RESPIRATORY SYSTEM

Embryology

Sheet Slide

Number:	-2
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I tried to include everything the doctor mentioned in both the lecture and his slides in the simplest way possible, so hopefully there would be no need for you to get back to the slides.

Last lecture we have talked about the development of the larynx, trachea, primary, secondary, and tertiary bronchi, in addition to bronchopulmonary segments. Remember that we said during development, the secondary bronchi undergo division in a dichotomous fashion to give off the tertiary bronchi, eventually giving off the bronchopulmonary segments; with 10 on the right and 8 on the left. By the end of the sixth month , approximately 17 generations of subdivisions have formed. Also after birth (postnatal), additional 6 divisions will happen leaving us with a total of 23 divisions completing the bronchial tree.

The bronchioles appear with further branching of the bronchopulmonary segments, and they are of two types: terminal bronchioles, and respiratory bronchioles. This marks the beginning of the maturation of the lung. By that, we mean the alveolar ducts, alveolar sacs, and alveoli.

In this sheet, we will be mainly covering the development of the respiratory bronchioles, and the lung, in addition to congenital anomalies of the lung.

Part A: Development

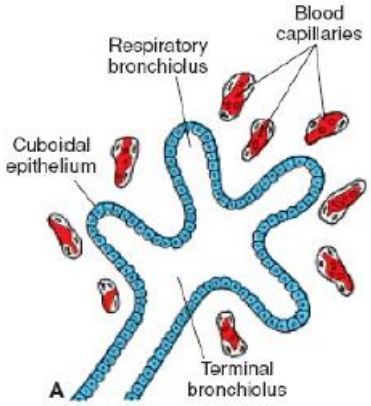
Now the development of the respiratory bronchioles and the lung is basically divided into 4 stages: To help you memorize faster divide each stage into 3 questions, when does it happen, what happens during this phase, and what kind of epithelium is there?

Stage 1: Pseudo glandular period

This period occurs from 5-16 weeks of gestation, which means it ends approximately at the 4.5^{th} month. At this point, the division has formed terminal bronchioles ONLY and there are no respiratory bronchioles nor alveoli. The epithelium present at this stage is simple cuboidal epithelium.

Stage 2: Canalicular period

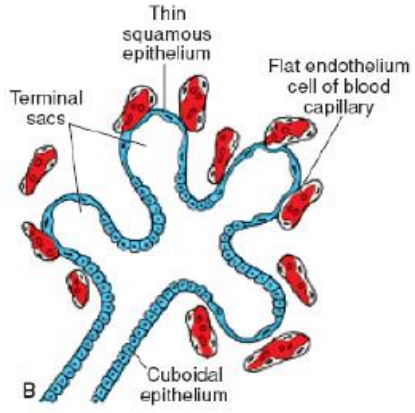
This stage occurs from 16-26 weeks; meaning approximately 6.5 months. The word "canalicular" is derived from "canaliculi" which refers to alveolar ducts. This helps you remember that in this phase, each terminal bronchiole will divide to form about 2 respiratory bronchioles, and each of those will divide to form 3-6 alveolar ducts. This means that epithelium will also start changing into simple squamous epithelium and alveolar capillaries will begin to appear as you realize in the picture on the right.



<u>Now this brings us to a question:</u> Can a baby born at this stage survive? The answer would be yes, because simple squamous epithelium would be formed and alveolar capillaries will also be present at this stage, so gas exchange can happen. We even realize that many babies around us are born at the 7th month of pregnancy which almost corresponds to this stage of development, and they are able to survive. Nowadays, with advanced technology, even a child born at 5.5th month of pregnancy can survive with adequate treatment and support.

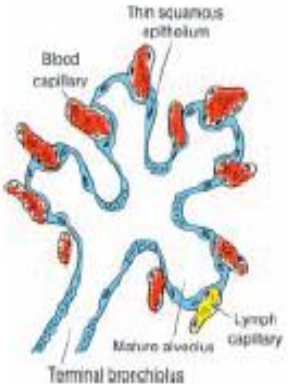
Stage 3: Terminal Sac Period

This period extends from the 26th week of pregnancy (approximately 7th month) until delivery. Terminal sac refers to the alveolar sacs and alveoli, which are formed at this period but are primitive alveoli (immature).These cells are intimately associated with numerous blood and lymph capillaries . As you can see in the picture, the alveolar capillaries have established close contact at this point with the alveolar sacs, and thin simple squamous epithelium is the dominant type of epithelium, which allows a high degree of gas exchange (respiratory membrane has been formed).



Stage 4: Alveolar Period

It is very important to note that this period starts from the 8th month of pregnancy and continues till the first 10 years of life after delivery. This period includes the maturation of alveoli. This means that maturation of alveoli only happens AFTER delivery and the alveoli continue to mature and divide up until 10 years after birth. As you can see in the picture on the right, at this point, the alveolar capillaries have formed complete contact with the alveoli and have formed the respiratory membrane; or what we can also call the "blood-air barrier" which is formed by the fusion between the endothelial cells of the capillaries, and type I alveolar cells lining the alveolar sacs.



What allows this close contact to be established is the fact that the type I alveolar cells become thinner at this stage to allow the alveolar capillaries to protrude into the alveolar sacs. Also, note that although lymphatic capillaries have started to appear in the previous stage, during the alveolar period they also achieve close contact with the alveolar sacs as seen in the picture. The table below summarizes everything mentioned:

TABLE 12.1 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.

The last thing we want to talk about concerning development of the lung is the type II alveolar cells. At the end of the 6th month, and the beginning of the 7th month and until the 8th month of pregnancy, the proliferation and development of type II alveolar cells takes place. Remember that those are the cells responsible for the production of surfactant, which reduces the surface tension at the liquid-air barrier in the alveolar sacs and increases the compliance of the lungs; making them easy to inflate. By the time where only 2 weeks are left for delivery, the peak in the production of surfactant takes place. Now let us divide the events into two parts for simplicity:

Before Birth: The lungs are full of fluid that contains a high chloride concentration, little protein, some mucus from the bronchial glands, and surfactant from the alveolar epithelial cells (type II). Before birth also, the breathing movements will start in the fetus causing aspiration of the amniotic fluid, and the importance of the amniotic fluid is that it stimulates further lung development and conditioning of the respiratory muscles to make the baby ready for pulmonary ventilation after delivery.

After Birth: At birth, when respiration begins, the fluid filling the lungs has to be resorbed. This happens by the help of blood and lymphatic capillaries, and also a small amount of fluid leaves through the trachea and bronchi during delivery. So now, we are only left with a liquid-air interface at the alveolar sac with the phospholipid surfactant deposited there. When the baby is first born, the doctor will tap his leg or his back and this will stimulate the skin receptors to send nerve impulses to the respiratory center of the brain, the brain will then respond by sending impulses through the phrenic nerve (motor nerve) to stimulate the diaphragm to contract. By mechanisms that we already covered in physiology, the lungs will now have to inflate to start the inspiration process. This is where the importance of the surfactant clearly shows. Reducing the surface tension means that we need less pressure to keep the alveoli open, so the presence of the surfactant is **actually important for expiration more than inspiration**, so that we keep the alveoli open and we prevent them from collapsing even when air is expelled. This is why when surfactant is missing, as soon as the baby expires, atelectasis (collapse) of the alveoli will happen and the next inspiration will be very hard.

The last concept to be discussed is simply a reminder of how alveoli mature AFTER delivery, where only **one sixth** of the adult alveoli number is present at birth. Alveoli remain to develop until 10 years of age. During this development, alveoli increase in both size and number, **but it is the increase in the number of alveoli and bronchioles that matters most for the growth of the lungs, and not the increase in size.**

PART B: Congenital Anomalies

1) RDS: Respiratory Distress Syndrome

From our previous talk about surfactant, we come to our first congenital anomaly which is the exact consequence of "missing surfactant at birth" that we have discussed above. In this case, during expiration, the newborn's alveoli will collapse due to loss of compliance and high pressure needed to overcome the collapsing force of the lung and to keep the alveoli open. This accounts for 30% of neonatal diseases, and 20% of deaths of newborns.

RDS can also be called **hyaline membrane disease (because of the high protein content and lamellar bodies) .**

The most important complication of RDS is intrauterine asphyxia, which is suffocation caused by deprivation of oxygen. This can cause irreversible damage to type II cells.

The treatment for this condition is administering glucocorticoids like betamethasone which stimulates surfactant production, which reduced the mortality associated with RDS. They have also found that thyroxine is the most important stimulator for surfactant production.

Remember when we said that a premature infant born at 5.5 months can still survive because of treatment and support? This is one of the treatments that help in the survival of those newborns.

2) Blind-ending trachea(atresia): Very Rare

3) Agenesis (absence or imperfect development) of one of the lungs

4) **Abnormal division of the bronchial tree resulting in supernumerary lobes:** The doctor gave an example on the left lung having 3 or 4 lobes for example instead of 2. These variations of the bronchial tree usually do not have functional significance but we might face an unexpected difficulty during bronchoscopy.

5) **Ectopic lung lobes:**
This means that the lung lobes are developing from somewhere outside the normal site which is the lung; in this case being the **trachea or esophagus.** This happens by the formation of additional respiratory buds of the foregut developing independently of the main respiratory system.

6) **Congenital cysts of the lung:**
These occur due to the dilation of terminal or larger bronchi. They could be small and multiple giving the lung a **honeycomb appearance on radiograph,** or restricted to one or more larger ones.
Cystic structures of the lung drain poorly and can frequently cause chronic infections.

7) **Lung Hypoplasia:**
The lungs here are much smaller than normal with a very small volume. They are characterized of being associated with **Congenital Diaphragmatic Hernia** which develops due to the compression of the abdominal viscera on the diaphragm. Most infants die because of pulmonary insufficiency as their lungs are too small and this mainly depends on whether the other lung can compensate or not. Plus, this condition can be treated.
Remember that the left side of the diaphragm is more prone to herniation.

8) **Oligohydramnios:**
This is where the amniotic fluid is reduced. Remember that amniotic fluid plays a very important role in the development of the lung, so if you

decrease it, severe pulmonary hypoplasia will take place, which takes us back to point 7.

The last thing you should know, is that you can easily tell if a newborn died after delivery, or if it is stillbirth. All you do is that you take a sample of the lung tissue and place it in water. If it floats, it means the lungs are healthy and fresh and the baby died after delivery. If it sinks, it means no air was present in the lungs at all and the baby did not take his first breath, so it is stillbirth.