Pathophysiology review

Lesch Nyhan

Mechanism: Absent HGPRT → increased de novo purine synthesis → increased uric acid production

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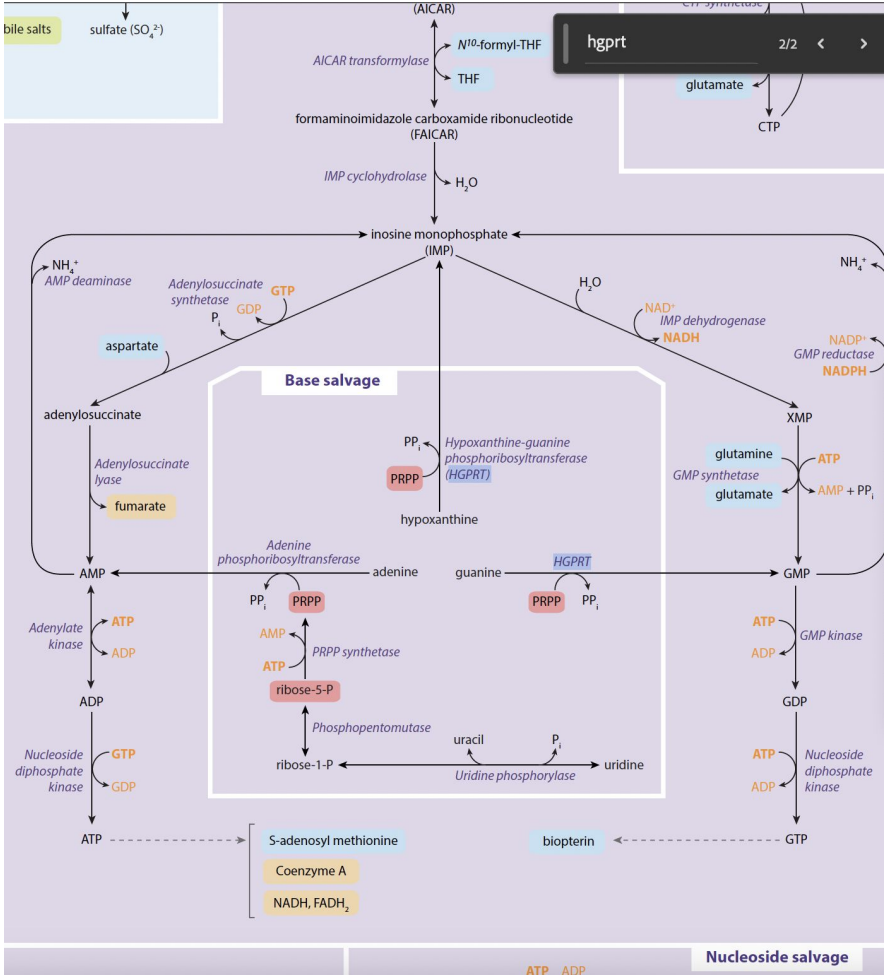
HGPRT:

- Hyperuricemia
- Gout
- Pissed off (aggression, self-mutilation)
- Red/orange crystals in urine
- Tense muscles (dystonia)



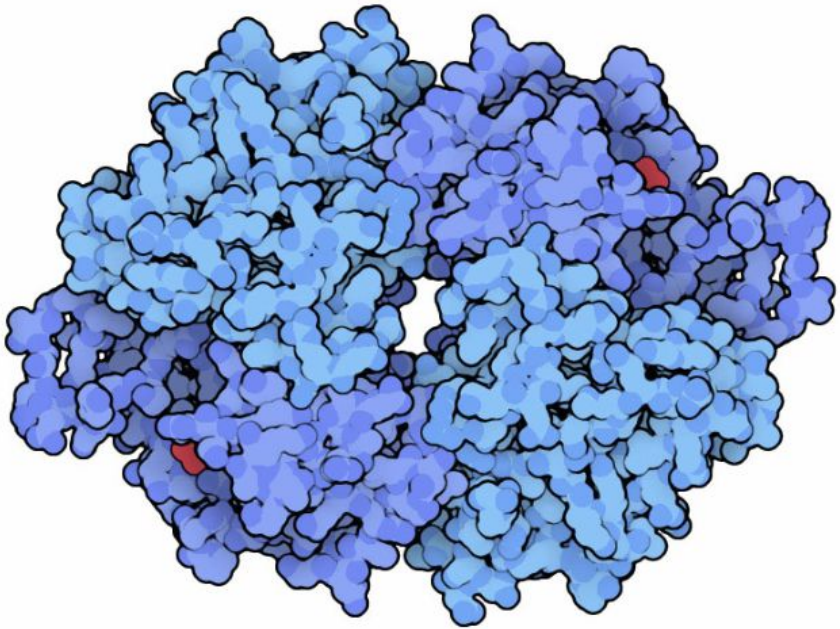
recycled. A complex set of salvage machinery is used to recycle these components.

Purine Salvage

The enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is one of the central enzymes that recycle the building blocks of RNA and DNA. It attaches a purine base (either guanine or hypoxanthine, a modified form of adenine) to a sugar, creating a nucleotide. The structure shown here (PDB entry 1hmp) is the human enzyme, which is composed of four identical subunits, each with its own active site. This structure includes the nucleotide product, guanine monophosphate, just before it is ready to be released for use by the cell.

Perils of Purines

As with all metabolic pathways, serious problems occur if steps in the pathway are blocked. Some people inherit a rare defective version of HGPRT, which leads to a serious illness termed Lesch-Nyhan syndrome. Since the enzyme is not active, purine bases build up causing severe neurological problems, including a dangerous compulsion for self-injury. In other cases, people with partially active HGPRT have problems with gout, as the pathways for discarding excess purines are overloaded and the waste products build up in the joints.



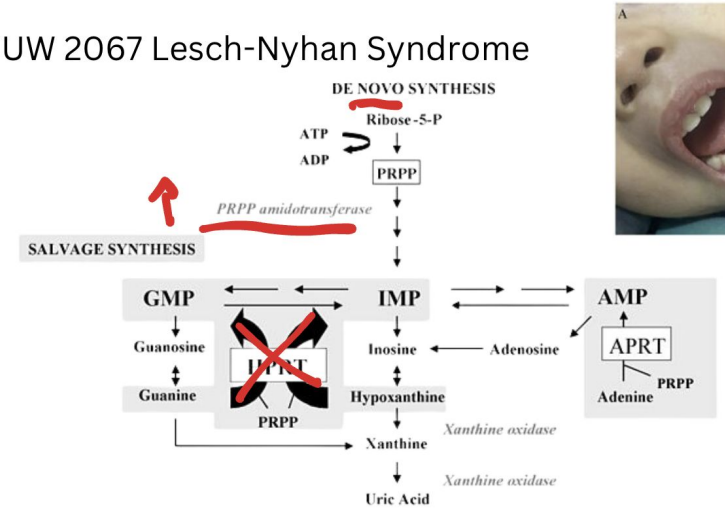
Human hypoxanthine-guanine phosphoribosyltransferase.

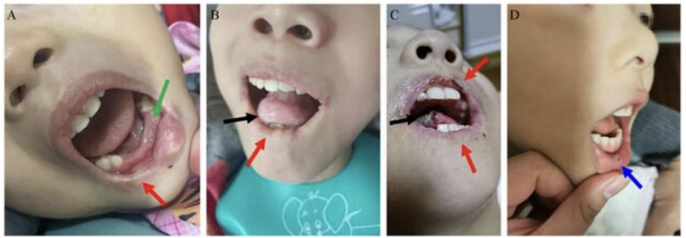
Download high quality TIFF image

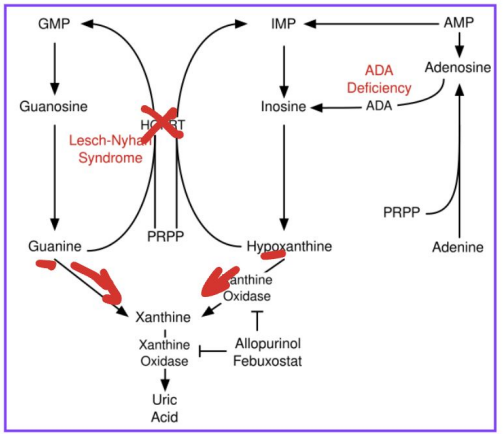
Purine Salvage Lesch Nyhan UWQID 2067

Play at 1:35

2067
Lesch-Nyhan syndrome (eg, dystonia, self-mutilation, hyperuricemia) is caused by a mutation in the gene encoding hypoxanthine-guanine phosphoribosyltransferase (HGPRT). Reduced HGPRT activity leads to impaired purine salvage and increased de novo purine synthesis, a process necessitating increased phosphoribosyl pyrophosphate amidotransferase activity.

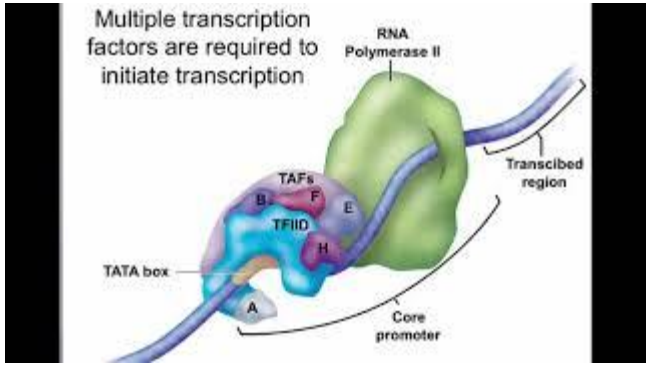






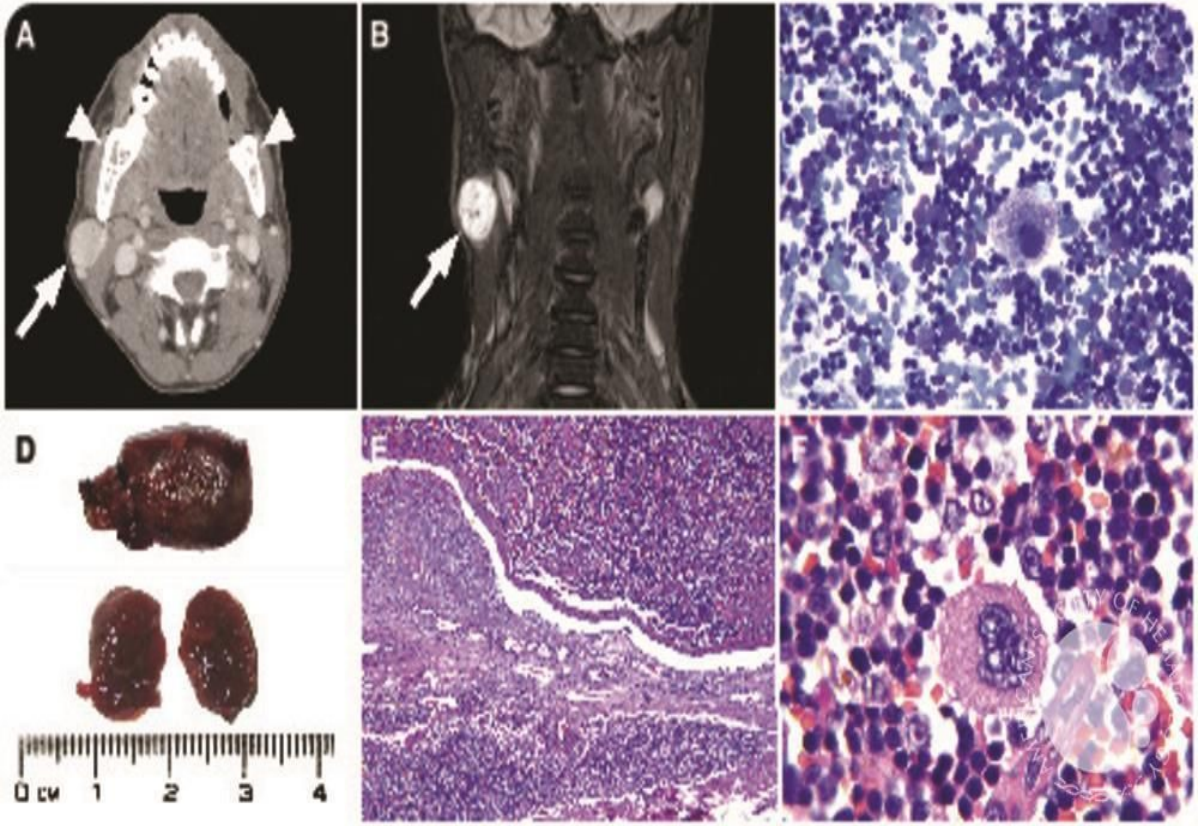
β-thalassemia

Mechanism: Mutation at splice site or promoter sequences → retained intron in mRNA
Page: 38, 424



33. SPICES:
mutation to the BETA globin gene can cause a mRNA splicing defect → fewer subunits produced

34. Corked CODON bottles:
mutation to the BETA globin gene can cause a premature stop codon → no subunits produced



A 24-year-old regularly transfused patient with β-thalassemia major presented with a lateral neck mass. Computed tomography and magnetic resonance imaging showed an enhanced mass 2.3 × 2 × 2.2 cm in the right parotid gland (panels A-B, arrows) with expansion and coarsening of the bony parts (panel A, arrowheads). Differential diagnosis included salivary gland tumors, metastases, hematomas, hemangioma, and extramedullary hematopoiesis (EMH). Fine-needle aspiration of the mass showed normal bone marrow elements (panel C), and EMH was suggested. Pathology showed a soft, dark red, clot-like mass (panel D) that was confirmed as nodal EMH (panels E-F).EMH and bone changes are well established in β-thalassemia. EMH is primarily seen in untreated or inadequately treated patients with thalassemia major or thalassemia intermedia and may not be prevented even by hypertransfusion regimens,whereas it is very rare in patients with thalassemia major who have received the appropriate treatment. Although EMH is usually primarily restricted to the liver or spleen, soft-tissue masses of EMH are rare. Biopsy is indicated when EMH occurs in very rare and unusual locations to exclude other differential diagnoses. If EMH is in a typical location and is not causing clinical problems, close monitoring without biopsy, in addition to attempts to suppress ineffective erythropoiesis or increase its efficacy, may suffice.


BETA THALASSEMIA
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HCP
PEER EXCHANGE
HCP Live
PEER EXCHANGE

Lynch Syndrome

Mechanism: Failure of mismatch repair during the S phase → microsatellite instability

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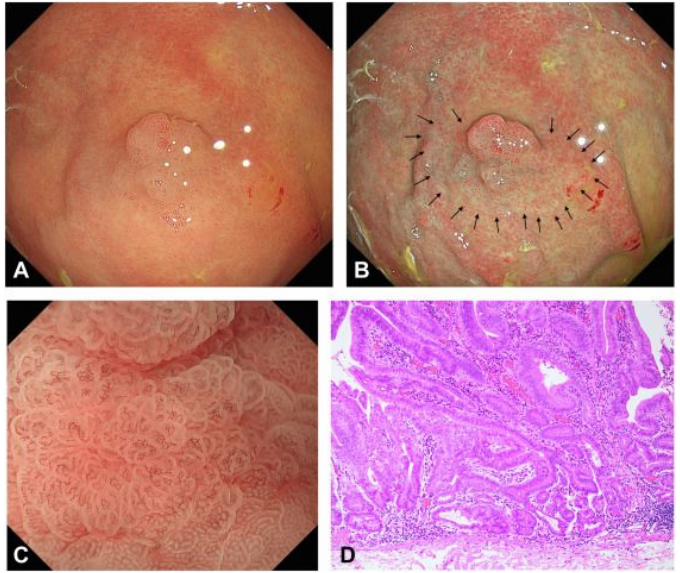
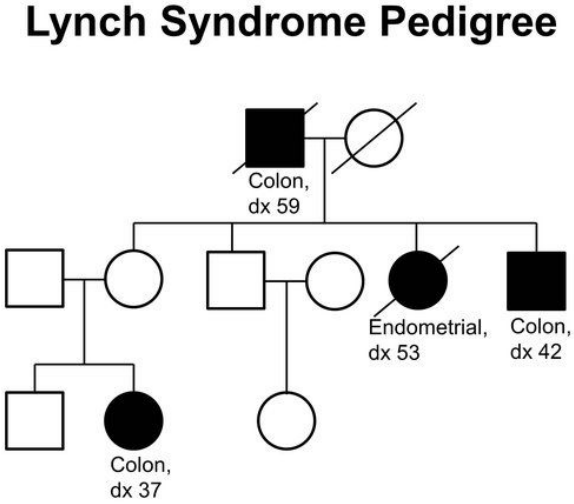
A 66-year-old woman with a diagnosis of Lynch syndrome with *MSH2* mutation was referred to surveillance EGD. Her medical history included multiple cancers: 3 gastric, a duodenal, 4 colorectal, an endometrial, and a bladder cancer. EGD showed a pale-colored, 2-tier raised lesion without a clear demarcation line in the upper part of the remnant stomach (A). Texture and color enhancement imaging enabled visualization of the clear boundary (B, *arrows*). Magnifying endoscopy with narrow-band imaging revealed a lobular surface structure that contained looplike microvessels, with a demarcation line (C). The results of serology and urea breath test for *Helicobacter pylori* were negative. These endoscopic findings suggested an early gastric cancer, which was extending laterally, measuring ≥10 mm. The lesion was subsequently resected en bloc by endoscopic submucosal dissection. On histologic examination, the tumor, 22 × 15 mm, showed monotonous proliferation of foveolar-like atypical tubules having enlarged nuclei and an irregular structure (D). The horizontal and vertical margins were free of tumor cells. Immunohistochemically, the tumor cells were positive for MUC5AC and MUC6 and negative for MUC2, CD10, pepsinogen I, and proton pump. Ki-67–positive cells were located at the whole mucosal layer. MLH1 and PMS2 were preserved, and MSH2 and MSH6 were lost. The final diagnosis was early gastric cancer of a gastric phenotype restricted to the mucosal layer, in Lynch syndrome, without lymphovascular invasion.



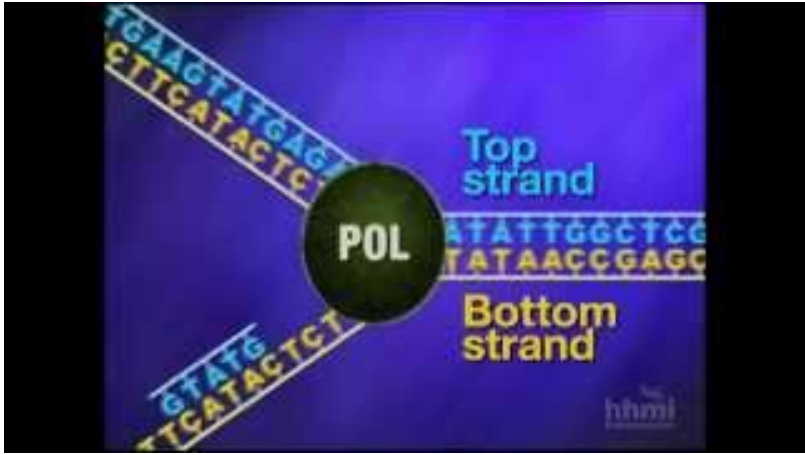
Lynch syndrome

UWQID 429 Hereditary nonpolyposis colon cancer (HNPCC), or Lynch syndrome, leads to occurrence of colonic adenocarcinomas at a young age (age <50) along with a predisposition for extraintestinal malignancies. Mutations of DNA mismatch repair genes are responsible for HNPCC.
MSH2

UWQID 2028 Lynch syndrome is an autosomal dominant disease caused by abnormal nucleotide mismatch repair. The mismatch repair system involves several genes, including MSH2 and MLH1, which code for components of the human MutS and MutL homologs. Mutations in these 2 genes account for around 90% of cases of Lynch syndrome.



- Typically due to mutation in an MMR gene: most commonly due to a germline mutation in *MSH2* or *MLH1*; less frequently due to germline mutations in *MSH6* or *PMS2*



- Mutation in MMR gene results in defective repair of DNA sequence mismatches, which most frequently occur in long, repetitive DNA sequences (such as seen in microsatellite regions, hence the term microsatellite instability [MSI])
- Accumulation of DNA mismatches lead to increased risk of developing malignant neoplasms

Pathologyoutlines

I-cell Disease

Mechanism:
N-acetylglucosaminyl-1-phosphotransferase defect → Golgi-mediated mannose residues phosphorylation failure (↓ mannose-6-phosphate) → increased cellular debris in lysosomes
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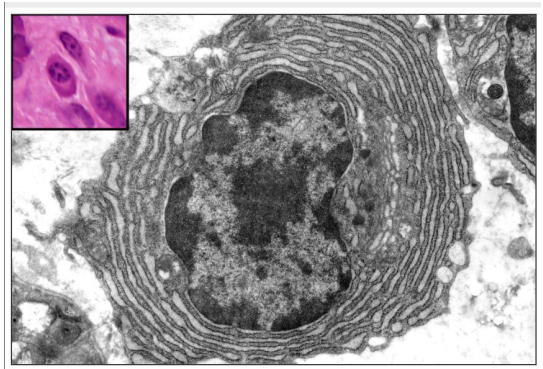
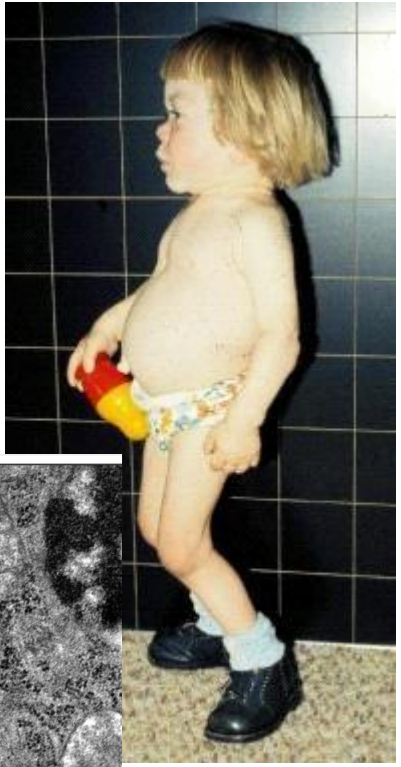
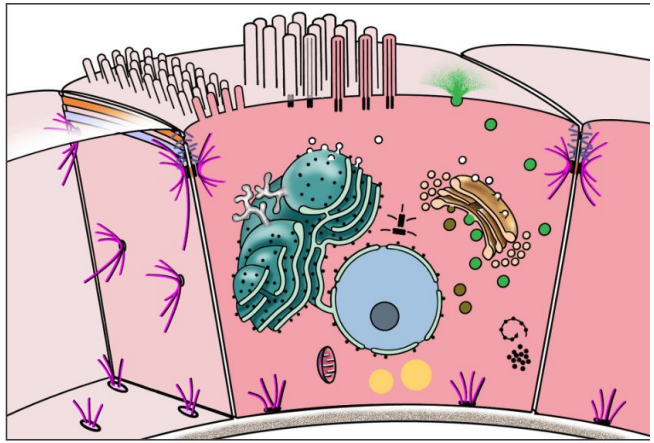


Golgi apparatus

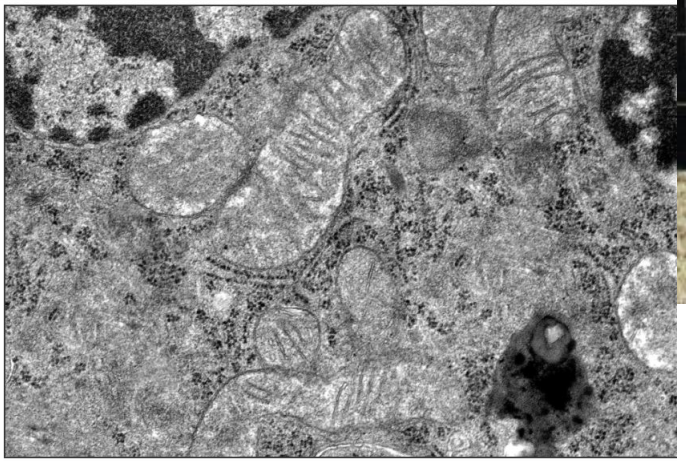
This electron micrograph shows a plasma cell with a very large Golgi apparatus. The light microscopic appearance of a similar cell is shown in the inset. This large Golgi lies adjacent to the nucleus and is surrounded by extensive RER. 10,000x





Golgi apparatus

The Golgi, usually located near the nucleus, consists of flattened, membranous sacs. These sacs receive newly synthesized proteins from the RER via transport vesicles. The vesicles fuse with the forming face of the Golgi, and their proteins are post-translationally modified, e.g., glycosylated or phosphorylated, and packaged on the maturing face of the Golgi for transport through the cell.



Lysosomes

This electron micrograph shows the irregular outline of a lysosome in the lower right corner of the image. The heterogeneous contents of the lysosome are breakdown products of recycled organelles and internalized materials. Note also the RER, ribosomes and mitochondria in this image. 30,000x

Osteogenesis Imperfecta

Mechanism: Type 1 collagen defect due to inability to form triple helices; mutation in COL1A1 and COL1A2 genes
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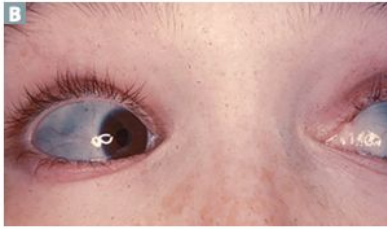
Osteogenesis imperfecta

Genetic bone disorder (brittle bone disease) caused by a variety of gene defects (most commonly *COL1A1* and *COL1A2*).
Most common form is autosomal dominant with ↓ production of otherwise normal type I collagen (altered triple helix formation).
Manifestations include:

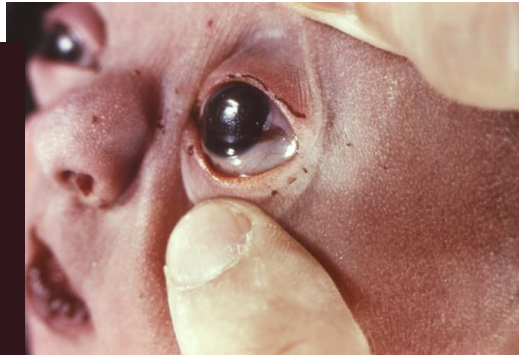
- Multiple fractures and bone deformities (arrows in A) after minimal trauma (eg, during birth)
- Blue sclerae B due to thin, translucent scleral collagen revealing choroidal veins
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)
- Hearing loss (abnormal ossicles)

May be confused with child abuse.
Treat with bisphosphonates to ↓ fracture
Patients can't **BITE**:
Bones = multiple fractures
I (eye) = blue sclerae
Teeth = dental imperfections
Ear = hearing loss



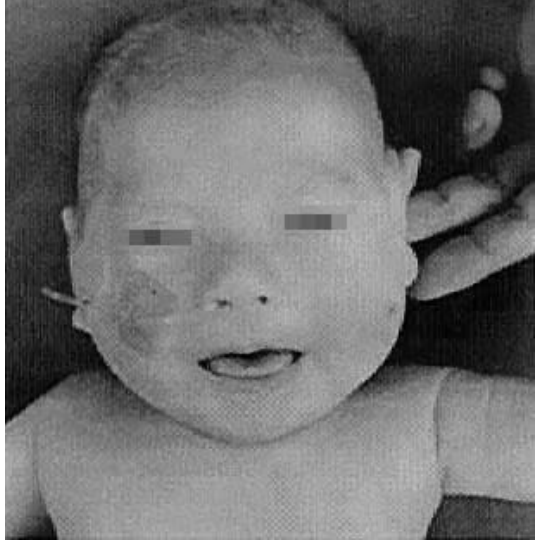
7. Brittle bone oar:

Type 1 collagen defects seen in **osteogenesis imperfecta (OI)**




Mild
Moderate
Severe
So Osteogenesis Imperfecta
is a spectrum of disorders...

Menkes Disease



Mechanism: Defective ATP7A protein → impaired copper absorption and transport → decreased lysyl oxidase activity → decreased collagen cross-linking
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Medscape

21. Monkey removing copper rings:

Collagen cross-linking defects are seen in **Menkes disease**

Marfan Syndrome

Mechanism: FBN1 mutation on chromosome 15 → defective fibrillin-1 (normally forms sheath around elastin)
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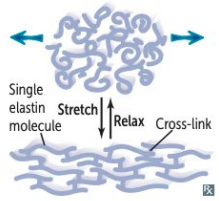
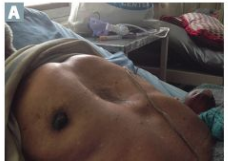
Elastin



Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, epiglottis, ligamenta flava (connect vertebrae → relaxed and stretched conformations).
Rich in nonhydroxylated proline, glycine, and lysine residues, vs the hydroxylated residues of collagen.
Tropoelastin with fibrillin scaffolding.
Cross-linking occurs extracellularly via lysyl oxidase and gives elastin its elastic properties.
Broken down by elastase, which is normally inhibited by α_1-antitrypsin.
α_1-Antitrypsin deficiency results in unopposed elastase activity, which can cause COPD.



Marfan syndrome—autosomal dominant (with variable expression) connective tissue disorder affecting skeleton, heart, and eyes. *FBN1* gene mutation on chromosome 15 (fifteen) results in defective fibrillin-1, a glycoprotein that forms a sheath around elastin and sequesters TGF-β. Findings: tall with long extremities; chest wall deformity (pectus carinatum [pigeon chest] or pectus excavatum A); hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic root aneurysm rupture or dissection (most common cause of death); mitral valve prolapse; ↑ risk of spontaneous pneumothorax.

Figure 2

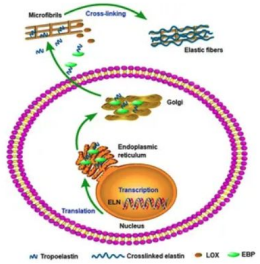
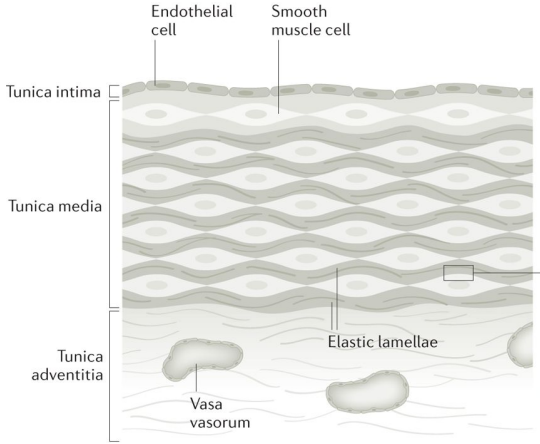
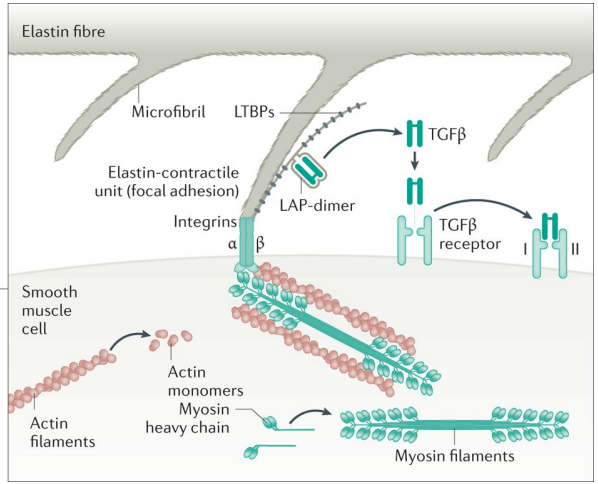
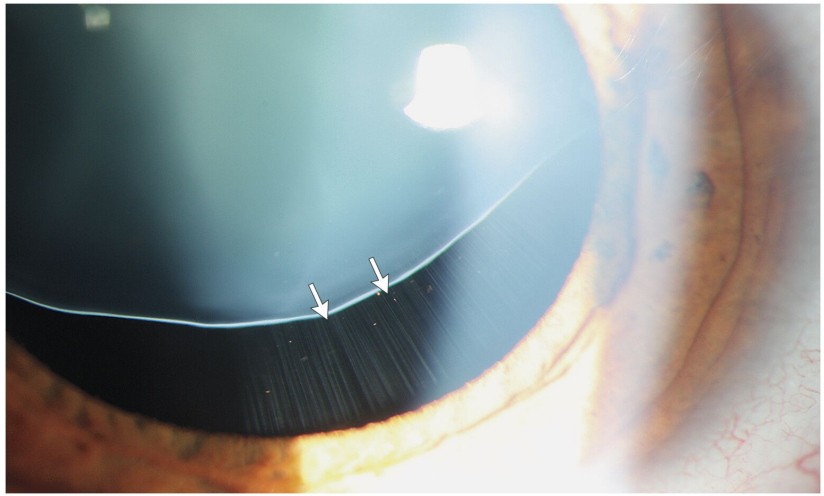


Figure 2. Tropoelastin secretory/assembly pathway. The synthesis of tropoelastin begins with the transcription of the ELN gene in the nucleus. In the endoplasmic reticulum, tropoelastin interacts with EBP and folds in structure. After the storage and transport of Golgi, the complex of EBP and tropoelastin is secreted to the cell surface for self-assembly. Then, tropoelastin dissociates from EBP and deposits onto the microfibril scaffold. In the presence of LOX, tropoelastin cross-links and eventually forms mature elastic fibers.

However, the precise molecular assembly pathway of the mechanical properties of elastin remains poorly understood.

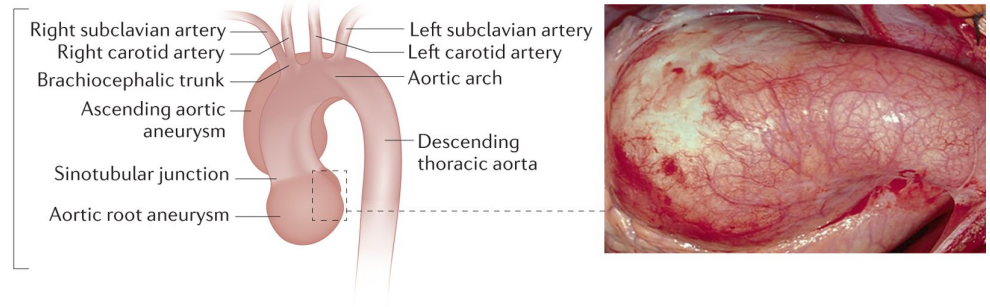






A 27-year-old woman with a diagnosis of Marfan's syndrome presented with worsening vision and glare in each eye for 1 month. On examination, visual acuity was 20/30 in each eye. Superotemporal partial subluxation of the lens was noted in each eye. On close inspection of the right eye, a decrease in the overall number of zonules was observed as widened spaces between zonules (arrows). Intraocular pressure was normal. Ectopia lentis is an ocular finding in Marfan's syndrome and typically develops between birth and 30 years of age. The lens subluxation is typically bilateral, symmetric, and in the superotemporal direction, although it may occur in other directions. Zonular fibers of the lens are few and are often attenuated and broken. Surgical intervention may be required if the refractive error cannot be managed conservatively or if uncontrolled glaucoma develops. Our patient was treated conservatively, and visual acuity improved with new prescription eyeglasses. The patient's condition has remained stable over a 2-year follow-up period.

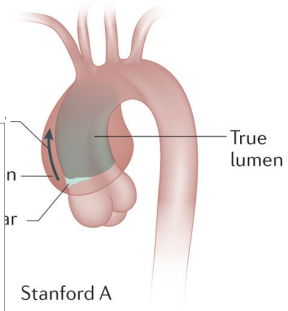
a

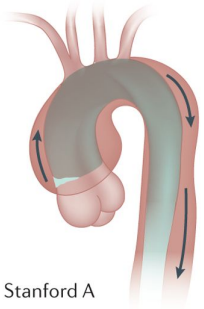


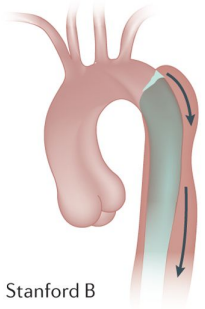
b Dissection involving the ascending aorta

c Dissection involving both the ascending and descending aorta

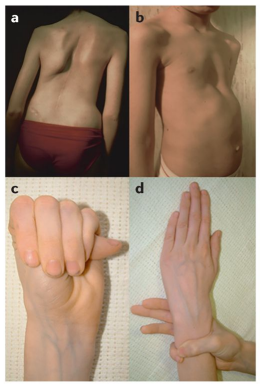
d Dissection not involving the ascending aorta

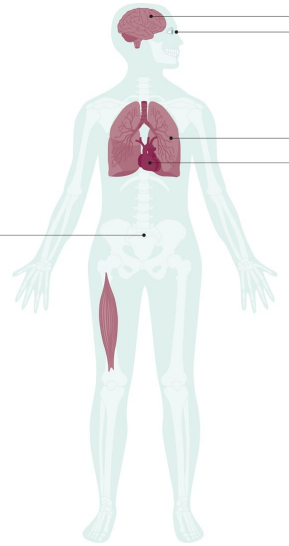






Musculoskeletal and integumentary systems
- Elongated digits (arachnodactyly)
- Disproportionately long legs and arms
- Scoliosis
- Dural ectasia
- Sternal deformity (pectus deformities)
- Joint hypermobility
- Stretch marks



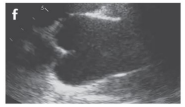


Psychosocial impact

Ophthalmic system
- Ectopia lentis
- Early cataracts

Respiratory system
- Pneumothorax
- Obstructive sleep apnoea

Cardiovascular system
- Aortic root aneurysm and dissection
- Mitral valve prolapse



Prader-Willi Syndrome

Mechanism: Uniparental disomy or imprinting leading to silencing of maternal gene. Disease expressed when paternal allele is deleted or mutated
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Angelman Syndrome

Mechanism: Silenced paternal gene leading to mutation, lack of expression, or deletion of UBE3A on maternal chromosome 15
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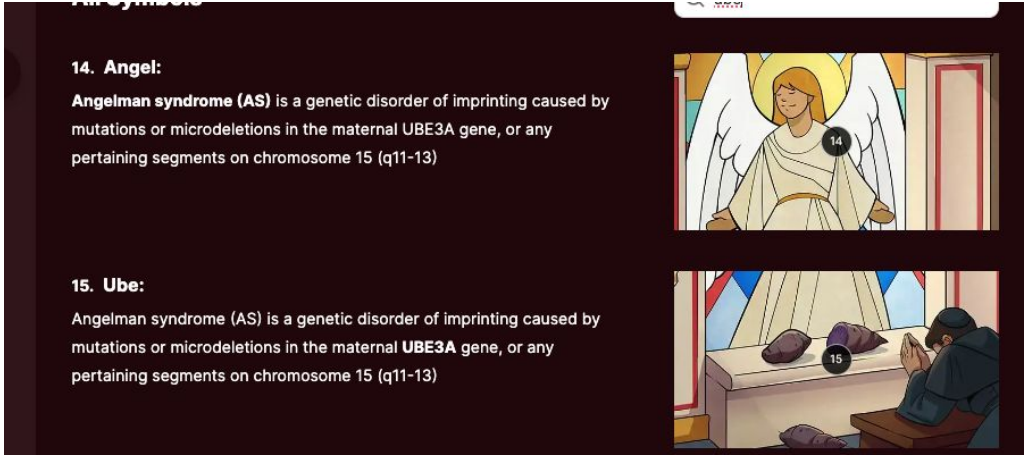

Cystic Fibrosis

Mechanism: Autosomal recessive ΔF508 deletion in CFTR gene on chromosome 7 → impaired ATP-gated Cl^- channel (secretes Cl^- in lungs and GI tract and reabsorbs Cl^- in sweat glands)
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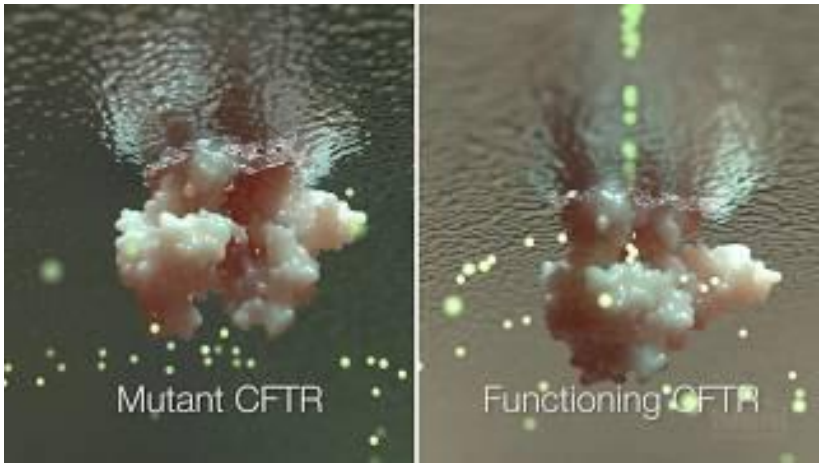
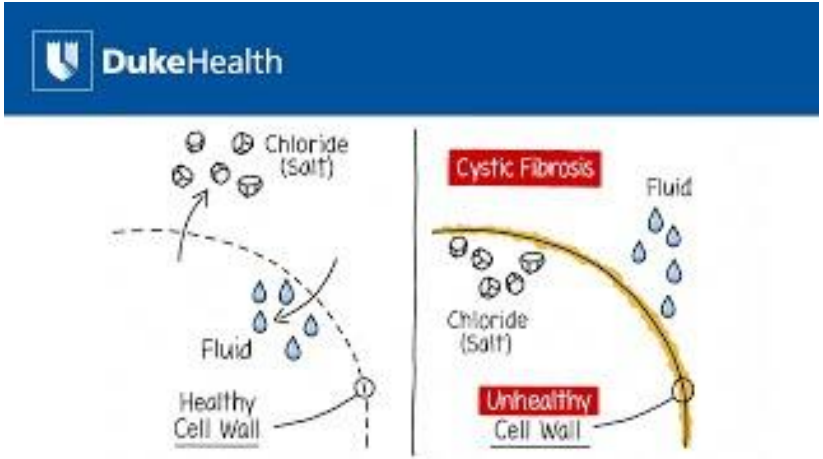
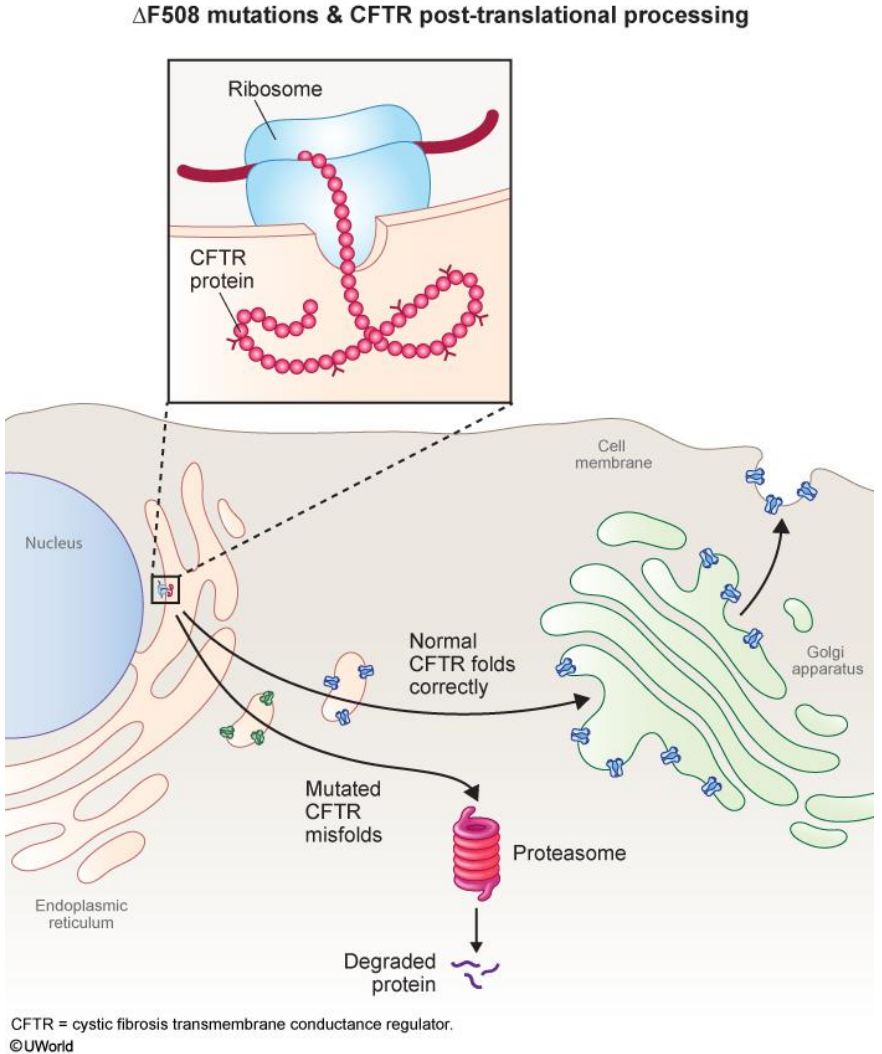


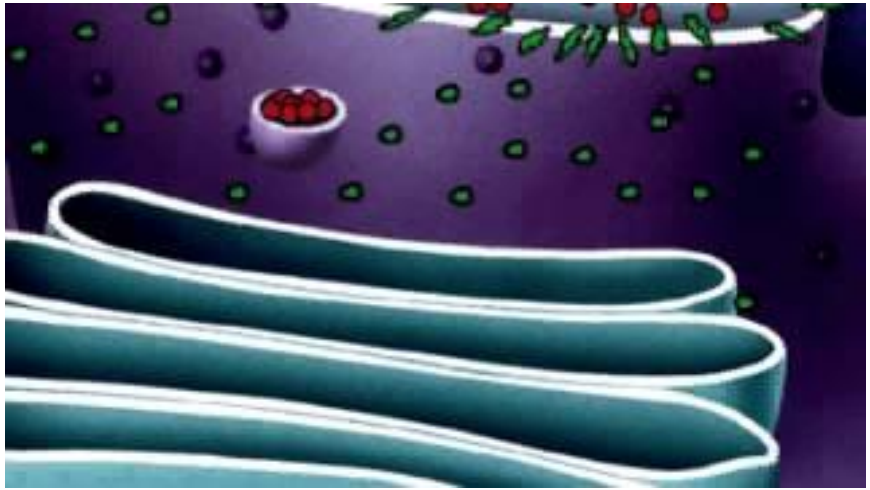


CFTR mutation

802 Cystic fibrosis (CF) is most commonly due to a 3-base pair deletion in the CF transmembrane conductance regulator (CFTR) gene at amino acid position 508 (ΔF508). This mutation impairs post-translational processing of CFTR, resulting in shunting of CFTR toward the proteasome, with complete absence of the protein on the cell surface. Elevated sweat chloride concentrations are found in most patients with CF.




PARIS
kaftrio 75 mg/50 mg/100 mg
film-coated tablets
ivacaftor/tezacaftor/elexacaftor
'MIRACLE' CYSTIC FIBROSIS DRUG
KAFTRIO IS CHANGING THE LIVES OF PATIENTS IN A BIG WAY
SCIENCE



Myotonic Dystrophy

Mechanism: CTG trinucleotide repeat expansion in DMPK gene → abnormal expression of myotonin protein kinase → myotonia
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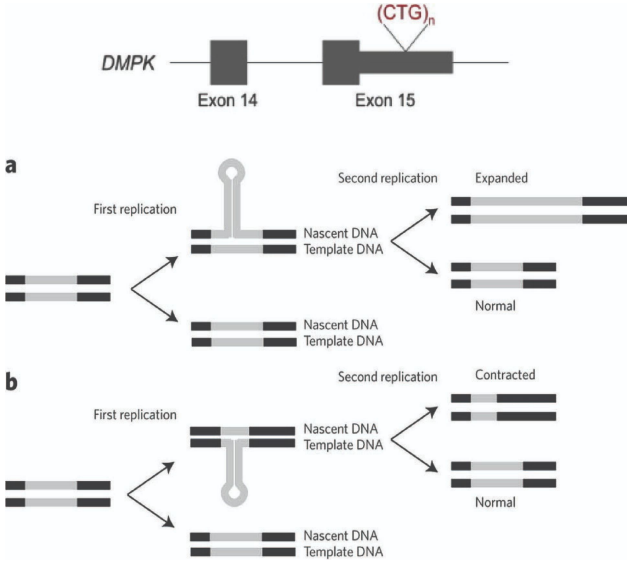
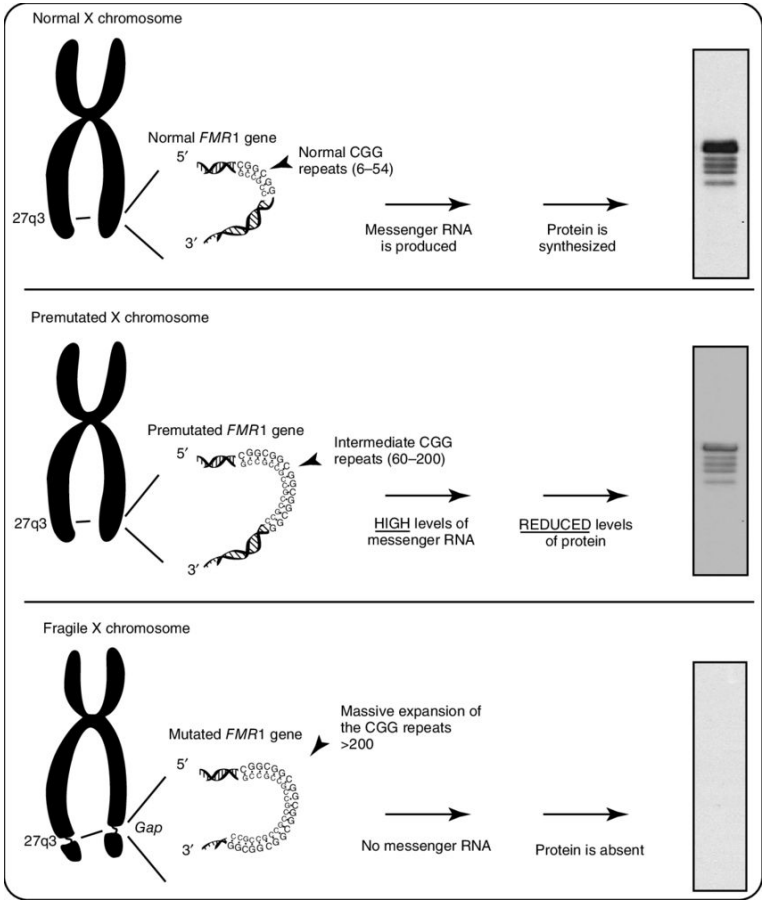
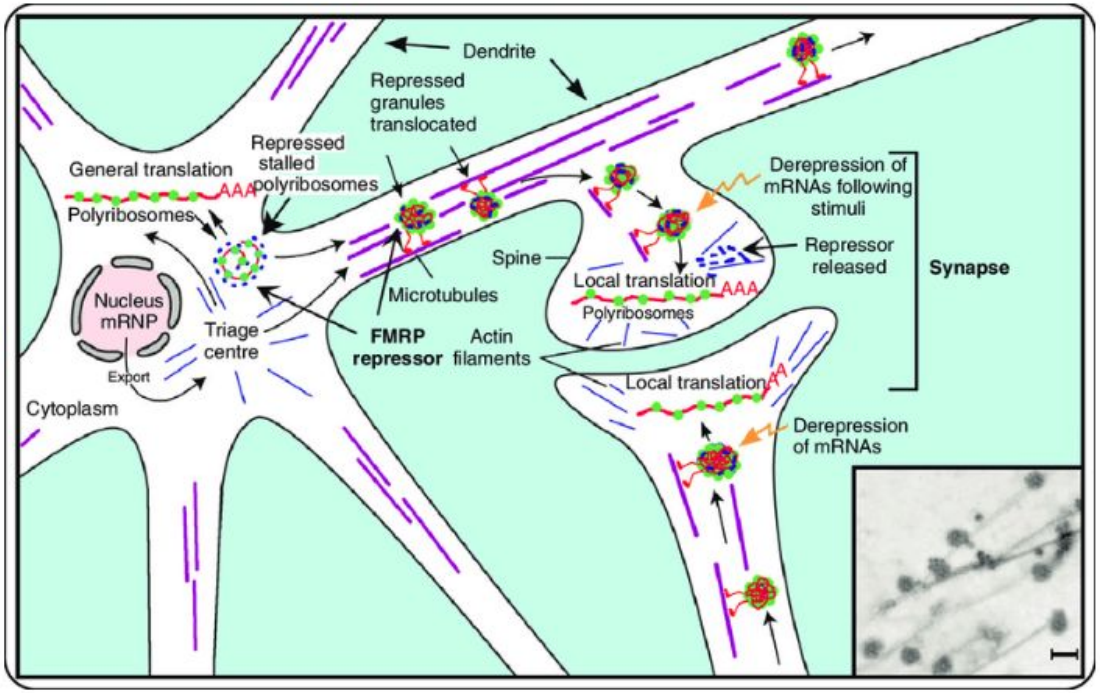


Myotonic dystrophy	Autosomal dominant. Onset 20–30 years. **CTG** trinucleotide repeat expansion in the *DMPK* gene → abnormal expression of myotonin protein kinase → percussion myotonia (eg, difficulty releasing hand from handshake), muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.	**C**ataracts, **T**oupee (early balding in males), **G**onadal atrophy. Muscle biopsy shows ring fibers and central nuclei.

Fragile X Syndrome

Mechanism: CGG trinucleotide repeat in FMR1 gene → hypermethylation → decreased expression
Page: 60





Model proposing the involvement of FMRP (fragile X mental retardation protein) in trafficking of neuronal granules containing mRNA (messenger ribonucleic acid) that are exported from the cell body (soma) to distal locations such as dendritic spines, synapses (one dendritic spine forms half a synapse) or axons. High levels of FMRP are present in granules to repress mRNAs. Inset: granules sliding on microtubules as seen by electron microscopy. Bar represents 500 nm. Adapted from Bardoni et al. (2006) © Cambridge University Press.

Trinucleotide repeat expansion diseases

Trinucleotide repeat expansion diseases — May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).

DISEASE	TRINUCLEOTIDE REPEAT	MODE OF INHERITANCE	MNEMONIC
Huntington disease	$(CAG)_n$	AD	**C**audate has ↓ **A**Ch and **G**ABA
Myotonic dystrophy	$(CTG)_n$	AD	**C**ataracts, **T**oupee (early balding in males), **G**onadal atrophy in males, reduced fertility in females
Fragile X syndrome	$(CGG)_n$	XD	**C**hin (protruding), **G**iant **G**onads
Friedreich ataxia	$(GAA)_n$	AR	Ataxic **GAA**it

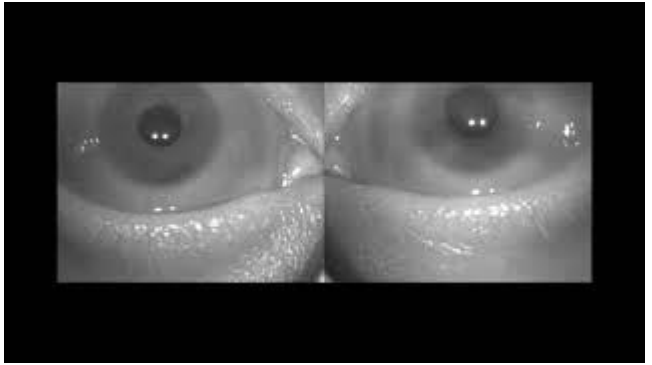
Bitot Spots in Vitamin A Deficiency

Mechanism: Decreased differentiation of epithelial cells into specialized tissue → squamous metaplasia
Page: 64

Recurrent sinopulmonary infections and exocrine gland fibrotic atrophy in a young patient are suggestive of cystic fibrosis (CF). CF can lead to pancreatic insufficiency, fat malabsorption, and a deficiency of vitamins A, D, E and K. Vitamin A maintains orderly differentiation of specialized epithelia, including the mucus-secreting columnar epithelia of the ocular conjunctiva, respiratory and urinary tracts, and pancreatic and other exocrine ducts. Avitaminosis A can cause squamous metaplasia of such epithelia to a keratinizing epithelium.

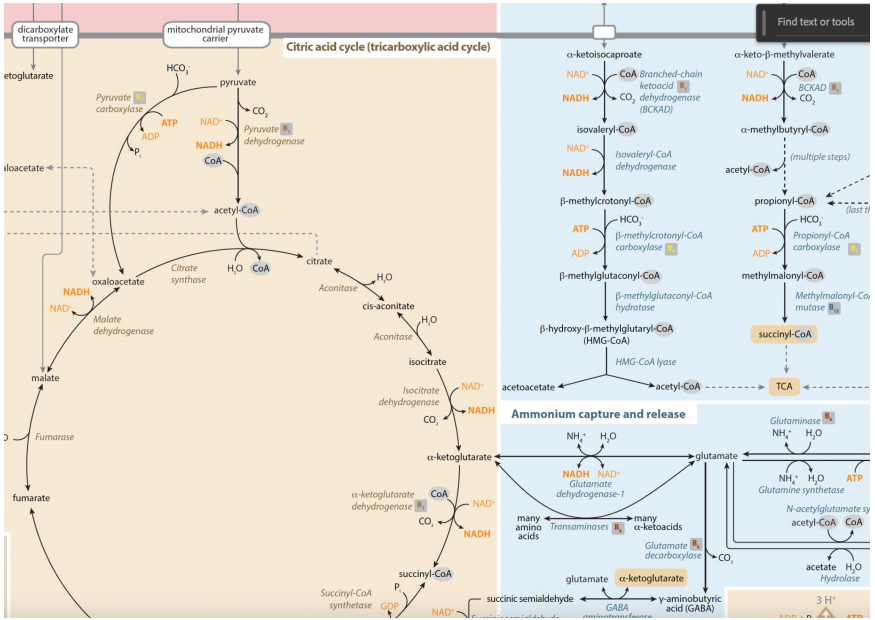
Sketchy

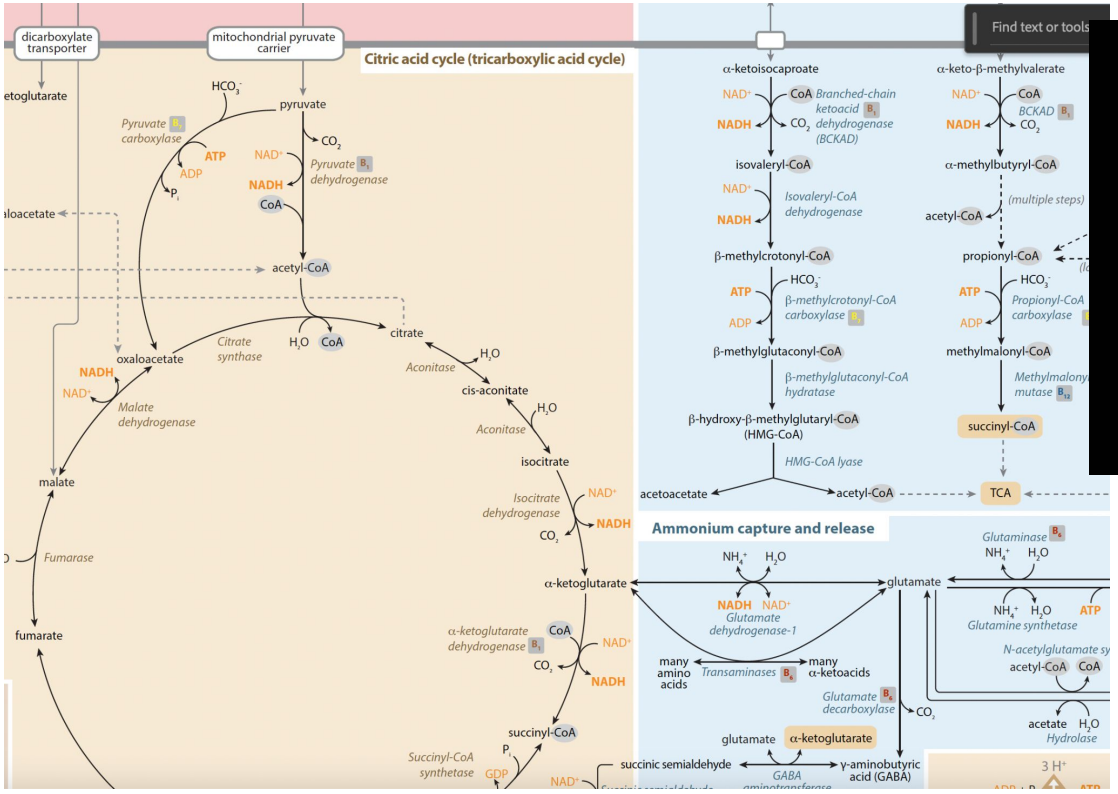
Wernicke Encephalopathy in Alcoholic Patient Given Glucose



Mechanism: Thiamine deficiency → impaired glucose breakdown → ATP depletion worsened by glucose infusion

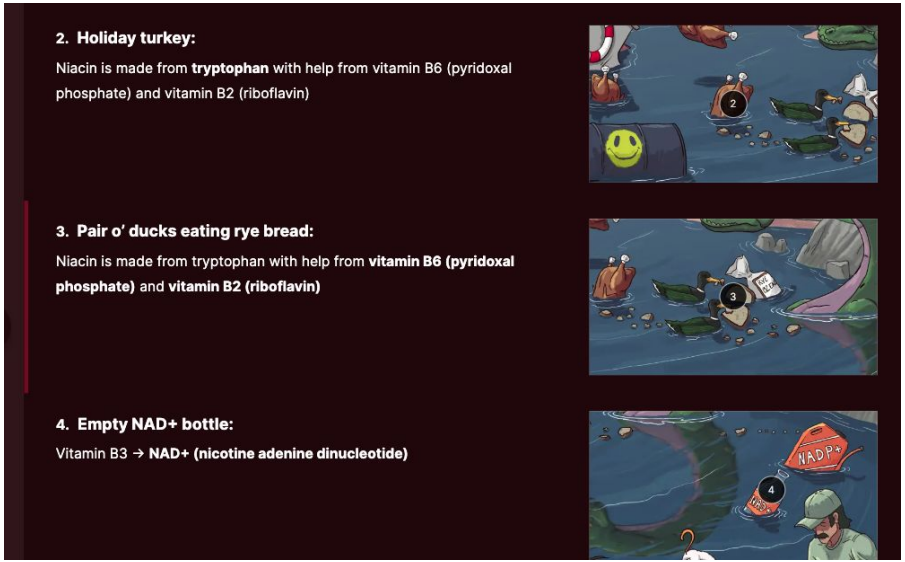
Vitamin B_1	Also called thiamine.	
FUNCTION	In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions (Be APT): ▪ Branched-chain ketoacid dehydrogenase ▪ α-Ketoglutarate dehydrogenase (TCA cycle) ▪ Pyruvate dehydrogenase (links glycolysis to TCA cycle) ▪ Transketolase (HMP shunt)	
DEFICIENCY	Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. In patients with chronic alcohol overuse or malnutrition, give thiamine before dextrose to ↓ risk of precipitating Wernicke encephalopathy. Diagnosis made by ↑ in RBC transketolase activity following vitamin B_1 administration.	
DISORDER	**CHARACTERISTICS**	
Wernicke encephalopathy	Acute, reversible, life-threatening neurologic condition. Symptoms: Confusion, Ophthalmoplegia/Nystagmus, Ataxia (CorONA beer).	
Korsakoff syndrome	Amnestic disorder due to chronic alcohol overuse; presents with confabulation, personality changes, memory loss (permanent).	
Wernicke-Korsakoff syndrome	Damage to medial dorsal nucleus of thalamus, mammillary bodies. Presentation is combination of Wernicke encephalopathy and Korsakoff syndrome.	
Dry beriberi	Polyneuropathy, symmetric muscle wasting.	Spell beriberi as Ber1Ber1 to remember vitamin B_1.
Wet beriberi	High-output cardiac failure (due to systemic vasodilation).	



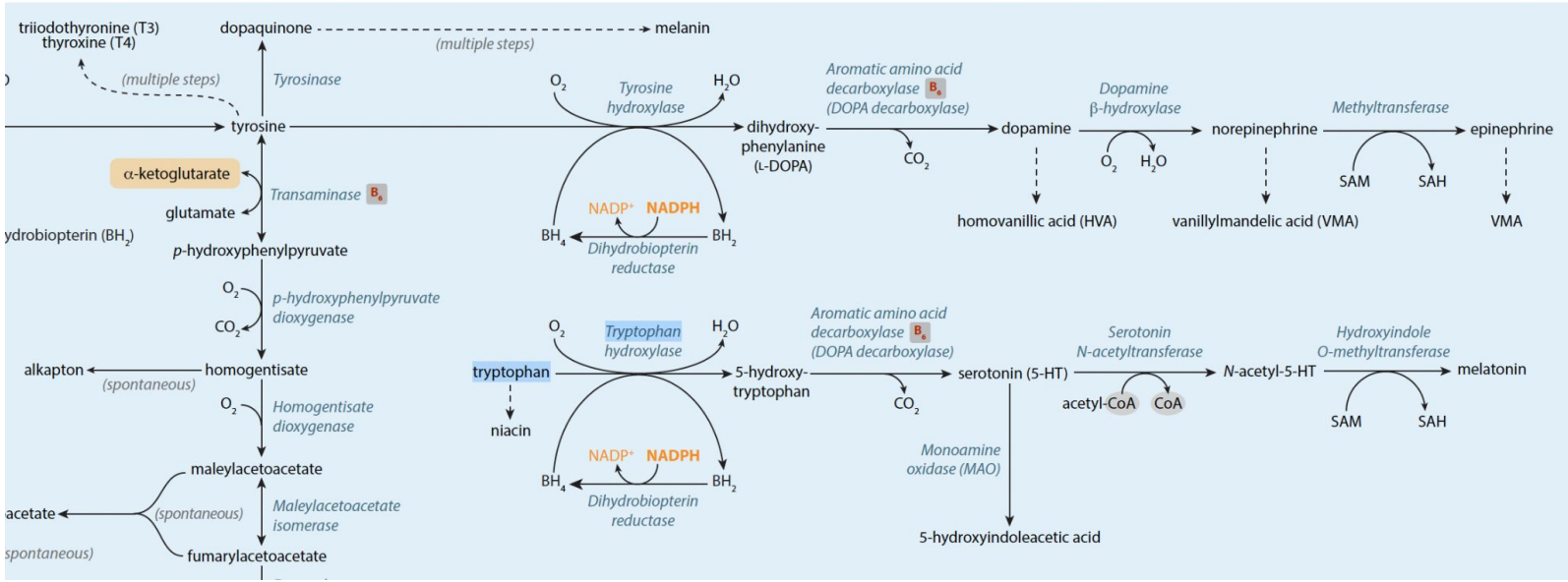


Pellagra in Malignant Carcinoid Syndrome

Mechanism: Tryptophan is diverted towards serotonin synthesis by tumor → B3 deficiency (B3 is derived from tryptophan)
Page: 65



UWQID74Carcinoid syndrome typically presents with episodic flushing, secretory diarrhea, and wheezing. It can lead to pathognomonic plaque-like deposits of fibrous tissue on the right-sided endocardium, causing tricuspid regurgitation and right-sided heart failure. Elevated 24-hour urinary 5-hydroxyindoleacetic acid can confirm the diagnosis.


triiodothyronine (T3)
thyroxine (T4)
dopaquinone
melanin
(multiple steps)
(multiple steps)
Tyrosinase
tyrosine
α-ketoglutarate
Transaminase B6
glutamate
ydrobiopterin (BH2)
p-hydroxyphenylpyruvate
O2
CO2
p-hydroxyphenylpyruvate dioxygenase
alkapton
homogentisate
(spontaneous)
O2
Homogentisate dioxygenase
maleylacetoacetate
acetate
(spontaneous)
Maleylacetoacetate isomerase
spontaneous)
fumarylacetoacetate
O2
Tyrosine hydroxylase
H2O
dihydroxy-phenylanine (L-DOPA)
NADP+
NADPH
BH4
BH2
Dihydrobiopterin reductase
Aromatic amino acid decarboxylase B6 (DOPA decarboxylase)
CO2
dopamine
Dopamine β-hydroxylase
O2
H2O
norepinephrine
Methyltransferase
SAM
SAH
epinephrine
homovanillic acid (HVA)
vanillylmandelic acid (VMA)
VMA
tryptophan
niacin
O2
Tryptophan hydroxylase
H2O
5-hydroxy-tryptophan
NADP+
NADPH
BH4
BH2
Dihydrobiopterin reductase
Aromatic amino acid decarboxylase B6 (DOPA decarboxylase)
CO2
serotonin (5-HT)
Monoamine oxidase (MAO)
5-hydroxyindoleacetic acid
Serotonin N-acetyltransferase
acetyl-CoA
CoA
N-acetyl-5-HT
Hydroxyindole O-methyltransferase
SAM
SAH
melatonin

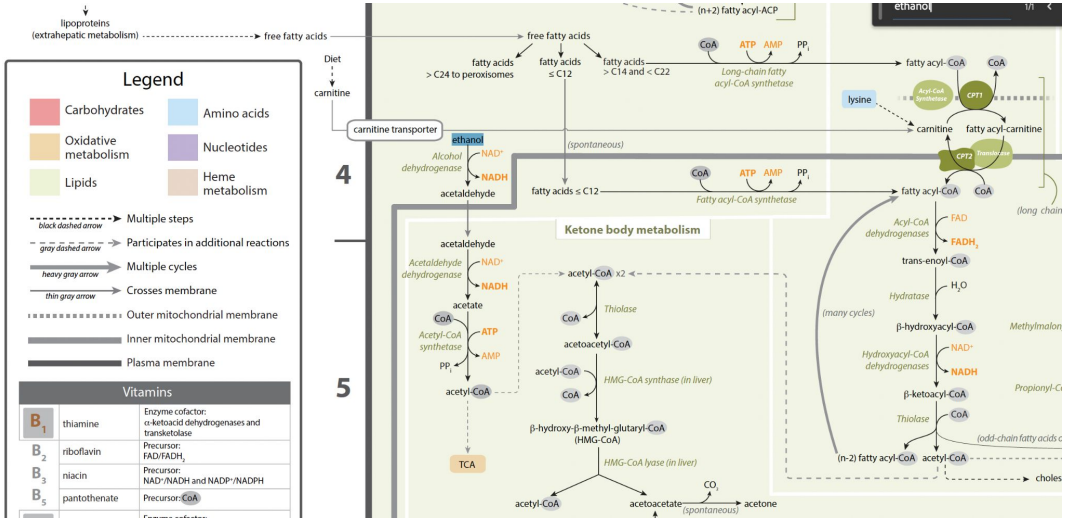
Kwashiorkor

Mechanism: Protein malnutrition → decreased oncotic pressure (→ edema), decreased apolipoprotein synthesis (→ liver fatty change)
Page: 69

Lactic Acidosis, Fasting Hypoglycemia, Hepatic Steatosis in Alcoholism

Mechanism: Increased NADH/NAD+ ratio due to ethanol metabolism
Page: 70

UWQID 370 The pathogenesis of alcohol-induced hepatic steatosis involves excess NADH production (via ethanol metabolism), which inhibits free fatty acid oxidation and promotes lipogenesis. Steatosis is microscopically characterized by clear cytoplasmic vacuoles within hepatocytes.



Aspirin-Induced Hyperthermia

Mechanism: Increased permeability of mitochondrial membrane → decreased proton [H+] gradient and decreased O_2 consumption → uncoupling

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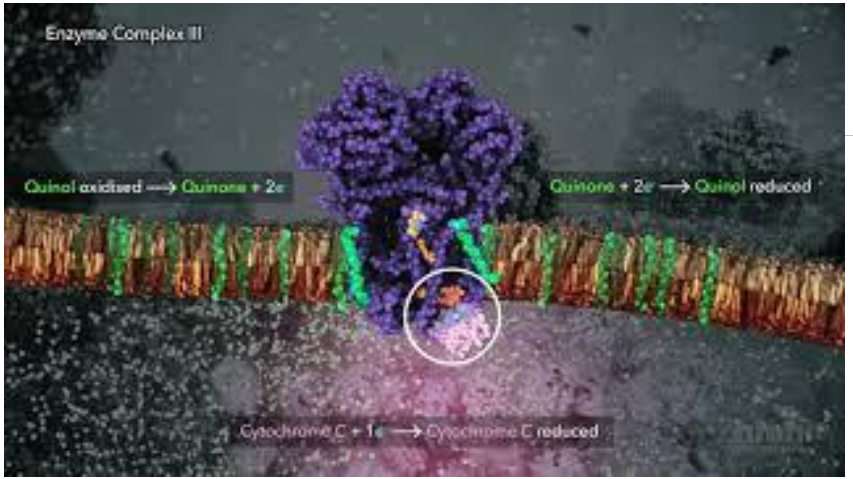
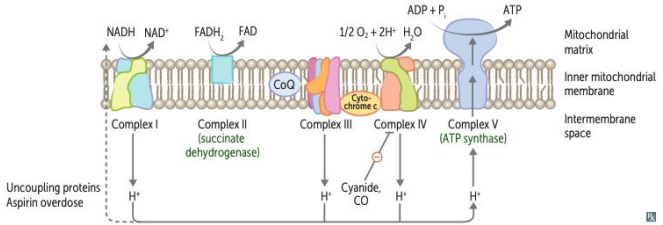


Electron transport chain and oxidative phosphorylation

NADH electrons are transferred to complex I.
$FADH_2$ electrons are transferred to complex II (at a lower energy level than NADH).
Oxygen acts as an electron acceptor to provide energy.
The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives ATP production. ATP hydrolysis can be coupled to energetically unfavorable reactions.
Uncoupling proteins (found in brown fat, which has more mitochondria than white fat) produce heat by ↑ inner mitochondrial membrane permeability → ↓ proton gradient. ATP synthesis stops, but electron transport continues.

1 NADH → 2.5 ATP; 1 $FADH_2$ → 1.5 ATP
NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle.
Aerobic metabolism of one glucose molecule produces 32 net ATP via malate-aspartate shuttle (heart and liver), 30 net ATP via glycerol-3-phosphate shuttle (muscle).
Anaerobic glycolysis produces only 2 net ATP per glucose molecule.
Aspirin overdose can also cause uncoupling of oxidative phosphorylation resulting in hyperthermia.



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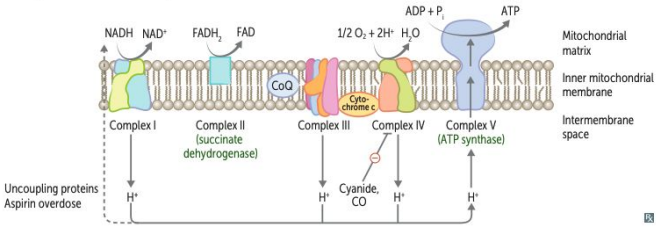
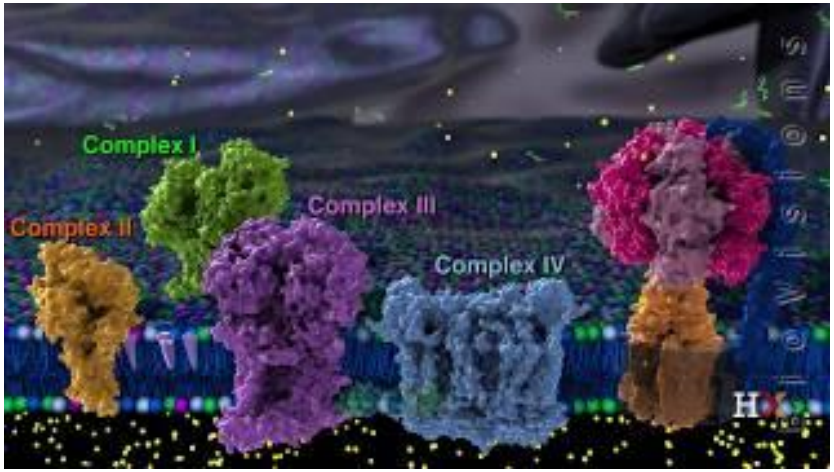
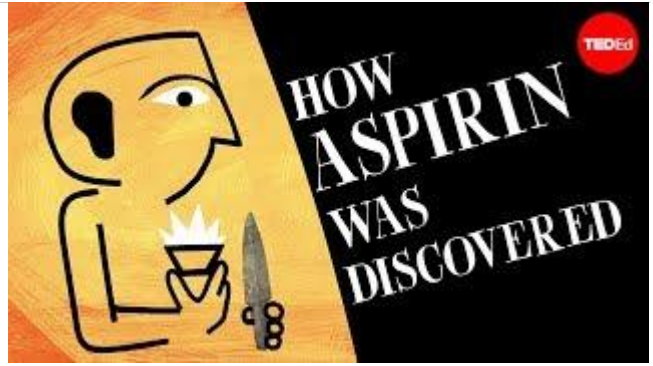






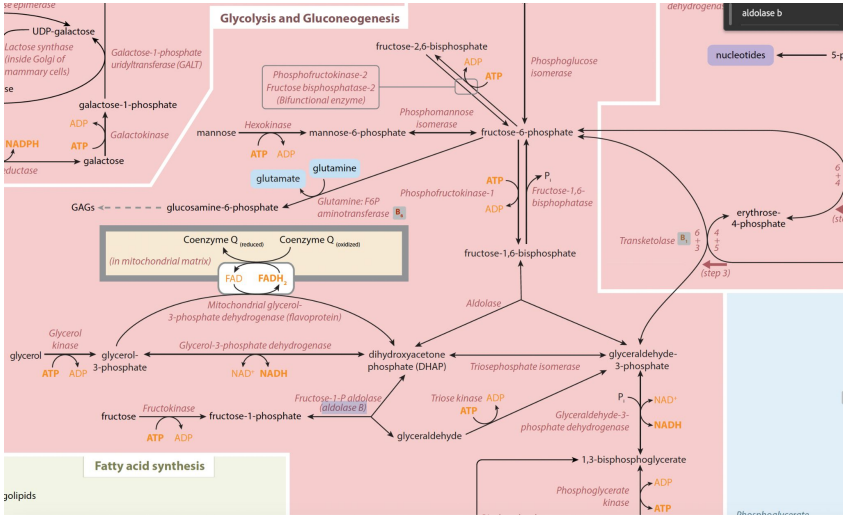
Hereditary Fructose Intolerance

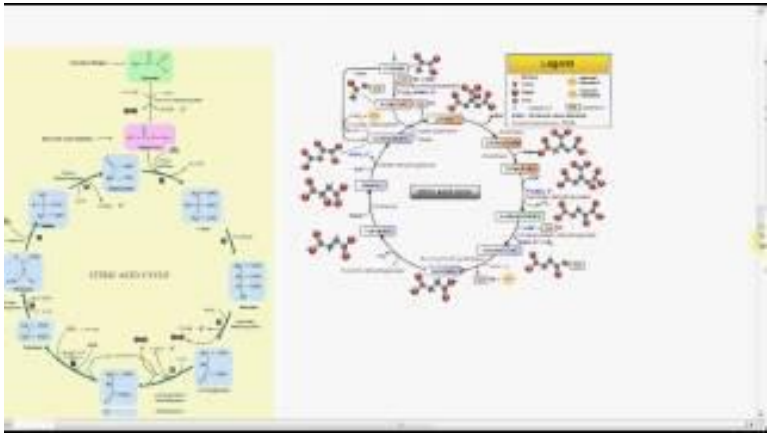
Mechanism: Aldolase B deficiency → Fructose-1-phosphate accumulates → decreased available phosphate → inhibition of glycogenolysis and gluconeogenesis
Page: 78

UWQID 1069 Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly.

-Acumulation of F1P depletes intracellular phosphate and inhibits activation of hepatic phosphorylase, and gluconeogeneis.

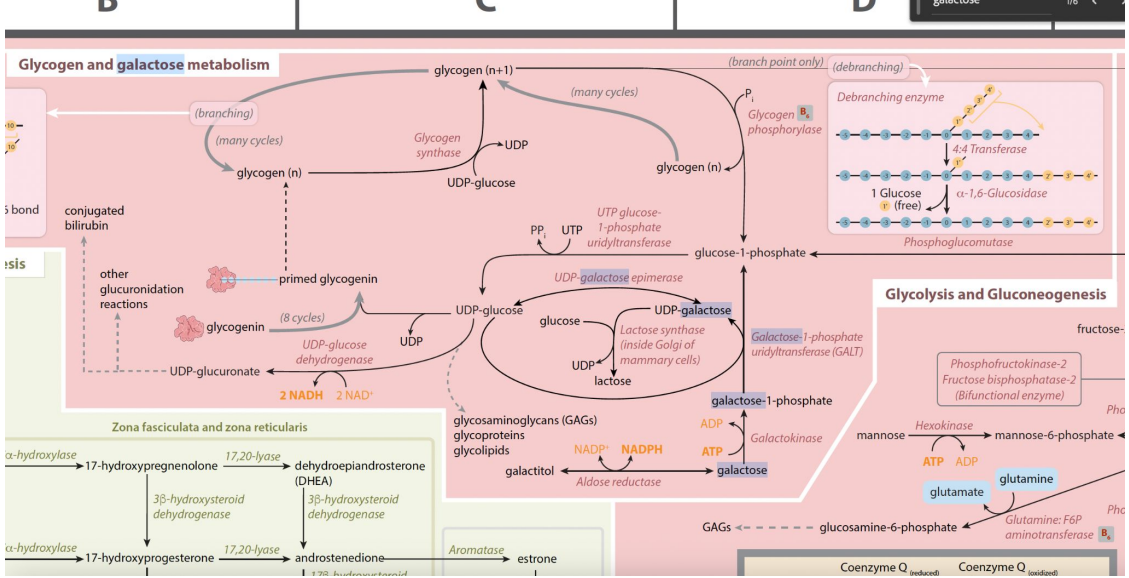
BB





Classic Galactosemia

Mechanism: Galactose-1-phosphate uridyltransferase deficiency → accumulation of toxic substances (e.g., galactitol in eyes)
Page: 78



UWQID 1071 Classic galactosemia results from deficiency of galactose-1-phosphate uridyl transferase. Clinical features include vomiting, lethargy, jaundice, and *Escherichia coli* sepsis. Cessation of breastfeeding and switching to soy milk-based formula is recommended.

-Caract can be the only sign in galactokinase deficiency.

-Classic galactosemia enz def : Galactose 1 phosphate uridyltransferase

Cataracts, retinopathy, peripheral neuropathy in DM

Lens, retina, Schwann cells lack sorbitol dehydrogenase -> □ intracellular sorbitol accumulation □-> osmotic damage

Recurrent Neisseria bacteremia

Terminal complement deficiencies (C5–C9) failure of MAC formation

Hereditary angioedema

C1 esterase inhibitor deficiency □ unregulated activation of kallikrein □ □ bradykinin

Paroxysmal nocturnal hemoglobinuria

PIGA gene mutation □ □ GPI anchors for complement inhibitors (DAF/ CD55, MIRL/CD59) □ complement-mediated intravascular hemolysis

Type 1 hypersensitivity

Immediate (minutes): antigen cross links IgE on mast cells degranulation release of histamine and tryptase

Late (hours): mast cells secrete chemokines (attract eosinophils) and leukotrienes inflammation, tissue damage

Type 2 hypersensitivity

Antibodies bind to cell-surface antigens □ cellular destruction, inflammation, cellular dysfunction

Type 3 hypersensitivity

Antigen-antibody complexes □ activate complement □ attracts neutrophils

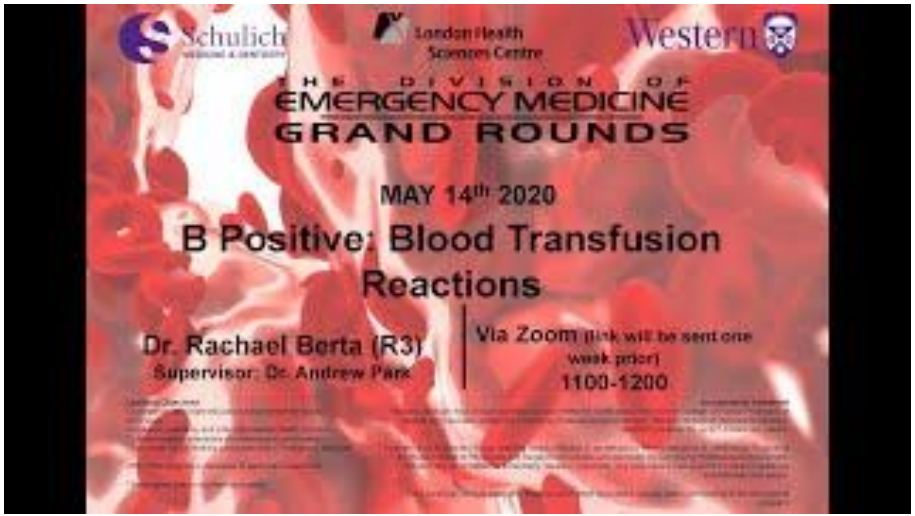
Type 4 hypersensitivity

T cell-mediated (no antibodies involved). CD8+ directly kills target cells,

CD4+ releases cytokines

Acute hemolytic transfusion reaction

Type II hypersensitivity reaction against donor RBCs (usually ABO antigens)



Adaptive Immune Arm

X-linked (Bruton) agammaglobulinemia

Defect in BTK gene (tyrosine kinase) □ no B-cell maturation □ absent B cells in peripheral blood, □ Ig of all classes

DiGeorge syndrome

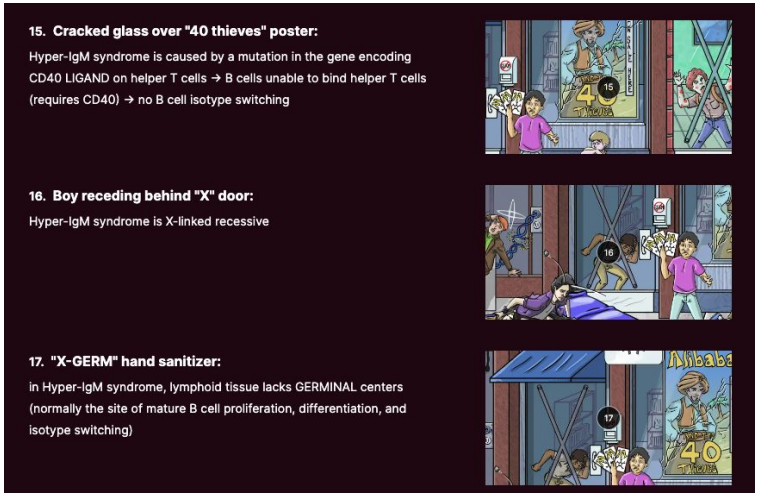
22q11 microdeletion □ failure to develop 3rd and 4th branchial (pharyngeal) pouches

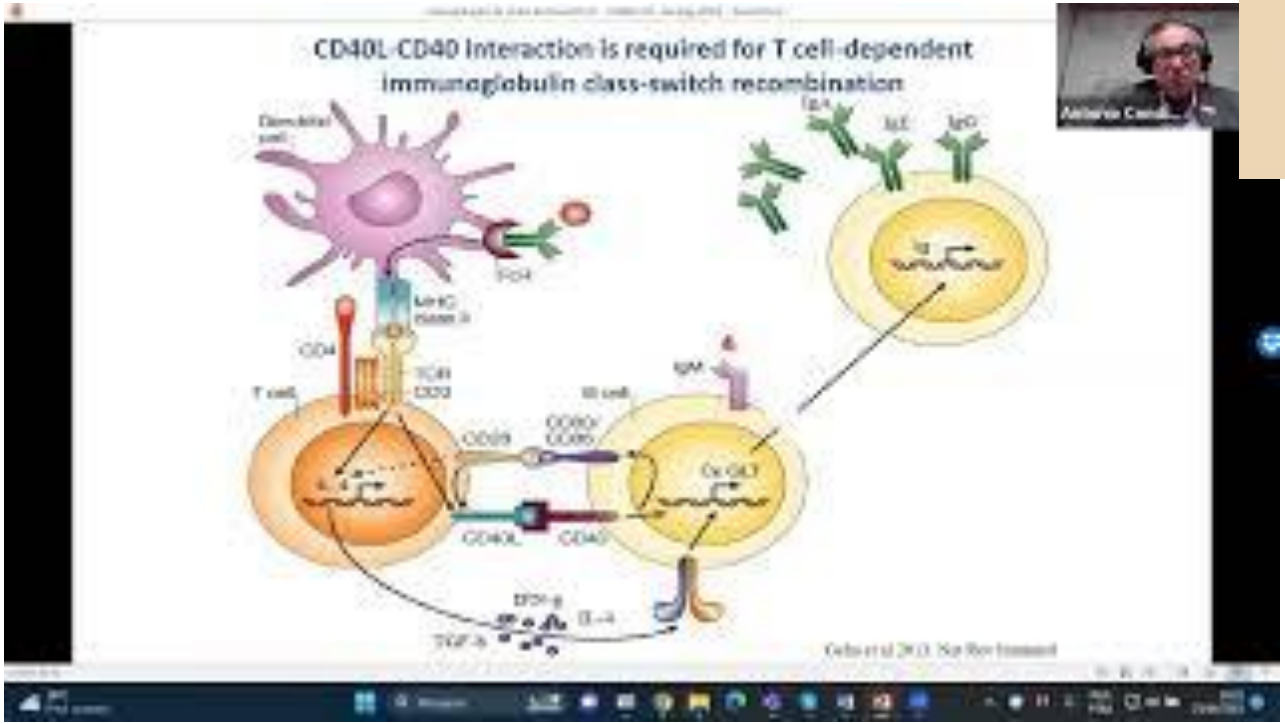
Pharyngeal pouch derivatives — Ear, tonsils, bottom-to-top: 1 (ear), 2 (tonsils), 3 dorsal (bottom = inferior parathyroids), 3 ventral (to = thymus), 4 (top = superior parathyroids).

POUCH	DERIVATIVES	NOTES
1st pharyngeal pouch	Middle ear cavity, eustachian tube, mastoid air cells	1st pouch contributes to endoderm-lined structures of ear
2nd pharyngeal pouch	Epithelial lining of palatine tonsil	
3rd pharyngeal pouch	Dorsal wings → **inferior** parathyroids Ventral wings → thymus	Third pouch contributes to thymus and both inferior parathyroids. Structures from 3rd pouch end up **below** those from 4th pouch
4th pharyngeal pouch	Dorsal wings → **superior** parathyroids Ventral wings → ultimopharyngeal body → parafollicular (C) cells of thyroid	4th pharyngeal pouch forms para"4"llicular cells

Hyper IgM syndrome

Defective CD40L on Th cells □ class switching defect

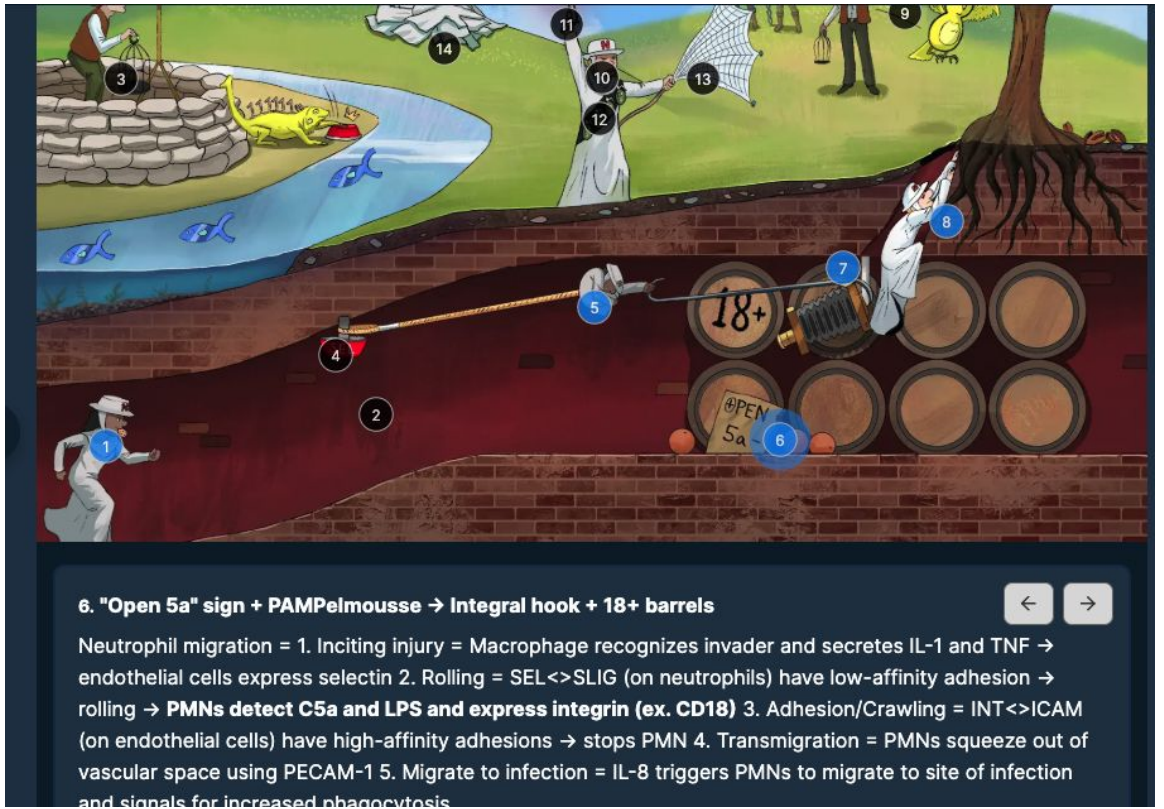



CD40L-CD40 Interaction is required for T cell-dependent immunoglobulin class-switch recombination
IgA
IgE
IgG
MHC class II
CD4
TCR
CD3
T cell
B cell
IgM
CD28
CD80/
CD86
CD40L
CD40
IFN-γ
IL-4
TGF-b


Defective class switching

Leukocyte adhesion deficiency (type 1)

LFA-1 integrin (CD18) defect □ impaired phagocyte migration and chemotaxis



Chediak-Higashi syndrome

LYST mutation microtubule dysfunction phagosome-lysosome fusion defect

Chronic granulomatous disease

NADPH oxidase defect □ □ ROS, □ respiratory burst in neutrophils

Candida infection in immunodeficiency

 granulocytes (systemic), T cells (local)

Graft-versus-host-disease

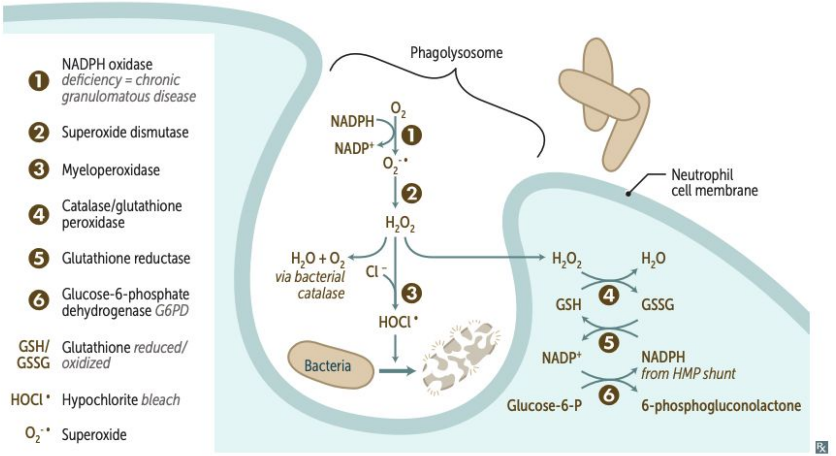
Type IV hypersensitivity reaction; HLA mismatch donor T cells attack host cells

Recurrent S aureus, Serratia, B cepacia infections in CGD

Catalase ⊕ organisms degrade H2 O2 before it can be converted to microbicidal products by the myeloperoxidase system

Respiratory burst

Also called oxidative burst. Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes O_2 as a substrate. Plays an important role in the immune response → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green, heme-containing pigment that gives sputum its color. **NO** Safe **M**icrobe (**N**ADPH **O**xidase → **S**uperoxide dismutase → **M**yeloperoxidase).



Phagocytes of patients with CGD can utilize H_2O_2 generated by invading organisms and convert it to ROS. Patients are at ↑ risk for infection by catalase ⊕ species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own H_2O_2, leaving phagocytes without ROS for fighting infections.

Pyocyanin of *P aeruginosa* generates ROS to kill competing pathogens. Oxidative burst leads to release of lysosomal enzymes.

Hemolytic uremic syndrome

Shiga/Shiga-like toxins inactivate 60S ribosome □ □ cytokine release

Tetanus

Tetanospasmin prevents release of inhibitory neurotransmitters (GABA and glycine) from Renshaw cells

Botulism

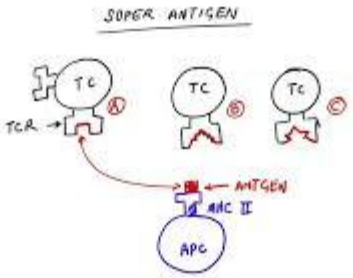
Toxin (protease) cleaves SNARE □ □
neurotransmitter (ACh) release at
NMJ

Gas gangrene

Alpha toxin (phospholipase/lecithinase) degrades phospholipids □ myonecrosis

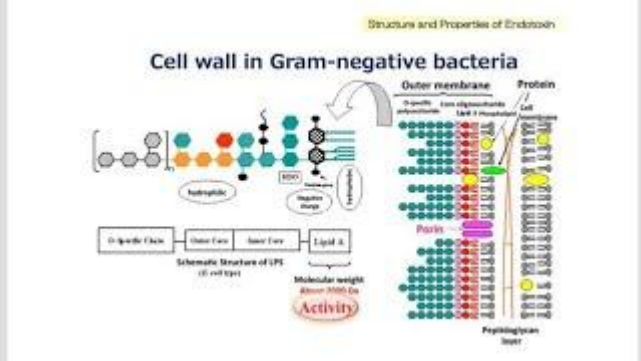
Toxic shock syndrome, scarlet fever

TSST-1 and erythrogenic exotoxin A (scarlet)
cross-link β region of TCR to MHC class II on APCs outside of antigen binding site □ □□ IL-1, IL-2, IFN-γ, TNF-α



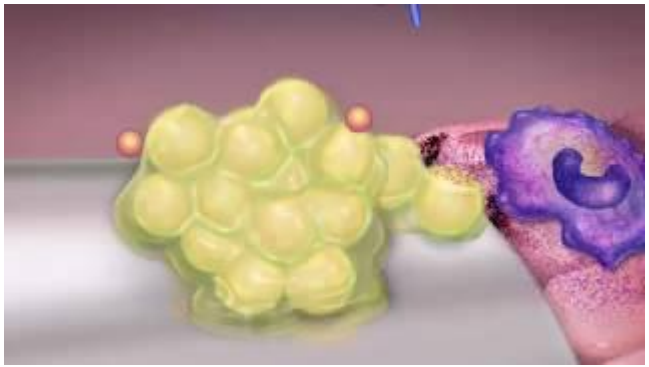
Shock and DIC by gram negative bacteria

Lipid A of LPS □ macrophage activation (TLR4/CD14), complement activation, tissue factor activation



Prosthetic device infection by S epidermidis

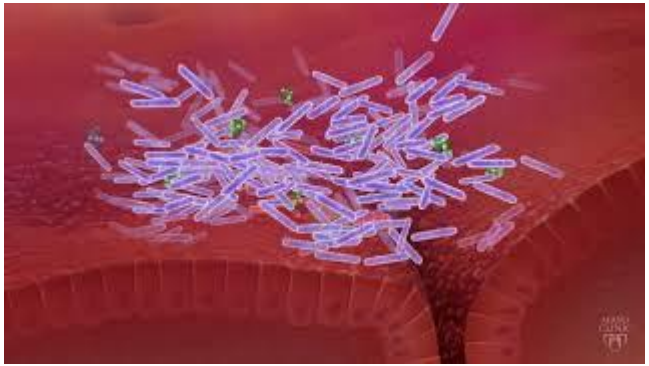
Biofilm production



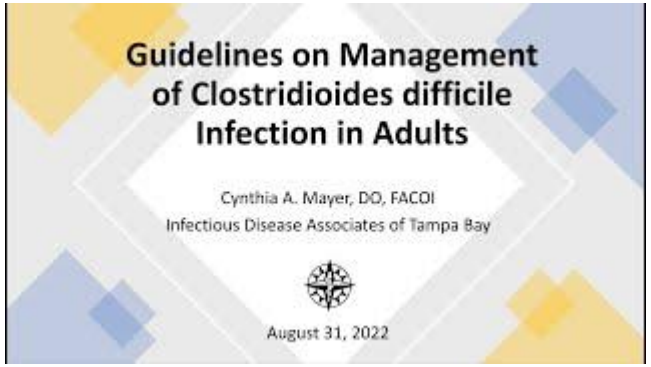
Endocarditis secondary to S sanguinis

Dextrans (biofilm) production that bind to fibrin-platelet aggregates on damaged heart valves

Pseudomembranous colitis 2 to C difficile

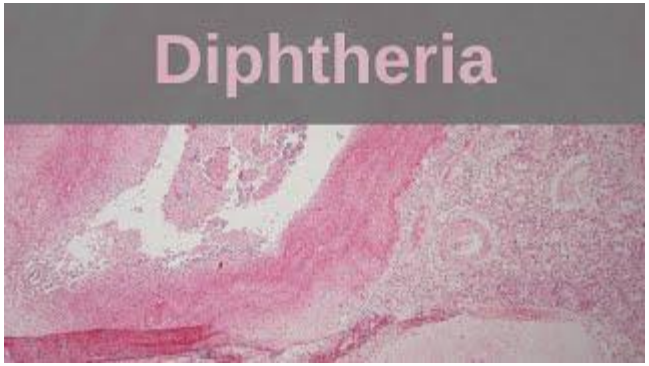


Toxins A and B damage enterocytes □ watery diarrhea



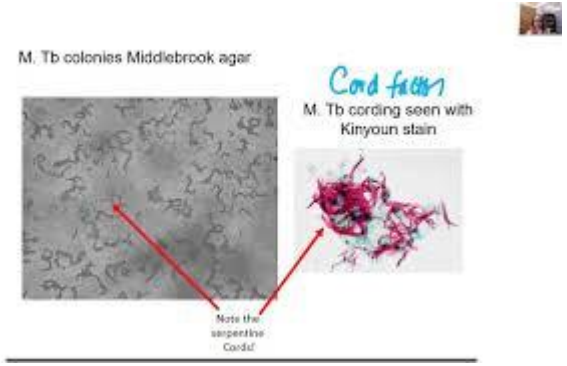
Diphteria

Exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2



Virulence of M tuberculosis

Cord factor activates macrophages (promoting granuloma formation), induces release of TNF-α; sulfatides (surface glycolipids) inhibit phagolysosomal fusion



Tuberculoid leprosy

Th1 immune response → mild symptoms

6. Jail cell 1:

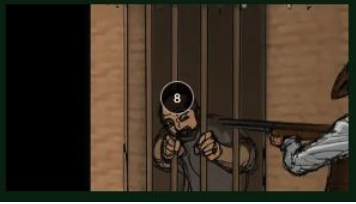
Tuberculoid leprosy elicits a **Th1 cell-mediated immune response**, resulting in macrophage activation and containment of the bacteria

7. Prisoner in jail cell 1:

A strong Th1 cell-mediated immune response induces **macrophage phagocytosis** of *Mycobacterium leprae* bacteria, resulting in the tuberculoid variant of leprosy

8. Bald prisoner:

Tuberculoid leprosy typically presents with a small number of skin lesions that are flat or mildly elevated, often **lacking hair**



No effective vaccine for N gonorrhea

Antigenic variation of pilus proteins

Cystitis and pyelonephritis by E coli

Fimbriae (P pili)

Pneumonia, neonatal meningitis by E coli

K capsule

Chlamydia resistance to B-lactam antibiotics

Lack of classic peptidoglycan due to reduced muramic acid

Influenza pandemics

RNA segment reassortment □ antigenic shift

Influenza epidemics

Mutations in hemagglutinin, neuraminidase antigenic drift

CNS invasion by rabies

Binds to ACh receptors □ retrograde transport (dynein)

HIV infection

Virus binds CD4 along with CCR5 on macrophages (early), or CXCR4 on T cells (late)

Granuloma

Macrophages present antigens to CD4+ and secrete IL-12 □ CD4+ differentiation into Th1 which secrete IFN-γ □ macrophage activation

Limitless replicative potential of cancer cells

Reactivation of telomerase □ maintains and lengthens telomeres □ prevention of chromosome shortening and aging

Tissue invasion by cancer

□ E-cadherin function □ □ intercellular junctions □ basement membrane and ECM degradation by metalloproteinases □ cell attachment to ECM proteins (laminin, fibronectin) □ locomotion □ vascular dissemination

Persistent truncus arteriosus

Failure of aorticopulmonary septum formation

D-transposition of great arteries

Failure of the aorticopulmonary septum to spiral

Tet spells in tetralogy of fallot

Crying, fever, exercise □ □ RV outflow obstruction □ □ right-to-left flow across VSD; squatting □ □ SVR □ □ right-to-left shunt □ □ cyanosis

Eisenmenger syndrome

Uncorrected left-to-right shunt □ □ pulmonary blood flow □ remodeling of vasculature □ pulmonary hypertension □ RVH □ right to left shunting

Atherosclerosis

Endothelial cell dysfunction □ macrophage and LDL accumulation □ foam cell formation □ fatty streaks □ smooth muscle cell migration, extracellular matrix deposition □ fibrous plaque □ complex atheromas

Thoracic aortic aneurysm

Cystic medial degeneration Rupture of coronary artery atherosclerotic plaque acute thrombosis

Myocardial infarction

Rupture of coronary artery atherosclerotic plaque □ acute thrombosis

Non-ST segment elevation MI

Subendocardial infarcts (subendocardium vulnerable to ischemia)

ST-segmenet elevation MI

Transmural infarcts

Death within 0-24

Ventricular arrhythmia

Death or shock within 3-14 days post MI

Macrophage-mediated ruptures: papillary muscle (2-7 days), interventricular septum (3-5 days), free wall (5-14 days)

Wolff-Parkinson-White

Abnormal accessory pathway from atria to ventricle bypasses the AV node □ ventricles begin to partially depolarize earlier □ delta wave. Reentrant circuit □ supraventricular tachycardia

Hypertrophic obstructive cardiomyopathy

Sarcomeric proteins gene mutations (myosin binding protein C and β-myosin heavy chain) concentric hypertrophy (sarcomeres added in parallel). Death due to arrhythmia

Syncope,dyspnea in HOCM

Asymmetric septal hypertrophy, systolic anterior motion of mitral valve □ outflow obstruction

□

Hypovolemic shock

preload □ □ CO

□

Cardiogenic shock

CO due to left heart dysfunction □

Distributive shock

SVR (afterload)

Rheumatic fever

Antibodies against M protein cross react with self antigens; type II hypersensitivity reaction

Most common form of congenital adrenal hyperplasia

21-hydroxylase deficiency□ □ mineralocorticoids, □ cortisol, □ sex hormones, □ 17-hydroxyprogesterone

□

Heat intolerance, weight loss in hyperthyroidism

Na+-K+ ATPase □ □ basal metabolic rate □ □ calorigenesis □ GAGs in interstitial space □ □ osmotic pressure □ □ water retention

Graves ophtalmopathy

Lymphocytic infiltration, fibroblast secretion of GAGs □ □ osmotic muscle swelling, inflammation

Primary hyperparathyroidism

Parathyroid adenoma or hyperplasia □ □ PTH □

Secondary hyperparathyroidism

Ca2+

and/or □ PO4 3–□ parathyroid hyperplasia □ □ PTH, □ ALP

□

Euvolemic hyponatremia in SIADH

ADH □ water retention □ □ aldosterone, □ ANB, □ BNP □ □ urinary Na+ secretion

Small/large vessel disease in DM

Nonenzymatic glycation of proteins; small vessels hyaline arteriosclerosis; large vessels atherosclerosis

Diabetic ketoacidosis

Insulin or □ insulin requirement □ □ fat breakdown □ □ free fatty acids □ □ ketogenesis

Hyperosmolar hyperglycemic state

Hyperglycemia □ □ serum osmolality, excessive osmotic diuresis

Zollinger-Ellison syndrome

Gastrin-secreting tumor (gastrinoma) of pancreas or duodenum □ recurrent ulcers in duodenum/jejunum and malabsorption

Duodenal atresia

Failure to recanalize

Jejunal/ileal atresia

Disruption of SMA □ ischemic necrosis of fetal intestine

Superior mesenteric artery syndrome

Diminished mesenteric fat compression of transverse (third) portion of duodenum by SMA and aorta

Achalasia

Loss of postganglionic inhibitory neurons (contain NO and VIP) in myenteric plexus □ failure of LES relaxation

Barret esophagus

Chronic GERD replacement (metaplasia) of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells)

Acute gastritis secondary to nsaids

PGE2 □ □ gastric protection

Celiac disease

Autoimmune-mediated intolerance of gliadin (found in wheat) malabsorption (distal duodenum, proximal jejunum), steatorrhea Transmural inflammation

Fistula formation inCrohn

Persistence of the vitelline (omphalomesenteric) duct

Meckel diverticulum

Loss of function mutation in RET □ failure of neural crest migration □ lack of ganglion cells/enteric nervous plexuses in distal colon

Hirschprung diseae

Loss of APC (□ intercellular adhesion, □ proliferation) □ KRAS mutation (unregulated intracellular signaling) □ loss of tumor suppressor genes (TP53, DCC)

Fibrosis in cirrhosis

Stellate cells

Aspirin β-oxidation by reversible inhibition of mitochondrial enzymes

Cirrhosis □ portosystemic shunts □ □ NH3

metabolism

Misfolded proteins aggregate in hepatocellular ER □ cirrhosis. In lungs, □ α1 -antitrypsin □ uninhibited elastase in alveoli □ panacinar emphysema

Mutated hepatocyte copper-transporting ATPase (ATP7B on chromosome 13) □ □ copper incorporation into apoceruloplasmin, excretion into bile □ □ serum ceruloplasmin, □ copper in tissues and urine

HFE mutation on chromosome 6 □ □ hepcidin production, □ intestinal absorption □ iron overload (□ ferritin,□ iron, □ TIBC □ □ transferrin saturation)

Fistula between gallbladder and GI tract □ stone enters GI lumen □ obstructing ileocecal valve (narrowest point)

Biliary tree obstruction □ stasis/bacterial overgrowth

Autodigestion of pancreas by pancreatic enzymes

Rh hemolytic disease of the newborn Rh ⊖ mother form antibodies (maternal anti-D IgG) against RBCs of Rh ⊕ fetus

Lead inhibits ferrochelatase and ALA dehydratase □ □ heme synthesis, □ RBC protoporphyrin.

Inflammation □ □ hepcidin □ □ release of iron from macrophages, □ iron absorption from gut

Defect in G6PD □ □ NADPH □ □ reduced glutathione □ □ RBC susceptibility to oxidant stress

Point mutation substitution of glutamic acid with valine in β chain low O2 , high altitude, acidosis precipitates sickling (deoxygenated HbS

polymerizes) anemia, vaso-occlusive disease

GpIb □ □ platelet-to-vWF adhesion

□

GpIIb/IIIa □ □ platelet-to-platelet aggregation, defective platelet plug formation

□

ADAMTS13 (a vWF metalloprotease) □ □ degradation of vWF multimers □ □ platelet adhesion and aggregation (microthrombi formation)