

Physiology

Marrow Edition 8

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Instructions

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HOMEOSTASIS

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Introduction

00:00:48

Homeostasis is the concept of **constancy**.
Central theme for bodily function.

Disturbance in homeostasis.



Disease.

Claude Bernard :

Coined the term **milieu interior** (Internal environment).

Walter Cannon :

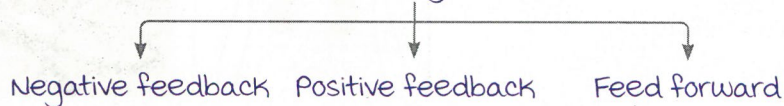
Coined the term homeostasis.

Control systems of homeostasis

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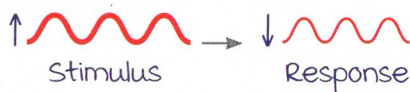
mechanisms of the body to maintain homeostasis.

Control systems



Negative feedback :

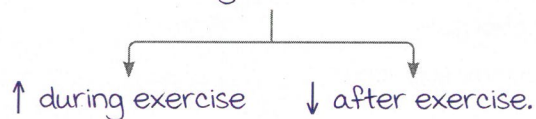
↑ in stimulus → ↓ parameters



Eg :

1. **Baroreflex** :

Changes in BP

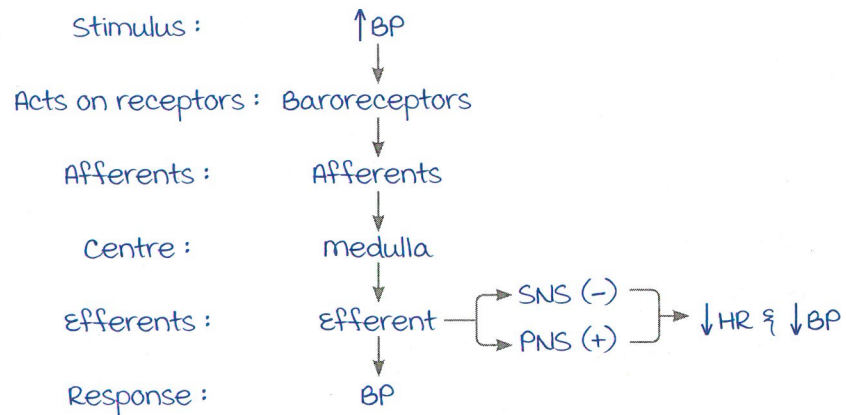


2. Endocrine hormone regulation (99%).

3. Gastric acid secretion.

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Components of -ve feedback :



SNS : Sympathetic nervous system.

PNS : Parasympathetic nervous system.

Assessment of effectiveness of -ve feedback :

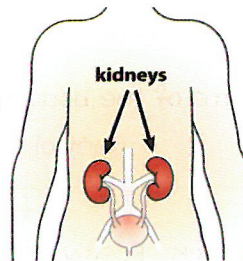
$$\text{Gain (G)} = \frac{\text{Correction by the system (C)}}{\text{Error remaining (E)}}$$

Infinite feedback gain :

When error becomes zero $G = \frac{C}{0} = \infty$

↓

Gain = Infinity



Eg :

Kidneys always correct blood pressure back to normal.

In HTN → Kidneys are affected → BP never comes back to normal.

Positive feedback :

- $\uparrow$ in initiating stimulus → Further $\uparrow$ in response.



- Amplification/cascade of reactions.
- AKA vicious cycle (Destabilizes our system).

Eg : CLAPS (mnemonic).

a) Coagulation cascade.

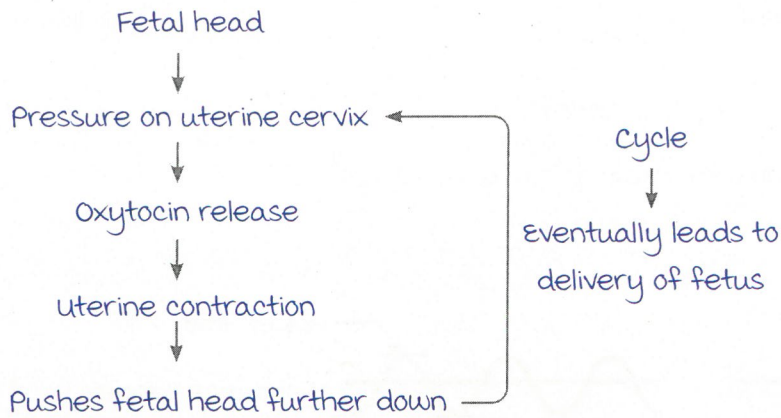
b) LH surge : Only exception for true feedback in endocrine hormone regulation.

c) Action potential.

d) Parturition (Normal delivery) :

AKA Ferguson reflex.

----- Active space -----



e) Shock :

Hemorrhagic shock (Eg : RTA) → Irreversible shock → Death (+ve feedback).

Feedforward control system :

Core theme : Anticipatory control system.

Body responds anticipating a stimulus (No actual stimulus).

Eg :

a) Anticipatory tachycardia & tachypnea : ↑RR and ↑HR before exercise.

b) Anticipatory motor control :

- Centre : Cerebellum
- Person driving on a highway → Applies breaks on seeing a cow (Anticipates danger).

c) Anticipatory regulation of core body temperature :

- Skin temperature → Shell temperature.
- Body organ temperature → Core temperature.

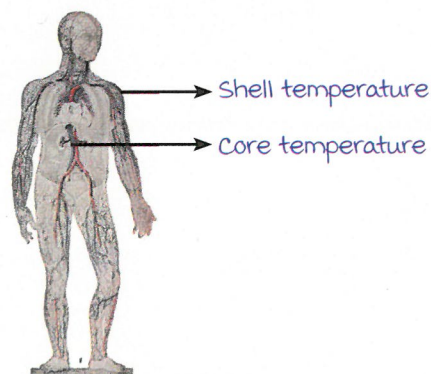
Cold environment.

↓ shell temperature.

Hypothalamus anticipates ↓ core temperature.

Corrective measures.

maintenance of core temperature.



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Properties of Homeostasis

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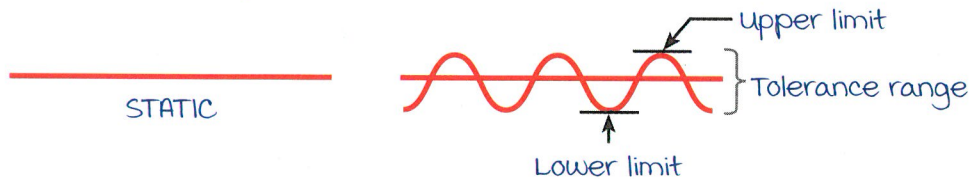
Dynamic constancy :

AKA *dynamic equilibrium*.

Homeostatic control systems maintain a "*range of values*"

Eg : Normal HR = 60-100bpm.

Normal RR = 12-18bpm.



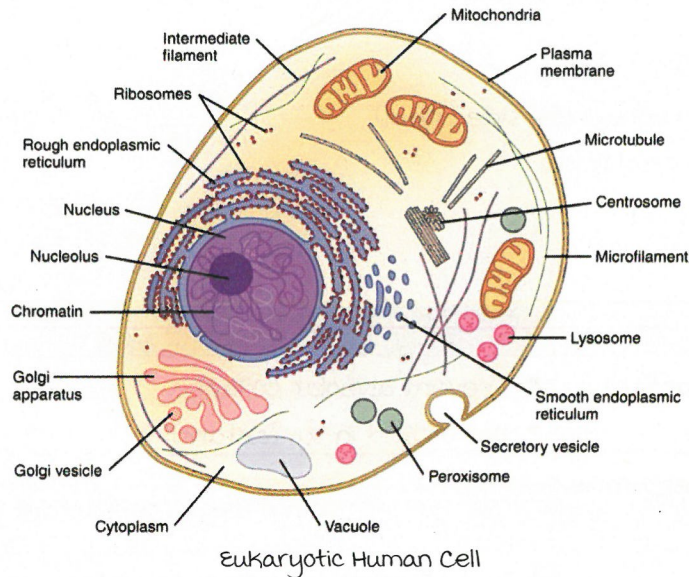
Prioritization of parameters :

- Priority of order of correction of parameters :
pH > BP > Temperature.
- pH changes are given more priority : As they affect the activity of enzymes
→ Death.

CELLULAR PHYSIOLOGY

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Cell is the fundamental unit of all living organisms.



Cell Membrane

00:01:13

AKA plasma membrane.

FUNCTION

It is an outer barrier with selective permeability in cell.

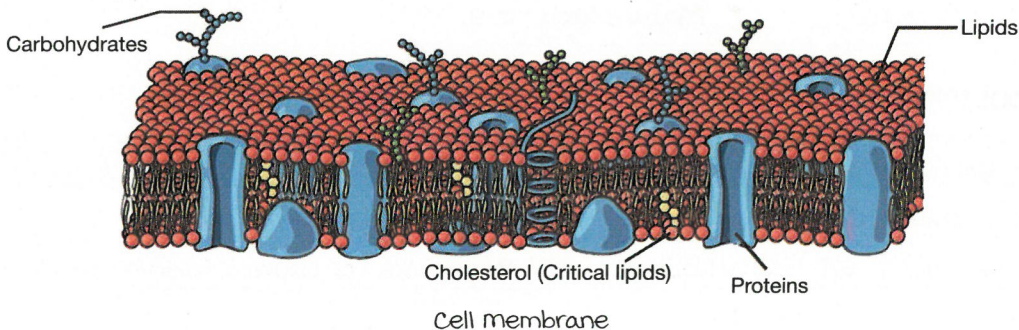
STRUCTURE

Fluid mosaic model of cell membrane. Proposed by Singer and Nicolson.

COMPOSITION

macromolecules :

1. Proteins (55%) : Arranged in mosaic pattern in cell membrane.
2. Lipids (40%) : Responsible for fluidity of cell membrane.
3. Carbohydrates (5%).



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Lipids

00:04:40

INTRODUCTION :**Structure :**

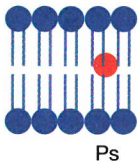
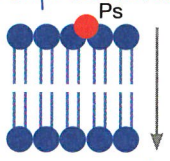
- Bilayer : Outer and Inner lipids.
- Asymmetry : Arranged specifically either on inner or outer side.

Types :

- Phospholipids (PO_4^{3-} group).
- Glycolipids (Carbohydrate side chain).
- Cholesterol (Critical lipid).

PHOSPHOLIPIDS :

major lipid.

Types	Site	Significance
Phosphatidyl choline (PC) AKA lecithin	Lungs : Surfactant	• Prevent alveolar collapse. • major lipid in surfactant.
Sphingomyelin	• Nerve cell membrane. • Surfactant.	minor lipid in surfactant
Phosphatidylinositol (IP3)	Endocrine cells	• Part of second messenger system ($\text{IP}_3 \rightarrow \text{DAG} \rightarrow \text{Ca}^{2+}$)
Phosphatidylserine (PS)	Inner surface of cell membrane in all cells 	If expressed on outer surface.  • Apoptosis (Programmed cell death). • Detected by Annexin V : Binds & forms complex with PS. (Annexin V staining).
Cardiolipin (CL)	Heart : mitochondria	In syphilis : Serum anti-CL antibody + (Detected by VDRL test)

Note :

$\frac{\text{L (Lecithin)}}{\text{S (Sphingomyelin)}}$ ratio :

- To assess fetal lung maturity.
- mature lung : ≥ 2 .

GLYCOLIPIDS :

Types	Site	Significance
Cerebrosides	CNS	-
Gangliosides	GIT	Gm-1 gangliosides : Receptors for cholera toxin-Fragment B.

CHOLESTEROL :

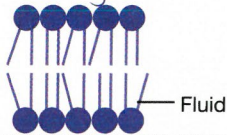
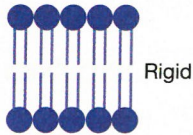
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Site : Cell membrane of skin.

Significance :

- Precursor of Vit.D.
- 7-dehydrocholesterol $\xrightarrow[\text{(Skin)}]{\text{Sunlight}}$ Vit.D
- **Fluidity buffer** : maintains membrane fluidity in optimal range.

MEMBRANE FLUIDITY :Lubricative property of lipid $\rightarrow$ maintain fluidity of membrane $\rightarrow$ Allows mobility.**Characteristics of Fluidity :**

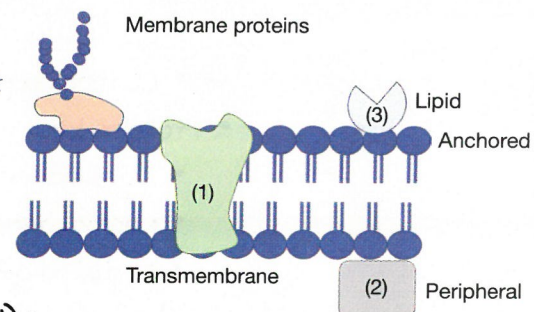
	Increased Fluidity	Decreased Fluidity
Effect on health	Good	Bad
Type of fatty acids	unsaturated (Essential)	Saturated (Trans)
Examples	• Linoleic acid. • Linolenic acid. • Arachidonic acid. • Omega-3 fatty acids : Abundant in fish. 	• Stearic acid. • Palmitic acid : (Abundant in junk food) 

Proteins

00:24:00

Classification based on location in cell membrane :

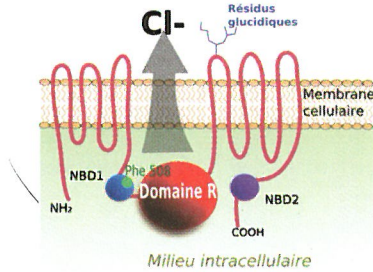
1. Transmembrane proteins/integral membrane proteins : Present throughout.
2. Peripheral proteins : Present peripherally.
3. Lipid-anchored proteins : Requires lipid for attachment.

**TRANSMEMBRANE PROTEINS (INTEGRAL MEMBRANE PROTEIN) :**

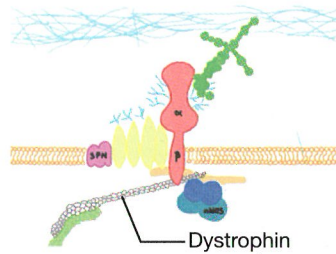
most important.

Functions	Examples
Hormone receptors (m/c)	GPCR (G-protein coupled receptors).
Pump channels	$\text{Na}^+ - \text{K}^+$ ATPase
Ion channels	• Cl^- channel (CFTR). (Cystic fibrosis transmembrane conductance regulator.) • In cystic fibrosis $\rightarrow$ CFTR mutation (+).

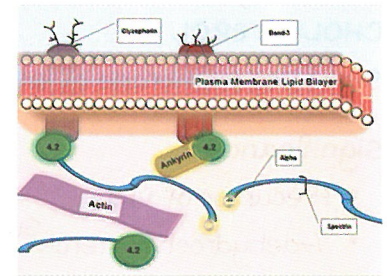
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Transmembrane protein :
Cl⁻ channel (CFTR)



Peripheral protein



PERIPHERAL PROTEINS :

Functions :

1. Support shape of cell :

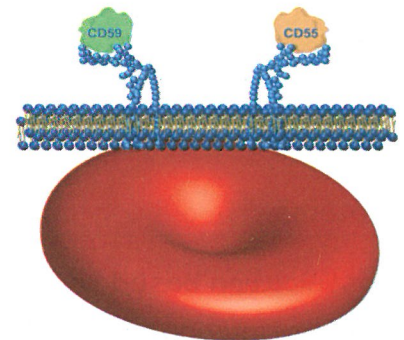
Cell	Protein	Diseases due to mutations
RBC (Biconcave disc)	Spectrin	Elliptocytosis
	Ankyrin	Spherocytosis
Skeletal muscle	Dystrophin	- Duchenne muscular Dystrophy (DMD). - muscular weakness. Typical presentation. - Gower's sign : Climb on own body to stand up (knee → Hip → Stand). - Respiratory paralysis (Weakness of diaphragm) → Death.

2. Cell surface receptors.

LIPID ANCHORED PROTEINS :

In Rbc :

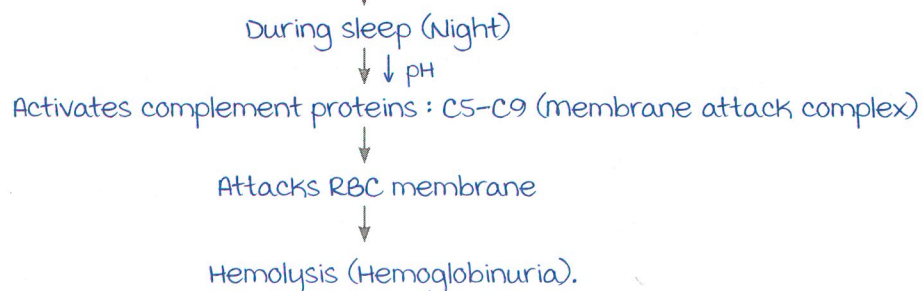
- PIGA (Phosphatidylinositol Glycan-A) gene synthesises proteins :
 - CD55 (Decay accelerating factor).
 - CD59 (membrane inhibitor of reactive lysis).
 - C8 binding protein.
- Proteins bind to lipid : **Phosphatidylinositol**.
 - Significance :
 - Normal gene : Prevent hemolysis.
 - mutated gene : Paroxysmal Nocturnal Hemoglobinuria.



Lipid anchored proteins in RBC.

Paroxysmal Nocturnal Hemoglobinuria

Pathology : mutated or absent PIGA gene.



Treatment :

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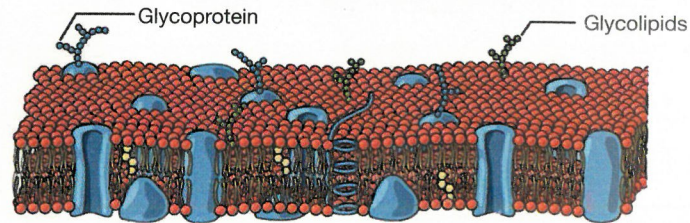
- Anti C5 monoclonal antibody : Supportive.
 - Eculizumab.
 - Ravulizumab (Long acting).
- Hematopoietic stem cell transplant : Definitive.

Carbohydrates

00:41:30

CLASSIFICATIONS :

1. **Glycoprotein** : Attached to proteins.
2. **Glycolipids** : Attached to lipids.



SIGNIFICANCE :

Glycolipids on RBC membrane : **Determine blood groups.**

	Blood Type			
	A	B	AB	O
Red Blood Cell Type				

Note :

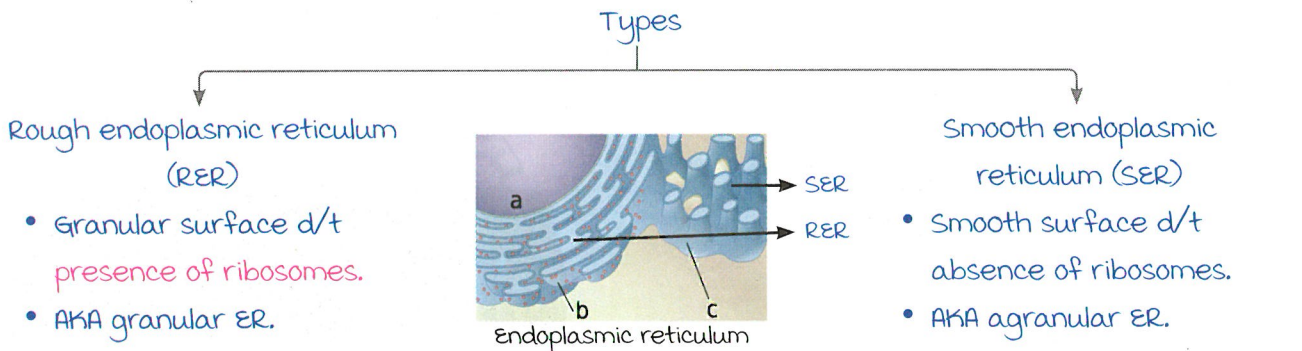
- membrane with highest protein : Inner mitochondrial membrane.
- In nerve cell membrane (myelin) : **Lipid (80%) : Protein (20%).**
- Repair of damaged cell membrane is by resealing of lipid bilayer.
- Deficiency of lecithin in pre-term baby : **Hyaline Membrane Disease.**

----- Active space -----

CELL ORGANELLES

Endoplasmic Reticulum

00:00:30



ROUGH ENDOPLASMIC RETICULUM :

Functions :

- Protein synthesis/translation.
- Folding of proteins : Using chaperones/heat shock proteins (HSP).
- Degradation of mis folded proteins & quality control of proteins by unfolded protein response or ER stress response.

↑↑ misfolded proteins → ER → 1. Halts protein synthesis.

2. Endoplasmic reticulum associated degradation (ERAD).

ERAD :

misfolded proteins are tagged to **ubiquitin** (kiss of death)

↓
Protein-ubiquitin complex

↓
moves to **proteasome** (Graveyard of the cell)

↓
Degradation.

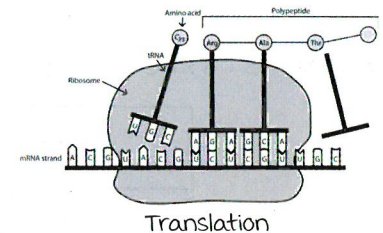
Applied aspect : misfolded protein diseases.

1. **Alzheimer's disease** : more common.

- Due to accumulation of misfolded **Aβ amyloid protein**.

2. Prion disease :

- PrP^C (Normal protein in CNS) → **PrP^{Sc}** (Prion protein : misfolded).
- Eg : Creutzfeldt Jakob disease (Very fatal).



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00:14:20



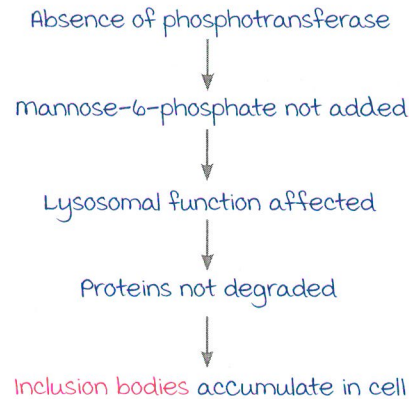
Vesicles

- 



tatus

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Applied aspect :**I cell disease :****Lysosomes**

00:23:30

Recycle bin of the cell.**Functions :**

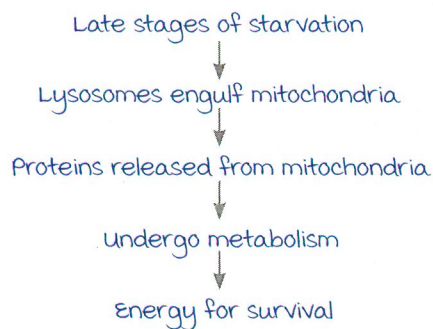
Acid mediated destruction.

- H^+ ATPase acid hydrolase.
- Acid hydroxylase enzyme.

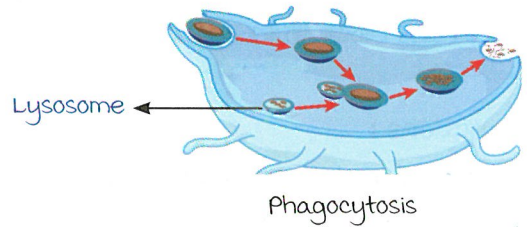
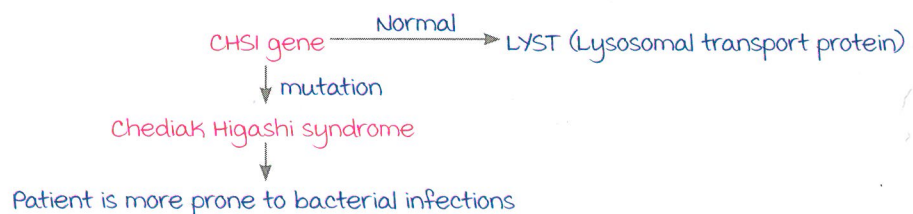
Note : Acid in the lysosome can destroy itself : Suicidal bags/residual bodies.

Autophagy :

Destruction of cell's own part.

**Clinical application :**

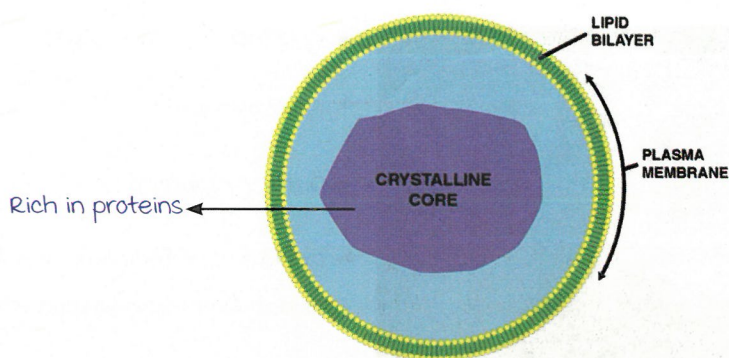
Neutrophil : High content of lysosomes.



Peroxisomes

00:31:55

----- Active space -----



Peroxisomes/microbodies

Function :

1. Oxidation of very long chain fatty acids (VLCFA's).
 - Generate H_2O_2 (Free radical).
2. Degradation of H_2O_2 : By **catalase**.
 - Pseudocatalase : Commercial/drug form of catalase.
 - Used to treat free radical mediated disorders. Eg : Vitiligo.

Enzymes produced by peroxisomes :

1. Plasminogens : Abundant in myelin sheath of nerve fibres.
2. Luciferase : Responsible for glow in fireflies.

Peroxisomal storage disorders :

Zellweger syndrome :

- **PEX** gene mutation.
 - PEX codes for **peroxins** (Proteins for peroxisome synthesis).
 - Features :
 - Accumulation of VLCFA's.
 - ↓ plasmalogens.
- } Neurological impairment

Refsum's disease :

- **PAHX** gene mutation.
- Defect in phytanyl CoA α hydroxylase.
- Defective oxidation of phytanic acid.

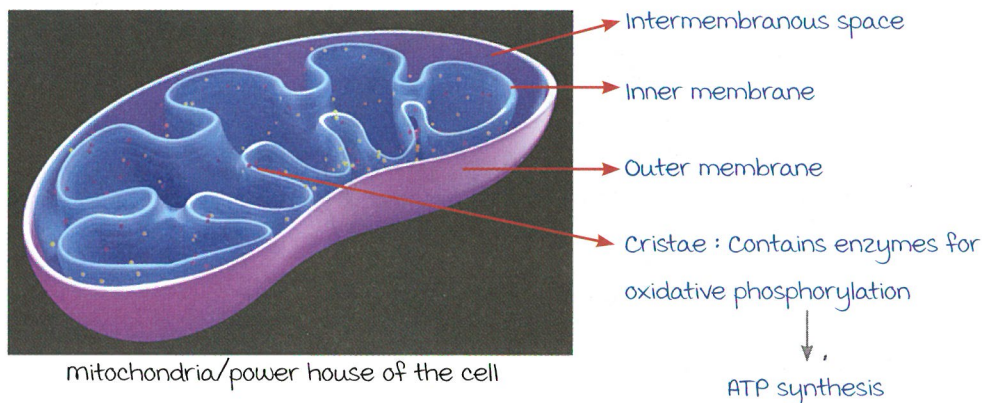
Adrenoleukodystrophy :

- Defect in **transport proteins**.
- ↑↑ VLCFA's → Neurological impairment.

----- Active space -----

Mitochondria

00:40:06



mitochondrial DNA :

- mitochondria has its **own DNA** (Endosymbiotic theory).
- Source : Ovum → Inheritance is always **maternal**.
- ds DNA with **16500** base pairs.
- **10 times** more prone for mutation than nuclear DNA.
 - Repair of mutations in mitochondrial DNA is ineffective.
- Cannot function without nuclear DNA (To produce enzymes for ATP synthesis).

mitochondrial disorders :

Affects organs with high metabolic requirements :

Features :

- Skeletal muscles : Contraction & relaxation is affected.
- CNS : Stroke like symptoms.
- GI tract is affected.
- ↑ susceptibility to infection.
- Lactic acidosis is common.

Mnemonic : MELAS.

- **M**itochondrial Encephalopathy.
- **L**actic Acidosis.
- **S**troke.

Nucleus

00:48:13

