal prominence
E) Palatal Prominence

ANSWER : D

  - **Maxillary Prominences**
    - Fuse with medial nasal prominences (**week 5**)
    - **Form lateral two-thirds of the upper lip**
    - Fusion completes in 2 weeks
    - Failure of fusion leads to **cleft lip** (unilateral or bilateral)

2. Cleft lip is a result of failure of fusion between maxillary prominence and
A) Lateral nasal process
B) Medial nasal processes
C) Mandibular prominence

ANSWER : A

  - **Nasal Septum** Developmental Parts
    - **Superior Part: Frontonasal Prominence**
    - **Inferior Part: Medial Nasal Prominences**
- Development of the **Nasal Cavities**
  - Division of Developing Nasal Cavity
    - Anterior – initial – part (Nares and Vestibule)
    - Posterior – deep – part (Definitive Nasal Cavity)
  - **Anterior** (Initial) Part Formation
    - Formed by **nasal pits** (**invagination of nasal placodes**)
    - Gives rise to external nares and nasal vestibule
    - Open to exterior early
  - **Posterior** (Deep) Part Formation
    - Formed by **medial and lateral nasal prominences**
    - Mesenchymal cells proliferate, filling cavity
    - Vacuolization and canalization recreate lumen
  - **Relationship to Oral Cavity and Palate**
    - Initially **separated by oronasal membrane**
    - **Membrane ruptures** → **Primitive Choana** (temporary communication)
    - **Formation of primary and secondary palates shifts choanae posteriorly** → **Definitive Choanae** (open into nasopharynx)
- Development of the **Paranasal Sinuses**
  - Origin
    - **Outgrowths from the lateral wall of the nasal cavity**
  - Initial Formation
    - Epithelial proliferation at openings into nasal cavity
    - Forms sinus duct
  - Cavity Formation
    - **Proliferating epithelium extends into adjacent bone**
    - **Canalization forms mucosa-lined cavity**
  - Growth and Maturation
    - Example: Maxillary Sinus
      - Opens into middle meatus via hiatus semilunaris
      - Proliferation forms duct, extends into maxilla
      - Canalization forms cavity within maxilla
- Primary and Secondary Palates
  - **Primary Palate**
    - Formed **from intermaxillary segment** (fusion of **medial nasal prominences**)
    - Continuous with inferior part of nasal septum
    - Contributes to initial division of nasal cavity
  - **Secondary Palate**
    - **Starts development week 6**
    - **From paired palatine shelves** (outgrowths of maxillary prominences/palatine bones)
    - Shelves grow medially above tongue
    - **Fuse in midline (week 7)**
    - Undergoes ossification → Hard Palate (anterior part)
    - **Palatine processes of maxilla + horizontal plates of palatine bones**
    - Posterior part remains non-ossified → **Soft Palate** and Uvula
    - Completely separates oral and nasal cavities
    - **Displaces primitive choanae posteriorly → Definitive choanae**
- Development of the **Incisive Foramen**
  - **Small opening** at junction of **primary and secondary palates**
  - Boundary between primary and secondary palates
  - **Allows passage** of **greater palatine nerve and vessels**
- Development of the **Soft Palate** and **Uvula**
  - Origin
    - **Posterior extensions of palatine shelves** (**do not ossify**)
    - Develop from paired palatine shelves
    - Requires midline fusion
  - Timeline
    - **Soft palate: around 8th week**
    - **Uvula: around 11th week**
  - **Bifid Uvula**
    - **Incomplete fusion of paired embryonic components**
- Development of the **Respiratory System** (General)
  - Gut Tube Segments
    - Pharyngeal gut
    - **Foregut (Gives rise to respiratory diverticulum)**
    - Midgut
    - Hindgut
  - Respiratory Diverticulum Formation (**Week 4**)
    - Stimulated by FGFs on ventral wall of **foregut**
    - Induces formation of **respiratory bud**
    - **Bud** expands to form respiratory diverticulum
    - Proliferates and differentiates sequentially: trachea, primary, secondary, tertiary bronchi, bronchioles, alveoli
  - Tissue Origins (Larynx, Trachea, Bronchi, Lungs)
    - Epithelium: Endodermal origin
    - Cartilaginous, **muscular, connective tissue: Splanchnic mesoderm** surrounding foregut
- Separation of the Respiratory Tract from the Foregut
  - Initial Formation
    - Ventral outpouching of foregut (respiratory diverticulum)
  - Formation of Tracheoesophageal Ridges (Week 5)
    - Paired longitudinal ridges **on lateral walls of foregut posterior to diverticulum**
  - **Dev**elopment of Tracheoesophageal Septum
    - Ridges proliferate and fuse in midline
  - Final Separation
    - **Septum** divides primitive foregut into:
    - **Anterior respiratory tube (trachea, lung primordium)**
    - **Posterior esophagus**

5. The development of the tracheoesophageal septum occurs at week:
A) 2
B) 3
C) 4
D) 5
E) 6

ANSWER : D

4. During early development of the respiratory system the laryngotracheal tube maintains in communication with the primitive foregut. Which of the following embryonic structure is responsible for partitioning these two embryonic structure ?
A) Laryngotracheal diverticulum
B) Tracheoesophageal septum
C) Tracheoesophageal fistula
D) Laryngotracheal septum
E) Tracheoesophageal fold

ANSWER : B

- Development of the **Laryngeal Orifice**
  - Only persistent embryonic communication between pharynx and developing respiratory tract
  - Remodels to form **adult laryngeal inlet**
  - Initially **slit-like**
  - Becomes temporarily **T-shaped**
  - Eventually forms adult-shaped laryngeal inlet
- Development of the Esophagus
  - Lengthening
    - Elongates due to descent of heart and caudal displacement of lungs
  - Muscular Development
    - Upper 1/3: Striated (skeletal) muscle
    - Lower 2/3: Smooth muscle
  - Innervation
    - Upper (striated) part: Vagus nerve (CN X) motor fibers
    - Lower (smooth muscle) part: Autonomic nerves from splanchnic plexus

8. wrong about tracheoesophageal fistula or atresia:

ANSWER : it causes pulmonary hypoplasia

11. an infant with polyhydraminous that was born with a lot of amniotic fluid in his mouth,which of the following is mostly the cause:

ANSWER : proximal esophageal atresia with TEF

- **Anomalies of the Trachea** and Esophagus
  - Esophageal Atresia and Tracheoesophageal Fistula (TEF)
    - Complications of Proximal EA with Distal TEF
      - During Fetal Life: Polyhydramnios (impaired amniotic fluid absorption)
      - After Birth:
      - Feeding difficulties (regurgitation)
      - Respiratory complications (chronic infections, pneumonia)
      - Abdominal distension (air enters stomach via fistula)
      - Surgical correction indicated immediately

7. baby suffers from vomiting and regurgitation upon feeding:

ANSWER : Esophageal atresia and trachea-esophageal fistula.

  - VACTERL Association
    - Constellation of anomalies often occurring with esophageal atresia:
    - V – Vertebral anomalies
    - A – Anal atresia
    - C – Cardiac defects (most common association, e.g., VSD, ASD, Tetralogy of Fallot)
    - T – Tracheoesophageal fistula
    - E – Esophageal atresia
    - R – Renal anomalies
    - L – Limb anomalies
  - **Tracheal Atresia and Stenosis**
    - **Rare** congenital abnormality
    - **Web-like** tissue **obstructs airflow**
    - Surgical correction indicated immediately
- Development of The Larynx
  - Tissue Origins
    - Epithelial lining: Endoderm
    - **Cartilages** and muscles: **Splanchnic mesoderm** of **4th and 6th** pharyngeal **arches**
- Development of the **Laryngeal Lumen**
  - Process
    - Epithelial proliferation → Temporary occlusion
    - Vacuolization and recanalization
    - Upper part: Reopens lumen
    - Below vestibular folds: Uneven breakdown → Laryngeal ventricles
    - Ventricles separate tissue into vestibular (false) and vocal (true) folds
    - Laryngeal saccules develop as superior extensions from ventricles

10. C-shaped trachea cartilage is derived from:

ANSWER : Splanchnic mesoderm

  - Stages
    - **Proliferation → Occlusion → Recanalization → Ventricles → Folds + Saccules**
  - Muscular Development and Innervation
    - **4th pharyngeal arch** muscles (**Cricothyroid**): **External laryngeal nerve** (branch of SLN)
    - **6th pharyngeal arch** muscles (**All other intrinsic laryngeal muscles**): **Recurrent laryngeal nerve**
- Anomalies of the Larynx
  - **Laryngeal Atresia**
    - Pathophysiological Changes
      - 1. **Enlarged**, echogenic lungs (**fluid accumulation**)
      - 2. **Flattened** diaphragm (**downward pressure from lungs**)
      - 3. Increased intrathoracic pressure → **Ascites**, **hydrops fetalis**
    - Diagnosis
      - Prenatal ultrasonography: **enlarged** echogenic lungs, **flattened diaphragm**, **ascites**, hydrops

3. Laryngeal atresia, all of the following statements are correct except :
A) Prenatal ultrasonography permits diagnosis of these anomalies
B) It is a rare anomaly
C) Distal to atresia the airways become constricted
D) It is accompanied with fetal ascites
E) It is known as congenital high airway obstruction syndrome

ANSWER : C

- Lungs and Bronchial Tree Development
  - Initial Development
    - Lung development begins with trachea formation **from respiratory diverticulum**
    - Trachea divides into right and left primary bronchi at T4 level
  - **Primary Bronchi**
    - First branching of bronchial tree
    - Enter respective lungs
  - Secondary **(Lobar)** Bronchi
    - Intrapulmonary divisions of primary bronchi
    - Correspond to lung lobes:
    - **Right lung: 3** (Superior, Middle, Inferior)
    - **Left lung: 2** (Superior, Inferior)
  - Tertiary **(Segmental)** Bronchi
    - Supply bronchopulmonary segments
    - **Right Lung: 10 Segmental Bronchi**
    - **Upper lobe**: Apical, Posterior, Anterior
    - Middle lobe: Lateral, Medial
    - Lower lobe: Superior, Medial basal, Anterior basal, Lateral basal, Posterior basal
    - **Left Lung:** 8–10 Segmental Bronchi
    - **Upper lobe**: **Apicoposterior**, Anterior, Superior lingular, Inferior lingular
    - **Lower lobe**: Superior, **Anteromedial basal**, Lateral basal, Posterior basal

9. The lack of the development of cartilage in the bronchus causes:

ANSWER : bronchial stenosis

- Malformation of The Respiratory Tract
  - Embryology
    - Lungs and Bronchial Tree Development
      - Respiratory Diverticulum Origin
        - Arises from the anterior wall of the foregut
        - Separation process divides respiratory and digestive systems
        - Begins with a longitudinal cleft (fold)
        - Develops into the tracheoesophageal septum
        - Completely separates the trachea from the esophagus
      - Laryngeal Inlet
        - Only remaining connection between pharynx and larynx
        - Changes from slit-like to T-shaped, then heart-shaped opening
    - Trachea, Bronchi, and Lungs Development
      - Trachea Development
        - Develops from bronchial buds (initially lung buds)
        - Arising from the endoderm of the anterior foregut
        - Endodermal cells form the epithelial lining
        - Cartilage, smooth muscle, and connective tissues from splanchnic mesoderm
        - Elongates caudally
        - At T4 level, divides into primary (main) bronchi
      - Bronchi Development
        - Primary bronchi divide into secondary bronchi
        - Three on the right, two on the left
        - Called lobar bronchi according to lung lobes
        - Secondary bronchi divide into tertiary (segmental) bronchi
        - Each supplies a bronchopulmonary segment
        - 10 bronchopulmonary segments in the right lung
        - Usually 8–10 in the left lung
      - Bronchioles Development
        - After tertiary bronchi, airways divide into bronchioles
        - Two types: conducting and respiratory
        - Conducting bronchioles divide dichotomously, forming tree-like branches
        - Branching occurs in the pericardioperitoneal canal
      - Lung Bud Expansion
        - With caudal and lateral growth, lung buds expand into the body cavity
        - Spaces for lungs and pericardioperitoneal canals narrow
        - Canals lie on each side of the foregut
      - Intraembryonic Coelom Subdivision
        - Subdivided into: pericardial cavity, two pleural cavities, peritoneal cavity
        - Pleuropericardial folds separate pleural from pericardial cavities
        - Pleuroperitoneal folds separate pleural from peritoneal cavities
        - Pericardioperitoneal canals persist as primitive pleural cavities

          18. The definitive pleural cavity is formed by:
          A) Incorporation from pericardial pleura
          B) Incorporation from peritoneal pleura
          C) Somatopleuric mesenchyme
          D) Splanchnopleuric mesenchyme

          ANSWER : C
      - Pleural Cavity Composition
        - Visceral pleura: from splanchnic mesoderm covering the lung
        - Parietal pleura: from somatic mesoderm covering the body wall
        - Space between them is the pleural cavity
      - Bronchial Tree Branching Generations
        - Secondary bronchi divide repeatedly to form tertiary bronchi (bronchopulmonary segments)
        - 10 tertiary bronchi in the right lung, 8 in the left
        - By end of 6th month: ~17 generations of subdivisions
        - Postnatal life: additional 6 divisions, totaling 23 generations
        - Branching signals: Fibroblast Growth Factor (FGF) family from mesoderm

          17. The number of segments in the lung after the postnatal period is
          A) 27
          B) 15
          C) 10
          D) 23
          E) 6

          ANSWER : D
    - Maturation of the Lungs
      - Definition
        - Development and functional differentiation of distal lung structures beyond bronchioles
        - Involves formation of respiratory bronchioles, alveolar ducts, alveolar sacs, alveoli
        - Alveolar-capillary (respiratory) membrane develops within alveoli for gas exchange

          12. Concerning the maturation of the lung, all the following statements are correct EXCEPT :
          A) Growth of lung after birth is mainly due to increase in the number of the alveoli .
          B) In terminal sac period, respiration is impossible .
          C) At the end of the 6th month type I and type II alveolar cells are developed .
          D) The canalicular period lasts from 16th to 26th weeks .
          E) In pseudoglandular period, no respiratory bronchioles or alveoli is present .

          ANSWER : B
      - Stages of Lung Maturation
        - Pseudoglandular Stage (up to 4 months)
        - Respiratory membrane not developed yet
        - Canalicular Stage (4–6 months)
        - Respiratory membrane developing
        - Terminal Saccular Stage (7–9 months)
        - Respiratory membrane is developing
        - Alveolar Stage (8 months – 10 years)
        - Extensive alveolarization
      - Clinical Implications of Maturation Stages
        - Viability of neonate governed by respiratory membrane development
        - Pseudoglandular stage: survival impossible (no gas-exchange membranes)
        - Late canalicular stage: survival possible with intensive care (surfactant, ventilation)
        - Terminal saccular stage: improved prognosis due to terminal sac expansion
        - Alveolar stage: postnatal growth primarily via increased alveoli number (1/6 at birth, 5/6 postnatally)

          20. Which of the following is wrong:

          ANSWER : the growth of alveoli after birth is mainly by increase in size

          number
      - Canalicular Phase Details (up to 7th prenatal month)
        - Bronchioles divide continuously into smaller canals
        - Most cells are cuboidal
        - Capillaries distant from air spaces
        - Respiration becomes possible when cuboidal cells flatten into thin cells
      - Terminal Sac Phase Details (7th month onwards)
        - Cuboidal cells thin out into simple squamous cells
        - Intimately associated with blood and lymph capillaries
        - Surrounding spaces: terminal sacs or primitive alveoli
        - Sufficient capillaries by 7th month for adequate gas exchange (premature infant survival) 7 month = 28 week

          16. A premature baby usually has difficulty breathing. However the respiratory system developed enough for survival by:
          A) 17 weeks
          B) 29 weeks
          C) 24 weeks
          D) 38 weeks
          E) none of the above

          ANSWER : C

          19. Wrong about terminal sac period of lung maturation:

          ANSWER : lack of respiratory membrane
      - Alveolar Phase Details (last 2 months prenatal and postnatal)
        - Number of terminal sacs increases steadily
        - Type I alveolar epithelial cells thin out, allowing capillaries to protrude
        - Blood-air barrier formed by intimate contact of epithelial and endothelial cells
        - Type II cells mature and increase surfactant production
        - Mature alveoli not present before birth
      - Surfactant Production and Lung Fluid
        - Type II alveolar epithelial cells produce surfactant
        - Surfactant reduces surface tension, allowing alveolar inflation
        - Before birth: lungs filled with fluid (high chloride, low protein, mucus, surfactant)
        - Surfactant amount increases in the last 2 weeks before birth

          21. Wrong about surfactant:

          ANSWER : Usually deficient in "term" babies
      - Fetal Breathing Movements
        - Begin before birth, causing amniotic fluid aspiration
        - Stimulate lung development and condition respiratory muscles
      - Respiration at Birth
        - Most lung fluid resorbed by blood/lymph capillaries
        - Small amount expelled via trachea/bronchi
        - Surfactant remains as a phospholipid coat on alveolar cell membranes
        - Prevents high surface tension with air entry
        - Prevents atelectasis (alveolar collapse during expiration)
      - Insufficient Surfactant Management
        - Medical intervention needed for respiratory distress
        - Exogenous (synthetic) surfactant administration
        - Prenatal stimulation: Betamethasone (corticosteroid) to mother
        - Thyroxine (thyroid hormone) stimulates Type II cell maturation and surfactant secretion
      - Postnatal Lung Growth
        - Respiratory movements bring air, lungs expand
        - Alveoli increase slightly in size
        - Postnatal growth primarily due to increased number of respiratory bronchioles and alveoli
    - Anomalies of the Lung
      - Clinical Notes: Respiratory Distress Syndrome (RDS)
        - Surfactant crucial for premature infant survival
        - Insufficient surfactant -> high air-water surface tension -> alveolar collapse during expiration
        - Leads to Respiratory Distress Syndrome (RDS)
        - Common cause of death in premature infants (30% neonatal diseases)
        - Partially collapsed alveoli contain: high protein fluid, hyaline membranes, lamellar bodies (from surfactant)

          15. Wrong about ARDS
          A) Thyroxine is the most important stimulator
          B) Causes collapsing of the alveoli
          C) Accounts for 2% of death in neonates

          ANSWER : C
      - Clinical Notes: Hyaline Membrane Disease
        - RDS also known as hyaline membrane disease
        - Accounts for ~20% of newborn deaths
        - Intrauterine Asphyxia can cause irreversible changes in Type II cells
        - Treatments: artificial surfactant, glucocorticoids (betamethasone) to stimulate production
        - Allowed survival of babies as young as 5.5 months gestation
        - Thyroxine is the most important stimulator for surfactant production
      - Clinical Notes: Other Anomalies
        - Gross abnormalities (e.g., blind-ending trachea, absent lungs, agenesis of one lung) are rare
        - Abnormal divisions of bronchial tree more common
        - Result in supernumerary lobules
        - Little functional significance, but can cause difficulties during bronchoscopies
      - Ectopic Lung Lobes
        - Arise from trachea or esophagus
        - Formed from additional respiratory buds of the foregut
        - No serious outcomes
      - Congenital Cysts of the Lung
        - Most clinically important anomaly
        - Formed by dilation of terminal or larger bronchi
        - Small and multiple: honeycomb appearance
        - Larger, restricted cysts possible
        - Poor drainage, frequent chronic infections, insufficient gas exchange
        - Treated by surgical excision
    - Lung Hypoplasia
      - Definition
        - Reduced lung size
      - Causes
        - Infants with Congenital Diaphragmatic Hernia (CDH)
        - Lung compressed by abdominal viscera (more common on left)
        - Reduced lung volume
        - Most infants die of pulmonary insufficiency
        - Severe Oligohydramnios (reduced amniotic fluid)
        - Retarded lung development
        - Severe pulmonary hypoplasia results

          13. Which of the following conditions are associated with oligohydramnios:
          A) Laryngeal atresia
          B) Tracheoesophageal fistula
          C) Congenital cyst of the lung
          D) Ectopic lung lobe
          E) Pulmonary hypoplasia

          ANSWER : E
    - Lungs of the Newborn Infant
      - Air-filled lungs
        - Fresh, healthy lungs contain air
        - Pulmonary samples float in water
      - Stillborn infant lungs
        - Lungs are firm and sink in water
        - Contain fluids, not air