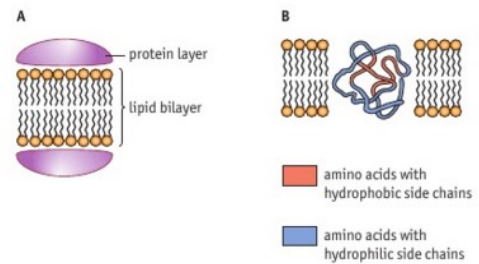


Some proteins are fixed within the membrane but others are not and can move around in the fluid phospholipid bilayer- **fluid mosaic model**.

Evidence for the fluid mosaic model

First accepted theory:

- Three layer protein-lipid sandwich
- Based on evidence from electron micrographs where dark outer layers thought to be proteins and lighter thought to be lipid



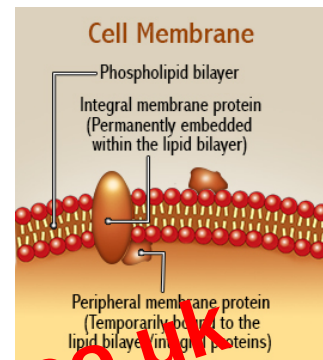
Problems:

- Doesn't allow hydrophilic phosphate heads to be in contact with water
- Doesn't allow hydrophobic amino acids on the outside of the membrane proteins to be kept away from water

Experiments show...

Two types of protein:

1. Easy to remove from membrane by increasing ionic strength of the solution
 2. Can only be removed by more drastic actions like detergents (most proteins)
- =
1. **Peripheral proteins**- loosely attached to the outside
 2. **Integral proteins**- embedded in the phospholipid (can span both layers)



Freeze fracture electron microscopy

The membrane is frozen and is fractured along the weak point between the lipid layers

- Inner layer is coated in heavy metal

3D images reveal a smooth mosaic like surface (lipid tails) interspersed by larger particles (integral proteins)

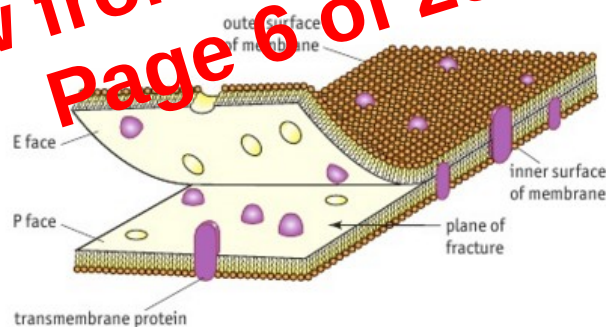


Figure 2.17 Freeze-fracture of membranes reveals the integral transmembrane proteins.

Labelled molecule test

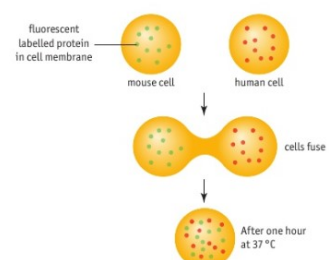
Plant proteins (lectins) bind to polysaccharides- labelled with ferritin (protein with ferric oxide core). When mixed with a membrane, the lectins only bound to the outer surface of the membrane- not the inner.

- Showed membrane is asymmetric (outside different to inside)
- Doesn't support to sandwich model (lectin would have bound to outside and inside)

Fusing mouse cells with human cells

Mouse protein- green label. Human membrane protein- red fluorescent label. Cells fused...

- 40 minutes
- 37 degrees



2. TOO LITTLE WATER IN THE MUCUS

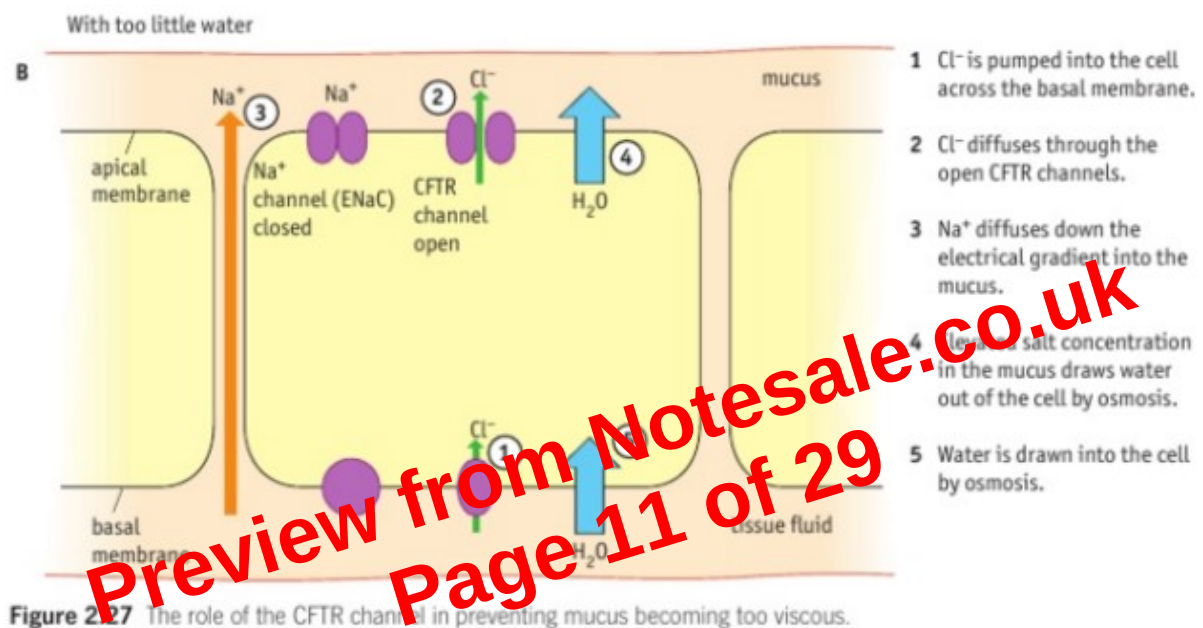
Chloride ions are transported across the basal membrane into the epithelial cell = concentration gradient- chloride ion concentration is higher in the cell than out.

People without CF have CFTR protein channels that open (gated channel protein), closing the sodium ion channels in the apical membrane.

- Cl^- ions diffuse out through the CFTR protein **down** the concentration gradient into the mucus.
- Build-up of Cl^- ions in the mucus creates an electrical gradient between the mucus and the tissue fluid

Sodium ions diffuse out of the tissue fluid through gaps between cells into the mucus. This movement of sodium and chloride ions into the mucus draws water out of the cells by osmosis until solutions are isotonic.

- This prevents the mucus becoming too sticky.



WHY CF LUNGS CAN'T REGULATE WATER IN MUCUS

CFTR protein may be missing or it doesn't function correctly.

- When there's too little water in the mucus, Cl^- ions can't be secreted
- Sodium ion channels aren't blocked and allow more sodium ions into the epithelial cell than normal
- Continuous absorption of sodium from mucus into the cells
- High concentration of sodium in cells draws chloride ions and water out of the mucus into the cells- osmosis

Mucus becomes even more viscous and cilia can't move it. Build-up of mucus reduces the effective ventilation of alveoli.

- Mucus becomes infected with bacteria
- Phagocytic cells that clear pathogens are over produced in response
- Break down of phagocytes makes mucus even stickier
- Airway inflammation and lung damage

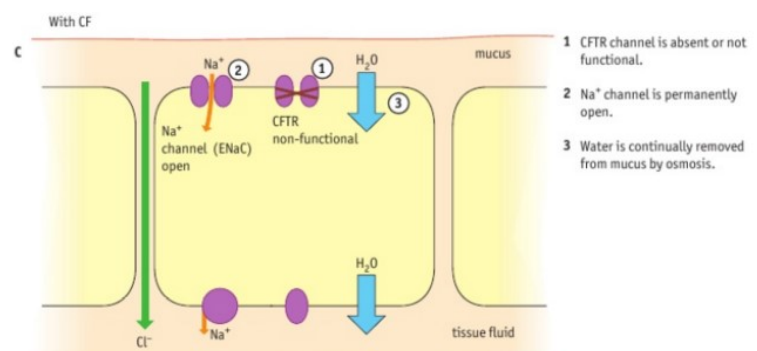


Figure 2.28 The effect of non-functioning CFTR channel on mucus viscosity.

- They allowed the bacteria to divide and their DNA to replicate once.
- They then extracted and centrifuged the DNA.

Heavy DNA (only ^{15}N) sinks to the bottom and light DNA (only ^{14}N) collects near the top. DNA of medium density is in the middle (heavy and light nucleotides).

Result:

- Single band of medium density DNA

No heavy DNA- conservative replication rejected.

- Fragmentational and semi-conservative replication would produce medium DNA after one round so they undergo two rounds of replication.

The DNA was extracted and centrifuged after two rounds of replication, giving two bands- one medium and one light.

- Presence of medium and light DNA bands confirmed semi-conservative model.

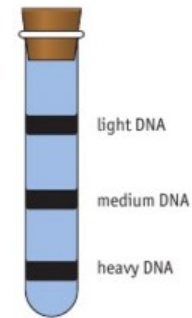


Figure 2.52 Position of DNA after density-gradient centrifugation.

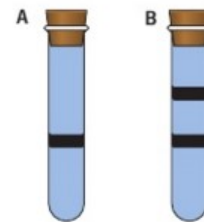


Figure 2.53 A Position of DNA after one replication. B Position of DNA after replicating twice.

Fragmentational replication would only produce one type of DNA containing a mix of heavy and light nucleotides.

Mistakes in replication

Inaccuracies can occur when building the 'new' strand of DNA = gene mutation.

Mutations can occur in the DNA of an ovary or testis cell that is dividing to form an egg or sperm. This can be passed onto future generations, present in every single cell produced by the fertilised cell.

Large amounts of DNA in a cell don't play a role in protein synthesis and so mutations here have no effect.

- Mutations only have an effect when a gene/new base triplet is created that codes for a stop signal or different amino acid causing a faulty acid
- Could cause a genetic disorder

Mutations in sickle cell anaemia

In sickle cell anaemia there is a substitution mutation in the gene that codes for one of the polypeptide chains in haemoglobin- the pigment in red blood cells that carries oxygen.

- Adenine replaces thymine at one position along the chain
- mRNA codes GUA instead of GAA
- result: protein produced contains non polar amino acid valine rather than polar glutamic acid
- haemoglobin becomes less soluble (not polar)
- when oxygen is low, the molecules form long fibres that stick together inside the red blood cell- distorts the shape.
- Resulting moon shaped cells carry less oxygen and can block blood vessels.

Mutation for Variation

Mutations can occur in somatic cells or germ cells. Germ cell mutations are passed along to progeny.

GERM CELL



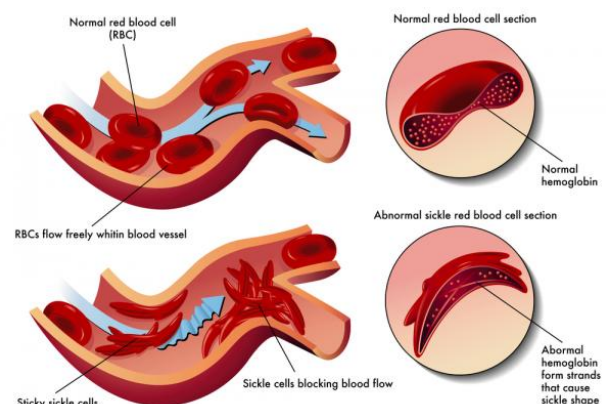
Germ cells are sex cells, like the sperm and egg.

SOMATIC CELL



Somatic cells are non-sex cells, like skin or muscle cells.

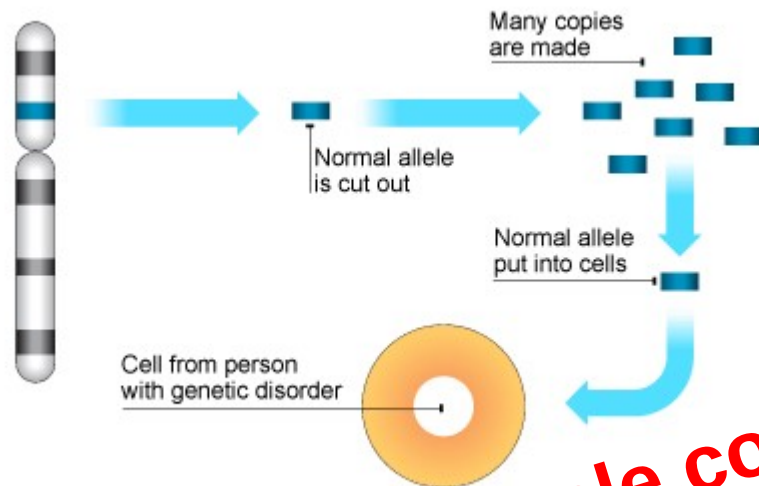
Sickle-Cell Anemia



Physiotherapy	- Rhythmical tapping of the walls of the chest cavity (percussion therapy) and use of a flutter device can loosen the mucus and improve airflow into the lungs - Regularly- twice a day
Heart and lung transplant	- Lungs can become very badly damaged and inefficient - Treatments may fail to relieve treatment

Future possibility:

Gene therapy



- Alters the genotype and phenotype of cells affected by the condition
- Normal alleles are inserted into target cells using a vector or a carrier mechanism (liposomes)
- The normal form of the gene is transcribed and translated, to produce a functioning protein
- A working CFTR protein is produced and incorporated into the cell membrane- restoring the ion channel

The effect of this is only temporary because cells are continually lost from the epithelium lining the airways- the transferred alleles would have to constantly be replaced.

- No cure for CF!!!

