Development of the Human Lung

Peter Rothstein, MD
Professor of Clinical Anesthesiology and Clinical Pediatrics
(Retired)

Learning Objectives:

- Understand the growth and functional development of the respiratory system
- Identify the stages of lung development and the major events of each stage
- Understand the physical and biochemical requirements for alveolar development and function
- Identify the developmental causes of neonatal respiratory failure, tracheoesophageal fistula and diaphragmatic hernia

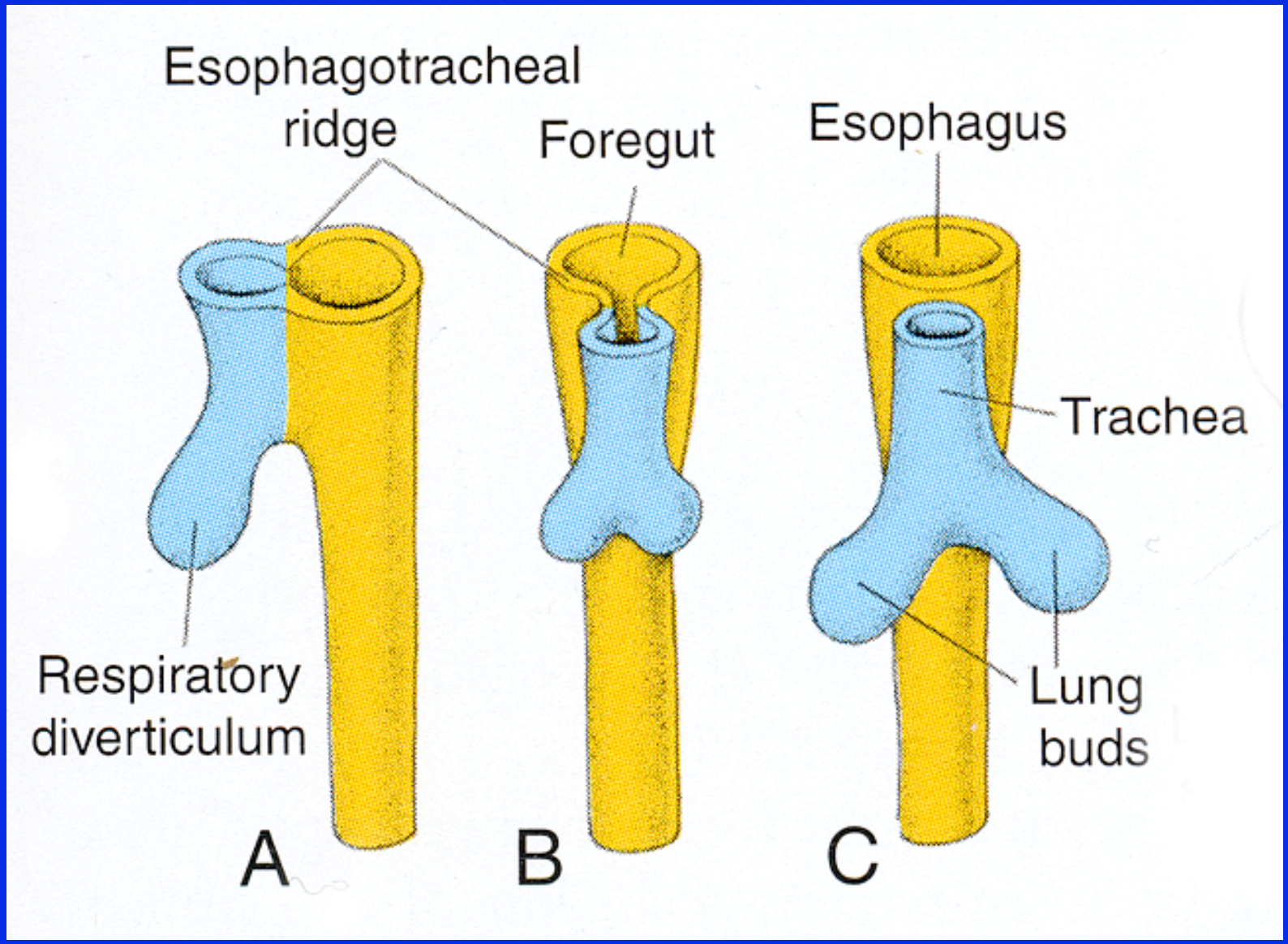
Phases of Lung Development

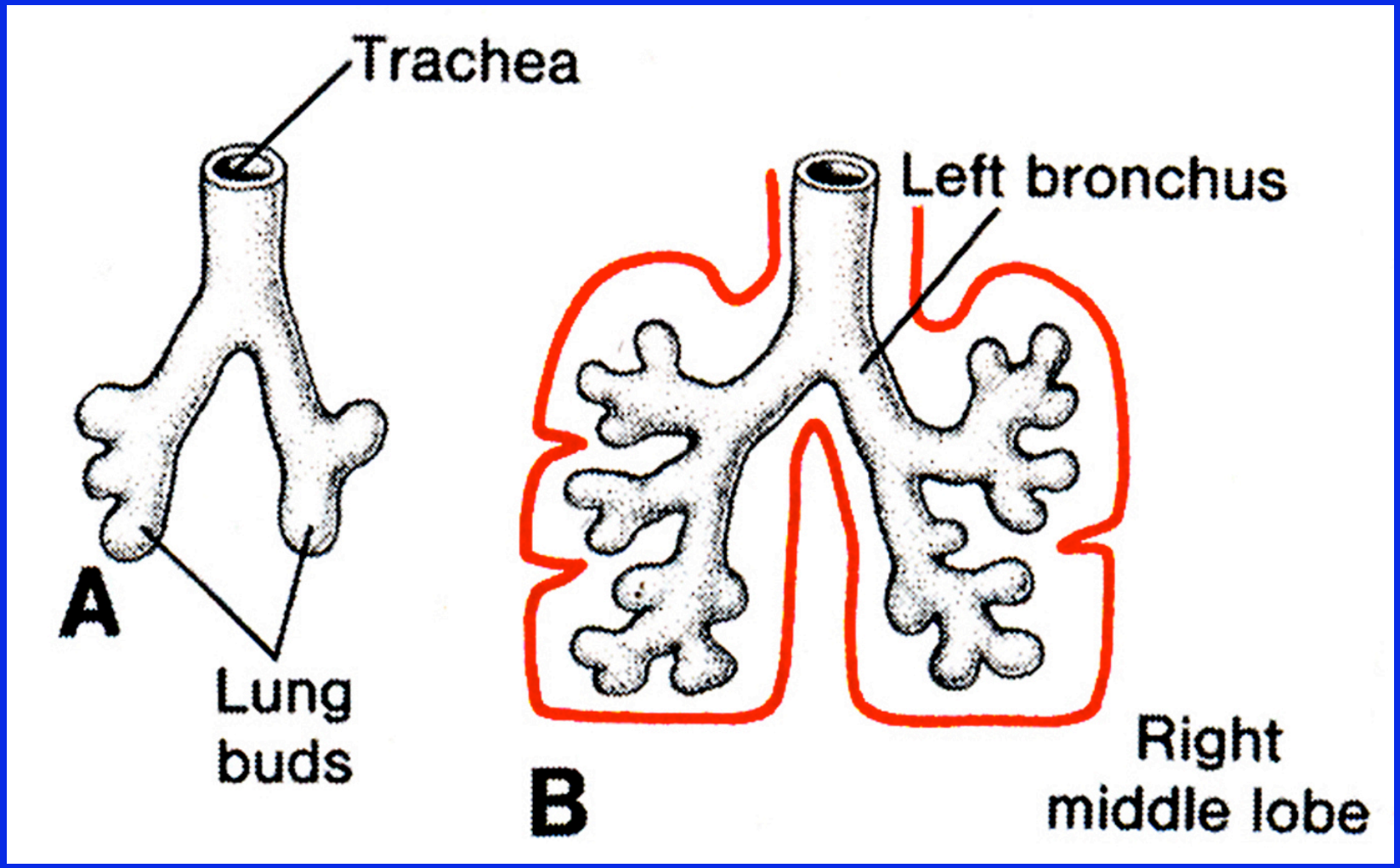
- Lung Growth
  - Structural development
  - Anatomic development
  - Affected by physical factors
- Lung Maturation
  - Functional development
  - Biochemical development
  - Affected by hormonal factors

The end result of the development of the lung is an organ with a tremendously large surface area that is approximately 50-100 m^2, capable of exchanging oxygen and carbon dioxide.

Maturation of the Lungs

Pseudoglandular period	5–16 weeks	Branching has continued to form terminal bronchioles. No respiratory bronchioles or alveoli are present.
Canalicular period	16–26 weeks	Each terminal bronchiole divides into 2 or more respiratory bronchioles, which in turn divide into 3–6 alveolar ducts.
Terminal sac period	26 weeks to birth	Terminal sacs (primitive alveoli) form, and capillaries establish close contact.
Alveolar period	8 months to childhood	Mature alveoli have well-developed epithelial endothelial (capillary) contacts.

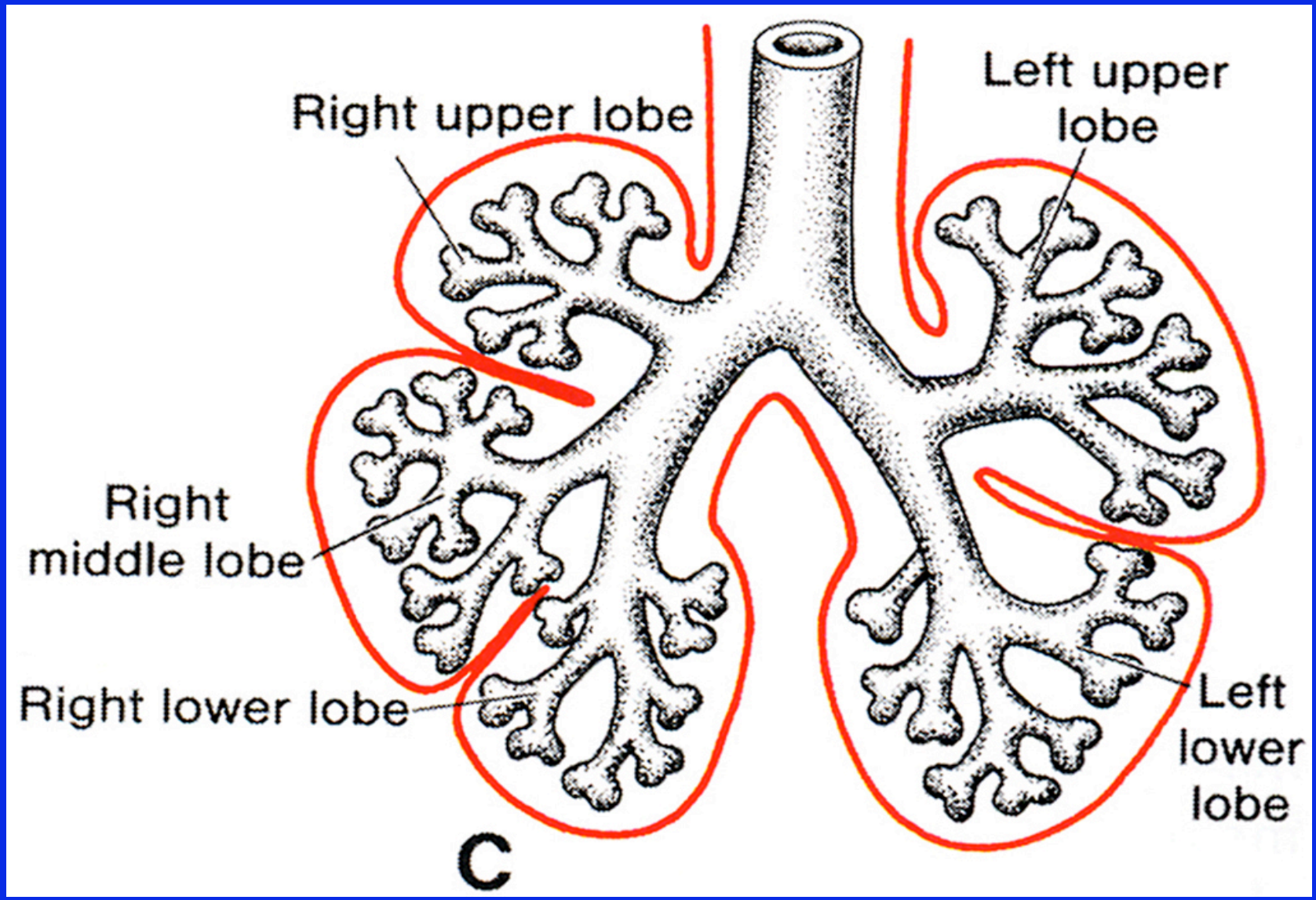

Esophagotracheal ridge
Foregut
Esophagus
Trachea
Respiratory diverticulum
Lung buds
A
B
C

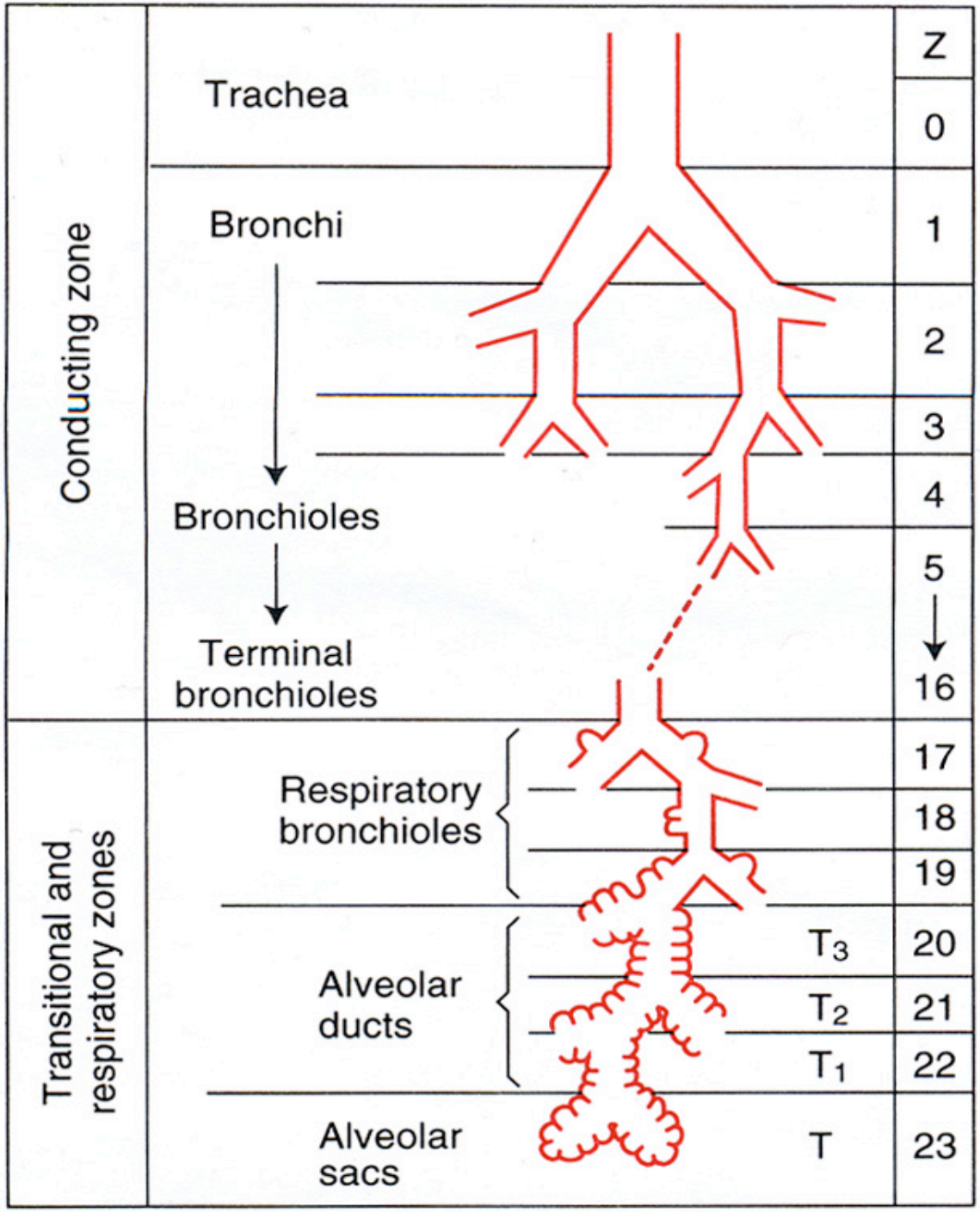

Trachea
A
Lung buds
Left bronchus
B
Right middle lobe

Derivation of lung elements

- Lung buds lined by **endodermally** derived epithelium—differentiates into respiratory epithelium, which lines airways and specialized epithelium that lines the alveoli
- **Ectoderm**-contributes to innervation
- **Mesoderm**- blood vessels, smooth muscle, cartilage and other connective tissue

- The **pseudoglandular stage** takes place between the 7th and 16th week of embryonic development


Right upper lobe
Left upper lobe
Right middle lobe
Right lower lobe
Left lower lobe
C

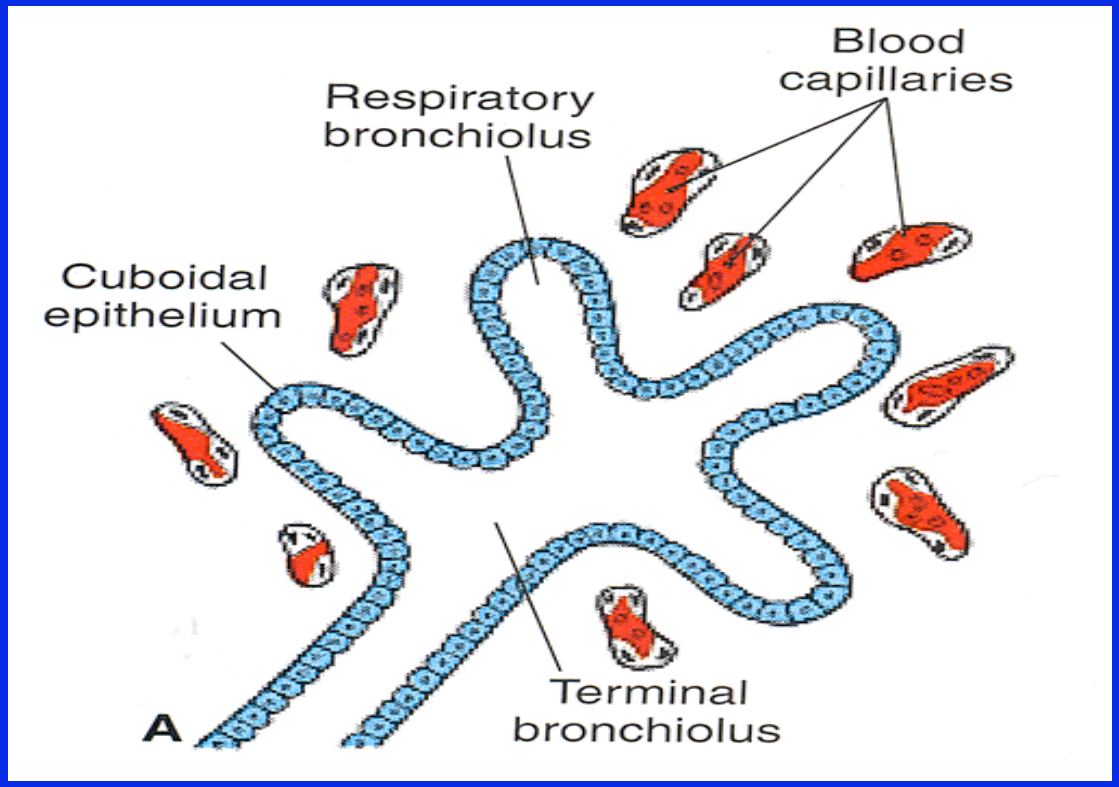

Conducting zone
Transitional and respiratory zones
Trachea
Bronchi
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sacs
Z
0
1
2
3
4
5
16
17
18
19
T3
20
T2
21
T1
22
T
23

- For branching to occur, bronchial mesoderm is required.
- The rate and extent of branching is proportional to the amount of mesenchyme present.
- After 16 weeks, further growth occurs by widening and elongation.

- Mesenchyme is necessary for epithelial differentiation to occur.
- Differentiation of mesenchyme requires the presence of lung epithelium.

- Cilia appear in the proximal airways by 13 weeks.
- There is a transition from bronchial epithelial cells (ciliated and columnar cells) to alveolar Type II cells.

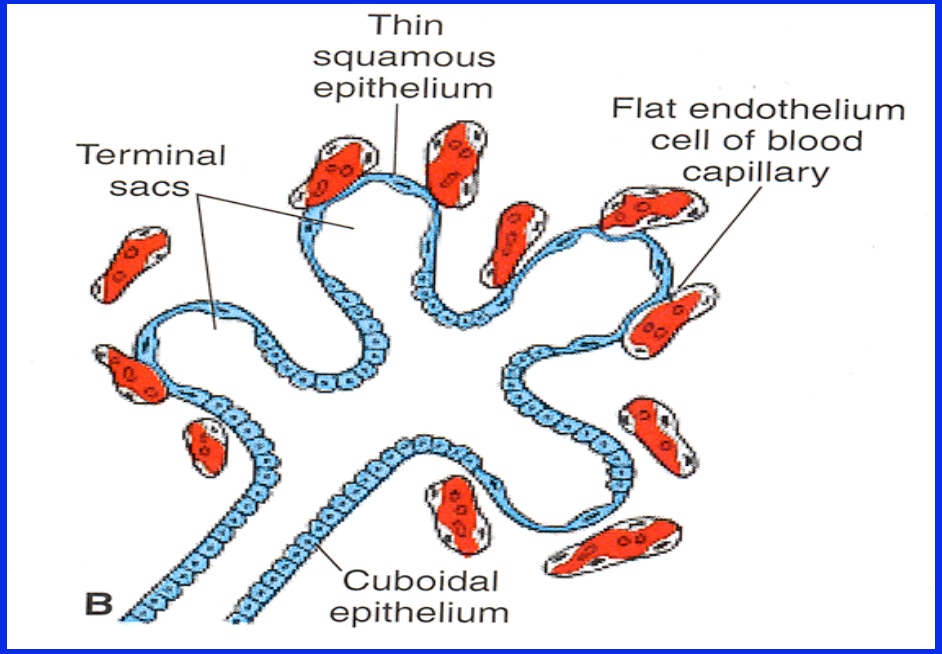
Canalicular Period 16-26 wk



- By 20 weeks the alveolar Type 1 cell is present
- Lamellar bodies start to appear in Type 2 cells

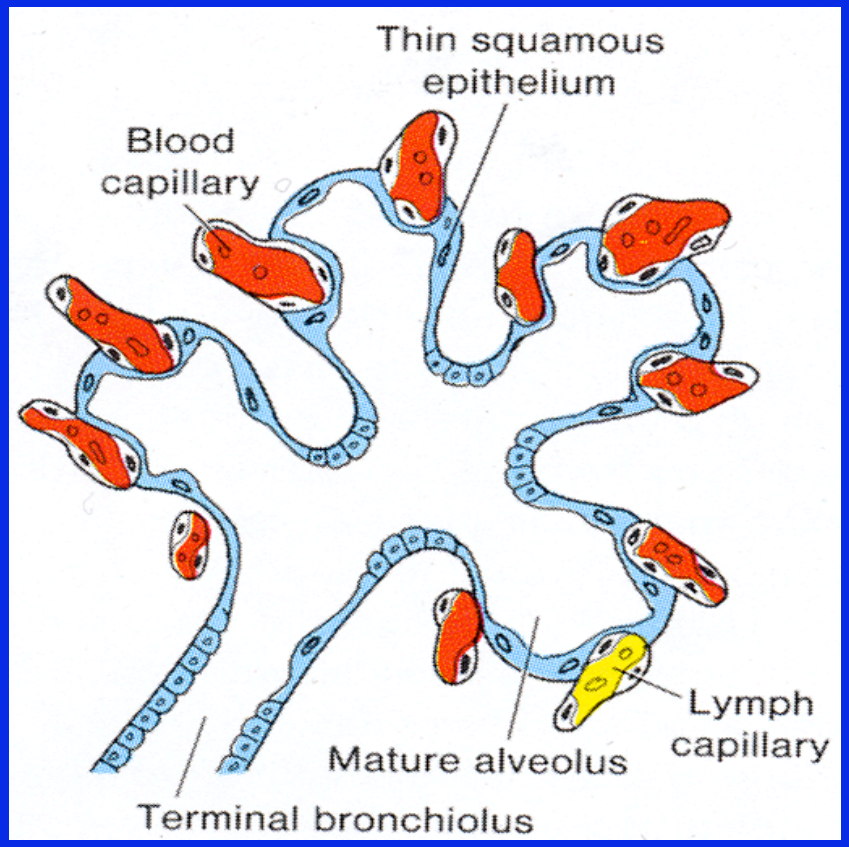
- By 20 weeks, the alveolar Type 1 cell is present.
- Lamellar bodies start to appear in Type 2 cells.

Terminal Sac Period 26 wk →



- Surfactant appears in lamellar bodies of Type 2 cells.
- Stability of the lung at birth correlates with the number of lamellar bodies present.

Primitive Saccule



- Approximately 20 x 10^6 saccules present at birth.

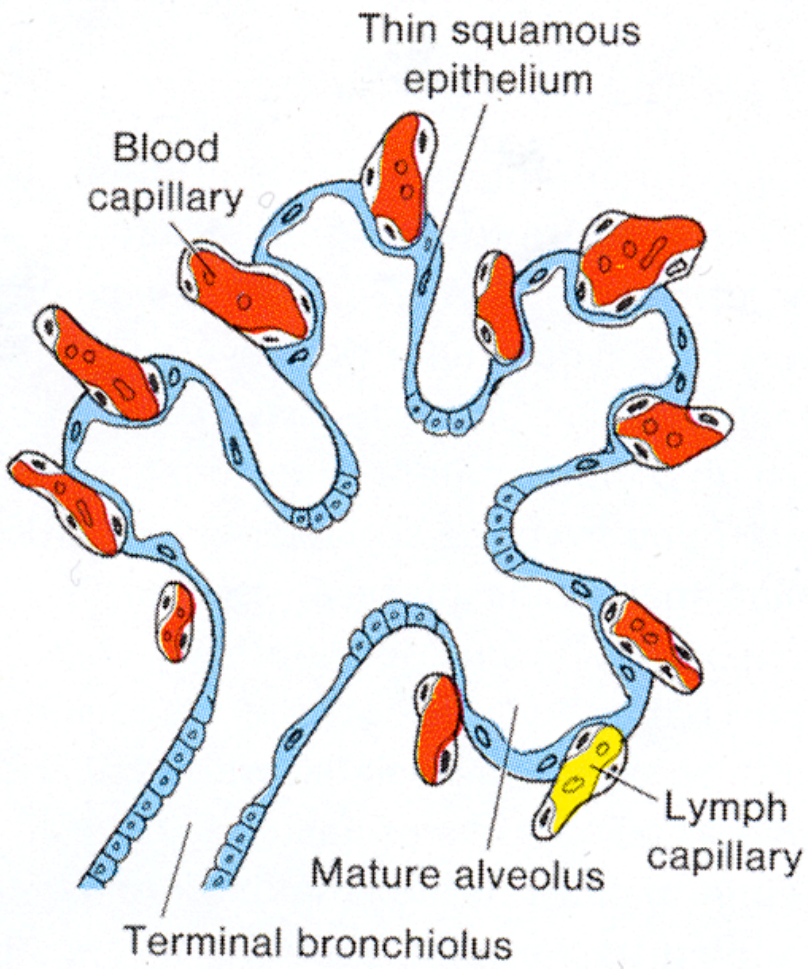


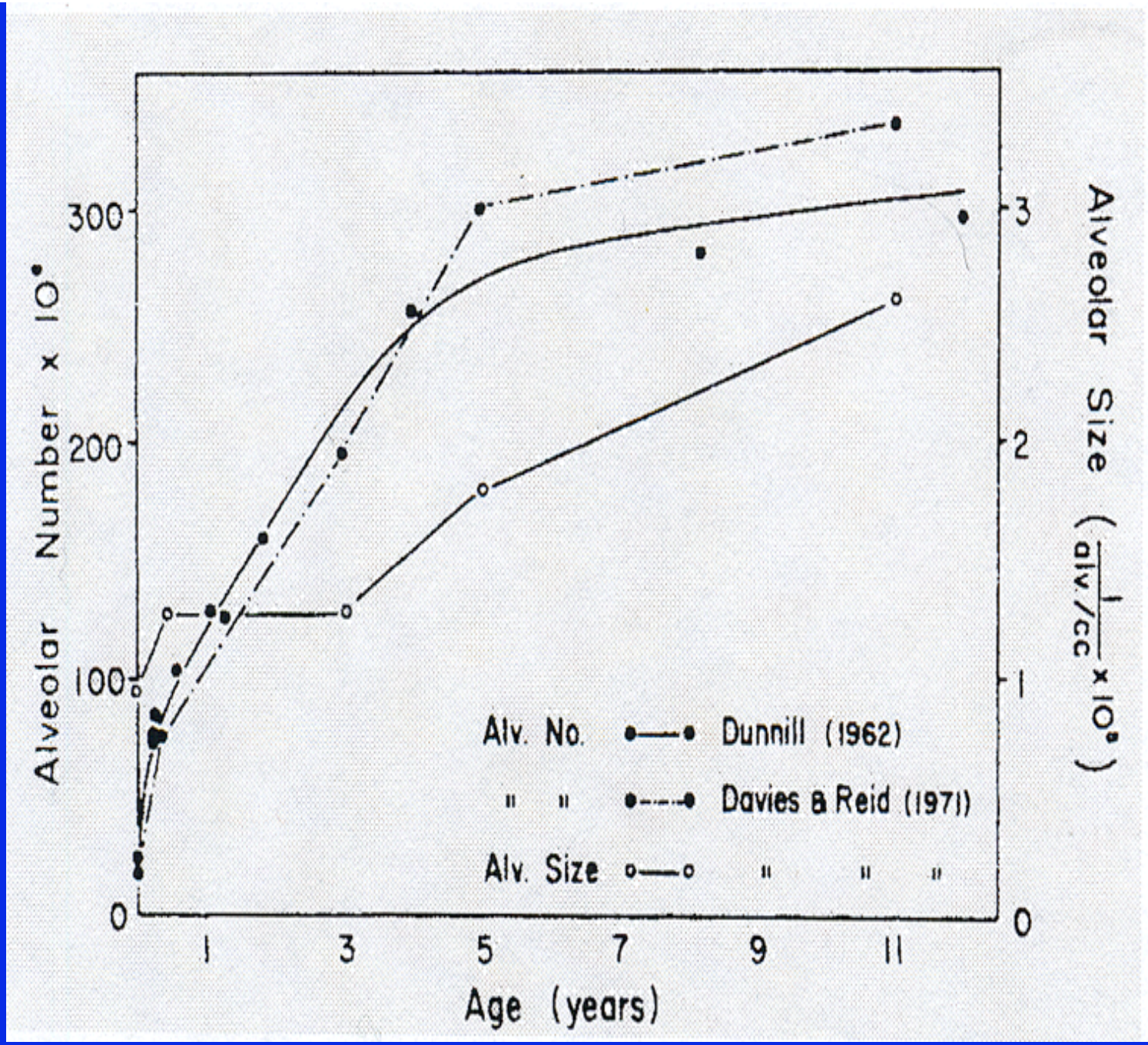
Figure 12.9. Lung tissue in a newborn. Note the thin squamous epithelial cells (also known as alveolar epithelial cells, type I) and surrounding capillaries protruding into mature alveoli.

Postnatal stage

“Adult” configuration reached by 5 weeks.

Characteristics of Mature Alveolus

- Connected to alveolar duct
- Lined with Type 1 cells, which are in intimate contact with capillaries
- Each capillary is exposed to 2 alveoli
- Contains surfactant
- Has interconnections with adjacent alveoli through pores of Kohn.


Alveolar Number x 10⁶
300
200
100
0
1
3
5
7
9
11
Age (years)
3
2
1
0
Alveolar Size (1/alv./cc x 10⁶)
Alv. No. Dunnill (1962)
" " Davies & Reid (1971)
Alv. Size " " "

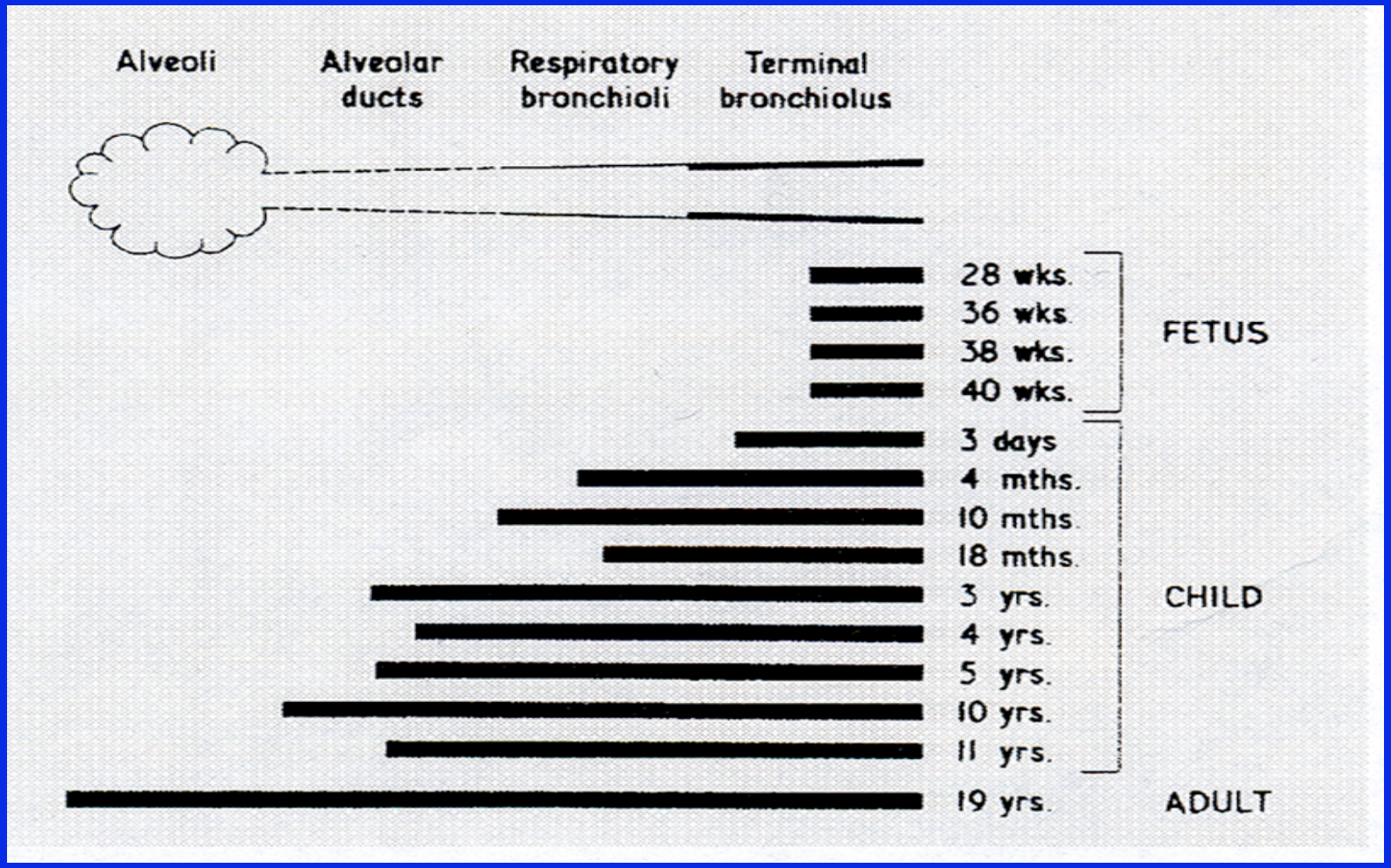
Hormonal Influence on the Lung

- Corticotropin stimulates cortisol
- Cortisol stimulates fetal lung fibroblast to produce fibroblast pneumocyte factor, which,
- Stimulates surfactant production in Type 2 cells
- Thyroid hormone is also necessary for surfactant production

Hormonal Influence on the Lung

- At birth, epinephrine and arginine vasopressin suppress fetal lung fluid production and play a role in its reabsorption

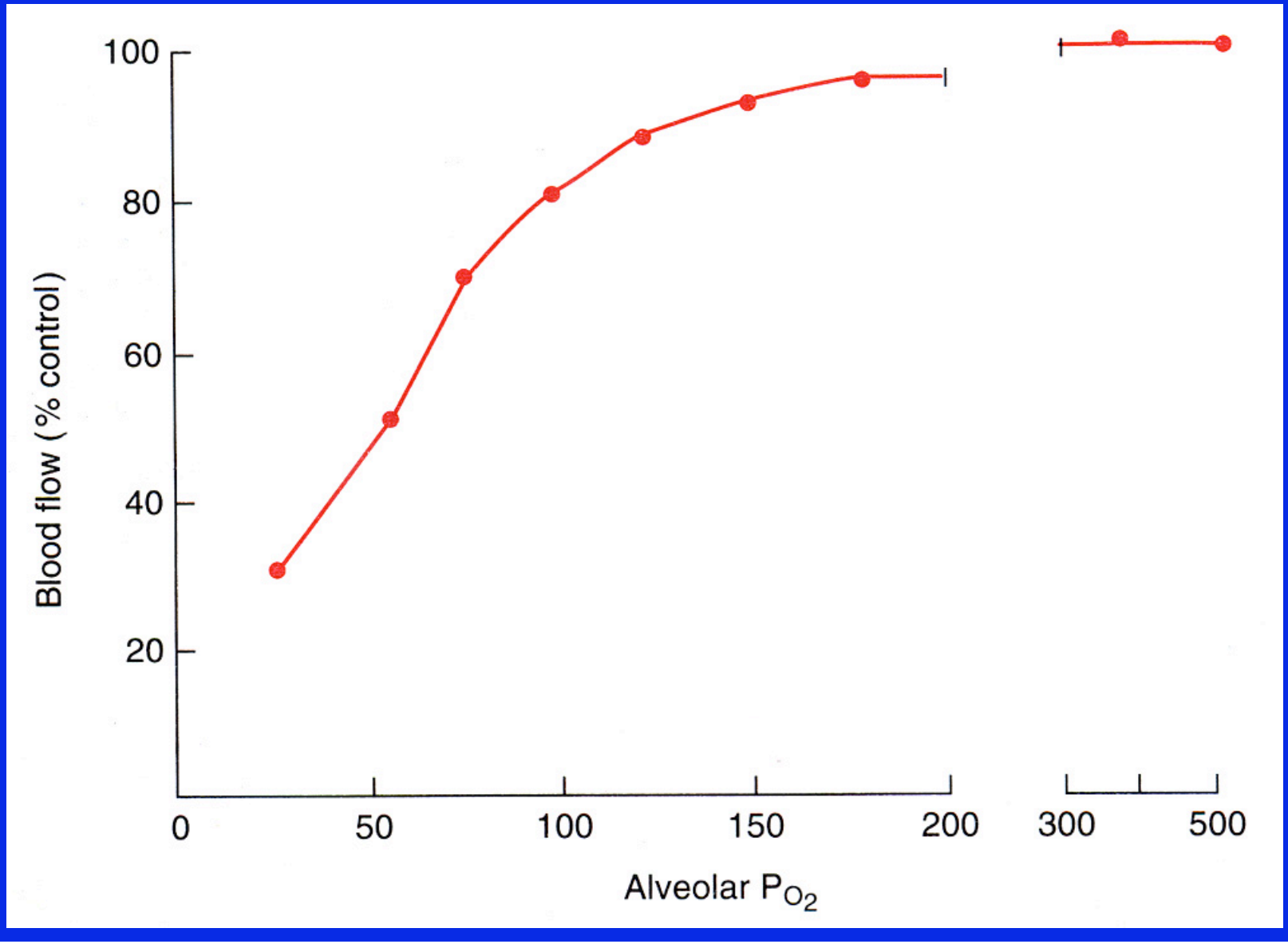
Development of Pulmonary Arterial Muscle

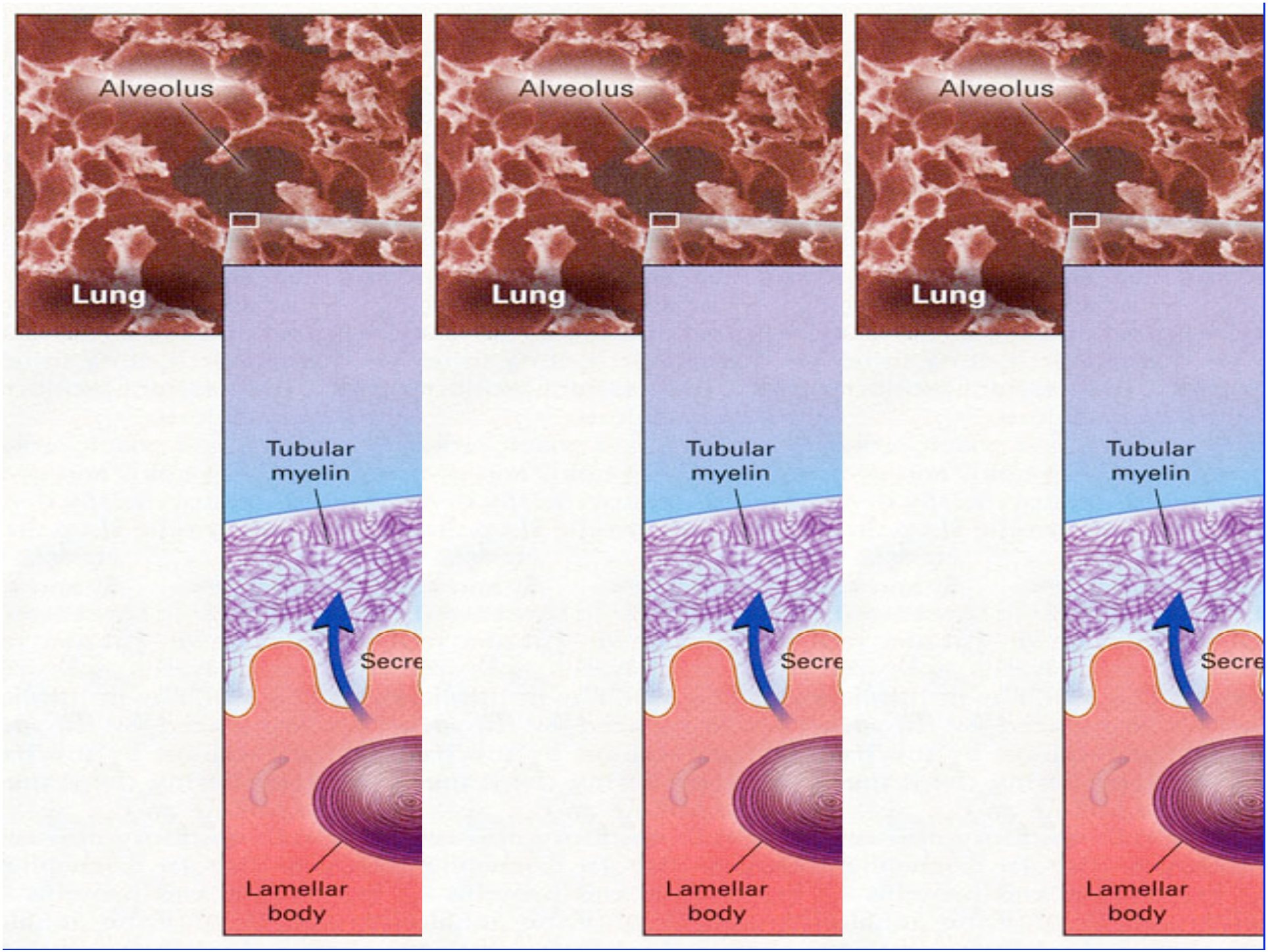


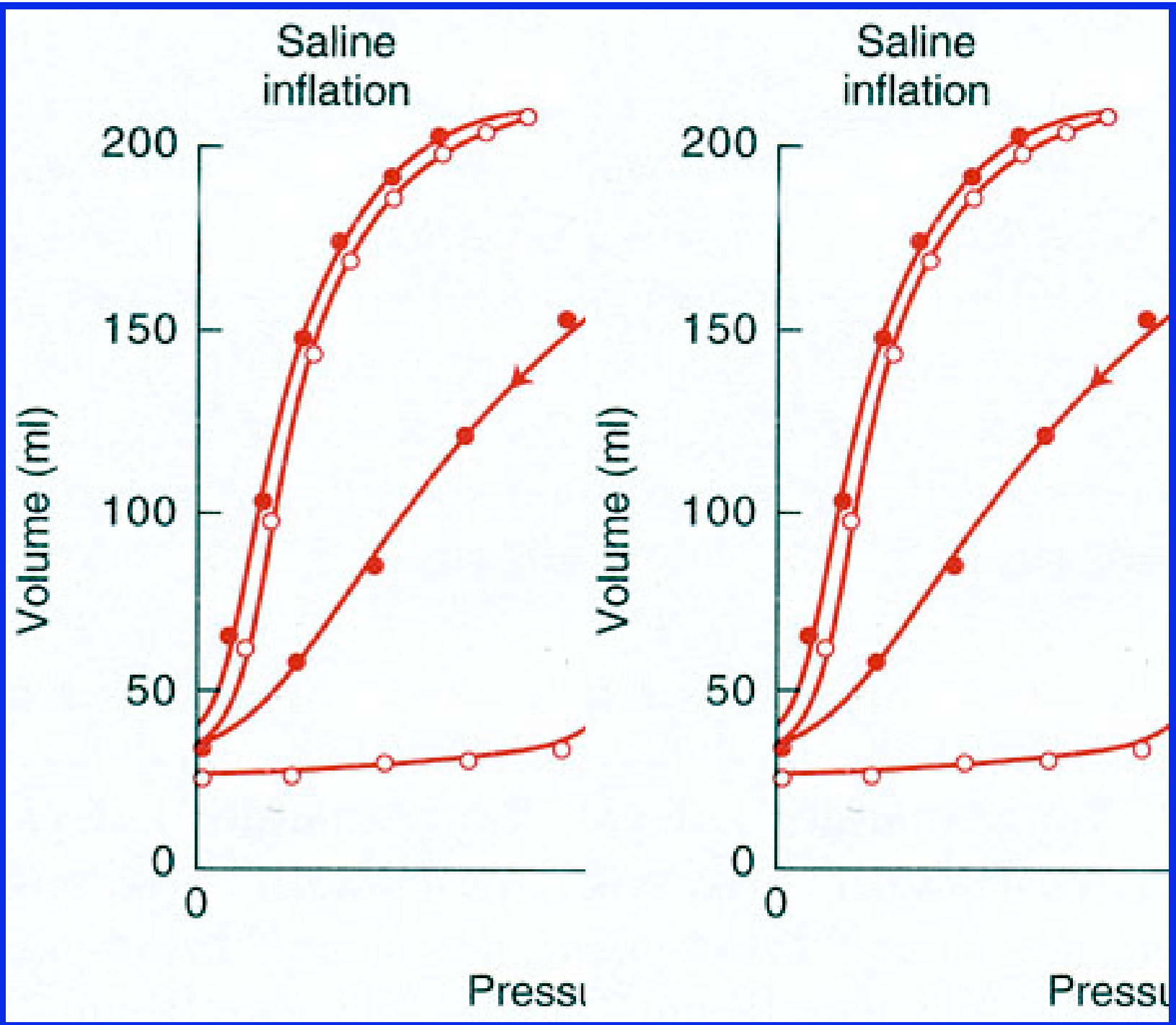
Control of Pulmonary Blood Flow

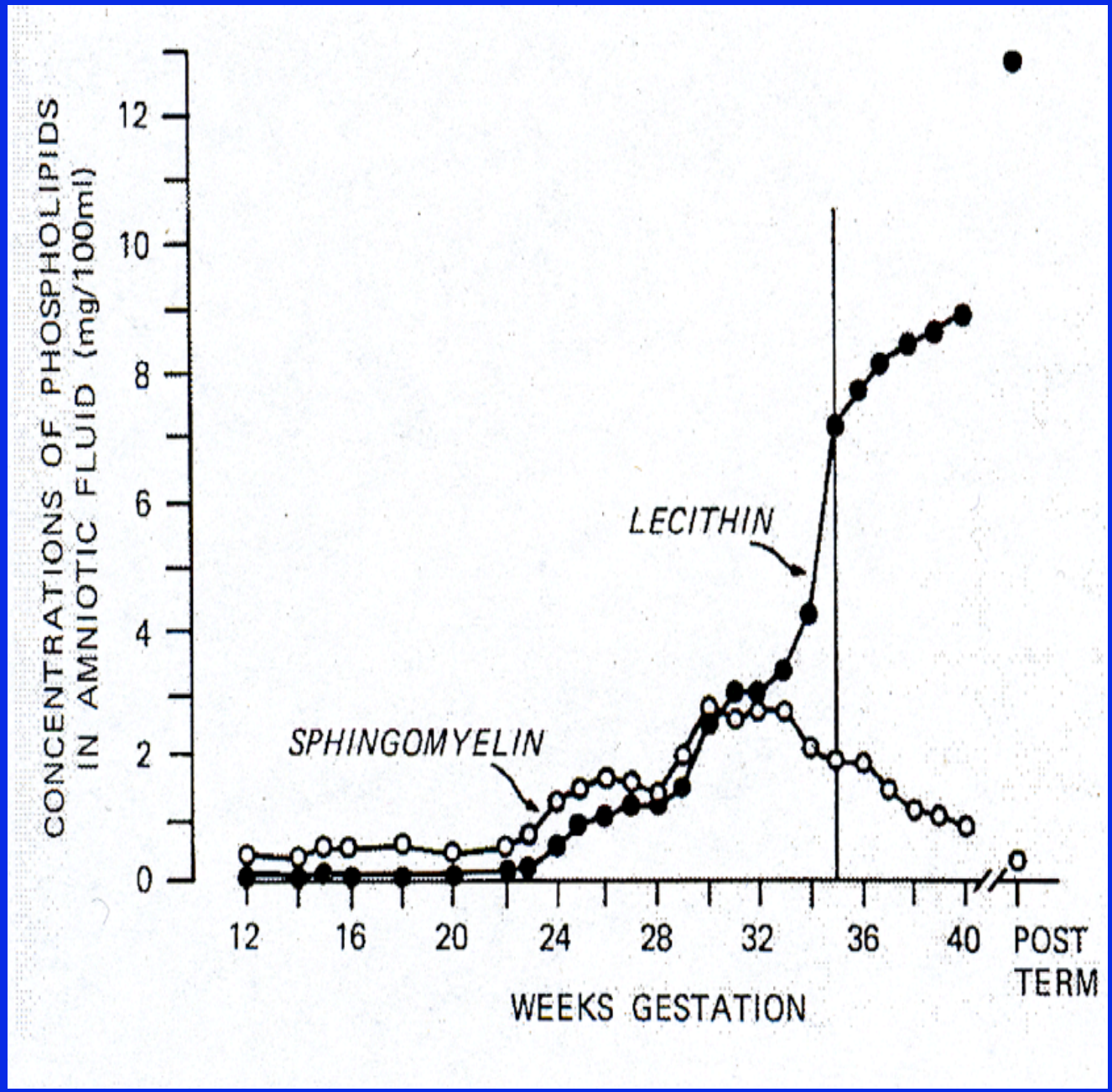
- Physical Location of Lung Unit
- Gravity
- Oxygen
- Nitric oxide

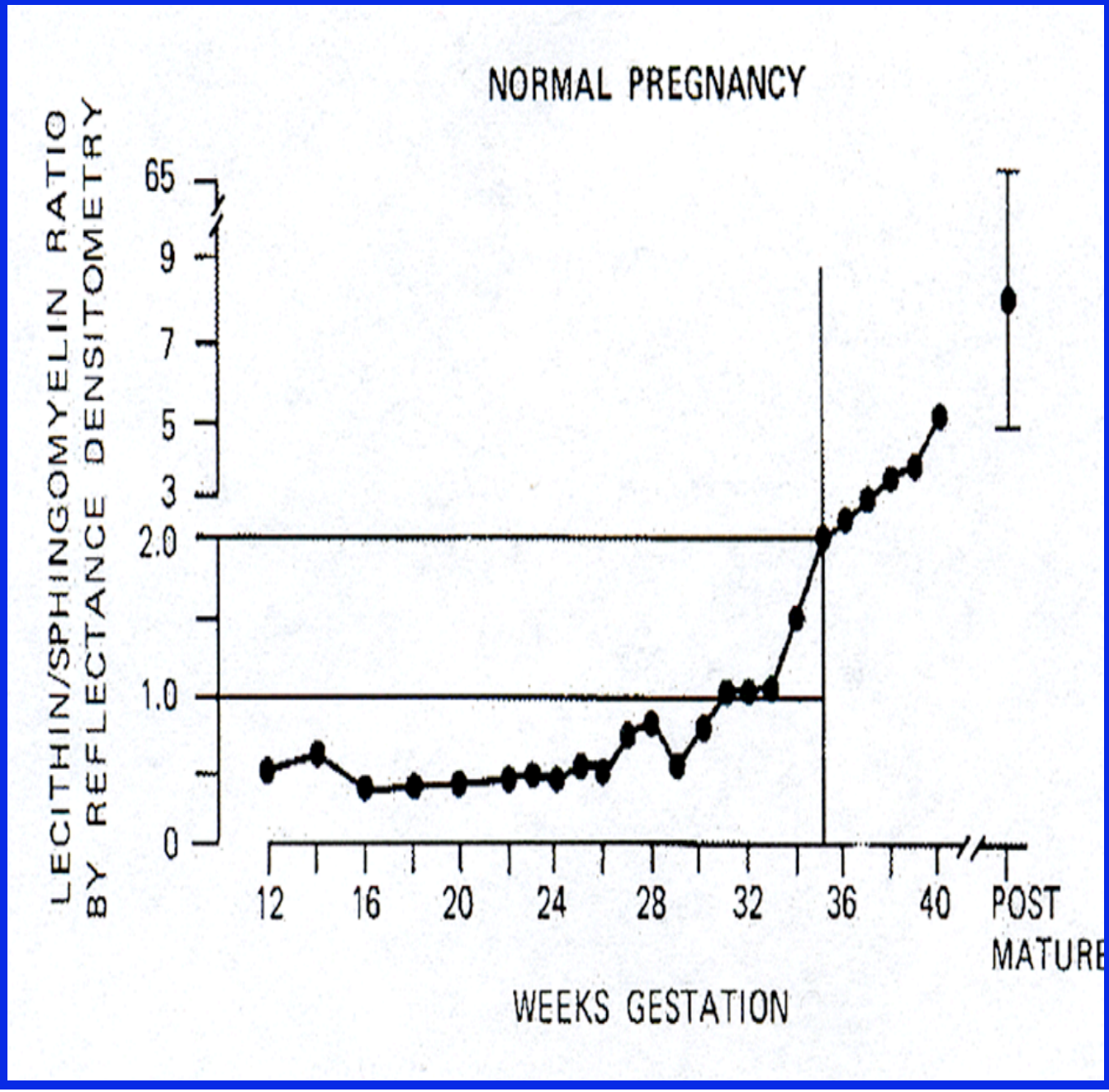
Hypoxic Pulmonary Vasoconstriction




Alveolus
Lung
Tubular myelin
Secre
Lamellar body
Alveolus
Lung
Tubular myelin
Secre
Lamellar body
Alveolus
Lung
Tubular myelin
Secre
Lamellar body

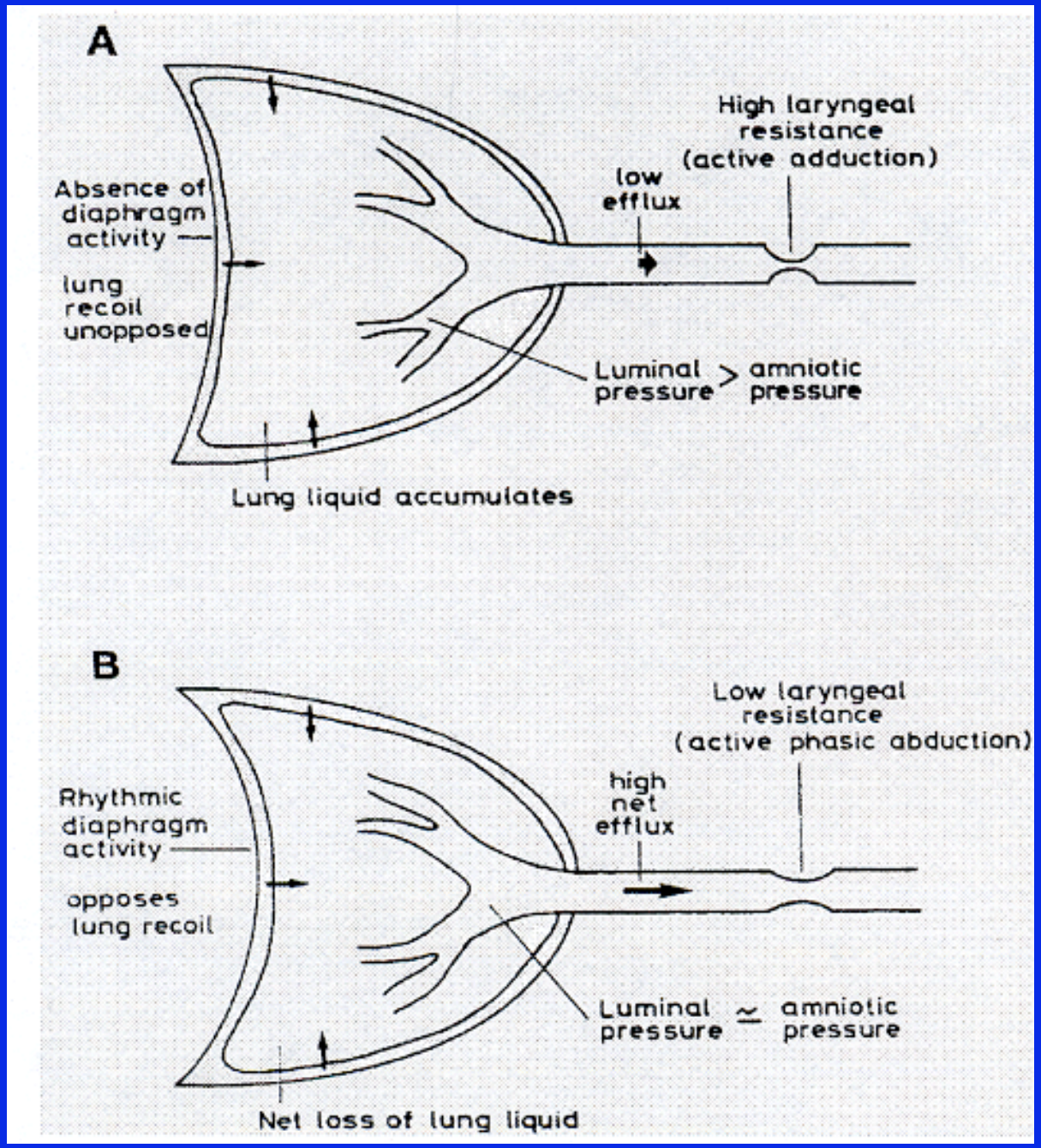

Saline
inflation
200
150
100
50
0
Volume (ml)
0
Pressu
Saline
inflation
200
150
100
50
0
Volume (ml)
0
Pressu


CONCENTRATIONS OF PHOSPHOLIPIDS
IN AMNIOTIC FLUID (mg/100ml)
0
2
4
6
8
10
12
LECITHIN
SPHINGOMYELIN
12
16
20
24
28
32
36
40
POST
TERM
WEEKS GESTATION


NORMAL PREGNANCY
LECITHIN/SPHINGOMYELIN RATIO
BY REFLECTANCE DENSITOMETRY
65
9
7
5
3
2.0
1.0
0
12
16
20
24
28
32
36
40
POST
MATURE
WEEKS GESTATION

Physical Influences on Lung Growth

- Lung Liquid


A
High laryngeal resistance (active adduction)
low efflux
Absence of diaphragm activity
lung recoil unopposed
Luminal pressure > amniotic pressure
Lung liquid accumulates
B
Low laryngeal resistance (active phasic abduction)
high net efflux
Rhythmic diaphragm activity
opposes lung recoil
Luminal pressure ≃ amniotic pressure
Net loss of lung liquid

Physical Influences on Lung Growth

- Amniotic fluid
  - Oligohydramnios→Potters syndrome

Physical Influences on Lung Growth

- Congenital diaphragmatic hernia
- Musculoskeletal abnormalities of the chest wall
- Space occupying lesions of the thorax, e.g. pleural effusions
- Oligohydramnios associated with renal or urinary tract abnormalities

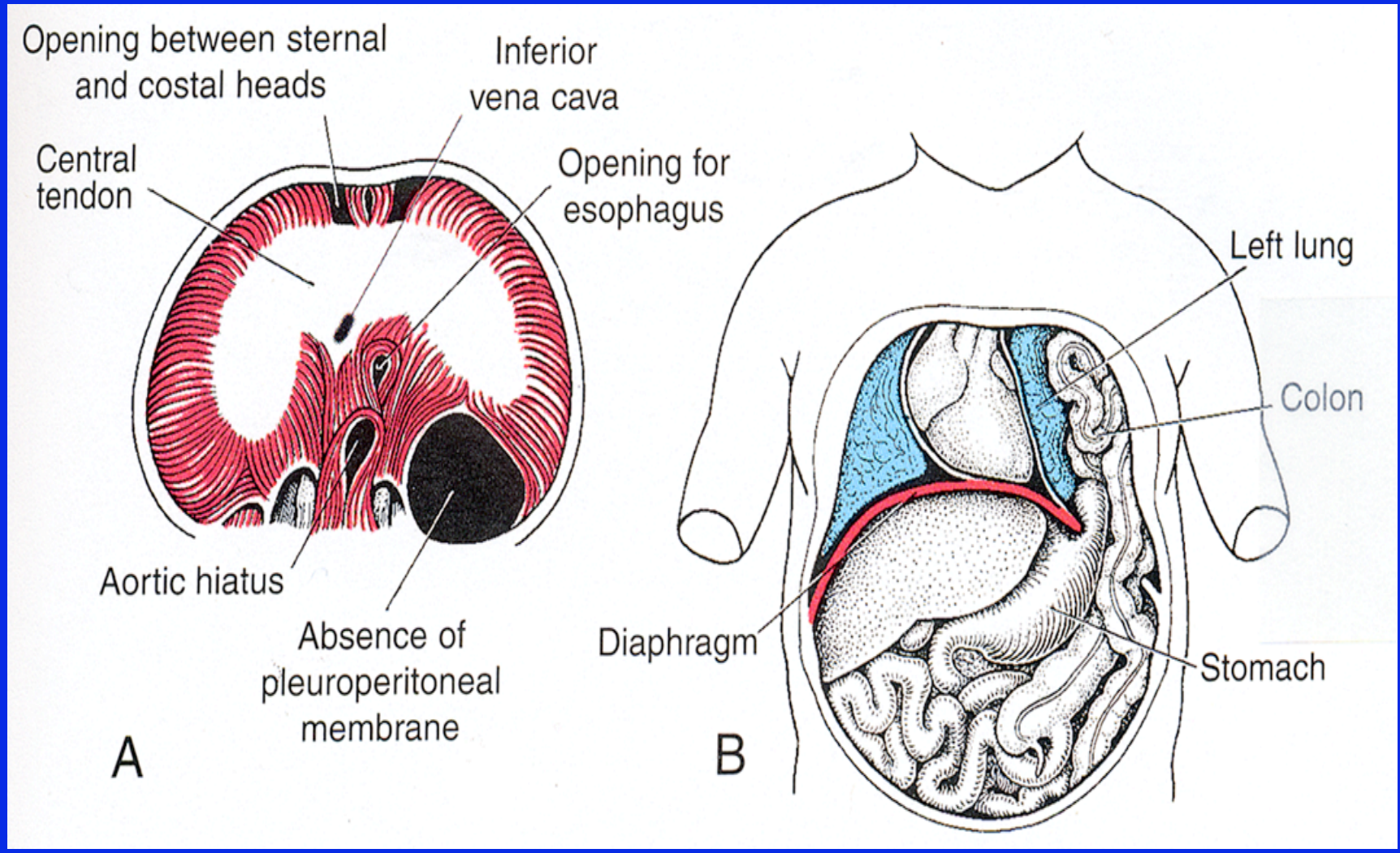

Opening between sternal and costal heads
Inferior vena cava
Central tendon
Opening for esophagus
Aortic hiatus
Absence of pleuroperitoneal membrane
A
Left lung
Colon
Diaphragm
Stomach
B

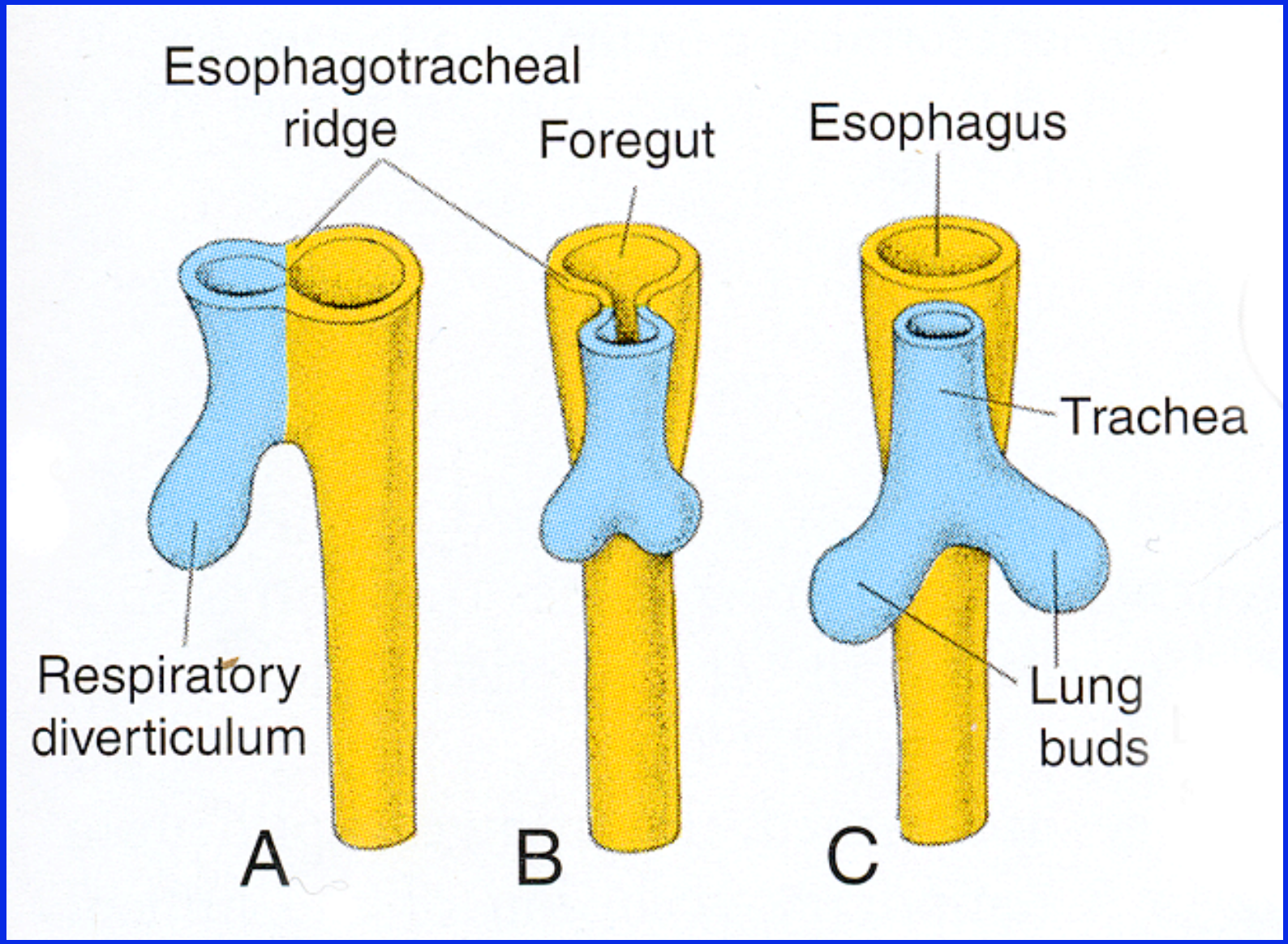
Fig 1. Annual mortality (
nancies involving CDH. T
of the new therapies are sh
horizontal boxes.

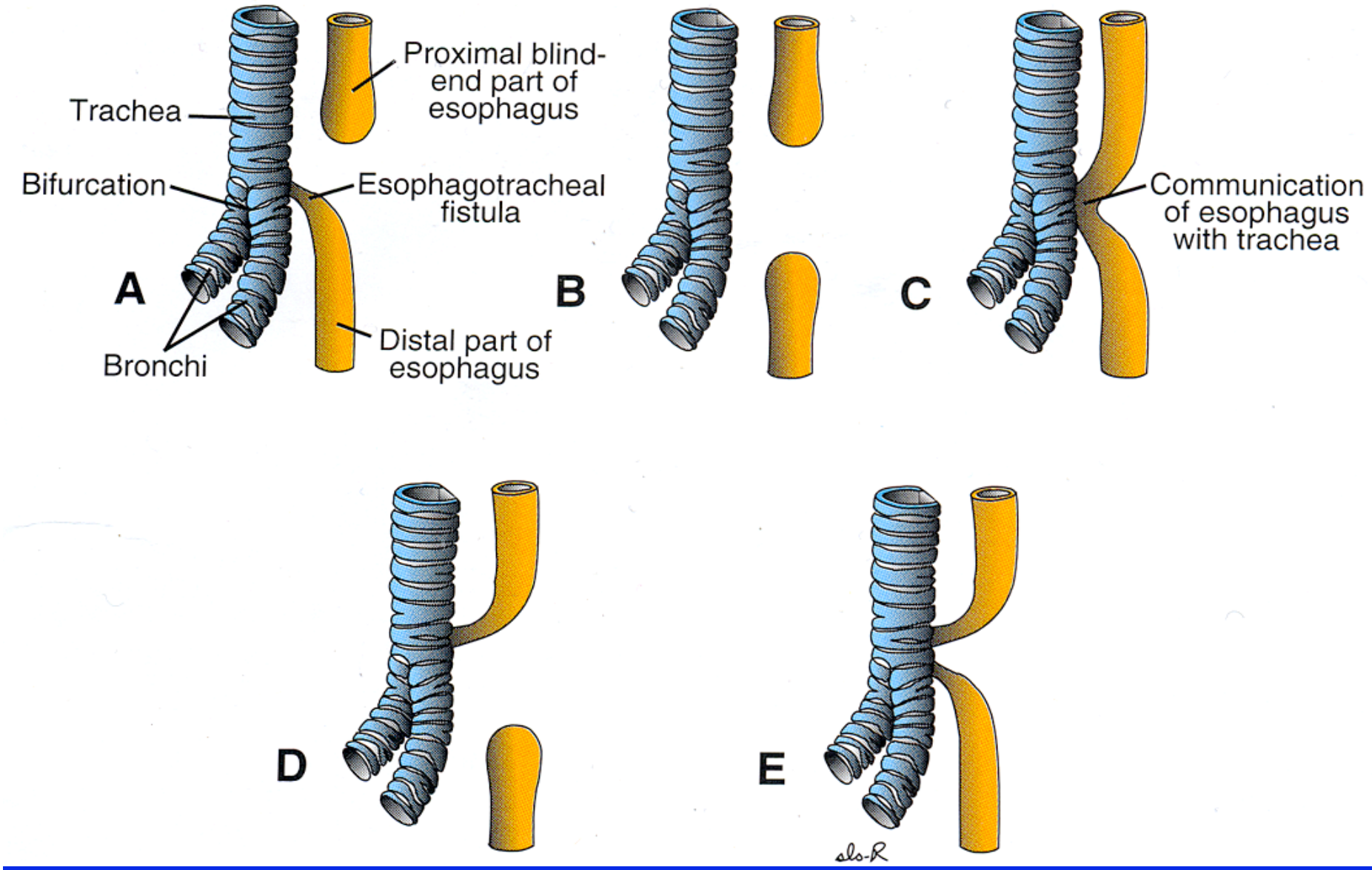
Fig 1. Annual mortality (
nancies involving CDH. T
of the new therapies are sh
horizontal boxes.

Fig 1. Annual mortality (
nancies involving CDH. T
of the new therapies are sh
horizontal boxes.

Fig 1. Annual mortality (
nancies involving CDH. T
of the new therapies are sh
horizontal boxes.

Fig 1. Annual mortality (
nancies involving CDH. Ti
of the new therapies are sh
horizontal boxes.


Esophagotracheal ridge
Foregut
Esophagus
Trachea
Respiratory diverticulum
Lung buds
A
B
C

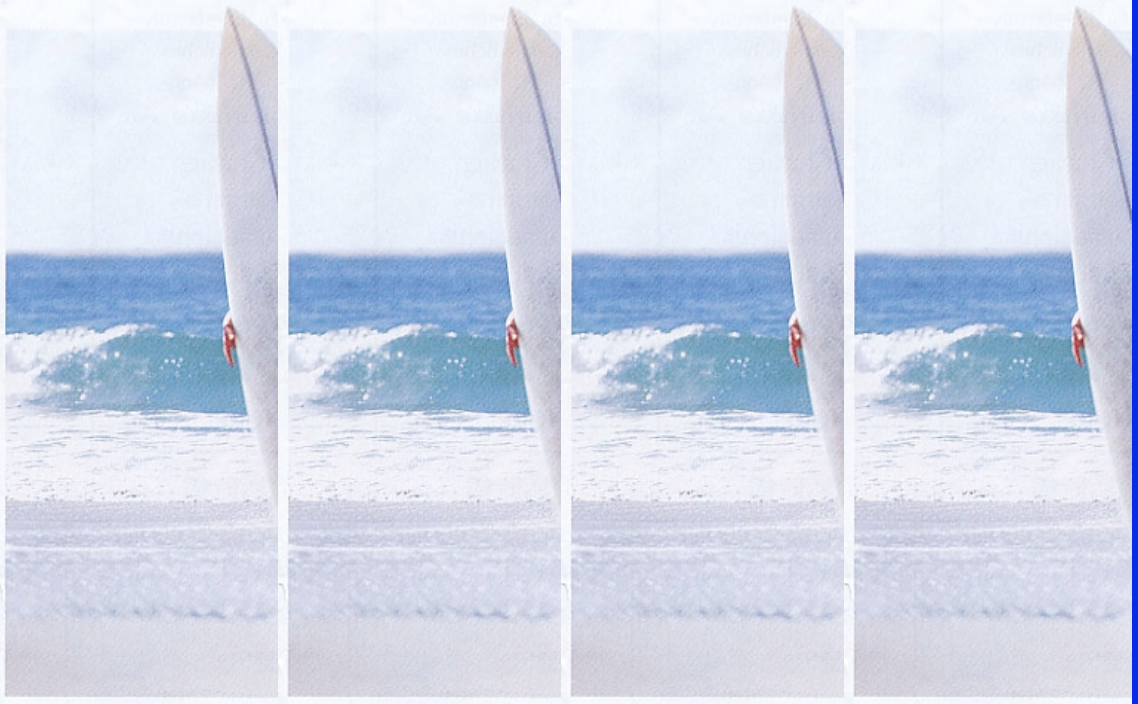

Trachea
Proximal blind-end part of esophagus
Bifurcation
Esophagotracheal fistula
A
Bronchi
Distal part of esophagus
B
C
Communication of esophagus with trachea
D
E
sls-R

The Problem of Prematurity

- Birth before 36 weeks may be associated with respiratory compromise and failure.
- 80,000 cases/yr of neonatal respiratory failure
- 8,500 deaths
- CNS injury in survivors
- Cost = $4.4 billion/yr

Sur Sur Sur Sur

A survi A survi A survi A survi



Mollie, newborn *Mollie, newborn* *Mollie, newborn* *Mollie, newborn*

Over 500,000 infants

You'd never know by looking
Today as an active, healthy te
premature and at risk for resp
given little chance of survival
was one of the first "Survan
celebration of safety and effic

* More infants treated by hospitals nati
Purchases 12 months ending February,

Please see the adjacent page for a brie

SURVANTA CAN RAPIDLY AFFE
clinical trials, the most commor
procedure: Transient bradycar
ETT reflux, fewer than 1% of c

Over 500,000 infants

You'd never know by looking
Today as an active, healthy te
premature and at risk for resp
given little chance of survival
was one of the first "Survan
celebration of safety and effic

* More infants treated by hospitals nati
Purchases 12 months ending February,

Please see the adjacent page for a brie

SURVANTA CAN RAPIDLY AFFE
clinical trials, the most commor
procedure: Transient bradycar
ETT reflux, fewer than 1% of c

Over 500,000 infants

You'd never know by looking
Today as an active, healthy te
premature and at risk for resp
given little chance of survival
was one of the first "Survan
celebration of safety and effic

* More infants treated by hospitals nati
Purchases 12 months ending February,

Please see the adjacent page for a brie

SURVANTA CAN RAPIDLY AFFE
clinical trials, the most commor
procedure: Transient bradycar
ETT reflux, fewer than 1% of c

Over 500,000 infants

You'd never know by looking
Today as an active, healthy te
premature and at risk for resp
given little chance of survival,
was one of the first "Survant
celebration of safety and effic

* More infants treated by hospitals natio
Purchases 12 months ending February,

Please see the adjacent page for a brie

SURVANTA CAN RAPIDLY AFFE
clinical trials, the most common
procedure: Transient bradycard
ETT reflux, fewer than 1% of d

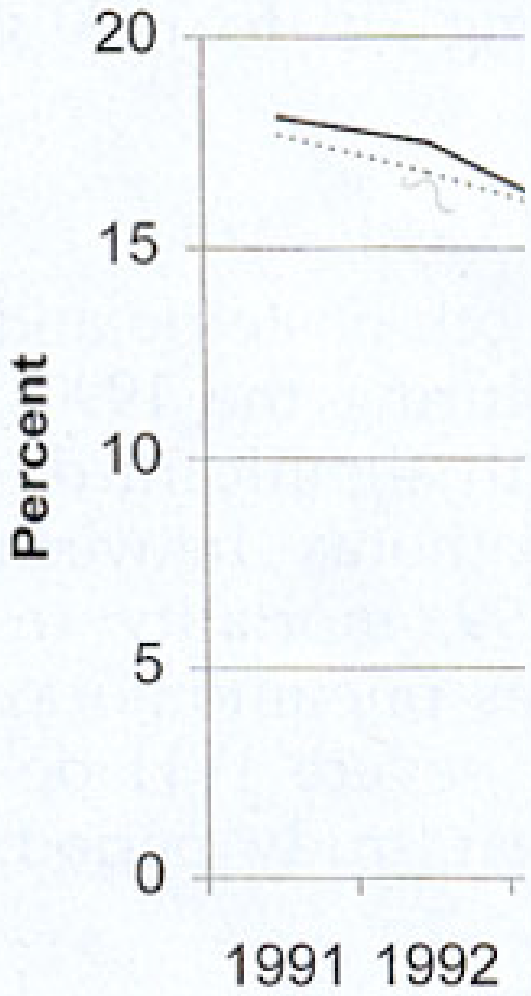


Fig 1. Mortality for i
network hospitals (sc
all 9 years (dashed li

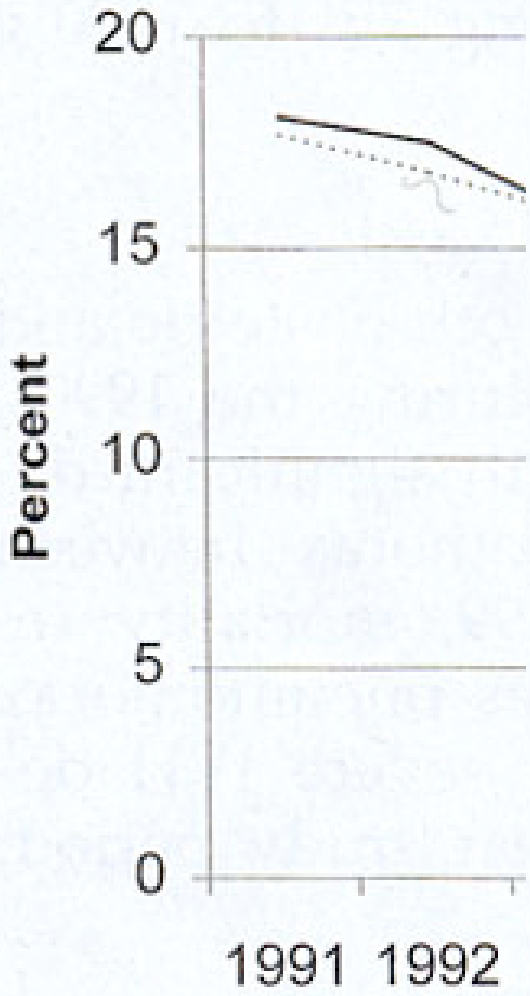


Fig 1. Mortality for i
network hospitals (sc
all 9 years (dashed li

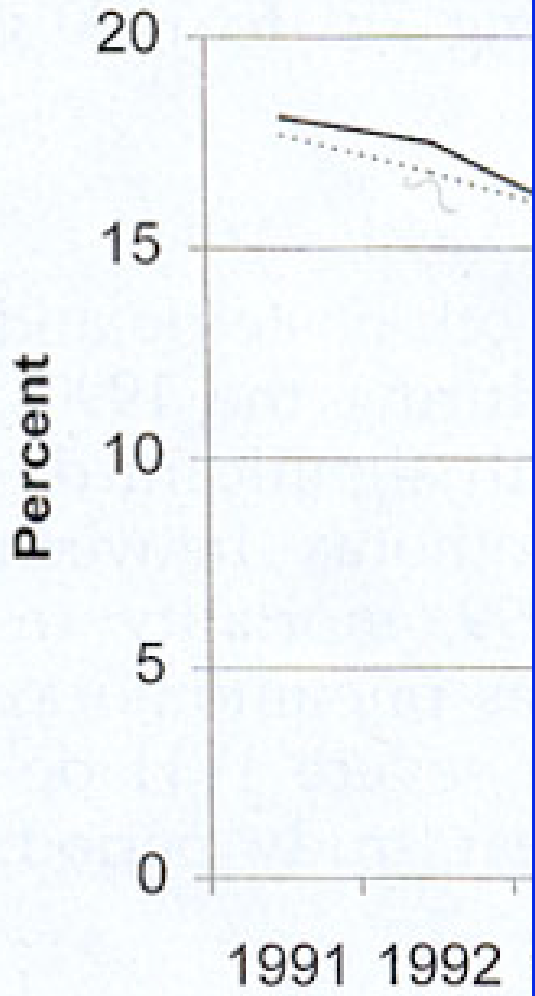


Fig 1. Mortality for i
network hospitals (so
all 9 years (dashed li

Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK.

Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure.

N. Eng. J. Med. 284:1333-40 , 1971

Neonatal Respiratory Failure

- Incidence
  - 20/1000 boys
  - 15.6/1000 girls
  - 29/1000 blacks

The lung is ignored only at your own peril!

DON’T HOLD YOUR BREATH!