Pathophysiology Two.

*** Course Summary ***

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Ch.1: Liver diseases:

1 Gallstone formation: [Cholelithiasis]

*In General:

- affect the complementary Parts of Liver. (not directly on the Liver)
  - ↳ gallbladder
  - ↳ biliary tract

∴ Gallbladder disorders:

group of disorders affecting the gallbladder and biliary tract.

1. Cholelithiasis (Gallstone formation)
2. Cholecystitis: inflammation in gallbladder or cystic duct
3. Cholangitis: inflammation in bile duct due to infection
4. Choledocholithiasis: affect all the biliary tract when obstruction due to accumulation of gallstone.

in normal:

Cholestrol from Liver → gallbladder → convert to bile salt → contraction of gallbladder to emptying its content → Small intestine → emulsification of cholestrol → reuptake

if accumulation of Stone:

accumulation → then obstruction → ∴ Choledo Cholithiasis.

*Cholelithiasis:

Formation of the stone in gallbladder or biliary tract

- cholestrol + Ca^{+2} → Yellow color → Cholestrol stone
- bilirubin + Ca^{+2} → Dark color (bile pigment) → bilirubin stone
- or both → mix → gallbladder stone

*Ca^{+2} → For hardness & crystalization of the mass

*Causes:

1. high cholestrol Level in the bile (not in the blood)

↑ conc. of cholestrol in the bile → Supersaturation → precipitation → crystalization → Formation of Stone + Ca^{+2} (Cholestrol Stone)

[2] High bilirubin Level in the bile

* bilirubin → metabolite of Heme from Hemoglobin from RBCs.
  - ↳ insoluble compound
  - ↳ Get rid of by liver, how?!

(non polar → polar)

by Glucuronic acid : bilirubin → conjugated bilirubin (soluble) → gallbladder → contraction

→ more to small intestine → large intestine → excretion by feces (90% feces, 10% Urine)

∴ ↑ conc. of bilirubin → precipitation → ∴ bilirubin stone

[3] Increase of mucin (glycoprotein) Secretion:

* mucin → monomer of mucus (↑ viscosity)

↑ mucin → ↑ mucus → ↑ viscosity → precipitation

[4] Hypomotility of gallbladder

Hypomotility → precipitation of soluble substance even if there is normal conc. of cholestrol / bilirubin

* Risk factors :

[1] Gender : women , multiparity (women more risk than men , multiparity more risk)

↑ Estrogen hormone → ↑ expression of LDL receptors → ↑ LDL reuptake → ↑ cholestrol → ↑ accumulation

∴ cholestrol stone

[2] Alteration of hepatic cholestrol catabolism

Catabolism → ∴ accumulation of cholestrol → ∴ cholestrol stone

[3] Obesity, ↑ cholestrol intake , use of oral contraceptives or estrogen supplements.

∴ Cholestrol stone

[4] Hemolytic anemia (Bile pigment stone)

Hemolytic → ↑ break of RBCs → ↑ Hemoglobin → ↑ Heme → ↑ bilirubin

[5] Cirrhosis

Live disease (non-functional) → Gallstone → Cholestrol
  - ↳ Bilirubin

[6] Biliary tract infection
  - ↳ bilirubin Stone
  - ↳ Cholestrol Stone.

* Pathogenesis:

bilirubin stones

• Pathogenesis of Bile pigment:

① if high conc.:

in normal:

bilirubin → to the liver → conjugation ≈ glucuronic acid → ∴ soluble → to gallbladder → contraction → excretion

in high conc.:

liver can't make complete conjugated of bilirubin → Conjugated and non-conjugated move to gallbladder → Precipitation of non-conjugated (insoluble) $+Ca^{+2}$ → crystal → accumulation.

② if infection:

infection in gallbladder → bacteria secrete β-glucuronidase enzyme → break the conjugated bilirubin → Convert from soluble to insoluble (unconjugated) → ∴ precipitation $+Ca^{+2}$ (form nucleus)

• Pathogenesis of Cholestrol Stone:

① if high conc.:

high conc. of cholestrol → Super Saturation → initiation of nucleus (Cholestrol crystal nucleation) (Cholestrol $+Ca^{+2}$) → more deposition of cholestrol on this nucleus → ∴ Cholestrol Stone.

② Decreasing gallbladder contractility:

(Hypomotility) → ↑ ability of crystal nucleation → aggregation → precipitation → deposition

③ infection: (inflammation)

infection → inflammation → inflammatory mediators activation by phospholipase A2 → Arachidonic acid → COX enzyme → Prostaglandin → ↑ mucus → ↑ viscosity → precipitation.
(formation of mucin-glycoprotein gel)

*Symptoms:

+ Asymptomatic disease in small stone state (small stones are "silent")

* ↑ size or movement of the stone → [1] severe waves pain (biliary colic)
↳ in abdominal region especially upper right area of abdomen and may in shoulder

[2] Nausa & vomiting

[3] Jaundice
Symptom of bilirubin stone.

[4] Severe pain with eating fatty meal
fatty meals need bile → ∴ ↑ contraction → ↑ Pain

✓ Treatment:

↳ Pharmacological:

Just ω Cholesterol stone and Small stone.

- bile acids binders

(bind ω bile acids in small intestine & pull it ↑ eliminate by feces)

∴ ↓ bile acids in gallbladder

↳ Non-pharmacological:

- Shock wave lithotripsy by high-energy Sound waves.

- Cholecystectomy

by laparoscope

- laparoscopic cholecystectomy.

2 Jaundice (Icterus, hyperbilirubinemia)

- ↑ bilirubin Conc. in the blood and characterized by yellowish color of the eyes & skin.
- may be primary or related to other disease.

Causes:

due to causes, it Classified to 3 categories
- based on the live function
  - Prehepatic
  - intra hepatic
  - Post hepatic

*normal Pathway of bilirubin:

RBCs → hemolysis → henoglobin → heme → bilirubin (unconjugated) → Liver → Conjugated bilirubin → gallbladder → bile → intestine → feces

[1] Prehepatic Jaundice:
(HemoLYtic Jaundice)
ex// Hemolytic anemia → ↑ degradation of RBCs → ↑ synthesis of bilirubin → ↑ unconjugated bilirubin
(Liver is functional but no capacity for all bilirubin) (Liver function is normal but unable to handle the additional bilirubin)
∴ Disease increase the synthesis of bilirubin
Because of

[2] Intrahepatic Jaundice:
- Due to ↓ of Liver function such as hepatitis or cirrhosis.
- normal level of bilirubin but Liver can't convert it to Conjugated bilirubin

[a]
∴ ↑ unconjugated bilirubin
due to disease directly effect the Liver.

[b] or ↑ conjugated bilirubin
due to inflammation in hepatic duct → swelling → obstruction → ↑ conjugated bilirubin back to circulation

[3] Posthepatic Jaundice:
- Normal Hemolysis, unconjugated bilirubin, Liver function
- ↑ of Conjugated bilirubin

due to abnormal Pathway of bile because of gallstone in bile duct
- Some of conjugated Pass to gallbladder
- other back to Circulation.

Symptoms:

- Characteristic symptom is Yellowish color start in eyes then skin, dark wine
  ↑ bilirubin in circulation

- Pruritus (itching) → Characteristic to 3rd catagory (Posthepatic)
  Because of bile accumulation (not bilirubin) → accumulation under the skin
  → stimulate mast cell → Histamine secretion.

Treatment:

- Phototherapy (blue color)
- Blood transfusion
- Drugs: Liver enzyme function.

3 Hepatitis:

- Inflammation of the Liver → acute inflammation (mild) → < 6 month
  → Chronic inflammation (severe) → > 6 month

Causes:

1 Idiopathic : fatty liver (hepatic steatosis)

accumulation of Cholestrol & TG inside the liver due to ↑synthesis or ↓ degradation → ↓ metabolism → Stimulate free radical → cell injury → inflammation

2 Infection : Virus (viral hepatitis), bacteria (bacterial hepatitis), Protozoa

3 Drug toxicity

(Most Drugs metabolite in the liver)

Some metabolites are toxic to the Liver → ∴ from high amount of them lead to damage in the Liver → ∴ Inflammation

ex// Paracetamol (high amount)

4 Alcohol consumption

Alcohol metabolism → aldehyde → damage in Liver → inflammation

5 Autoimmunity

Body recognize some cells in the liver as foreign substance → attack by immune system

- Viral hepatitis :-

→ Hepatitis A Virus (HAV)
→ Hepatitis B virus (HBV)
→ Hepatitis C virus (HCV)
→ Hepatitis D Virus (HDV)
→ Hepatitis E virus (HEV)

Disease	Agent	Transmission	Incubation Period	Carrier / chronic
Hepatitis A (self-limited)	RNA virus	Oral - fecal (especially in children)	< 6 month (acute)	None (acute)
Hepatitis B (complex virus) composed from 3 proteins: .S: on surface .c and e: inside the virus	DNA virus	Blood & Body fluids (Blood transfusion, from mother to baby)	> 6month (chronic)	Carrier and chronic may be either symptomatic or asymptomatic.
Hepatitis C	RNA virus	Blood & Body fluids	> 6 month	Carrier and Chronic
Hepatitis D	RNA virus requires presence of HBV. (S protein) virus D دايمًا لازم يكون معاه B	Blood & Body fluids	< 6 month	"Acute بسيط" but Chronic Viral D alone → incomplete RNA but requires the presence of Hepatitis B virus to replicate & Produce active infection
Hepatitis E	RNA virus	Oral - fecal	< 6month	None

Pathogenesis :

(Hepatitis C and Hepatitis B)

Cell injury by 2 pathways → Direct pathway (Hepatitis C) Direct killing by virus

→ Cell-mediated immune response (Hepatitis B) killing immune cells

[1] Direct Pathway (hepatitis C):

virus enter the hepatocyte to replicate and duplicate → due to duplication by using enzymes and Proteins in hepatic cell → duplication of virus C → Cells get out from hepatic cell to other cell → damage in hepatic cell

virus C attack hepatocyte → enter the nucleus → using hepatocyte enzymes to replication and duplication for genetic materials of the virus → genetic material of the virus move to cytoplasm → Coating by proteins → release from hepatic cell (exit) → ∴ killing the cell (distruction due to virus exit)

[2] Cell-mediated immune response (hepatitis B): "ذكي"

virus attack hepatic cell → enter the cytoplasm → to nucleus (to use host cell enzymes for duplication and Form a new copies) → duplication for virus genetic materials → to cytoplasm → Coating

virus B contain protein S and Protein e (Complex virus) → manufactering by cell enzymes as mRNA → mRNA get out and translated by ribosome → ∴

Symptoms:

Acute:-

- Preicteric or Prodromal Stage → related to immune system (fever, pain) and elevation in Liver enzymes → ALT, AST (No ↓ in Liver functions)
- Icteric or Jaundice stage → damage in liver → ↓ functions → no normal conjugation of bilirubin → Jaundice
- Posticteric or recovery stage → Self limited

Chronic:

The same 1st and 2nd stages then fibrosis

4 Liver cirrhosis:

- It is a progressive destruction of the liver tissue due to long-term liver disease
- Liver fibrosis → The first stage
- fibrosis (inflammation) → damage → continous damage → No ability for repair / regenerate → scar tissue → Fibrosis → Liver cirrhosis
- Chronic disease (gradually)

Classification:

1. According to morphology:
   - ① macromodulas
   - ② micromodulas

2. According to cause:

1 Alcoholic liver cirrhosis (Portal or Laennec's cirrhosis):

Large amount of consumption of alcohol → accumulation of alcohol metabolites → cell injury → inflammation → Chronic → ∴ Liver cirrhosis

2 Biliary cirrhosis:

Stones in biliary tract → injury → ↑↑ injury → inflammation → Liver cirrhosis

3 Postnecrotic cirrhosis:

- after necrosis process: chronic inflammation, chronic hepatitis or long-term exposure to toxic material
- necrosis → inflammation

4 Metabolic cirrhosis: (such hemochromatosis / wilson's disease)

due to some metabolic disorders especially: in some metals → Liver control its absorption & distribution and storage for this metals (iron, cupper)

in normal:

- iron:
  - control and passage by ferroportin protein (Protein in the inner membrane of small intestine) → cytoplasm → circulation by ferroportin → transferrin to Liver → storge → distribute
  - Synthesis control by Liver
- in hemochromatosis: (accumulation of the iron in the body)
  - toxic conc. of the iron (due to genetic problem) → chronic inflammation → injury → ..
- wilson's disease: accumulation of the cupper in the body
  - in normal: Liver distribute the cupper and get rid of excess amount by the bile.
    Cupper from Liver → gallbladder by wilson's cupper transporter synthesis by Liver.
  - in wilson's disease: accumulation of cupper in Liver → chronic inflammation → ..

Pathogenesis :

Healthy liver → Chronic exposure → Ireversible injury → chronic inflammation → Liver cirrhosis

- Main cell is macrophage.
- macrophage in the Liver (kupffer cells)
- chronic inflammation → activation kupffe cells → secrete cytokines → activation Lymphocytes → cytokines → activation hepatic stellate cells (Quiescent HSC for storage fats) → activated HSC → cytokines (TGF-β) (Transforming growth factor) → transdifferentiation → myofibroblast, fibroblast (activated HSC ↑) → ECM synthesis (collagen) → ∴ fibrosis → Liver cirrhosis. (Gradually)

Symptoms :

depends on (related to) → either liver as function
→ or due to Hardness in portal vein due to scars and fibrosis.

1. Fatigue, anorexia, indigestion, weigh loss:
due to metabolic dysfunction in liver such as ↓Gluconeogenesis, ↓ bile for digestion, Portal hypertension

2. General edema : accumulation of fluids.
- liver responsible for catabolism of aldosteron
liver cirrhosis → ↑aldosteron → Na^+/H_2O retention → accumulation → edema
- liver responsible for catabolism of anticliuretic hormone synthesis by kidney (collecting duct)
liver cirrhosis → ↑antidiuretic hormone → ↑fluid → accumulation → edema
- liver synthesis the Albumin
→ major protein in blood, for normalization of osmotic pressure
↑ Albumin → ↑ Fluid From interstitial fluid → blood
↓ Albumin → ↑ fluid From blood → interstitial Fluid
Liver cirrhosis → ↓ amount of albumin (not sufficient) → ↓ Osmotic pressure → accumulation of fluid → ∴ edema
- Congestion (accumulation of fluids in the organs)

fibrosis → Problem of valve in portal vein (Hardness) → round-trip blood → No suitable distribution of blood to surrounding organs ↑ → accumulation of fluids → especially in abdominal area → ∴ Congestion

3. Splenomegaly → congestion in spleen (main cause : congestion)

" Explanation above"

[4] **Ascites** : special type of edema, accumulation of fluids in the abdomin region

"Same to edema"

[5] **Anemia**:

-hemochromatosis → accumulation of iron in the body

①Liver cirrhosis → ↓ absorption / storage of iron → ↓ iron → ∴ anemia

②Liver cirrhosis → ↓ absorption/ storage of Vit. B12 → ↓ Vit. B12 → anemia

③ Spleen play imp. role in production of RBCs and

Liver cirrhosis → Splenomegaly → ↓ efficiency of spleen → ↓ production of RBCs → anemia

④ Bleeding due to:

[6] **Increased bleeding and purpura** → Purple colored spots on the skin due to bleeding → pressure on cappilares

① Liver cirrhosis → ↓ no. of clotting factors → ∴ bleeding (high risk)

Liver is responsible for synthesis of clotting factors

② Liver cirrhosis → ↓ no. of platlets (thrombocytopenia) → ∴ bleeding.

③ ↓ absorption of vit. K — synthesis by Liver

[7] **Leukopenia and thrombocytopenia** :

↳ ↓ in WBCs ↳ ↓ in platlets

- Leukopenia: spleen play important role in lymphocytes synthesis (mature lymphocyte)

Liver cirrhosis → Spleenomegaly → no suffucient no. of WBCs → ∴ Leukopenia

- thrombocytopenia & Leukopenia: & anemia due to ↓RBCs:

Liver cirrhosis → accumulation of amonia conc. → ↓ efficiency of Hematopoetic stem cells (bone marrow depression)

→ ↓ Hematopoesis → ↓ no. of blood cells: WBCs, RBCs, platlets

Cells responsible for formation of all blood cells from the bone marrow.

[8] **Encephalopathy** (Hepatic encephalopathy):

↳ disorder in brain

due to accumulation of the ammonia. → Liver responsible for convert ammonia → urea to get rid of it.

- Liver cirrhosis → ↓ dysfunction → inability to remove ammonia → accumulation of amonia → ↑ammonia conc. in blood → to CNS → Passing BBB → to brain → accumulation in brain → encephalopathy
  - → Coma
  - → tremors
  - → Confusion

9 Gynecomastia, impotance and irregular menses : (Sex hormones, especially estrogen)
(- Excess amount of estrogen → metabolism in Liver) in normal

Liver cirhosis → ↓ dysfunction → accumulation of estrogen → homoral Balance in femals →
→ Gyncomastia in mals
↑ size of breast
irregular menses.

10 Jaundice

11 Pruritus litching

Liver cirhosis → billary obstruction → ↑ bile salts (accumulation) → ~~itching~~ some back to gallbladder and other in circulation → accumulation under the skin → itching

12 Esophageal varices / hemorrhoids :

The main reason:
Liver cirhosis → fibrosis → obstruction (Hardness) in portal vein → NO normal blood flow and blood return into spleen ~~and~~, small intestine, and stomach → continuous pressure on valves of Portal vein → ↓ efficiacy of the valves → broblem in blood distribution → pressure on other branch → destination ~~and thickening~~ of wall of vein → high observation in thein vein especially esophagus → twisting and coiling → ∴ Esophageal varices .

Treatments :

- Life style management :
  - ↓ protein → to avoid ammonia accumulation
  - ↓ Na^+ intake → to avoid H_2O and fluids accumulation
  - ↑ carbs, ↑ vitamins → ↑ Liver functions
- Paracentesis:
  technique used for remove exces amount of fluid from abdomen (ascites)
- Albumin transfusion
- Neomycin → ↓ normal flora and formation of ammonia
- End stage : Liver transplantation.

Ch. Respiratory Disease

1 Covid-19 :

Respiratory Diseases

- Infectious diseases (bacteral/virus)
  - Sinusitis
  - Influenza (Covid-19)
- Obstructive diseases
  - Asthma
  - Chronic obstructive Pulmonary disease
  - Cystic fibrosis

+Covid-19:

- Infection disease (viral infection) affect the Respiratory system by a newly discovered virus Coronavirus
- 85% matching with SARS-CoV (Severe acute Respiratory Syndrome Coronavirus) genetic material.
- ∴ Called it SARS-CoV-2 (the virus) and called the disease Covid-19

NOTE/ Corona viruses are group of virus classified into 2 classes → α → affect animals.
→ β → affect humans.

- SARS-CoV-2 Structure:
- In general: general structure for SARS-CoV-2 Similar to SARS-CoV (β-Coronaviruses)
- Spherical structure under the microscope
- has Corona structure / Crown structure / Solar-like structure

* Corona viruses especially β-Corona viruses, The main source for it is the bats (خفافيش). but it's not directly ~~transmitted~~ transmitted to human, but by intermediate animal.

virus → in bats → intermediate host → human

- SARS → Civet cats are ~~most~~ intermediate host
- MERS → Camels are intermediate host
- SARS-CoV-2 → Pangolin are intermediate host.
  or - Snacks / cats / dogs.

• Structure:

- RNA virus.
- Surrounded by phospholipids membrane and expression some Proteins & embedded in it some others (:- at surfaces and within it)

4 Proteins:

↳ [1] Spike glycoprotein (S protein)

- at surface
- Responsible for infection process by interaction blw the virus & host cell in Respiratory. Receptor → endocytosis
(main protein which is Required for the interaction blw the host cell and the virus).
- Similar to S protein in SARS-cov-1
- Make up from 2 domains

S_1 domain
to interact w receptor

S_2 domain
fusion blw virus & host cell (virus membrane & cell membrane of host cell) (volpoll)
to start endocytosis of virus into host cell.

[2] Membrane glycoprotein (M Protein)
[3] Envelope glycoprotein (E Protein)

- Embedded inside the membrane
- For supporting the structure of the virus
- Stimulate B cells to start synthesis antibody against them

The first Part that B cells start synthesis antibody against it is "The M Protein" then "E Protein"

[4] Nucleocapsid protein (N protein)

- Inside the virus bind with RNA
- Stabilization of RNA
- Protection of RNA from RNAase by inhibition it.
↳ enzyme in host cell, break up RNAs which have problem to avoid mutation

Pathogenesis:

1. How virus enter the cell and how it's work.
2. How immune system responsiveness against this virus.

1 Virus entery :-

- The interaction blw virus & host cell in lung by ACE-2 receptor [Angiotensin converting enzyme 2] (90% expression in Respiratory, 10% on other organs)

SARS-coV-2 binds with ACE-2 on lungs by S_1 domain Protein → S_2 domain →
↳ more affinity for ACE-2 than SARS-coV-1 ∴ more dangerous

endocytosis → reach inside the host cell → uncoating by host's cell enzyme → RNA for Polyproteins
remain RNA → translation of RNA → Convert RNA to Polyproteins → Proteolysis to non-structural proteins → Proteins combinate with itself and form Viral replicase transcriptase responsible for transcription & replication
(different than S, M, E, N)

Complex → transcription & replication of other virus genetic material → 2 copies of RNA
→ one consider as main copy of virus to bind with N protein
↳ other responsible for formation structural proteins which enter translation process to form
N, S, E, M proteins → N protein binding with new RNA to Stabilization RNA virus → S, M, E
Proteins go to endoplasmic reticulm in ERGIC (endoplasmic reticulum Golgi intermediate compartment)
→ The new virus buds are generated inside → exit the cell as vesicle → exocytosis →
death of the cell → and the viron containing vesicles move and fuse with the plasma membrane to release the newly formed viruses inorder to infect new cells.

2 Immune Response :-

Virus enter the cell → replication & duplication → expression of the virus antigen by MHC-I →
Denteric cells recognize it → recognition → Antigen-presenting cell (APCs) → on MHC-II →
T-H_0 → differentiation to TH1 IL-2 → activation CD_8 → Cytotoxic CD_8 → secrete perforin and granzymes against viral infected cell → apoptosis
↳ T-H2 IL-4 → activated B cells to Plasma B cell to start synthesis antibodies against it for second exposure

- Strong enough immune system → Can kill all cells contain SARS-coV-2

- In weak immune system:

weakness in immune system → ↑ delayed response → accumulation of cytokines

∴ Continous activation of immune system → Continous Secretion of cytokines, chemokines, inflammatory mediators → Causes **Cytokines Storm**

The main cause of death
because it is very toxic for cells ☹

Cytokines storm → inflammation → Damage (in lung ☹ Firstly) then, to other organs because cytokines move with blood.

Symptoms:

☹ In general: Fever, loss of sense of smell & taste, muscle-pain, fatigue, difficult breathing, —

In progressive cases (cytokine storm): liver dysfunction, necrosis, acute renal failure, dysfunction of spleen & lymph node which ↓ lymphocytes no., myocarditis, immune cells chemotaxis, —

Diagnosis:

1- Symptoms

2- PCR → Main test (Polymerase chain Reaction) → detect the nucleic acid either DNA or RNA by nasopharyngeal Swamp.

3- Serological test → by detect IgG, IgM in blood analysis

Treatments:

- Antiviral agents
- Anti-inflammatory drugs
- Convalescent Plasma
- Vaccines.

2 Asthma :

"Obstructive Lung Disease"

any disease causes limitation in airflow. because of environmental / congenital cause

In normal :-

* Smooth muscles in lungs (bronchial smooth muscles) → Control airflow
* Homeostasis blw bronchodilation & bronchoconstriction (bronchospasm) Controlled by ANS.
  - Sympathetic → adrenaline is its NT → Relaxation in bronchial muscles
  - Parasympathetic → Ach is its NT.

(ANS: Sym. / Para.)

+ Sympathetic :-
* β_2 receptor present in lungs (bronchial smooth muscles), adrenaline/noradrenaline bind ☜ it → Relaxation → bronchodilation

+ Parasympathetic :-

Acetylcholine → binds ☜ M_1 or M_3 receptors on bronchial smooth muscles → contraction → ∴ bronchospasm.

* Bronchial asthma :

Obstructive lung disease / obstructive airway disease (∴ Problem in airflow)
because of narrowing / bronchospasm / inflammation / increasing airway secretion

(Reversible) but Chronic disease.

- (Reversible) → not permanent
- inflammation → edema → swelling → obstruction; inflammatory mediators (Histamine)
- secretion → viscous → ∴ ↑ secretion cause narrowing.
- Chronic disease ↓
  - if asthmetic patient
    ∴ chronic disease
  - acute if not diagnosis.

* The main cause is : Hyperresponsiveness of the smooth muscles : (General cause)
  asthmatic patient exposure to x factor → hyper response → ↑contraction → ↑ spasm → ↑ secretion → may inflammation.
  (Related to how my body accept this factor (normal response or hyperactive)).

classifications of asthma: (due to Risk factors)

1. Extrinsic asthma (allergic /atopic) → Immune system-mediated reaction (Type 1)
2. Intrinsic asthma (non-atopic) →

Risk-factors :- (Triggers)

→ extrinsic triggers:

Air Pollution, Pollen, Animals, chemicals, Tobacco Smoke, moldy, Dust, Viruses

∴ Immune mediated asthma

→ Intrinsic triggers:

medicines, physical ~~exercise~~ exercise, cold air, Stress.

Pathogenisis:

1. Extrinic triggers:

• asthma → Delayed response.

exII Pollen

Pollen → immune system → Ds or macophage → recognize it as foreign sub. → ~~asthma~~

Phagocytosis → expression on MHC-II by APC → allergy → TH_0 → TH_2 → B cells → ~~sym~~ Antibodies (IgE) → On mast cell → binds ω mast cell (sensitization) → interaction blw Pollen and IgE on mast cell (Degranulation) → Histamine Production / PG or Leukotraines → bronchospasm → ↑ secretions → ∴ asthma

but

In Virusis → activation TH_1 and immune cells in lung → IL-4 in lung → ↑inflammation and mucus secretion in lung and ↑damage of epithelial cells in lng.

↳ secretes when virus attack

2. Intrinsic triggers:

• Physical activity:

Physical activity → ↑ contraction of muscles → ↑O_2-demand → ↑ H_0R_0 → ↑ Cardiac Output → hyperventelation (to accelerate Pulmonary circulation) → no humidification and warming of air → ~~contraction~~ Stimulate mast cell → mediators → bronchospasm

• Cold air:

Cold air → body can't adaptation for temp. → hyperresponsiveness → ∴ asthma.

" physical ~~was~~ activity "

• Stress:

Stress → ↑ parasympathetic innervation in lung → ↑Ach → ↑contraction → ↑secretion → obstruction in airway.

• DRUGS:

NSAIDs → most common drugs cause asthma

In normals

Phospholipase A2 → arachidonic acid → LOX → Leukotriens (main mediator of asthma)
→ COX → prostaglandin (PG)

NSAIDs:

NSAIDs → inhibition of Cox enzyme → ↑↑↑ activation of LOX enzyme → ↑↑↑↑ Leukotriens → more secretions, ↑bronchospasm, ↑inflammation → initiation of asthmatic attack

but Cortecosteroids:

(Drug of choice for asthma)

Cortecosteroid → inhibition Phospholipase A2 → inhibition of LOX and COX (No Cox/Lox) → NO Leukotriens / PG. (↓ decreasing).

Symptoms:

- During asthmatic attack

1. Wheezing (shortness of breath with whistling) because of bronchiol obstructive & bronchospasm
2. cough
3. Tachycardia

asthma attack → shortness in respiration → ↓ Gas exchange → ↓ O_2 reach to organs → as normal reflux → ↑ cardiac output → ↑ HoR.

4. Difficulty breathing
5. Pale & wet skin
6. dyspnea
7. Chest tightness

* at night in all People:
↓ cortisone & ↑ Melatonin hormone
→ ↑ Histamine secretions.
∴ asthmatic attack increase in night.

Diagnosis:

- by symptoms
- Laboratory findings (extirinsic asthma by IgE) (blood analysis)
- Pulmonary Functions by spirometer
  ↳ measure Pulmonary Functions (VC / FVC / FEV1)
- Airway responsiveness: histamine / cholinergic agonist / cold air

3 Chronic Obstructive Pulmonary Disease (COPD)

- It is a progressive disease, characterized by chronic & recurrent obstruction, may be reversible of air flow in the lungs.
  ↳ if mild

main characteristic symptom: Progressive (mild then Severe)

* Reversible → in mild case
* Irreversible → in more Progressive cases.

Causes:

- environmental (Smoking)
- Chronic infection
- Genetic

* COPD: defficiency in Protein (enzyme) α_1 antitrypsin

Consequences: (of causes)

1. Chronic inflammation → Fibrosis
2. Hypertrophy of submucusal layer in lung → ↑ mucus secretion (hypersecretion) → obstruction
   ↳ responsible of mucus secretion
3. Loss of lung elasticity
   - elastin Protein → responsible of elasticity
   - elastase → break elastin
   - α_1-antitrypsin → break Protein elastase (antiprotease) (antielastase)

Types of COPD:

1. Emphysema
2. Chronic obstructive bronchitis (chronic inflammation)

1 Chronic obstructive bronchitis:

Obstruction in air way due to hypersecretion and fibrosis (chronic inflammation) of the bronchiolar wall which associated with chronic irritation from smoking & recurrent infections. (Environmental factors)

2 Emphysema: "انتفاخ الرئة"

Hepatitis الالتهاب + الكبد

Loss of elasticity and abnormal enlargement of the air spaces with destruction of the alveolar walls & capillary beds.
↳ because of ↑ trapped air (residual air)

elastin → ↓ folding → ↓ surface area
↳ ↓ contractility → ↑ trapped air → ↑ size → accumulation of air → emphysema

Types of emphysema:

- Centriacinar emphysema → damage in bronchiol, normal alveoli, from smoking
- Panacinar emphysema → damage in bronchiol & alveoli, start in alveoli then bronchiol
  ↳ because of defficiacy of α_1-antitrypsin
  ↳ loss of elasticity

Causing:

- Smoking
- α_1-antitrypsin defficiency

Pathogenesis:

• acute inflammation → innate immune response (neutrophil, macrophage in alveoli)

Smoking (Nicotin & Free radicals) → mild inflammation → immune cells (neutrophil) → Cytokines
& macrophage → elastase and metallo proteinases ↳ elastase

in normal:
α_1-antitrypsin → break elastase

Chronic inflammation → ↑↑↑ immune cells → ↑↑ elastase → degradation of elastin → No sufficient amount of α_1-antitrypsin → damage in tissue (alveoli) → loss of elasticity due to accumulation of elastase.

due to Free radicals / genetic problem

∴ Smoking → ↑ elastase
↳ ↓ α_1-antitrypsin efficiency

Symptoms:

- Cough → emphysima: low degree
  → Chronic bronchitis: cough due to hardness of bronchial & accumulation of mucus
  → Irritation → cough reflux (Productive cough)

- Shortness of breath → Characteristic to Chronic bronchitis: accumulation of mucous in bronchoil → narrowing → Shortness
  → emphysema: No Shortness bc no bronchospasm

- dysprea → Chronic bronchitis
- tachypenea → emphysema
- Recurrent Infection → because of acc. of mucous

± Pink Puffer → emphysema
because of tachypenea

- blue bloater → Chronic bronchitis
because of cyanosis (shortness of breath → $\downarrow O_2$, $\uparrow CO_2$)

- Wheezing
- Barrel chest
- Respiratory failure (diaphragm fatigue)

Diagnosis:

- Pulmonary function: by spirometer

TLC, VC, FVC, FEV_1, FEV_1/FVC
↳ Total lung capacity

COPD patients have ↑ TLC & ↓ in other values.
because of decreasing expiration

- Chest Radiology
- Hemoglobin Saturation % ~~arterial~~ arterial blood gases.
($\downarrow O_2$, $\uparrow CO_2$, oversaturation of Hemoglobin)

4 Cystic Fibrosis:

- It is a genetic disorder Can affect the exocrine glands (lungs, Pancreas, Liver, GIT, sweat glands) (mutation in specific gene)
- Most common symptoms is problems in Respiratory
- Change in compisition of the secretion is happened (become more sticky)

+ in normal:

Removing of mucus by cilliary hemolytic mechanism / mucocilliary mechanism.
(The excess amount of mucus).

[+ If sticky mucus → body Can't remove it → accumulation → :- obstruction.]

• in Lung:

- Lung has mucus (in alveoli) for lining internal surface of cells (epithelial cells).
- Epithelial cells covered with mucus For:

① Protection (Prevent direct contact blw dry air & epithelial cells)
② Humidification of air.

NOTE// Mucus (Mucin Protein) is very suitable medium for bacterial infection.
- In mucus composition: there is an antibacterial activity (antiseptic) by Nacl.

+ In cystic fibrosis:

Change in mucus composition → more sticky due to genetic problem → accumulation of mucus → :- obstruction Lung disease.

Cause:

Mutation in DNA (chromosome 7) : in CFTR gene / chloride channel / chloride transport
(as function)

Cystic Fibrosis Transmembrane regulator

regulation Cl^- movement

Pathogenesis:

- In all exocrine glands

in Lung:

Normal condition:

Submucusal cells → secrete mucus

Nacl → For prevent mucus from infection

CFTR → Control movement of Nacl from interstitial fluid → mucus.

Water → Control (maintain) the consistency of mucus by follow Na^+

∴ No infection because of Nacl & No sticky because of H_2O.

Abnormal condition:

Mutation in CFTR

Normal secretion of mucus from submucusal

but

- No Cl^- movement to mucus & No Na^+

∴ No Nacl → Suitable medium for bacterial infection → ∴ infection.

- No H_2O movement to mucus & water withdrawing From mucus to → Circulation due to hyperosmolar conc. of Nacl

∴ Sticky mucus → accumulation → obstruction.

- Infection → immune system → neutrophil & macrophage → Secrete elastase → degradation of elastin → loss of elasticity → as consequence COPD & emphysema

Symptoms:

- Chronic respiratory problems.
- Weight loss & poor growth:

Because of Pancreatic abnormal function (exocrine gland) → No normal absorption of food.

trypsinogen → trypsin → Protein metabolism

- GIT Problems (cramping and diarrhea):

especially ⊃ fatty foods:

No bile → No emulsification of fats → No absorption → cramping & diarrhea.

- Hyperglycemia (↑ of glucose in blood):

Cystic Fibrosis → obstruction of Pancreatic chanels → normal synthesis of insulin but ↓ in insulin secretion amount → hyperglycemia.

- Salty-tasting skin:

↑ conc. of Nacl

Sweating in normal condition:

- Sweat move from ductal lumen → skin surface.
- Sweat composition is water & minerals, the body reabsorbed some minerals in sweating as Na^+, Cl^-.

-In lumen, there is Na-k-cl co-transporter → moving Na^+, k^+, Cl^- from interstitial fluid to lumen → Sweat → on skin, then, reabsorbed Na^+ & Cl^- back to interstitial fluid (circulation) by Na transporter & Cl-transporter (CFTR)

∴ reabsorbed Cl^- from sweat to interstitial fluid (circulation)

In cystic fibrosis:

Co-transporter → movenat of Cl-Na-k from interstitial fluid to sweat → genetic Problem in CFTR (cl-transporter) → No reabsorbed of Cl^- → ∴ No movenet of Na^+ → ∴ excretion of Nacl with sweat → accumulation on skin → ∴ Salty skin

Diagnosis:

for newborn bc. it's a genetic disease:

- DNA test:

analysis for chromosome 7 especially for CFTR gene.

- Carrier screening:

analysis of DNA in fetus if pregnant woman has CF.

- Immuno Reactive Trypsinogen (IRT):

Trypsinogen → precursor for many enzymes which secrete by Pancrease

∴ in normal condition, trypsinogen conc. is low (due to consuming it)

in CF: obstruction in Pancreas → ↓ synthesis of Pancrease enzymes → ∴ accumulation of trypsinogen

- Sweat chloride test:

Cholinergic agonist (pilocarpine) on baby skin → ↑ of sweat secretion → measure the % of Cl^-

Treatment:

No treatment for it bc. it's a genetic problem, but to delay its progression:

- Antibiotics
- Chest physical therapy which include chest Percussion & Postural drainage.
- Mucolytic agents
- Nutritional therapy including Pancreatic (or GIT) enzyme replacement

Ch.3 : Endocrine disease

1 Thyroid gland disorders :

* Thyroid gland: Butterfly-shaped organ located in the neck.

main function: Synthesis & secretion of Thyroid hormones → Thyroxine (T_4) → 90% of Thyroid hormone
↳ Triiodothyronine (T_3) → 10%

* ~~Pituitary~~
* Hypothalamus Pituitary axis control the endocrine system.
  ↳ Posterior Pituitary gland
  ↳ Anterior Pituitary gland → control most of hormons (as Thyroid hormons)

How hypothalamus control hormones? (Thyroid)
by
Hypothalamus - Anterior Pituitary axis :

Stimulus (cold or stress) → activation hypothalamus → secretion TRH (Thyrotropin-releasing hormone)
→ work on anterior pituitary gland → secretion TSH (Thyroid-stimulating hormone) → work
directly on thyroid gland → activation thyroid cells → secretion thyroid hormones T_3 & T_4 →
Circulation → most of thyroid hormones bound with plasma proteins (99%) (1% free)
Responsible for physiological function & Negative feedback

* 3 plasma proteins are responsible for interaction ω thyroid hormones:
1- Thyroid binding globulin
2- Albumin
3- Transthyretin

* Negative feedback:
The body inhibit the main source (main organ) which stimulate the glands
↳ hypothalamus
↳ Pituitary gland axis
when increasing the concentration of the hormones.

* ↑ T_3 & T_4 → inhibition hypothalamus → inhibition TRH
↳ inhibition Pituitary gland (anterior) → inhibition TSH
→ inactivation thyroid gland → ↓ T_3 & T_4 secretion.

Physiological effects of thyroid hormones:

1- Metabolism:

(↑ catabolism)

- ↑ glucose absorption from gut
- ↑ gluconeogenesis
- ↑ lipolysis
- ↑ Proteolysis

2- Cardiovascular system:

- T_3 ↑ cardiac output
- T_3 ↑ chronotropic (heart rate) & inotropic (contractility of the cardiac muscle)
- T_3 ↓ vascular resistance. (by vasodilation effect)

3- Sympathetic Nervous System:

- ↑ synthesis of β-adrenergic receptors in cardiac & skeletal muscles & adipocytes (heterologous up regulation).

+ Thyroid disorders:

classified into: 1- Hypothyrodism → ↓ in function of thyroid gland → ↓ synthesis & secretion of thyroid hormones

2- Hyperthyrodism → ↑ in function of thyroid gland → ↑ synthesis & secretion of thyroid hormones

* Goiter:

"Symptom associated with thyroid disorders"

is an increase in the size of the thyroid gland which can occur in hypothyroid & hyperthyroid state.

[1] Hypothyrodism:

is an inability of thyroid gland to produce enough thyroid hormones (insufficient)

Causes:

1- Congenital defect:

(certinism → nonfunctional thyroid gland in children due to congenital problem)
↳ impaired physical & mental development

2- Acquired defect:

↓ in thyroid hormones due to (x) factor

- Primary
- secondary
- tertiary

1- Primary hypothyroidism. 2- Acquired hypothyroidism

Primary hypothyroidism

- Defect in Thyroid gland itself due to:
- Damage in thyroid gland due to infection / radiation /.. etc
- Surgical removal of thyroid gland (Thyroidectomy)
- Chronic use of antithyroid drugs w large doses.
- Iodine deficiency
  ↳ Precourser for synthesis of thyroid hormones.
- Excess amount of Iodine:
  Thyroid gland can't deal w large amount of iodine → hypothyroidism.

Secondary hypothyroidism

- Defect damage in anterior Pituitary gland
∴ No secretion of TSH
∴ No synthesis of Thyroid hormones.

Tertiary hypothyroidism

- Defect in hypothalamus
∴ No TRH
∴ No activation of anterior Pituitary gland (No TSH)
∴ No synthesis of thyroid hormones.

3- Autoimmune Disease : Hashimoto's thyroditis.

Body synthesis antibodies against thyroid cells → No production of thyroid hormones

Pathogenesis of Hashimoto's thyroiditis :

- immune system work against some proteins which are expressed on the surface of the thyroid epithelial cells → activation of innate immune cells (APCs) → activation adaptive immune cells (CD_4)
→ TH_0 → TH_1 major Pathway → IL-2 → activation CD_8 (naive CD_8) → cytotoxic CD_8 T-cell →
Perforin & granzyme → apoptosis of thyroid epithelial cells (degradation)
(T-cell-mediated cytotoxicity)

minor Pathway → IFN-γ → activation monocytes macrophage → macrophage → phagocytosis of thyroid epithelial cells (degradation)
(Thyrocyte injury)

→ IFN-γ → activation B cells → plasma B cell → IgG → binds with proteins on thyroid epithelial cells and CD_{16} on Nk cell → activation of Nk cell → Perforin & granzymes → apoptosis of thyroid epithelial cells.
(Antibody-dependent cell-mediated cytotoxicity (ADCC)).

Symptoms:

hypothyroidism → ↓ catabolism
↳ ↓ CVS functions

1. Unexplained weight gain
. accumulation of carbohydrate & lipids.
2. Constant fatigue & Tiredness
No utilization of glucose → No energy
3. Muscle Soreness & pain (spasm)
4. Cold intolerance (No energy)
5. Hair loss / Hair dryness (Poor nutrition)
6. Yellow skin (Poor nutrition)
7. Puffy face (accumulation of lipids in face)
8. Horse voice (goiter → Pressing on vocal cords)
9. Bradycardia (Negative chronotropic)
10. Dry & Flaky skin (Bad (Poor) nutrition)
11. ↑ cholesterol level (No degradation of cholesterol)
12. Poor conc. & memory
13. Myxedema "Characteristic symptom"
(glycosaminoglycans deposition)
due to accumulation of glycosaminoglycan under the tissues.
14. EDema (Fluids accumulation)
Bradycardia → ↓ cardiac output → ↓ Blood flow to the kidney → ↑ secretion of Renin → activation of RAAS system → angiotensin → aldosteron → Na^+/H_2O Retention → :. EDEMA.

Diagnosis:

- Symptoms
- Blood analysis (measure the level of Thyroid hormones (T_3 & T_4), TSH)

Treatment:

T_3 / T_4 replacement therapy.

[2] Hyperthyrodism: (Thyrotoxicosis)

It is a condition characterized by excessive production & secretion of thyroid hormones.

Thyrotoxicosis → Severe case of hyperthyrodism.

Causes:

- Tertiary hyperthyroidism → Defect in hypothalamus → ↑ TRH → ↑ TSH → ∴ ↑ Thyroid hormone
- Secondary hyperthyroidism → Defect in anterior pituitary gland → ↑ TSH → ↑ T_3/T_4
  (↓ TRH because of Negative feedback)
- Primary hyperthyroidism → Defect in Thyroid gland → ↑ T_3/T_4 due to:
  (↓ TRH / ↓ TSH because of Negative feedback)

1. Thyroiditis (acute):

- inflammation in thyroid gland (acute inflammation)
  - because after synthesis of thyroid hormones, they storage in vesicles and gradually secrete to the body, so in acute inflammation, irritation & activation of these vesicles is happened and overproduction of thyroid hormones happened.
- if chronic → hyperthyroidism.
  ↓
  due to continous damage.

2. Thyroid adenoma:

[adenoma / adenocarcinoma]
- adenoma → benign cancer
- adenocarcinoma → malignant cancer

- adenoma → increasing in size of the gland.

∴ increasing in size of thyroid gland (benign cancer) → abnormal cell division → ↑ cells → ↑ synthesis & secretion of thyroid hormones → ∴ hyperthyroidisim.

3. Iodine Containing agents:

↑ Iodine consumption → ↑ Iodine → ↑ synthesis of thyroid hormone.
(high iodine consumption after this lead to hypothyroidism (discussed before).

4. Grave's disease:

Pathogenesis of grave's disease:

immune system recognize TSH receptor as foreign substances → innate immune cells → APCs activate CD_4 → TH_0 → TH_1 (minor Pathway) → IFN-γ → activate B cells → Plasma B cell → secrete IgG → bind on TSH receptor on thyroid cells → activation receptor → activation Thyroid cell → secretion thyroid hormones → ∴ hyperthyroidisim.

also this Pathogenesis for characteristic symptom in grave's disease:

Exophthalmos → bulging or protruding eyeballs (abnormal contraction of eyes)

- Orbital muscles in eye have TSH-receptors:

Grave's disease → IgG antibodies → binds on TSH receptors on orbital muscles and stimulate

Orbital fibroblast → activation fibroblast → formation ECM (collagen, --- glycosaminoglycan) →

Fibrosis → ∴ hardness in muscles → ∴ Exophthalmos

Symptoms:

opposite to hypothyroidism

- Heat intolerance

↑↑ catabolism → ↑↑ ATP

- Sweating
- Enlarged thyroid
- Rapid /irregular heart beat / Palpitation
- weigh loss
- Increased sensitivity to heat
- Increased in appetite
- Hand tumors
- Difficulty in sleeping
- Thining of the skin
- Irregular menstrual cycle
- fine & brittle hair
- fatigue & muscle weakness
- Diarrhea
- Nervousness anxiety & irritability
- Protruding eyes.

Diagnosis:

- Blood analysis (measure of T_3 / T_4)

Treatment:

- Surgical removal of thyroid gland (Thyroidectomy)
- β- adrenergic blocking agents
- Antithyroid drugs (propylthiouracil and methimazole) → ↓ Synthesis of thyroid hormones
- Eradication (irradiation) of thyroid gland ω radioactive iodine

* Thyroid Storm (crisis):-

- Severe case of thyrotoxicosis.
- excess amounts of T_3 / T_4

Causes:

- non-adherent patient of hyperthiroidism.
- ↑ iodine consumption by hyperthiroidism patient
- take aspirin by hyperthyroidism patient

hyperthyroidism → ↑ percentage of free thyroid hormones

- Aspirin → binds ω proteins in circulation (high affinity to plasma proteins than thyroid hormones) → displacement for thyroid hormones → ↑ conc. of free thyroid hormone

→ crisis (in hyperthyroidism patient).

2 Adrenal gland (cortex) disorders:

+ Adrenal glands:
Small structures found at the apex of each kidney divided into 2 parts:
- medulla: inside tissue of the gland (20% of the gland), secrete adrenaline.
- Cortex: The external layer (80% of gland), secrete 3 groups of hormones: glucocorticoid (glucocorticosteroids) (cortisol), mineralocorticoids (aldosterone), adrenal androgens (dehydroepiandrosterone).

Cortisol & aldosterone:
- Synthesis by cortex of adrenal gland → Secretion to circulation → binds with proteins:
  Cortisol → binds ω globulin
  aldosterone → binds ω albumin

What control the adrenal cortex? Hypothalamus - Anterior Pituitary axis
How?!

- 1 Cortisol:
- when body need cortisol → Stimulus (stress, infection, Pain, Hypoglycemia, sleep, Hemorrhage, trauma,...)
→ Stimulate hypothalamus → Secrete CRH (Corticotropin - releasing hormone) → Stimulate anterior Pituitary gland → secrete ACTH (adrenocorticotropic hormone) → circulation → binds ω receptor on adrenal cortex → synthesis cortisol from Cholestrol → storage → Secrete to circulation.
- when sufficient amount is reached:
Negative feed back by inhibition hypothalamus & pituitary gland → No secretion of CRH / ACTH

2 Aldosterone:
By kidney (RAAS (Renin-angiotensin-aldosterone system))
any ↓ in cardiac output → ↓ in Renal Perfusion
So: ↓ in B.P, ↓ in blood volume → Renin release from kidney → work on angiotensinogen protein (inactive) → convert to angiotensin 1 (active) (intermediate) → ACE (angiotensin-converting enzyme) release from lung and convert angiotensin 1 to angiotensin 2 in kidney → Stimulate the adrenal Cortex → secrete the aldosterone → Na^+/H_2O Retention (in kidney, especially collecting duct) →
∴ ↑ cardiac output.

Physiological effects of cortisol (Functions):

* Under the homeostasis *

↑ synthesis of cortisol:

1- Skeletal muscle mass atrophy (↓ size) → ↓ mass of the cell → by catabolism of protein in the cell
& by ↓ anabolism of new protein synthesis
∴ Atrophy

2- ↑ cortisol → hyperglycemia:

● in muscles:

① ↓ glucose uptake by muscles → ↑ glucose conc. in circulation → hyperglycemia.

② ↓ glycogen synthesis (due to excess glucose) → ∴ ↑ conc. of glucose in circulation → hyperglycemia

in adipose tissue:

③ ↑ lipolysis → ↑ degradation of TG_s to free fatty acids → fat redistribution/mobilisation → ∴ accumulation of fatty acids in face, neck, abdomen (moon face)

④ ↓ insulin sensitivity (↑ insulin resistance) → body secrete sufficient amount of insulin but No sufficient interaction between insulin & receptors → ∴ hyperglycemia

in Liver:

⑤ ↑ Glycogenolysis → ↑ break glycogen in Live to glucose → ↑ glucose → hyperglycemia.

⑥ ↓ Glycogenosynthesis → hyperglycemia

in GIT:

⑦ ↓ Incretin Secretion
↳ control GIT motility by control GER:
↑ motility (contractility) → ↓ GER → sufficient time for digestion → avoid excess absorption → avoid constipation (neither constipation nor diarrhea).

∴ ↑ cortisol → ↓ Incretin Secretion → ↑ GER → ↓ motility → ↑ absorption → ↑ conc. of glucose in blood → hyperglycemia

in Pancrease: due to

⑧ ↓ β-cells Function ← ↓ Incretin
↳ important for normal Secretion of insulin

↑ Cortisol → ↓ Incretin → ↓ insulin → hyperglycemia

in bone:

⑨ ↓ Osteocalcin
↳ hormone secrete by osteoblast → take Ca^{+2} → bone → ↑ bone density (strength).

↑ Cortisol → ↓ osteocalcin → Osteoprosis
↳ reflux of Ca^{+2} from bone to blood.

NoTE// Steroid diabetes → hyperglycemia due to increasing in cortisol level

[1] Adrenocortical insufficiency:
Decreasing in production & secretion of the adrenal cortex hormones (commonly: glucocortecosteroids, mineralocorticosteroids)

Hypocortisolism → ↓ in cortisol

3 types:

[1] Tertiary adrenocortical insufficiency:
Defect in hypothalamus → ↓ CRH → ↓ ACTH → ↓ Adrenal Steroids

Primary & tertiary ... aldosterone

[2] Secondary adrenocortical insufficiency:
Defect in anterior Pituitary gland → ↓ ACTH → ↓ Adrenal Steroids
↑ CRH due to Negative feedback (continous stimulus to pituitary gland)

[3] Primary adrenocortical insufficiency:
Defect in adrenal cortex → ↓ adrenal steroids, due to:
↑ CRH, ↑ ACTH as Negative feedback
- Infection (viral, bacterial, fungal)
- use of some drugs like "ketoconazole"
  → antifungal → as systemic → ↓ synthesis of cortisol
- Hematochromatosis
  → metabolic disease → accumulation of iron → Ppt. of iron on adrenal cortex → damage.
- Autoimmune disease (Addison's disease)

Pathogenesis of Addison's disease:
- immune system recognize 21-hydroxylase enzyme in adrenocortical cells as foreign substances →
  → Play imp. role in synthesis of glucocorticoid & mineralocorticoid.
engulfment by APCs → express antigen on HMC-II → activation CD_4 → TH_0 → TH_1 →
two pathway major → IL-2 → activate Naive CD_8 → cytotoxic CD_8 → Perfoin & granzyme →
degradation of all adrenocortical cells contain 21-hydroxylase enzyme.
minor → IFN-γ → macrophage → Phagocytosis adrenocortical cells
→ activate B cells → plasma B cells → Secrete IgG
→ opsonization for adrenocortical cells
→ activation NK cells → distruction adreno... cells by ADCC mechanism.

Symptoms:

especially in primary:

• ↓ aldosterone:

- hyponatremia due to ↑ Na^+ secretion
- hypovolemia (↓ Na^+ → ↓ H_2O (↑ H_2O secretion)
  ↳ ↓ Blood volume
- ∴ Hypotension
- Hyperkalemia due to ↑ Na^+ output → ↑ K^+ input → ↑ K^+ conc.

• ↓ cortisol:

- hypoglycemia
- diarrhea
- abdominal pain → ↑ incretin
- Hyperpigmentation (Parsonage color) due to ↑ ACTH → binds to melanocyte cells → ↑↑ melanin
  ↳ as structure, it looks like melanin releasing hormone.
- Vitilligo (Characteristic symptom for addison's disease).

addison → autoimmune response against melanocyte cells → ↓ melanin → vatilligo

* adrenal crisis:

Severe case of addison's disease include:

- fever
- hypoglycemia
- Hypovolemia
- Convulsions
- Hyponatremia
- Severe vomiting & diarrhea.

Diagnosis:

- Symptoms
- Blood levels of cortisol, aldosterone, ACTH

Primary → ↑ CRH, ↑ ACTH, ↓ adrenal steroids

Secondary → ↑ CRH, ↓ ACTH, ↓ adrenal steroids

Tertiary → ↓ CRH, ↓ ACTH, ↓ adrenal steroids

- Stimulation Test

To differentiate blw Primary, Secondary or tertiary, injection of ACTH then management of cortisol level in blood before and after injection.

Treatment:

Hormones replacement Therapy.

[2] Cushing syndrome: (Hypercortisolism)

It is a condition caused by either excessive production of cortisol by the adrenal glands or excessive cortisol-like medication.

NOTE// Patient who using cortisone (cortisol-like drugs) shouldn't stop taking it suddenly (sudden withdrawing), They must stop it gradually to avoid hypocortisolism.

Causes:

1- Cushing's disease:

↑ conc. of cortisol in circulation due to: Defect in anterior pituitary gland or Hypothalamus → ↑ ACTH → ↑ Cortisol.

2- Adrenal form cushing: (Primary)

Defect in adrenal cortex → ↑ Cortisol

3- Ectopic Cushing syndrome:

↑ cortisol conc due to: ↑ ACTH (non-pituitary gland ACTH)

ex// Tumor in Lung → ↑ ACTH (stimulate ACTH secretion).

4- Iatrogenic Cushing's syndrome:

long-term using of Cortisol-like drugs → ↑ Cortisol-like drugs conc.

Symptoms:

- Redistribution of fat especially in face, neck & abdomen → ↑ in body weigh (visceral obesity) → moon face, Buffalo hump (↑ fat in neck).
- High blood pressure: ↑ Cortisol → ↑ aldosterone → ↑ Na^+/H_2O retention
- More susceptibility to infection:

↑ Cortisol → ↓ immune response → immune suppresent.

- High Risk for bone facilitates & osteoprosis:

↑ Cortisol → ↓ osteocalcin → migration of Ca^{+2} from bone to circulation → weakness in bones.

- Muscle Aches & Pain:

↑ cortisol → ↓ utilization of glucose in the muscles.

- Hypoglycemia
- Peptic ulcer:

↑ Cortisol → inhibition of Phospholipase A_2 → ↓ Arachidonic acid → ↓ COX → ↓ Prostaglandin → ulcer

- Imbalance in sex hormone ⁂ irregular period, overgrowth of hair, bad mood.

↑ Cortisol → ↑ activation of cortex → ↑ androgen hormones.

- Purple Straie (stretch marker):
  → in membranes of blood vessels.

↑ Protein catabolism due to ↑ cortisol → Skin become very thin → Vasodilation in Cappillaries & blood vessels. ⁂ more elasticity.

- Hyperpigmentation (Just in Cushing's disease & ectopic Cushing's syndrome).

Diagnosis:

- Symptoms
- Blood levels of Cortisol & ACTH
- Suppression test: measure ACTH then injection ω
  High dose of dexamethasone (synthetic corticosteroid drugs)
  after 1-2 hours, measure ACTH again:
  if The same → ∴ adrenal form Cushing's syndrome or ectopic Cushing syndrome.
  if decrease → ∴ Cushing's disease

  [∴ suppression test using for detect the type of Cushing's syndrome].

Treatment:

- Surgery
- Radiation
- Drug inhibit Cortisol Synthesis.

Ch.4: Kidney Disease:

Inflammatory Disorders:

1 Glomerulonephritis (Nephritic Syndrome):

* Inflammatory diseases:

- Inflammation Process inside the kidney.
- Inflammatory response against the kidney structure especially **glomerulus.**

The most organ affected by the ↵ inflammation (either cells or blood vessels inside it).

* Glomerulonephritis:

- It is an inflammation process that involves glomerular structures
- Inflammatory affect the cortex, cells & blood vessels.

II Causes:

- Immunological: Type II & Type III hypersensitivity reactions // Infection
- Non-immunological: Hypertension (HTN), DM (diapetic nephropathy), toxic sub., Chemical

- If the primary cause of the Nephritic Syndrome is a direct immune response → ∴ Immunological cause.
- If the Primary cause of the disease is <u>not</u> direct immune response →. but this primary cause <u>initiation</u> of the inflammation in the glomerulus → ∴ Non-immunological cause.

III Immunological Causes:

Type II:

Goodpasture Syndrome → body synthesis antibodies against specific proteins in glomerulus (basement membrane)

* Body synthesis antibodies (IgG) → circulation as free antibodies → to basement membrane → bind to specific proteins → antigen-antibody interaction → activation Complenat proteins (C_3 / C_5) → ~~activation~~ conversion to C_{3a} / C_{5a} → Inflammation process

Type III :

Body synthesis antibodies against x ~~protein~~ Protein in circulation /either tissues/... (IgG) → interaction b/w antibody & antiga (Protein) but not in basement membrane → formation of complex → precipitation in some tissues such as: basement membrane of glomerulus → activation CP (C_3 / C_5) → C_{3a} / C_{5a} → inflammation process.

The difference b/w Type II & Type III

Type II → Antibodies as a free antibodies in circulation and antigen in basement membrane of glomerulus.

Type III → antibodies as antibody-antigen complex

Infection : (main cause of immunological cause)

- Bacterial infection (β- hemolytic streptococcus), major in children 3-7 years.

* Acute poststreptococcal glomerulonephritis (APSGN): is a nephrotic syndrome due to β-hemolytic Streptococcus.

Pathogenesis of APSGN :

Bacterial infection (streptococcal infection) → recognition by innate immune system → adaptive immune → activate B cells → plasma B cell → formation of specific antibodies against bacterial antigens (Streptolysin O, Streptokinase) & antibodies are ASO (anti-Streptolysin O), ASK (Antistreptokinase) → secretion of antibodies to circulation → interaction b/w antigen & antibody → formation of complex (similar to Type III) → precipitation of complex in glomerulas → activation Complenat system (C_3/C_5) → C_{3a} / C_{5a} → Inflammation Process by Chemotaxis of immune cells → Cytokines → inflammation (acute inflammation)

•acute inflammation has characteristic symptoms:

- ↑ Permeability due to histamine & other mediators

↑ Permeability of kidney (gof glomerulas) → ↑ secretion of proteins & RBCs → ∴ Hematuria
↑blood in urine

& albuminuria
↳ ↑ of albumin in urine

-↓Swelling & Thickness of glomerulas → ↓ of efficiacy of Filtration mechanism → ↓ GFR
congestion

(glomerulus Filtration Rate) → ↓ urine formation & secretion → Oliguria → ↑ in serum urea
↳determine urine output ↳↓ in Urine Output

-due to ↓ in urine output → Stimulation of RAAS → ↑ Renin secretion → angiotensinogen
→ angiotensin I → angiotensin 2 → aldosteron secretion → Na/H_2O
retention → ↑ blood volume → ↑ cardiac output.

• Most of APSGN cases are full recovery after disappear of causative agent (B-hemolytic S.C)
and some others: → acute Renal failure due to:
- Damage of the membrane
- Dysfunction of the kidney
the Recovery / Chronic inflammation → Fibrosis → Chronic Renal failure.

Symptoms of APSGN:

↳ Symptoms related to kidney:
- Porteinuria & Hematuria due to ↑ permeability → - - -
- Oliguria : thikness of glomerulus membrane (basement membrane) → ↓ GFR → ↓ urine output
- Dysuia (Difficult in urination)
- Dark color urine (RBCs & Protiens)

↳ Symptoms related to inflammation:
- Fever
- Headache
- Edema :

Start in Face (under the eyes) → Facial & Periorbital edema → then general edema → weight gain.
- ↑ B.P & Tachycardia due to RAAS.

Diagnosis:

-Blood test:
• Characteristic antibodies (ASO(ASK) & AntiDNAse B.
• Determenation of serum urea (↑ in serum urea level) & ↑Creatinine (main Parameter which detemine kidney funtion)
• Metabolic acidosis (↑ bicarbonate) → ↓ PH.

② Nephrotic Syndrome: (Nephrosis)

- It is a kidney disorder characterized by high protein (inflammatory) in the urine, low blood albumin levels (hypoalbuminemia), lipiduria, high blood lipids (hyperlipidemia), Significant swelling (massive edema)

- Nephrosis is Secondary Outcome to other disease:
- Renal disease: glomerulonephritis (acute)
- Other disease: HTN / DM / SLE / Some drugs.

* Differences blw Nephrotic & Nephritic is:

- Quality of protein urea:

  > 3.5 g/day → ∴ Nephrotic Syndrome

  < 3.5 g/day → ∴ Nephritic Syndrome.

- The hypoalbuminemia (for Nephrotic)
- Lipid urea (in Nephrotic) due to Severe damage in the kidney → very high permeability
- ↑ lipid in blood (Nephrotic)
- Significant swelling due to massive edema (Nephrotic)

Pathogenesis:

- any cause causing Severe damage in glomerulus → Loss of basement membrane functions →
∴ ↑ Permeability → more loss of Proteins, lipids & electrolytes → Hypoproteinemia (Hypoalbuminemia) →
  - ↓ Osmotic Pressure → move of Fluids from blood to tissues → massive edema
  - activation of liver:

loss of albumin (↳ Synthesis by liver) → as compensatory mechanism → activation of the liver to synthesis Protein → Synthesis of high amount of VLDL → LDL in Circulation → ∴ hyperlipidemia. (↳ main terminal lipoprotein)

Symptoms:

- Proteinuria
- Hypoalbuminemia
- lipid urea
- ↑ TGs & cholesterol in blood
- Anasarca (massive & excessive of edema)
- RAAS symptoms
(Tachycardia, HTN ↑ cardiac output).

Urinary tract Obstruction:

Obstruction in urinary tract (kidney, nephron, bladder, ---)
- ↓ or slowing in urine flow (decreasing in urine Output)
- No problem in urine formation (kidney is functional) but

due to x factor, → Narowing in passage/flow of urine → ↓ Urine Output
∴ obstruction in urinary tract.

Causes:

1. Renal stones → more common → inside the kidney
   ↳ Ureter
   ↳ bladder
2. Benign prostatic hyperplasia.

Renal stone / kidney stone / Renal calculi / Urolithiasis
↳ Formation of Stone in any part of urinary tract.

Stone components:
electrolytes (Ca^{+2} / phosphorous / oxalate / carbonate)
- other components

General causes of kidney stones:
- ↑ conc. of electrolytes in Urinary tract / in filtrate (hyper conc. of electrolytes) → Concentrated urine → injury in epithelial layer.
- ↓ intake of fluids (water)

Types of Renal stones:
1. Calcium salts stones (oxalate / carbonate / Phosphate) → 75% of total stones
2. Uric acid stones
3. Cystine stones (amino acid)
4. Struvite stones (ammonium / magnesium / phosphorus / phosphate)

1. Ca^{+2} salt stones:

Causes:
① hypercalcimia → ↑ Ca^{+2} conc. in blood → kidney → Filtration
- [redacted]
in normal:
filtration → reabsorption of body need From Ca^{+2} → excretion of excessive amount.

- ↓ water intake

② Alkaline PH → No converting to oxalic acid / Phosphoric acid / Carbonic acid which are important to elimination of the electrolyte

∴ Ppt of oxalate / phosphate / carbonate (No elimination) → insoluble Ca^{+2} salts (binds $\bar{w}$ Ca^{+2})

③ Vegetinan people (special for Ca oxalate)

vegetable contain high amount of oxalate → ↑ oxalate conc. → ↑ oxalate in filtration → oxalate + Ca^{+2} → ppt.

④ Infection → ↑ PH value → alkaline urine → →

⑤ Hyperparathyroidism → ↑ in Parathyroidism hormones (The most is Calcium phosphate stone)

↳ homones make balance of Ca^{+2} conc. in blood by ↑ absorption of Ca^{+2} from small intestine to blood & kidney & Reabsorption of Ca^{+2} to blood & kidney & ↓ Phosphate absorption in kidney.

∴ ↑ Phosphate conc. & hypercalcimia → insoluble complex → ppt.

2 Uric acid Stones:

① ↑ amount of Red meat eating (gout disease)

↳ Contain high amount of purin which metabolized to uric acid.

High amount of Red meat → ↑ purin → ↑ uric acid → hyperuricemia in blood → kidney → PPt → uric acid stones.

∴ main cause is hyperuricemia.

② ↓ PH value (acidic urine)

acidic urine → No convert of uric acid to urate (salt of uric acid) and still as Uric acid → ∴ PPt.

3 Cystine stones:

↳ amino acid (Protein) in circulation

in normal:

- Shouldn't pass to filtration (insoluble amino acid)
- If pass: Cystine transporter → Circulation (back)

abnormal:

If genetic mutation in cystine transporter (rarely) → ppt of cystine (Rare condition)

4- Struvite stones:

- In vegitirian people

Contamination / infection of Sol-bacteria → metabolism of N → Convert urea to ammonia → binds ω Mg, P → ppt (stones)

- In normal conditions:

There is balance blw urinary promoters & urinary inhibitors.

all contents of stones ↵

↳ Substances inhibit the synthesis of the stones.

if imbalance → ↑ Promoters or ↓ inhibitors → Stones formation.

Inhibitors :

① Citrate:

Citrate degradation of stones & elimination of salts if Presence

∴ Prevent accumulation of Ca^{+2}.

Citrate as drug: (when small stones)

1- At First → alkaline media (↑ PH value) for uric acid Stones

2- ↑ effinity to bind ω Ca^{+2} (for Ca^{+2} stones) → Soluble Complex formation

∴ ↓ citrate → ↑ Stone formation.

② Pyrophosphorus / pyrophosphate:

Compound stimulate the binding blw 2 stones (Phosphate + phosphate) → ↓ binding of phosphate ω Ca^{+2}

∴ Pulls up phosphate from filtrate → ↓ conc. of phosphate → no binds ω Ca^{+2} → ∴ ↓ ability of Stone formation

∴ ↓ Pyrophosphate → ↑ stone formation

③ Uromodiolin:

Protein in kidney, nephron, loop of henle → reabsorption of Ca^{+2} → ↓ Ca^{+2} conc. in filtrate → ↓ stone formation.

∴ ↓ Uromodulation → ↑ stone formation.

Symptoms:

- Severe pain (renal colic)
- ↓ in urine flow (
- ↑ frequence of urination sensation:

obstruction → accumulation of urine in bladder if the stone in bladder → no complete emptying of bladder → ↑ sensation of urination.

- Incontinence (Pain in urination process & abnormal blood flow)

عسر البول

- Blood in urine due to large stones
- UTIs (Urinary tract infections) → stones → injury → infection
- Nausea & vomiting.

Vascular disorders:

"disorders in blood vessels of the kidney"

Nephrosclerosis:

Hardness of the wall of the blood vessels of the kidney (narrowing of the blood vessels)

Causes:

- Aging:

↓ function of the kidney → accumulation of epithelial cells due to damage ↑ / thickness → hardness.

- HTN:

as a chronic complication for non-adherent patients → Hypertensive nephrosclerosis.

- Diabetes:

Diabetic nephrosclerosis.

Pathogenesis of Hypertensive nephrosclerosis:

HTN → No normal perfusion to the organs → ↓ blood flow to kidney → ↓ Perfusion → Renin → angiotensin I → angiotensin II

Direct & indirect effect:

* Direct:

- Vasoconstriction → ↑ peripheral resistance → ↓ blood supply to kidney
- ↑ Na^+/H_2O retention (reabsorption) → ↑ blood volume → ↑ cardiac output → HTN

* Indirect:

- activation of sympathetic nervous system → ↑ cardiac output and resistance
- activation secretion of aldosterone → Na^+/H_2O retention

∴ ↓ blood supply to kidney (chronic decrease) → Ischemia → damage of renal tissues by Necrosis.

∵ Chronic → ∴ No repair → ∴ Fibrosis atrophy → ↓ in kidney size → Chronic renal failure.

Diagnosis:

- Blood test (creatinine & urea)
- Urine analysis
- Ultrasound of the leidney

Congenital disorders:

"defect during development of the kidney, it may be structural defects ω normal functions or structural and functional defects"

1. Vesicoureteral reflux:

Congenital disorder (structural & functional), it's a defect on the formation of the valve blw the ureter & bladder

2. Agenesis:

Congenital disorder (structural & functional), failure of one kidney to develop.

3. Hypoplasia:

Congenital disorder (structural & functional), failure of one kidney to develop the normal size.

4. Ectopic kidney:

Congenital disorder (structural), one kidney & its ureter are not located in the normal position which found in the lower part of the abdomen or in Pelvis, and its function is normal.

5. Horseshoe kidney:

Congenital disorder (structural) which connection and fusion occur blw 2 kidneys during development & the function of kidneys are normal.

6. Nephroblastoma (wilm's tumor)

It is a defect in the tumor suppression gene (wilm's tumor gene) at Chromosome 11 leading to cancer in one kidney.

Renal failure:

Inability of kidney to function sufficiently.

(The kidney is functional)

0% function → End stage of renal failure.

Types:

- acute → Rapid onset & reversible
- Chronic → Slow, gradual destruction & irreversible.

I Acute renal failure / Acute kidney disease:

Causes:

- acute inflammation → damage in nephrons → ↓ in function
  When treat the infection → recovery ∴ reversible.
- acute hypovolemia / acute ↓ in blood supply (ischemia) → RAAS → vasoconstriction → overload in kidney → damage.
  - → Heart failure → ↓ Cardiac output → ↓ Perfusion → ischemia
  - → Severe burns → acute hypovolemia (Hypovolumic Shock)
  - → Severe destructions in RBCs (hemolytic anemia) → ↑ Hemoglobin → ppt. → damage in nephrons.
    ↳ toxic for kidney
  - → Severe damage in skeletal muscles → ↑ myoglobin → ppt. → damage of nephrons.
    ↳ toxic for kidney.
- Nephrotoxins:
  (most from drugs (NSAIDs))
  overdose → accumulation in kidney → ↑ Damage → ↓ functions
- Chemical obstructions:
  Obstruction due to → blood clots, kidney stones, tumor → damage → acute renal failure.

2 Chronic renal failure:

Causes:
- Chronic inflammation
- Chronic disease (DM/HTN) for non-adherant patients.
- Chronic use of nephrotoxins
- People w tumor
- No treat of causative agent of acute renal failure.

Stages of Chronic renal failure:
- Early stage (decrease reserve)
- Second stage (renal insufficiency)
- Last stage (end stage renal disease).

* To reach End stage of chronic renal failure or not, depend on:
- Severity

↑ Severe cause ⟶ ↑ degradation.

- Exposure time of causative agent

↑ Exposure time ⟶ ↑ damage.

1 Early stage: (around normal function)
- Damage of 60% of the kidney

Other 40% adaptation ⟶ ↑ capacity of filtration to compensate the loss

∴ Functional kidney (80%)

+ What determines kidney functions?

Parametes: - Creatinine (most imp.)

normal: 1 – 1.2 (< 1.5)

renal dysfunction: > 1.5

• in early stage the creatinine at maximum level of normal (1.3 → 1.5)

- Urea (metabolite of ammonia)

normal: < 30 mg/dL

• in early stage (40 → 50 mg/dL) (around the normal)

• No problems in Urination (urine process) is normal because the kidney is functional (80%)

2] Second stage (renal insufficiency)

Now there is a clear problem in kidney function
75% damage of kidney.
25% of the past 40% are functional
↳ can't adapt
- Clear decreasing in function of kidney.
- ↑ in creatinine (reach 3)
- ↑ in urea (70 → 80 mg/dL)
- electrolyte imbalance → Hyponatremia, Hypocalcemia, Hyperkalemia, hyperphosphorolemia
- Diluted urine formation:
Osmotic diuresis: ↑Ca^{+2}, ↑Na^{+2} in Filtrate, So body absorbed water from ISF (circulation)
→ water excretion w urine →∴ diluted urine

3] End stage Renal disease (ESRD):

90% and more damage of kidney (nephrons)
- (10% → 0%) Functional kidney
- Some people reach to Unurea (No urination) → Edema.

Symptoms (ESRD):

- Itching:
due to accumulation of phosphorus
- Hyperpigmentation:
accumulation of melanocyte stimulating hormone
↳ Stimulate the melanocyte → melanin → pegmintation and excretion by kidney
∴ Renal failure → No kidney function → No excretion to melanocyte stimulating hormone (elimination) → accumulation → hyperpigmentation.
- Peripheral neuropathy:
due to electrolytes imbalance
- Sexual dysfunction:
due to electrolyte imbalance.
- Arrythmia (irregular heart rate):
due to hyperkalemia (k^{+})
- Encephalopathy (Renal encephalopathy):
No excretion of urea → accumulation of urea in blood → CNS → encephalopathy
- Tetany (severe and rapid spasm)
due to hypocalcemia
- Uremic frost (accumulation of urea on the skin)
Urea excretion by the sweat due to accumulation
- Infection
- Anemia
(all people suffer from renal failure has anemia but w different severity due to the stage)
due to ↓ in erythropoietin
↳ synthesis & secretion by kidney → bone marrow → activation Red blood cells synthesis & production

- Edema → (due to) No urination (general & Pulmonary)
- Osteodystrophy (bone demineralization / bone resorption):
Decreasing in bone density → osteoprosis due to:
* Hypocalcemia:
• No activation of Vitamin D (kidney is responsible for Vitamin D activation), No converting to calcitriol (1,25-Dihydroxycholecalciferol)
↳ active form of Vitamin D
∴ No absorption of Ca^{+2} from the intestine → ↓ conc. of Ca^{+2} → Hypocalcemia
• Hyperphosphorolemia:
↑ Phosphorus conc. → activation of Parathyroid glands → secretion Parathyroid hormones → make homeostasis for ↓ Phosphorus secretion
Parathyroid hormones control of Ca^{+2} conc. in the blood by Ca^{+2} resorption from bone → ↓ Ca^{+2} conc. in bone → ↓ bone mass → osteoprosis.

Diagnosis:

- Blood test: Creatinine, Urea
- PH value (acidosis (↓ PH) for Second & End stage)
↳ الغسيل الكلوي (main indication of Dialysis)

Diabetes Mellitus:

- It is a chronic metabolic disorder charecterized by chronic hyperglycemia due to multiple causes
  ↳ because diabetes has a main relation ω metabolism of carbohydrates and some of lipids & proteins
- It should be chronic hyperglycemia to call it diabetes.
- main cause is: imbalance blw insulin need and insulin availability
  ↳ hormone which control glucose blood level (+glucagon)

↑glucose level → insulin secretion → more utilization of glucose → ↓ glucose level (to reach normal)
↓glucose level → glucagon secretion → more glucose production to reach normal.
∴ Hemeostasis.

- when imbalance (chronic) → chronic hyperglycemia.

Causes:
- Absolute insulin deficiency (No insulin) due to damage in β-cells
- Impaired insulin secretion → Insufficient amount of insulin
- Insulin resistance

Normal insulin level but Problem in secretion → no interaction blw insulin & insulin receptors

or

- Increased glucose production (chronic increased glucose production)

Normal insulin but high glucose level → Insulin can't deal ω Pt

Classification of DM:

2 main types:
1- Type 1 DM
2- Type 2 DM

other type:
- Secondary DM
- Gestational DM

[1] Type 1 DM:

- 5 → 10% of total diabetes
- Absolute insulin deficiency (No insulin) due to: destruction of β cells
- Classified into: (2 subtypes)

Type 1 A (immune-related diabetes mellitus type 1)/(autoimmune diabetes mellitus type 1)/(Juvenile Diabetes)

- Type 1B (Idiopathic diabetes)

* Type 1A:

Body recognize β cells as foreign substances → destruction of β cells → absolute insulin difficiency

* Type 1B:

Destruction of β-cells due to ~~idose~~ unknown cause (Idiopathy)

[2] Type 2 DM:

- 90 → 95%
- Impaired insulin secretion / Insulin resistance (more common) / Increase glucose production
- Insulin is ~~copper~~, no complete destruction of β-cells

insufficient amount
due to:
1. impaired insulin secretion
2. insulin resistance
3. increase glucose production

∴ The main differences b/w Type 1 & Type 2 is Insulin

in type 2 may be high level / low level / normal level but ⇒ hyperglycemia

- Low level → impaired insulin secretion
- high level
  - insulin resistance (no interaction b/w insulin & insulin receptors, stimulate β cells to secrete more insulin ∴ high level of insulin)
  - increased glucose production

at first, normal insulin level but increase glucose production → hyperglycemia → more stimulation → more insulin secretion & more glucose production and The body can't utilize all glucose amount ∴ → Chronic hyperglycemia.

* Insulin resistance:

- most common subtype of type 2
- main cause is: obesity
- may be genetic factor (mutation in gene responsible for synthesis of insulin receptors, ∴ No interaction)
- Obesity → thickness in adipose tissue → covering of insulin receptor → No interaction b/w insulin & insulin receptors → hyperglycemia

Secondary DM:

- Related to other cause (disease/drugs)

ex: Cushing's Syndrome → ↑ cortisol → Steroid diabetes

- Pancreatitis (infection in pancrease) → defect in β cell (in function) → ↓ insulin synthesis → hyperglycemia

- Related to Drugs: Corticosteroids / oral contraceptive / diuretics (specially thiazide) in chronic use → Secondary DM.

+ When treat the cause → treat the hyperglycemia (DM).

[4] Gestational DM:

- Diabetes during pregnancy
- 7% of all pregnancies
- Risk Fachers → family history
  → obesity (obese pregnant women)
  → 5 or more pregnancies (5 babies or more)
  → advanced maternal age (>35 age)

Pathogenesis of Type 1A: (autoimmune)

body recognize beta cell as foreign sub. (specific proteins) → dentric cells recognize the antigen → engulfment → expression by MHC-II → APCs → activation CD_4 cells → TH → major → activation of naive CD_8 cell → Cytotoxic CD_8 → Perforin & granzymes → apoptosis

→ minor → IFN-γ → Stimuli

B cells → plasma B cell → synthesis & secretion IgG → binds to beta cells → opsonization → activation other immune cells → destruction of beta cells

:- Absolute Insulin diffeciency.

Pathogenesis of Type 2 DM: (due to genetic/environmental factor)

[1] Insulin resistance

Envirnomental / Genetic factor → obesity → insulin resistance → Covering of insulin resistance in tissue → No interaction blw insulin & insulen receptors → ↓ glucose uptake lutilization → accumulation of glucose in blood → hyperglycemia → Chronic → :. Type 2 diapetes.

[2] Impaired insulin secretion or increasing in glucose production:

no normal production of ATP → body send signals to liver → liver Produce glucose by glycogen degradation → ↑ production of glucose to circulation → more hyperglycemia → :. Type 2 DM

because at first there was hypoglycemia & due to abnormal utilization
2 more production of glucose by the liver.

Symptoms:

- Symptoms in Type 1 → suddnely (Absolute insulin difficiency)
- Symptoms in Type 2 → gradually (impaired insulin secretion)
- The main charecteristic symptom is 3 Polys
  - → Polyuria
  - → Polydipsia
  - → polyphagia

1 Polyuria:

- excess of urination / frequent urination
- main cause is hyperglycemia
- hyperglycemia → ↑ blood glucose level → hyperosmolar blood soln. due to accumulation of glucose → movement of water from ISF & tissues to circulation → ↑ blood volume → ↑ cardiac output & ↑ B.P. → maintain the increasing by activation urinary system → ↑ filtration & ↑ urine production → ∴ frequent urination.

2 Glycosuria (accompanying polyuria):

- ↑ glucose in the urine
- In normal there isn't glucose in the wine
- hyperglycemia → ↑ glucose conc. → high amount of glucose reach the kidney → ↑ filtration of glucose and no reabsorption → ∴ glycosuria.

3 Polydipsia:

- excessive thirst
- hyperglycemia → hyperosmolar soln. → fluid & water from ISF & tissues → circulation → dehydation of tissues → activation thirst center in hypothalamus → polydipsia

4 Polyphagia:

- excessive hunger
- Appear clearly in Type 1 (but not characteristic of Type 1)
- Just in advanced cases of Type 2.
- Hyperglycemia → No insulin (in Type 1) → No utilization of glucose for ATP Production → alternatal source for ATP as lipid & Protein → TGs, free fatty acids → ATP production → amino acids
- ↓ catabolism of lipid & protein → starvation of cells → stimulate hunger center in hypothalamus (activation) → ∴ Polyphagia.

symptoms:

- fatigue & weakness

No normal production of ATP

- Infection

hyperglycemia → ↓ immune system activity and ↓ healing process

- Blurred vision

hyperglycemia → metabolizm of glucose → accumulation of glucose metabolites in retina → blured vision

Charecteristic symptoms of Type 1 DM:

- nausea, Vomiting, abdominal pain → due to keto acciclosis
- Smell of acetone (Breath) (Fruity smell)

due to catabolism of TG_s → glycerol & Free fatty acids → excess amount of glycerol & Free fatty acids metabolism by liver → formation of keton bodies (acetone) → ↑ keton bodies in circulation → ∴ ketoacidosis

accumulation of keton bodies → body excretion it by kidney & breath (acetone is volatile) → ∴ acetone smell.

- kussmaul breathing (hyper-ventilation)

↳ Deep breathing → deep inspiration & deep expiration

↓ PH Value due to accumulation of keton bodies, So the body use bicarbonate to maintain acid-base balance → sharp ↓ in bicarbonate level

So, body should get rid of acid → by kussmaul breathing → hyperventelation, deep ventilation

To get rid of large amount of CO_2.

- weight loss.

"Same to polyphegia"

but ON the other hand:

weight gain in type 2:

Main cause of Type 2

Diagnosis:

- Blood test: measurment of blood glucose level
- Urine test: measurment of glucose & ketone (complement to blood test)

Blood tests:

by capillary blood glucose mointoring

(must be chronic → diabetic Patient)

Blood tests:

[1] FPG: "Fasting plasma glucose test"
- measurment blood glucose after 8 hours of fasting
- normal FPG: < 100 mg/dL or < 5.6 mmol/L
- 100 mg/dL → 125 mg/dL → impaired fasting glucose level (pre-diabetic)
- ≥ 126 mg/dL → diabetic patient.

[2] Casual Blood Glucose Test:
- measurment of blood glucose level without any care about time of meal.
- ~~Unreliable~~
- Unreliable
- normal: < 200 mg
- > 200 mg + symptoms → ∴ diabetes Mellitus

[3] OGTT: "oral glucose tolerance test"
- measure the body ability for utilization of glucose either break down (catabolism) or converting it to glycogen for storage in Skeletal muscles & Liver
- when high result ῶ FPG → give the patient sugar soln. (75 g (very conc.) → measure the tolerance → if body can catabolite or storage of glucose
or not
then after 2 hours → measure the blood glucose : after administration
- normal: < 140 mg/dL
- 140 → 199 mg/dL → Impaired glucose test (Pre-diabetes)
- ≥ 200 mg/dL → Diabetic patient

[4] Glycated Hemoglobin test (HbA1C or A1C)
- measure sugar stock.
- Hemoglobin appears in RBCs, when synthesis (RBCs) in bone marrow → hemoglobin not bind ῶ glucose → RBC need glucose, Utilization done without insulin (insulin-independent)
→ Some of glucose binds ῶ hemoglobin (irreversible)
∴ ↑ hyperglycemia → ↑ glucose entrance ῶ RBC → ↑ interaction blw glucose & insulin → (irreversible)
- normal: < 6 %
- 6.1 → 6.4 % : Prediabetic
- ≥ 6.5 % : Diabetes millitus.
- Non-repeated test (no need for repeat the test) because A1C is indicate glucose level during 2-3 months (before 2/3 months) because binding process blw glucose & Hb is slow & irreversible

Diagnosis DM:

Chronic hyperglycemia by A1C ≥ 6.5%.
- repeated FPG ≥ 126 mg/dL
- OGTT ≥ 200 mg/dL after 75 g sugar soln. (2 hours from adm.)
- Casual ≥ 200 mg/dL w/ symptoms

- For Gestational:
  - Fasting → 92 mg/dL
  - after 2 hours of OGTT → < 153 mg/dL or < 155 mg/dL

Complications of diabetes:
- Acute complications
- chronic complications

Acute Diabetic complications:

Groups of complications which doesn't occur rapidly after diagnosis of DM (after month → Year) in all diabetic patients:
- ketoacidosis
- hyperosmolar hyperglycemia
- hypoglycemia

I. ketoacidosis:
- Diabetic ketoacidosis
- ↑ ketonbodies in the body (ketonemia)
- ↓ PH value of blood
- Characteristic for DM Type 1
- may happen in Type 2 but when the cause is Insulin resistance

Characteristic for type 1 ? Type 2

- Insulin difficiency → No utilization of glucose via skeletal muscle & other tissues → No ATP
→ alternate source (adipose tissues) → lipolysis process → TGs to glycerol + free fatty acids
→ Free fatty acids Catabolism → ATP
→ Excess amount of fatty acids → Liver → Catabolism → Convet to ketonbodies
→ Glycerol → liver → Convet to glucose
∴ hyperglycemia

- have acidic characters → ↓ PH value (metabolic acidosis)

- ketonuria may happen.

Symptoms of ketoacidosis:
- ketonemia
- ketouria
- metabolic acidosis
- hyperglycemia & all consequence of it such as: hyperosmolar, dehydration, Polyuria
- Hypotension because of Polyuria

HTN as chronic compl. → hypotension?
- Tachycardia as compensatory of hypotension
- Fruit smell / acetone smell
- ↓ bicarbonate level

2 Hyperosmolar hyperglycemia:

- Happen in Type 1 & Type 2 but more common in Type 2
  - Type 1 ← glucose 250-300 mg
  - Type 2 → reach 600 mg

- in type 1: before treatment / nonadherent patient
  The body compensat glucose difficiency by adipose tissues → "discussed before"
- in Type 2 "except insulin resistance": "gradual resistance"
  Sufficient amount of insulin but can't deal w glucose → ↓ utilization of glucose but not
  Sufficient production of ATP → ↓ Production (not completly absent) → adipose tissue → →
  body try compensate
  but appear of bicarbonate neutralize keton bodies → ∴ No metabolic acidosis.

bicarbonate في type 2 ليش
بتقدر تعادل keton bodies
type 1 في ليش ؟

3 Hypoglycemia:

- In 2 types, more common in Type 1
- glucose < 60 mg → ∴ hypoglycemia
- Main cause is: Increase in insulin dose
  - → take insulin without food
  - → Overdose of insulin
  - → No balance btw insulin dose & food intake
  - → Change the site of injection
  - → Change in insulin type (ليش ؟)
- The characteristic symptoms is:
  - fainting
  - heavy sweating

(Characteristic for hypo.. & hyper...)

- other symptoms:
  - confusion & headache
  - Seizurier & coma
  - Hungry
  - Difficulty speaking
  - Sleepiness

Complications of Diabetes: (chronic Complications) (Long term complications)

- Not for all diabetic Patients
- For non-adherant Patients & after diagnosis (10-20 Years)
- Depend for the Patient & his life-style management

Causes of Chronic complications:

1. accumulation of glucose metabolites, ex/ Sorbitol ⇒ accumulation in tissues → Problems.
2. Glycated proteins: hyperglycemia → Stimulate binding of glucose ω x protein → forming glyco-Protein
   - in normal, no bind of glucose ω Proteins
   - has sticky characteristic
3. Accumulations of free radicals:
   chronic hyperglycemia → ↑ chemical reactions → ↑↑↑ free radicals → body can't utilization this Free radical → ∴ accumulation
4. accumulation of glycoproteins in blood vessels → damage in endothelial layer → LDL to intima → atherosclerosis → narrowing → ↓ blood supply → ↓ organ perfusion.

Chronic complications:

- Microvascular
- Macrovascular

II Microvascular:

① Eye: (diabetic retinopathy)
- Glucoma → (↑ Pressure in eye)
- Cataracts → (water in eye)

hyperglycemia → ↑ glucose metabolism → ↑ Sorbitol → accumulation in eye → hyperosmolar conc. (aqueous humor) → move of fluid from circulation to eye → ↑ water in eye

② kidney:
diabetic nephropathy
hyperglycemia → accumulation of glycoproteins (sticky characteristic) in circulation → to kidney for filtration → but sticky sub. → accumulation → closing the nephron → kidneys problem (chronic)

③ Neuropathy:
- at first, umbness → after long Period → loss of Pain sensation
- hyperglycemia → accumulation of Free radicals, accumulation of sorbitol → damage in Myelin sheath around neurons → ↓ pulse transmission → Loss of Pain sensation.
- hyperglycemia → accumulation of glycoproteins → binds ω nociceptors → loss of Pain sensation
  - nociceptors: Pain receptors

[2] Macrovascular:

① Heart:

- Cardiovascular disorders
- Most of diabetic patients have hypertension
- hyperglycemia → accumulation of free radicals
  → accumulation of glycoproteins
  → damage in endothelial layer → Passing of LDL → ↑↑ LDL → atherosclerosis → narrowing → HTN
- Most of diabetic patients have ↑ Haemophilia (زيادة سيولة الدم)

Hyperglycemia → accumulation of glycoproteins → binds ω receptors which responsible for platelet & Clotting factors binding → Prevent aggregation process → more bleeding.

② Brain:

- In very advanced case
- Ischemic attack / brain stroke may happen

hyperglycemia → ~~accumulation~~ narrowing of blood vessels which supply the brain

③ Extremities:

- Foot ulcer
- Diabetic patients have very slow regeneration process due to weakness of immune system
- May lead to gangrene
- Problem in growth factor → no normal healing

Ch.5: CNS Disorders:

1 Multiple Sclerosis:

* Neurodegenerative disorders:

- Degeneration / destruction of neurons (CNS)
- Progressive (gradual) diseases
- Its main cause (in general) is ppt / aggregation of specific proteins in a specific region in CNS.

Examples//

1. Disease affect the hippocampus: Al-Zheimer's disease (degradation in hippocampus neurons)
   - hippocampus → region in CNS, Control the behavior, memory, language, ...
2. Disease affect the basal ganglia: (Control the movement)
   - → hypokinetic: Parkinson disease (degradation in excitatory neuron)
   - → hyperkinetic: Huntington disease (degradation in inhibitory neuron)
3. Disease affect the cerebellum: ataxis (uncontrolled movement) (Control the movement)
4. Disease affect the myelin sheath: Multiple sclerosis

Multiple Sclerosis:

- It is a progressive neurodegenerative disorder / Progressive myelin sheath disorder characterized by demyelination of the CNS neurons
  - as consequence → damage in neurons
- Schwann cells → cells responsible for produce / synthesis the myelin sheath of the Peripheral nervous system neurons.
- Oligodendrocytes → cells responsible for synthesis the myelin sheath of CNS neurons.
- More common in women by 2:1 ratio

myelin sheath disorder
- Demyelinated diseases → for normal myelinated neuron → destruction of myelin sheath → demyelinated disease
- Dismyelinated diseases → For normal abnormal neuron

Causes:

- The main cause is: Autoimmune response
- Risk factors:
  - → Infections in CNS
  - → Genetics Problem in CNS.
  - → Drugs have toxic effects on CNS.

Pathogenesis :

* BBB → Prevent Passing of immune cells from Blood (Peripheral) to CNS

∴ No immune cells in CNS.

* Damage in BBB → Passing of immune cells to CNS
* Microglia → responsible For immune response in CNS
  ↳ (work as immune cells in CNS)

MS :-

Autoimmune disease → response against myelin sheath :

*Recognition of Protein from myelin sheath component as antigen / Recognition phospholipid or lipid as foreign substance (antigen) / one component of oligodendrocyte cell as foreign substance

→ antigen ↑ Pass to circulation → recognition by immune cells → Macrophage → APCs → activation

TH_0 → TH_1 —IL-2→ CD_8

TH_0 → TH_{17} → secrete IL-17

and TH_1 minor Pathway —IFN-γ→ B cells → Plasma B cell → antibodies

NOW If: (Risk factors)

- Infection (inflammation) → ↑ Permeability → Passing through BBB
- Genetic problem in BBB (mutation) → :
- Toxic Drugs of CNS → Damage in Pores of BBB → Passing through BBB

∴ CD_8 , TH_{17} , antibodies → CNS → immune response against myelin Sheath

→ degradation of Myelin Sheath → degradation of axon → Degradation of neuron.

Symptoms :

according to damaged neurons:

- In Cerebellum : - loss of balance
  - Ataxia & tremor
- Cranial nerve : - Diplopia → double vision
  - Loss of vision
- Motion nerve Tracts : - weakness
  - Paralysis
- Damage to sensory Nerve tracts : - Paresthesia - Pickling
  - burning sensation

Diagnosis :

- Symptoms
- Imaging : CT / MRI* → white plaques for demyelination.

*magnetic resonance imaging

- Evoked potential : by activation 1 neuron and measure the speed of transmission (less speed ∴ demyelinated)
- CSF : Cerebrospinal fluid measure the immune cells & cytokines , if presence ∴ M.S

Parkinson disease :

- It is a progressive ~~Adeno~~ Neurodegenerative disorder, characterized by hypokinetic movement disorder (hypokinesia) in basal ganglia (substantia nigra)
  that caused by loss of dopaminergic neuron

- Aggregation of α-synuclein in substantia nigra → damage in dopaminergic neuron → hypokinetic → ∴ Parkinson. (general cause)

- mainly affect the motor neurons.

Causes:

- Primary P.D :- aggregation of α-synuclein in substantia nigra → damage in neuron but the cause is unknown (Idiopathic)
  - elderly as risk factor

- Secondary P.D :- encephalitis (inflamation in CNS) → damage in substantia nigra (no need for α-synuclein aggregation, the inf: directly damage the neuron)
  - Vascular disease : Ischemia (↓ in blood supply in substantia nigra) → damage in dopaminergic neuron.
  - Dopaminergic antagonists (blocking dopamine receptors): has Parkinson-like effect (extapyramidal symptoms) (syndrome)

Pathogenesis:

aggregation of α-synuclein in substantia nigra → damage of dopamine neurons → ↑Ach, ↑ Glutamine (excitatory) → ↑ GABA → ∴ Inhibition (hypokinetic)
(more activation of striatum which release more amount of GABA)
∴ Imbalance blw Ach / dopamine → ↑GABA

Symptoms:

- main symptoms are:
  - tremor at rest.
  - Postural instability
  - Rigidity (due to severe contraction of involuntary)
  - Bradykinesia (hypokinetic) (slowed movement)

- Tremor in Parkinson has 2 characteristic → at rest, start in hands, then nick
  - involuntary movement
  - → Pell-rolling shape
- Rigidity: muscles when severe contraction → become rigid

ALZheimer's disease:

* Dementia: "جنون"

+Dementia is cause of ALZheimer ⟺

- CNS disorder, It is a Progressive chronic disease, in which the Cerebral Cortical function of the brain is decreased.
- atrophy / shrinking in CNS, when reach to hippocampus → Alzheimar
- If damage happened at hippocampus, then continous & spreading to damage in cortex ∴ → Dementia.
- Cortex → Control Cognetive skills (language, speak, memory, thincking, Judgment, ...)

* ALZheimer's disease:

- It is a progressive neurodegenerative disease, characterized by damage / atrophy and loss of neurons in hippocampus.
- Cerebral cortex atrophy may happened in advanced age.
- More common in women.
- General Causes: Unknown but:
  - Aggregation of B-amyloid and tau Proteins (No interaction blw thm, each one aggregate individually)

Risk Factors:

- Age (<74 Years)
- Genetics
- Oxidative Stress (Free radical)

+Aging: (main risk factor)

- 65 → 74 Years (3%)
- 75 → 84 Years (20%)
- >85 Years (50%)

Pathogenesis:

- Alzheimer → aggregation of Tau protein and/or β-amyloid protein

Tau protein:

- 6 proteins, interaction ω microtubule (cytoskeleton for neuron's axon for stabilization the shape of axon)
- for stabilization of microtubule (axon)

β-amayloid protein:

- synthesis From Amyloid precursor protein in cell membrane of neuron.
  - Functions: 1- For management of the growth of neuron
    2- Regeneration of damaged neuron

- 2 enzymes (β-Secretase, ϒ-Secretase) work on the precorsor (internally & extenally)

→ synthesis β-amyloid protein (moneman)

- Functions: - Controlling of signalling in synapse.
  - antioxidant activity (↓ accumulation of free radical)
  - Activation of kinase enzymes

Now in ALZheimer:

* Aging /any risk factor → aggregation of β-amyloid → forming amyloid plaques → (aggregated form of β-amyloid)

1. distrubtion in internal Ca^{+2} conc → cell injury → death of neuron
2. damage in mitochondrial membrane → cytochrome C → activation procaspase enzyme → apoptosis
3. ↑ accumulation of free radicals → ↑ damage
4. Overactivation of kinase enzymes → overphosphorylation → phosphorylation of other Proteins (1 of them is Tau protein) → aggregation.

* Aging /overphosphorylation of Tau protein/ any risk factor → aggregation of Tau protein → forming Neurofibrillary tangle (aggregated form of Tau protein)

→ damage in axon of neuron (No support of microtubule) → damage

Symptoms:

* Depending on the progressive of the disease:
  - mild case of Alzheimer:
    - Loss of short-term memory
  - Advanced case:
    - Loss of Long & short-term memory (memory loss)
    - Confusion with time & location
    - Difficulty completing familiar Tasks
    - Misplacing items
    - Difficulty solving problems
    - Poor jugment
    - Unfound emotions
    - Diffuclty ω words
    - Trouble ω images & spaces
    - withdrawal From social activities

Diagnosis:

- Symptoms
- Imaging (CT/MRI)

- by seeing the atrophy/shrinking in the cortex or hippocampus
- more advanced case → more atrophy or appearance of plaques/tangles.
- The plaque of β-amyloid is externally in surrounding area of neuron (not in neuron cell)
- The tangle is internally (inside the neuron cell)

Ch.6: Cancer

- Is a group of diseases characterized by abnormal & uncontrolled cell growth with the potential to invade or spread to other parts of the body.

Cell cycle:

- sequence of events which can control the cell devision / cell growth
- Highly control cycle
- Divided into 3 or 5 phases:
  1- Interphase
  2- Mitosis phase (M phase)
  3- Cytokinesis phase (C phase) (Separation phase)

بالكتاب كاين 4 phases؟

if 5:

1- Interphase divided into 3 phases:
   1- G_1 phase
   2- S phase
   3- G_2 Phase
   4- M phase
   5- C phase

- Each phase has some process and at the end the outcome is: 2 dauter cells have the same morphology, the same characteristics, the same functions.
- If this condihions aren't acheived → apoptosis except the cancer is happened.

Ex// - In G_1 → duplicahion of proteins, enzymes which play roles in cell devision process
- S phase → duplicahion of genetic material (DNA)
- G_2 phase → continuous duplicahion
- M Phase → Mitosis (Nuclear division)
  ↳ give 2 fuse cells (identical) → 2 daughter cells

- Controlled by: - growth factors work in nucleus → initiation cell devision.
- Check Points → after G_1
  - after G_2
  - after M & during M

G_1 check → sufficient nutrition, sufficient growth factor, normal cell size, normal DNA
- If normal → Pass
- If abnormal → apoptosis (damaged DNA)

Check points:

G_1 checkpoint → Pass this checkpoint if:
- nutrients are sufficient
- growth factors (signals from other cells) are present
- Cell size is adequate
- DNA is undamaged.

G_2 checkpoint → Pass this checkpoint if:
- Chromosome replication is successfully complete
- no DNA damage

M checkpoint → Pass this checkpoint if:
- All chromosomes are attached to mitotic spindle.

The Cancer:

- Group of diseases, affect the cell cycle / cell devision / cell growth

Terminology:

- Oncology → Sience which studies the cancer
- Neoplasm → Tumor → increasing in size, formation of the mass,
  2 types → benign
  → malignant
- Neoplasia / carcinogenesis → mechanism of the disease / process of cancer development / Pathogenesis of the cancer

Benign & malignant Tumor:

Similarities: - 2 are tumor (mass)
- Uncontrolled cell devision

differences:

	Benign	Malignant
- Cell Characteristics	well-differentiated, as morphology & characteristic similar to normal	undifferentiated cell, atypical Shap, Apnormal appearance
- Rate of Growth	Slow growth, progressive (gradual) "malignant ≠ بطيئ"	Rapid growth; Variable due to organ
- Mode of Growth	as expansion, because it surrounds by capsule (encapsulated mass)	No capsule → No expansion but infiltration & invasion → Result of metastasis
- Metastasis *transfer of malignant tumor from the origin site to another site" "Secondary tumors"	NO metastasis, Just localized "Doesn't cause Death but dysfunction" "Death when appear in vital organ"	There is metastasis "Dysfunction & Death"

inology:

Tumors are named by adding the suffix -oma

Tissue type	Benign tumors	Malignant tumors
① Endothelial → gland	-oma	-carcinoma
	+ Adenoma "benign tumor in epithelial cells of the gland"	Adenocarcinoma "malignant tumor in epithelial cells of the gland"
② Connective tissue	-oma	-Sarcoma
↳ Fibrous	Fibroma	Fibrosarcoma
↳ Adipose	Lipoma	Liposarcoma
↳ Bone	Osteoma	osteosarcoma
③ Muscle	-oma	-Sarcoma
↳ Smooth	Leiomyoma	Leiomyosarcoma
④ Neural tissue	-Oma	- blastoma
↳ Nerve cell	Neuroma	Neuroblastoma
Hematologic		
↳ Granulocytic (neutrophil, ...)	" NO Benign of Blood cancer"	Myelocytic leukemia → = "Myeloid leukemia"
↳ Erythrocytic		Erythrocytic leukemia
↳ Plasma cells		Multiple myeloma → of B cell xxxx (Plasma ✓)
↳ Lymphocytic (B cells)		Lymphocytic leukemia or lymphoma → = "lymphoid leukemia" ↳ Cancer hematological in lymphocyte in blood ∴ Malignant cancer of lymphocyte in the blood

Adenoma is benign tumor in the gland? ... "in epithelial ... ok"

Solid Cancer "mass" "dimension" due to ↑ no.

Blood Cancer "Hematological malignancy" "↑ number" "mobile phase"

↳ malignant cancer of lymphocyte in lymph node

Pathogenesis:- (carcinogenesis / Neoplasia)

- Carcinogenic agent → Cancer causing agent → has the ability to Perform/change normal cell to cancer cell by mutation in genetic material of genes which control the cell cycle
  - ↳ in general: mutation of DNA of the cell

How?!

- By 2 or 3 phases :- - initiation phase
  - Promotion phase → Benign tumor "2 phases"
  - Progression phase → malignant tumor "3 phases"

II Initiation phase :-

Exposure of the normal cells to the carcinogenic agent "The First step" ⇒ Result in mutation in genes which control the cell cycle

2 Promotion phase:

- Second phase of carcinogenesis, characterized by uncontrolled cell devision → ↑ no. of cells → ↑ size → ∴ formation of mass
- "initiation of uncontrolled cell devision" how ?!

2 categories of genes which control cell devision:

- Oncogenes → Group of genes, transcript the growth factors which initiation the cell cycle / cell devision
- Tumor suppressor genes → Enzymes of the check points

- Carcinogenic agent → mutation in Oncogenes & tumor suppressor genes → more growth factors → ∴ ↑↑ cell devision → ↑ no. of cells
  - ↑ Oncogenes expression
  - ↓ tumor suppressor genes

∴ Benign tumor / premalignant tumor

↳ Reversible by apoptosis the cells then regeneration of other normal cells

- When continuous exposure of carcinogenic agent: "↑ exposure of causing agent"

Pre malignant → become malignant

& benign → if damage of capsule → become malignant

• Relapse → recurrence occurs when the cancer comes back after treatment

3 Progression phase:

Third phase of carcinogenesis, development of benign / premalignant tumor to malignant tumor due to continuous exposure to carcinogenic agent → ↑ damage → ↑ mutation → ↑ expression of oncogenes & ↓ tumor suppressor genes → ↑ uncontrolled cell devision → uncapsulated → malignant tumor

Metastasis: "for malignant cancer"

- Transfer of the cancer cell (malignant cancer cell) from the orgin site to another site (1 or more)
- also called Seconday cancer
- Occur by 3 steps → infiltration
  - invasion
  - Metastasis

1 infiltration: meta

movement of malignant tumor cell from one tissue to another tissue in the same organ by: cytokines secreted from malignant tumor cells & enzymes causes adaptation for surrounding environment → this enzymes precloud the matrix in the organ → ∴ movement / transfer of cells from one tissue to other tissues.

Invasion:

Movement of the malignant tumor cell from the tissue to the circulation → blood or lymphoid system

- angiogenesis occur to ↑ blood supply for more O_2 & nutrition for malignant tumor cell
  - ↳ Formation of new blood vessels (cappilleries)
- Tumor malignant cell → Secrete Vascular endothelial growth factor (VEGF) "in no limitation" → ↑VEGF → ↑ angiogenesis → ↑ Generation of new blood vessels → ↑ blood supply for malignant tumor cell → adaptation → expresion of adhesive molecules on surface of malignant tumor cell

∴ "malignant tumor cell surrounding c̄ network of cappillaries"

→ binds c̄ Proteins on the surface of blood vessels → interaction b/w molecules & receptors → transmigration → Secrete enzymes → break down of tight junctions for passing →

∴ movement from tissues to circulation → to heart → pumping to different organs ex// lung → interaction b/w adhesive molecules of cancer cell & receptors on endothelial layer in lung → mediators → destruction of tight junctions → passing into lung tissues → uncontrolled cell devision → ↑ no. of cells → formation a new mass → new malignant tumor formation in Lung → called it Secondary tumor.

and this is **metastasis**.

لو اجانا نكتب الـ metastasis
منو وين نبدأ؟

* هل ممكن الـ benign انه يصير
metastasis ولا مستحيل؟

Causes & Risk factors:

- Hormones
- Smoking
- Pollution
- family history
- immune deficiency
- Aging
- Other illnesses viruses
- Exposure to radiation.

Staging & grading Cancer:

- Stratiges using for evaluation the cancer (mild, moderate, advanced)
- Grading: technique for Classification of Cancer according to type & metastasis (1 → 4), (I – IV)
- Staging: technique for determination of cancer, size of the cancer, infiltration, invasion or metastasis
- (American joint Committee on Cancer (AJCC)) according TNM method:

T → tumor size (0–4):
- 0 → No cancer
- 1 → Small size
- 2 → moderate / intermediate size
- 3 → large / big size
- 4 → + large

N → involvement on the lymph node (0–3):
- 0 → no involvement
- 1 → limited involvement
- 2 → intermediate
- 3 → high involment

M → extent of metastasis involvement: 0 → No metastasis
1 → metastasis.

ex// T2N1M0 ?
There is a moderate size tumor ☐ limited involvement to the lymph node ✕ No metastasis

T3N0M1, explain the staging of this tumor:
There is a big/large size tumor ☐ No involvement of the lymph node ✕ metastasis

Diagnosis

. By Imaging (MRI/CT/Ultrasound/Ultrasonography)
- Biopsy → Remoual of a tissue from specific organ for analysis
- Immunohistochemistry → Use of antibodies to facilitate the identification of cell products or surface markers ✕ must be flourescent antibody
* antibody binds ☐ X protein in tumor cell (if preset), seen by microscope if binding *
- Microarray technology → Quantification ✕ Qualification for DNA
- Tumor Biomarkers "ref"

* Tumor Biomarkers:
- Each cancer has characteristic protein/proteins → CA "Cancer antigen"

Ex//
- CA 15.3 → Tumor marks for tracking breast cancer, or Liver, or Lung (according the source of biopsy)
- CA 27.29 → metastasis breast cancer / Seconday breast cancer
- PSA → Prostate cancer * the source → epithelial cells lining the acini ✕ ducts of prostate "Prostatic specific antigen"
- CA-125 → Ovarium cancer " source: Produced by mullerian cells of ovary"
- CD antigens → Determine the type ✕ level of differentiation of leukocytes involved in different "cluster of differentiation" types of leukemia ✕ lymphoma

CD_{33} → Characteristic biomarker for leukemia (in general)

CD_{30} → For lymphoma

CD_{19} or/and CD_{20} → (blood cancer) B cell cancer

$CD_{3/4/8}$ → T-cell cancer

CD_{19} ✕ CD_{30} → Cancer B cell lymphoma

CD_{19} ✕ CD_{33} → Cancer B cell leukemia

Breast Cancer:

- Type of cancer disease in breast tissues, Characterized by uncontrolled cell devision

* Breast tissue consist of,

3 main parts:- lobe, lobule, bulb → cells which produce the milk

lobe consists of lobules

lobules consist of bulbs

each breast contain 15-20 lobes

∴ bulbs → lobules → lobes → connect ☐ duct

- Duct → tubes which can transfer the milk from the lobe to the nipple

may be connection blw 2 lobes for the same duct

- fatty tissues "Stroma" → Matrix of the breast

* Cancer may be either in Duct (more common) or lobe (less common)

∴ Breast cancer (malignant) → Ductal Carcinoma "malignant cancer in the epithelial cells in duct / Lobule of the breast"
→ Lobular Carcinoma

* Impossible found cancer in all ducts / all lobes.

* 7 types:

① Ductal carcinoma in situ ("localized") (DCIS)

∴ localized in one tissue (no infiltration)

- malignant breast cancer in the epithelial layer of the duct & there is No infiltration

② Lobular Carcinoma in situ (LCIS)

malignant cancer in the ~~breast~~ (breast) epithelial layer of the lobule & there is No infiltration

③ Invasive ductal carcinoma (IDC) "more common"

malignant breast cancer in epithelial layer of the duct & there is infiltration & invasive.

(movement from tissue to other or to circulation)

④ Invasive lobular carcinoma (ILC)

malignant breast cancer in epithelial layer of the lobule & there is infiltration & invasive

(movement from tissue to other / circulation)

⑤ Inflammatory breast cancer (IBC) "aggressive"

- Invasive ductal carcinoma, having appearance of breast similar to inflammation symptoms

- No inflammation, but invasive ductal carcinoma → infiltration & invasion of malignant tumor cell to lymph node of the skin of the breast → blocking it → redness, swelling, warmness

- blocking lymph node of the breast → swelling, Redness & warmness

⑥ Triple-negative breast cancer (TNBC)

- breast tissue → contain 3 types of receptors → estrogen receptors, progestron receptor, human-epidermal receptor → control cell devision of breast tissue

in cancer → ↑ expression of receptors

∴ TNBC → No estrogen receptors & progestron & human-epidermal receptors

"Can't use hormonal therapy for it"

⑦ Baget disease: "very rare"

malignant cancer in the cells of the nipple

Risk factors:

- Age & Gender
- family history
- Personal history of breast cancer
- Menstrual cycle
- Childbirth
- Hormone replacement therapy (HRT) or oral contraceptives
- Obesity
- Radiation
- Benign breast cancer

Symptoms:

- Painless (when present deeply, Painful superficially), hard mass that has irregular edges, but Sometimes it can be soft, and rounded
- swelling of all or part of the breast
- skin dimpling
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness, or thickening of the nipple or breast skin
- Nipple discharge (may be bloody, clear to yellow, green & look like pus)
- Skin ulcers
- swelling of one arm (beside the breast ∪ cancer)

Staging:

- To clarify the progression of the disease (Mild cancer / advanced / Hemostasis or not / --)
- In breast cancer 5 stages: - stage 0 " include ductal / lobular")
  - Stage 1
  - Stage 2
  - Stage 3
  - Stage 4

Stage 0:
- In situ carcinoma (either ductal or lobular) "localized" → No infiltration → in 1 tissue "no mass"

2 Stage 1:
- Infiltration → movemat of cancer from 1 tissue to another tissue "not requirement of metastasis"
- detectable mass (< 2 cm), no involvement of lymph node

3 Stage 2:
① Size 2-5 cm
② < 2 cm but involvement of lymph node of axilla
③ size 2-5 cm and involvement to lymph node.

4 Stage 3:
- > 5 cm
- involvement of lymph node of axillary
- involvement of chest muscle (may or not)
  ↳ which surrounded the breast

5 Stage 4:
- Any size (> 5 cm) (advanced case)
- Involvement of lymph node of axillary
- Involvement of chest muscle
- Metastasis (Just stage 4)

Diagnosis:
- Breast self-exam (BSE)
- Clinical breast-exam (CBE)
- mammography
- Breast ultrasound (sonography)
- MRI
- Immunohistochemistry: Estrogen, progesterone, HER2 receptors
- Microarray
- Tumor markers: CA 15.3 & CA 27.29
  ↳ For metastasis breast cancer / seconday breast cancer
- Biopsy
  - ↳ Excisional biopsy:
    Surgery → opening → removal all the mass → analysis by any method
    (removing the total mass)
  - ↳ Incisional biopsy:
    Surgery → opening → removing part of the mass → analysis
  - ↳ Core biopsy: (wide needle)
  - ↳ Fine-needle aspiration (thin needle)

  → NO surgery, deperd on needle (if can reach the mass by needle)

Treatment:

* Surgery "→ the"

- most efficient treatment (depend on stage)
- 2 Types:

- Breast-conversing Surgery "no total remove of breast" → Lumpectomy → removing of total mass & part of surrounding normal tissue " look like excisional biopsy"
  → Partial mastectomy → removing of part of the breast "including the mass"

- Total mastectomy

Removing the breast (depend on the Stage)

- Modified radical mastectomy

Removing the breast and some of the chest muscles

* Blood Cancer :- "Hematological Malignancies"
+ Lymph

↳ Leukemia
↳ Lymphoma
↳ multiple myloma

* Leukemia → malignant cancer in blood cells either in bone marrow or circulation.
Precorser of Blood cells

* Lymphoma → malignant cancer affecting lymphocyte ("myeloid / Lymphoid") / affecting blood cells in Lymph nodes.
↳ in Lymph node

* multiple myloma → malignant cancer affecting plasma cells (Plasma B cells)

[1] Leukemia:
Malignant cancer which can affect the bone marrow precourser / blood cells in the circulation

* Leukemia types according the origin:
[1] Acute leukemia:
malignant blood cancer which can affect the hematopoietic stem cells (HSC) / precourse → ↑ the innature blood cells in bone marrow & circulation → :- Non-functional stem cells.

[2] Chronic leukemia:
malignant blood cancer which can affect the blood cells in circulation → ↑ the innature cells / ↑ the mature

* according to pathway:
[3] Myeloid leukemia:
malignant cancer which can affect the myeloid precourser in the bone marrow / myeloid cells in the circulation
acute ↵ ↳ chronic

[4] Lymphocytic leukemia:
malignant cancer which affect the lymphoid precourser in bone marrow / lymphoid cells in circulation
acute ↵ ↳ chronic

:- Acute myeloid Leukemia (AML)
Chronic myeloid Leukemia (CML)
Acute lymphoid Leukemia (ALL)
Chronic lymphoid Leukemia (CLL)

* AML → malignant blood cancer which can affect the myeloid precourser → innature myeloid cells in the circulation.

* ALL → malignant blood cancer which can affect the lymphoid precourser in bone marrow
"The most aggressive cancer & more common in children"
lead to over expansion or uncontrolled cell devesion → large no. of innature lymphoid cells in the blood.

* CLL → Blood cancer affecting lymphocyte in the circulation (Blood)

* CML → Blood cancer affecting the myloid cells in circulation → ↑ no. of the blood cells → non-functional cells

* Hairy cells leukemia → Charachteristic type of CLL which can affect the B cells. (B cell chronic Leukemia)
↳ change in morphology (surrounding hair like stru.)

2 Lymphoma:

Cancer in Lymphocytes precourser in the lymph node

"CLL" يشبه

2 types:

- Hodgkin Lymphoma (HL)
- non-Hodgkin Lymphoma (NHL)

	HL	NHL
1	- Less common	- more common
2	- only affect B cells	- affect T cells, B cells & NK cells
3	- affecting younger people (15 - 20 - 30 - - -)	- affecting older people (50 & more)
4	- has Charachteristic morphology: (Reed-Sternberg cells Shape) ↳ muttinucleated cells	- no Reed-Sternberg cells shape
5	in upper lymphonode (Localized) ⇒ specific Lymphnode "upper عالي"	- in all of the body "upper + lower" or/and (Generalized)