TABLE OF CONTENTS:

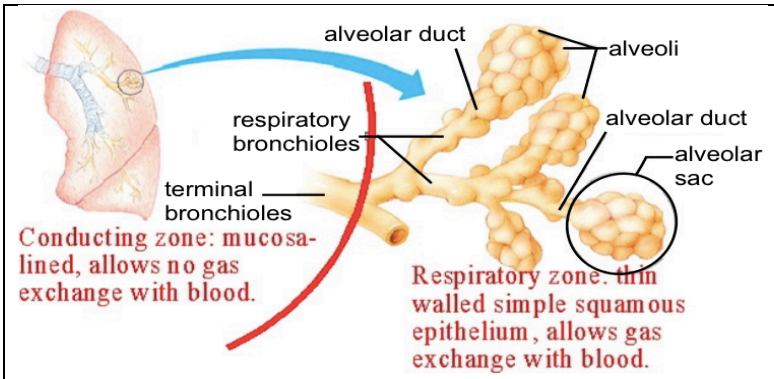
Notes to reader:

- Drugs and drug classes are highlighted in green and bolded (e.g. **Ivacaftor**).
- Drugs that are not approved for clinical use, are highlighted in grey and bolded (e.g. **Ataluren**).

LECTURE 22 Respiratory System and Cystic Fibrosis 23/04/18

Review of the Respiratory System:

- ***Note***: The respiratory system begins in the upper airways (in the nose)!



- The airways are a series of branching tubes.
- The **trachea** branches into bronchi, which branch into **bronchioles**, which branch into **terminal bronchioles**, which branches into the **respiratory bronchioles**, which branch into **alveolar ducts**, which form **alveoli** (air sacs).

- The **acini** (singular: **acinus**) refer to the portions of the lung involved in **gas exchange** and consist of the respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli.

Five Stages of Lung Development:

Stage:	**Time**:	**What happens?**
Embryonic	0-6 weeks gestation	• **Lung bud** appears (4 weeks gestation) via ventral outpouching of the primitive foregut (*endodermal origin*). Branching of the airways occurs in a proximal fashion into the surrounding mesoderm.
Pseudo-glandular	6-16 weeks gestation	• Branching occurs to the level of terminal bronchioles (final part of the **conducting zone**). 16 generations have occurred.
Canalicular	16-26 weeks gestation	• Earliest development of the acini (**respiratory zone** where gas exchange occurs) occurs. But at this stage, there is not enough gas exchange to allow a foetus to survive outside the uterus. • Thinning of the peripheral epithelium occurs. • Type I (gas exchange) and II (surfactant) pneumocytes develop (which will later make up the alveoli).
Sacular (alveolar)	26-36 weeks gestation	• Sacules form into alveolar ducts and alveoli. Alveoli form around 30 weeks gestation. Sacules become thin walled. Sacules and alveoli form further generations of alveoli by **septation**.
Postnatal	Birth (2 years until adult)	• At birth, there are 1 x 10^8 alveoli (4 m^2 of SA). As an adult, there are 3 x 10^8 alveoli (10 m^2 of SA). So continued alveolisation occurs post-birth.

Functions of the Lung:

Function:	**Notes:**
Gas exchange	• Gas exchange occurs in the acinus, predominantly in the alveoli, which are lined by Type I (alveolar) cells and Type II (surfactant-secreting) cells. - The majority of cells are Type I, which are thin-walled to facilitate gas exchange. O_2 diffuses into the capillaries and CO_2 can diffuse out of the capillaries. - Type II secrete surfactant, reducing surface tension, to prevent alveolar collapse.
Defence	• The lung has a role in defence against particles that may adhere to the lung epithelium: **1.** Physical (airway): ○ Upper airway filter: The nose contains hairs that filter out large dust particles. Turbinates of the nose help dust and larger particles to deposit. ○ Reflexes (e.g. cough, sneeze): To expel particles ○ **Mucociliary escalator** (*impaired* in CF) **2.** Cellular (alveolar): ○ Phagocytes (e.g. alveolar macrophages) migrate, ingest foreign particles in lung

LECTURE 24 Current and Future Therapies for Cystic Fibrosis 27/04/18

Goals of Treatment:

1. Maintain lung function:
   - By treating infections
   - By assisting airway clearance
   - By reducing exacerbations: If exacerbations occur and the patient loses lung function, they unlikely to recover to baseline function
2. Adequate growth:
   - By diet
   - By supplementation
3. Managing complications
   - Such as CFRDM
   - Such as liver disease

Treatments Used in Cystic Fibrosis:

- CF requires multidisciplinary care involving: Physicians, nurses, physiotherapists, dieticians, geneticists, psychologists, social workers. When care is delivered by **centres of excellence**, where groups of CF patients have access to multidisciplinary team, this is associated with better outcomes.

Therapy:	Purpose:	Mechanism:	Notes:
Physiotherapy:			
Gravity assisted drainage	• Improve mucociliary clearance. Doesn't make you feel better in short-term, but is better in long-term	• By positioning body into gravity-assisted positions	• e.g. 5-position technique in infants
Active cycle of breathing technique		• Active breathing technique performed by patient	• e.g. Blowing games
Autogenic drainage (**AD**) (or assisted AD)		• Controlling urge to cough until enough of a build-up occurs, so that mucous can be cleared more easily	
Positive expiratory pressure (**PEP**)		• Pressure prevents airway closure, helping mucous move into larger airways.	• Started at age 2 • e.g. Bubble PEP (blow in water)
Physical activity and exercise			• Any sport • e.g. Trampoline
Mucolytics:			
Pulmozyme	• To reduce mucous viscosity.	• rhDNase: Cleaves DNA in mucous, reducing viscosity	
Hypertonic saline		• Draws water in by osmosis thereby reducing viscosity	
Mannitol		• Draws water in by osmosis thereby reducing viscosity	
Anti-microbials: Either as prophylaxis or to treat exacerbations			
Anti-inflammatories: Prednisolone, inhaled steroids and ibuprofen have unfavourable risk-benefit ratio. While they showed significant improvements in lung function, there were severe adverse effects.			
Azithromycin (an aminoglycoside)	• For chronic infections with *P. aeruginosa* • Neutrophilic inflammation	• Inhibits protein synthesis by binding to small subunit of ribosome, disrupting the reading frame.	• ***Improves***: Weight, FEV_1, exacerbation • Increases risk of infection by NTM • Deafness
Prednisolone	• Used judiciously due to adverse effects	• Glucocorticoid mechanism to reduce inflammation	• ***Improves***: FEV_1 (i.e. lung function)
Ibuprofen (an NSAID)	• Used more so in US (not much here)	• Inhibition of COX blocks synthesis of PGs, TXs	• Minimally improves lung function
Nutrition: CF patients have higher energy requirements (but it is variable).			
Managing pancreatic insufficiency:			
Creon (contains enteric-coated pancreatic enzyme microspheres)	• To treat CF patients who are pancreatic insufficient • Taken with any meal containing proteins, lipids or carbohydrate	• Contains lipase, amylase, protease. A maximum of 10,000 units lipase/kg/day.	• Derived from porcine extract • May involve 2-3 pills for a snack • May involve 4-5 pills for a meal

LECTURE 28-30 Malaria 07/05/18, 10/05/18, 11/05/18

- **Malaria** is one of the leading causes of child mortality and morbidity.
  - Around 1 billion people have parasites, with 200-300 million people getting sick. 0.5 million deaths occur, mostly involving children. Why do some people get sick and die, while others do not?
  - Malaria involves technical (e.g. lack of effective vaccine, insecticide resistance, anti-malarial drug resistance) and non-technical barriers (e.g. healthcare system barriers, unaffordable treatment).
  - Because of drug resistance (we're currently on our last line of anti-malarial drugs, the **artemisinins**), there is desperation for new drugs and preferably, a vaccine.
- While malaria deaths are not as widespread across the world, the number of malaria cases are. For example, South America has a lot of *P. vivax*. So while there may not mortality, there is a lot of morbidity. In India and South-East Asia, there's *P. vivax* or *P. falciparum*, with access to better treatment.
- Malaria hinders social and economic development, causing high rates of work and school absenteeism.

Taxonomic Classification of the Parasite Involved In Malaria:

- Phylum: *Apicomplexa* (relates to the shape, has an apical complex)
- Genus: *Plasmodium*
- Species (that are known to infect humans): *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*
  - *P. falciparum* results in the most lethal form of malaria.
  - *P. vivax* is less lethal. Most of us would recover from *P. vivax*, but in developing countries, when mixed with other infections and nutrient deficiencies, it can cause significant problems.
    - Most of the West African population are Duffy-negative (Duffy is an antigen on RBCs). *P. vivax* uses Duffy to enter RBCs, selecting those with a Duffy-negative phenotype.
    - **Relapsing malaria**, where there is infection again and again and again due to a latent form that persists in the liver, is only caused by *P. vivax*.
  - *P. ovale*, *P. malariae* and recently *P. knowlesi* (Malaysia, Indonesia) are lesser known species.

Life Cycle Involves Three Stages:

1. Mosquito stage (sexual reproduction: 1-2 weeks): A female *Anopheles* mosquito infected by *Plasmodium* will transmit *Plasmodium* to humans during a blood meal. Only females drink blood to mature eggs.
   - ***Note***: Only some species of *Anopheles* will cause malaria.
   - The mosquito is the definitive host of the *Plasmodium*, where sexual reproduction occurs (and sexual reproduction is what eukaryotes do best, because it facilitates genetic diversity).
     - But *Plasmodium* uses mammalian hosts as a mechanism to be transmitted from mosquito to mosquito. When the uninfected mosquito then bites the mammalian host, there is transmission.
2. Liver stage (asexual reproduction: 1-2 weeks): The *Plasmodium* that are injected by the mosquito into the skin, get into the blood vessels (**sporozoites**), and move into the **liver** and infect a small number of **hepatocytes**. There is no disease in the liver, since only a small number of hepatocytes are affected. The *Plasmodium* multiplies in these infected hepatocytes producing **merozoites**.
3. Blood stage (asexual reproduction cycle: 2-3 days) Merozoites enter the bloodstream and infect RBCs, undergoing a cycle of maturation, replication, and burst. Major amplification stage for *Plasmodium*.
   - Some of the *Plasmodium* change to produce female and male **gametocytes**.
     - ***Note***: These gametocytes will go on to form **gametes** when are taken up by a feeding mosquito. Once they are in the mosquito, fertilisation occurs and sexual reproduction occurs.

Virulence and Immune Escape:

- When a person is infected with malaria, parasitaemia occurs, but then the immune system kicks in and it gets cleared. But then they go up again, and then drops off, and goes up, then drops off. Why?

Cytoadherence and Sequestration:

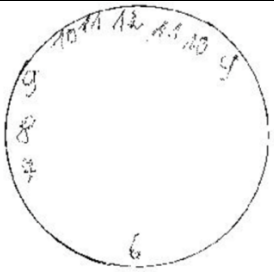
- The spleen has mechanisms to determine whether RBCs are normal or not, and can kill cells that are abnormal. **Cytoadherence** describes the process of how infected cells latch onto the endothelial cells of the blood vessels, which enables the infected RBCs to avoid splenic clearance..

LECTURE 34-35 Alzheimer's Disease (AD) 21/05/18, 23/05/18

- **Alzheimer's disease** (**AD**) is the most common cause of dementia. It is a disease associated with ageing.
- 25% of people over the age of 85 have dementia (not necessarily AD) with ~400,000 Australians with dementia. It is expected to rise to ~1,000,000 by 2056.
- 55% of people with AD are female and 45% are male. Women have an increased risk of AD compared to men, even if we account for the fact that females tend to live longer than males.

Mini Mental State Exam (MMSE):

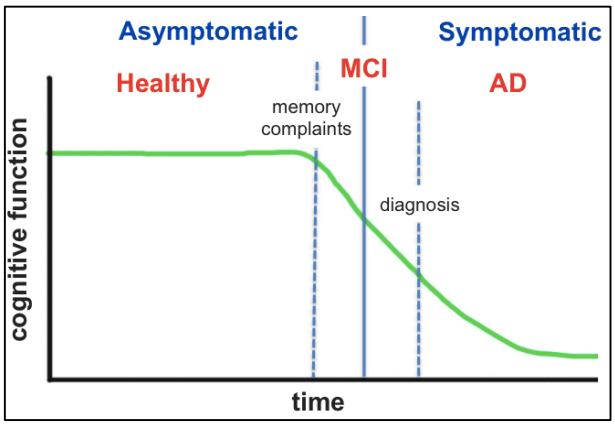
- Neurologists can do different tests to determine whether there are memory problems or just a bit forgetful. One test is a **mini mental state exam** involving orientation, registration, attention, calculation, recall, etc.
- **Clock drawing test**:



- A MMSE score of 16 (left) represents a person with quite significant dementia. They can't put the numbers in the right places.
- With a MMSE score of 12 (right), the ability to draw a clock (an object they would have seen all through life) from memory is severely impacted.

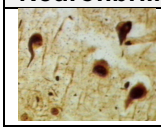
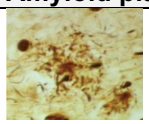
Natural Progression of Alzheimer's Disease:

- A **prodromal period** (up to 5 years): There is a decline in cognition, characterised by impairment of short-term memory and possibly impairments of working memory, but the person does not present with clinical symptoms (still part of asymptomatic phase). Usually precedes formal diagnosis of AD.
  - ***Note***: For some, these declines in cognition do not necessarily indicate AD. It could just be that they have these impairments of short-term and working memory and don't have AD.
- Some develop **mild cognitive impairment** (**MCI**) where there is clearly a significant cognitive defect.
- A certain percentage will progress beyond MCI and develop AD. Some people will not progress further.



Pathological Hallmarks of Alzheimer's Disease:

- There is significant neuronal loss in AD (refer to brain images on p. 4). Remember, cell loss is a common feature in the pathology of age-related neurodegenerative disease (e.g. PD, AD, HD).
- There is protein deposition in AD, including **neurofibrillary tangles** (NFTs) and **amyloid plaques**.

Neurofibrillary tangles (NFTs):		**Amyloid plaque:**	
	Intracellular protein aggregates (inside neuron) that is composed of: Hyperphosphorylated tau		Extracellular protein deposit that is primarily made up of: Aβ peptide

Neurofibrillary tangles:

Tau:

- **Tau** is a part of the cytoskeleton. It interacts with tubulin to stabilise microtubules and regulate axonal transport. It is mainly present in **axons**. Microtubule binding is mediated via its **microtubule-binding repeats** (**R1**, **R2**, **R3**, **R4**). Tau affects the transport of motor proteins (e.g. dynein, kinesin: which are proteins that transport either organelles, proteins or vesicles along axons) along microtubules.

REVISION CHECKLIST FOR MODULE 4, MODULE 5 AND MODULE 6:

About MST 2:

- In 2018, MST 2 ran for 50 minutes (5 minutes reading time, 45 minutes writing time). It was worth 20% of our final mark. MST 2 tested our understanding of Module 3 (Muscular Dystrophies) and Module 4 (Cystic Fibrosis).
- ***Note***: The order of modules can differ each year. In 2018, the first two modules were B-cell diseases and rheumatoid arthritis, but in the past other modules were done first. So don't assume that your MST 1 will involve the same modules as the 2018 MST 1.

Class Results from MST #2:

- In 2018, the average mark was 31.13 / 40 and the median mark was 32 / 40. No questions were removed from our score this time. I found Modules 3 & 4 to be slightly easier compared to Modules 1 & 2.

Preparing for MST 2 and Exam:

Revision Checklist for Module 3 (Muscular Dystrophy):

- ***Note***: This revision checklist is in the first half of my notes for this subject.

Revision Checklist for Module 4 (Rheumatoid Arthritis):

- Here's a checklist:

From:	Content:	
Lecture 19	• What are examples of the systems that CF can affect?	
	• What are the most common causes of death in people with CF?	
	• Do two individuals with the same *CFTR* mutations necessarily have the same disease severity? Why or why not?	
	• What are the respiratory clinical features of CF?	
	- Explain why each of these clinical features occur.	
	• What are the digestive clinical features of CF?	
	- Explain why each of these clinical features occur.	
	• What are the reproductive clinical features of CF?	
	- Explain why each of these clinical features occur.	
Lecture 20	• What is the *CFTR* gene?	
	- What chromosome is the *CFTR* gene on?	
	- What does the *CFTR* gene encode?	
	- When was the *CFTR* gene discovered and how was it identified?	
	- How many exons does the *CFTR* gene have?	
	• What is the CFTR protein?	
	- The CFTR protein is a member of which protein family?	
	○ Unlike other members of this protein family, CFTR is unique in what respect?	
	- The CFTR protein is regulated by what kinase?	
	- What does the CFTR protein regulate?	
	- In what tissues, is CFTR protein expressed?	
	- On what side of epithelial cells, is CFTR protein expressed?	
	• What is the structure of the CFTR protein?	
	- What are the five domains of the CFTR protein and what are each of their functions?	
	- Explain the molecular mechanism for opening the CFTR protein.	
	- Explain the other roles of the C-terminal domain of CFTR protein.	