Dr.Najeeb General Pathology By Dr NIDO

This Pdf Contains :

* **Apoptosis** (3 Videos)
* **Inflammation** (4 Videos)
* **Necrosis** (2 Videos)
* **Neoplasia Nomenclature** (3 videos)
* **Neoplasia (Gene nd Cancer)** (10 Videos)

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1. **Insta:Dr NIDO**

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PATHOLOGY

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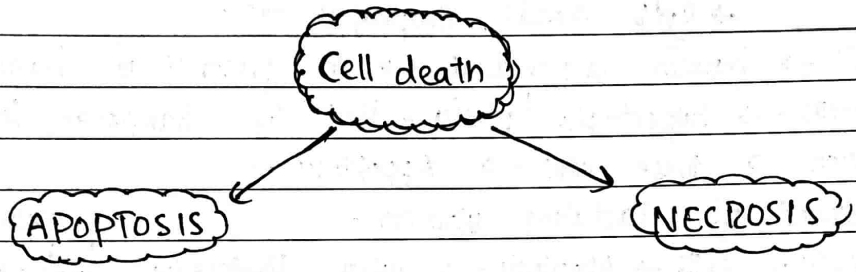
APOPTOSIS

* Literally → leaves falling from a tree.
* Programmed cell death → Apoptosis.



* Sucidal death of cell.
* Usually one cell is involved.
* May be due to external or internal factors.
* Cells → shrinks usually.
* Cells → membranes → disrupted → enzyme/lysosome → affed nearby healthy cells → Inflammation → → so necrotic Tissue have Inflammatory Zone Around it.

* Mass Murder of cells.
* Group of cell/Tissue → involved.
* Usually due to external factors.
* cells → swells up.

* Apoptotic cells → into Apoptotic granules → express "Opsonins" on its Surface → phapocytozed by macrophapes → → Sorrounding cells → not disrupted.

* Apoptosis → may be physiological or pathological.
* Necrosis → Alway → Pathological.

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WHY APOPTOSIS OCCURS? / Significance ?

Physiological

* Embryological → Different structure → undergoes apoptosis → to achieve adult functional shape.
  → e.g: hands, esophagus etc.
* Some cells → harmone dependant → In presence of harmones → → these cells → hypertrophy / plasia - But if harmonal support → → withdrawn → these cells → Appoptosis.
  → e.g: → Breasts of lactating women.
  → Endometrial cells → Apoptosis → when Progesterone ↓↓↓ → Before menstrual Bleeding
  → Prostatic Atrophy after Testis castration.
* Deletion of Some Immune cells.
  → e.g: Auto-Reactive T-cells deletion → in Thymus.
* Bone Marrow + GIT + Skin → cells → Continuously Proliferating → Appoptosis as well → so cell count → balanced.

Pathological

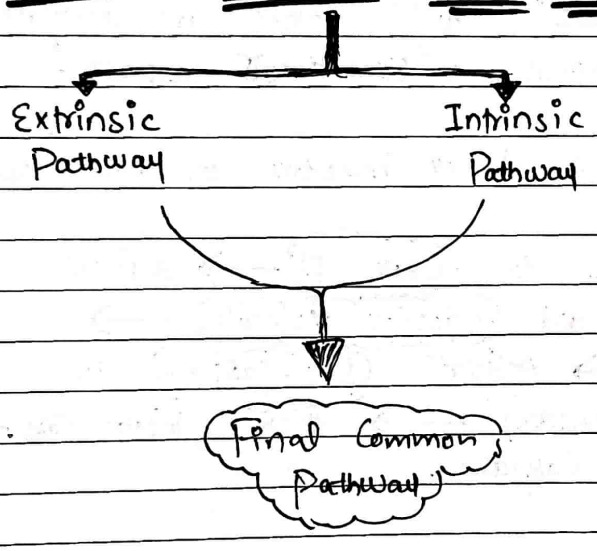
* When Genetic material of the cell → So badly damaged that it cannot be repaired → the apoptosis should occur.
* In Severe Thermal injury or hypoxia → Apoptosis.
* Hepatocytes → loaded wd virus → In hepatitis → Appoptosis.

* Endoplasmic Ret- stress → loaded wd too much un-folded proteins → E.R stress → Sucidal death.

* Duct of glandular structure → blocked → Appoptosis.

* Mutation in genes → too much → P53 gene → Activated → → force the cell to Commit Suicide.

Molecular Mechanism OF APoptosis :



P53

→ Guardian of Genome.
→ Stops cell cycle & activate repairing enzymes during mutation.
→ If no repair → then forces the cell → to Apoptosis.
→ In People who have difficiency of P53 → → chances of Cancer → ↑↑

Extrinsic Pathway :

→ Depends upon special receptors on cell membrane → → called → "Death Receptors".

e.g: FAS molecules or TNF- Receptor.

"Death Inducers" (FAS-Ligand) binds wd Death Receptors.

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→ Death Receptors have intracellular "Death Domain" into w/c "Adoptor Molecules" binds w/c also have "Death domain".

→ Now cell have proteoletic Enzymes (CASPASES) w/c have cystiene containg in their Active pockets and have cutting activity at Aspartate specific.

→ Initially they are inactive → Pro-Enzyme (Pro-CASPASES) → then Activated.

→ Some caspases are activated at inital phase of Apoptosis → "Initiator Caspases" while other are activated at Advance phase of Apoptosis → "Executioner Caspases."

→ Almost All the cells have Death Receptors on their Surface.

→ First (Death Inducers) binds to (Death R) → Activate its Death Domain → Binds wd (Adoptor Molecules) → → Activate it Death Domain → Activate (pro-caspase) to Active (Caspases): (Initiator Caspase) → then initator Casp. → → activate Executioner Caspases.

→ Then Executioner Caspase causes proteolysis of:

* Cytoskeleton of cytoplasm-
* Scafolding Protian for Nucleus-
* Activate DNAases enzymes w/c dipest Inter Nucleosomal DNA-

→ As a result most of Pratiens, nuclear material etc is dipested → & cell membrane undergoes some chanpes & & bud out → make Apoptotic Bodies.

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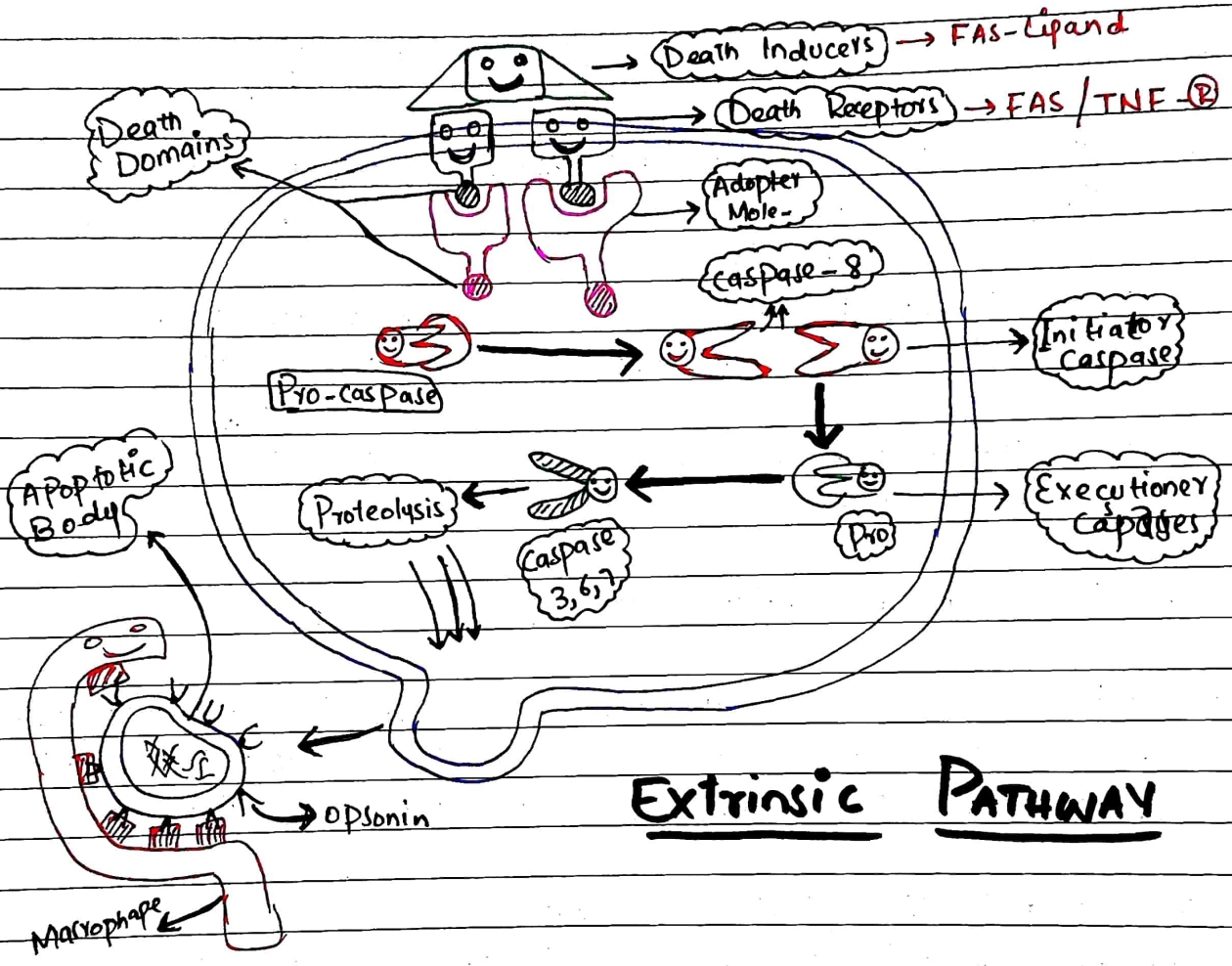
→ These Apoptotic bodies express special molecules → "Opsonins" w/c is a signal for Macrophages & they also secrete molecules w/c binds wd opsonins & phagocytosis occurs.



Extrinsic Pathway

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Intrinsic Pathway

* Also called → Mitochondrial Pathway.

Why Different cells have Different Life Span?

→ Actually Every cell have "Pro-Apoptotic / Pro-Death" genes & "Anti-Apoptotic / Pro-Life" genes. There is balance b/w these ② types of Genes → w/c determine life of cell.

→ If Pro-Apoptotic genes expresses more → Apoptosis occur early & vice versa if Anti-Apoptotic genes expresses more.

* Pro Apoptotic → Bad, Box, Bak
* Anti- " → Bcl2, Bcl-x

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* The Real bad Poison are Present in Mitochondria.

→ Mitochondria have cytochrome-c & Apoptosis Inducing Factor (AIF).
→ There are channels in mitoch- membrane → (Mito- Permeability Transition Pores) → thro. w/c cyt-c & AIF can Escape out.

→ Normally the products of Pro-life genes make Homo-Dimers wd each other or Hetero-dimer wd pro-death genes product and block / plug the Transition pores & also inhabits. Apoptosis Activating Factor w/c is present in cytoplasm. (AAF)

→ when cell is going to die → the Process reverses → Pro-death genes Products → dimer → cannot plug the Pores and thus cyt-C and AIF Come out of mito.

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→ AIF → inhabits Anti-Apoptosis Factor / Bcl-2, x etc.

→ Cyt-c along wd AAF activates initator Caspases w/c will inturn activate Executioner caspases & remaining Pathway is same as Extrinsic pathway.

● Activation of Pro-life & Pro-death Genes is dependant upon Growth Factors, Harmones etc.
i.e If Growth Factors are present → they signal Pro-life Gene positively & Pro-death genes nepatively.
→ But if G.F aren't they Pro-death genes are activated & Apoptosis occurs.

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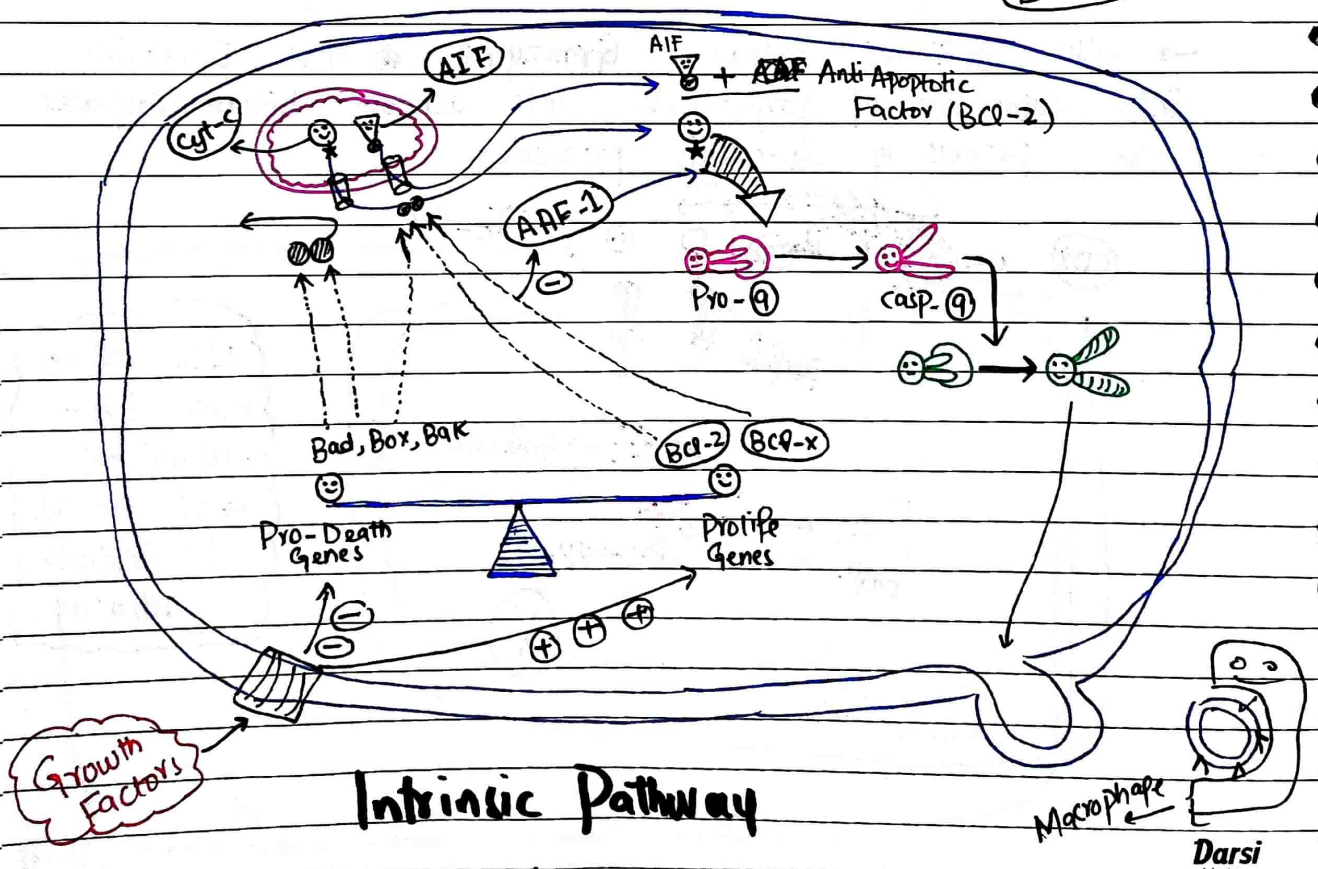

Intrinsic Pathway

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How Cytotoxic T-cell Kill the Cell / Apoptosis :

→ When a cell is infected wd virus → viral protiens are expressed on surface of cell along wd class-1 MHC molecule.

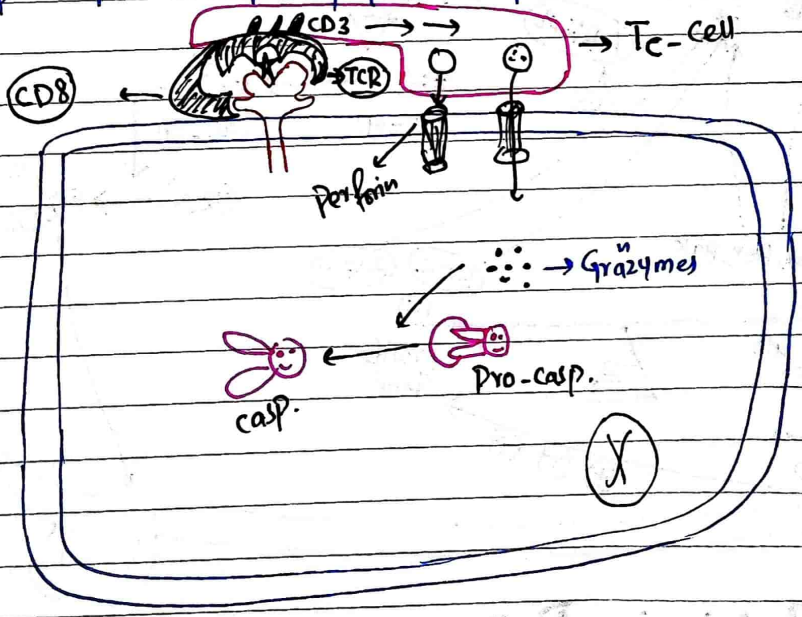
→ Cyt-T cell → attach to viral protien thru TCR (T-cell Receptor) &p also thru CD-8 to MHC to confirm whether viral protien is present or not.

→ When binds then → it give signals to the CD_3 molecule.

→ Cyt-T-cell become activated → it come near to ~~prear~~ cell →

→ release pre-formed peptides (Perforins) → w|c make holes|pores in cell surface membrane.

→ Also cyt-T cell release Granzyme thru perforins into cytoplasm of target cell w|c activate initiator caspases &p process of apoptosis proceeds.



NK-cell → have FAS-Ligand → → Kill the cell By Extrinsic pathway.

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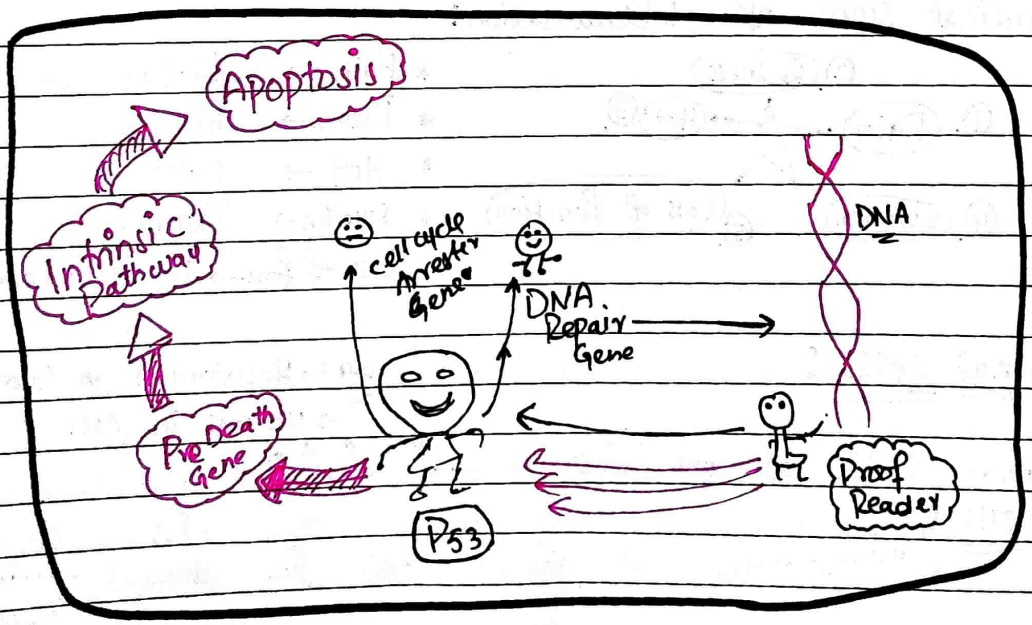
How P53 Gene Induce Apoptosis:

* P53 → Guardian of Genome.

Normally when DNA Replication is going on → there are Proof reader Genes w/c check the mismatched pair in DNA. When error occurs → proof reader signals the P53 gene w/c activate cell cycle Arrest gene to Arrest the cell cycle & P53 also activate DNA repair gene to repair the error.

→ But If Irrepairable loss occur to DNA → Proof reader Stimulate / Irritate P53 too much that it activate another pathway → Stimulate Pro Apoptotic gene & inhabit Anti-Apoptotic genes → As as result →
→ Intrisic pathway is activated → & Apoptosis occurs.



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INFLAMMATION

→ "The response of vascular connective tissue towards injury ——."

Purpose OF Inflammation :

* To destroy / wall-off the cause of injury.
* To remove necrotic cell so that to open the way for tissue repair.

Types :

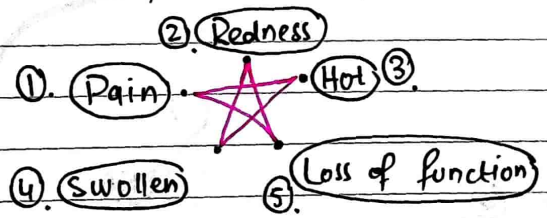
① Acute Inflammation

→ Tissue response to the injury Rapidly & Transiently (short-duration)

② Chronic Inflammation

→ Response for long duration.

→ ⑤ Cardinal signs of Inflammation:



* Pain → Dolar
* Redness → Rubor
* Hot → calor
* Swollen → Tumor
* Loss of func. → Functiono Losia

Paranchymal cells :

→ "Functional cells of any tissue ——."

e.g :→ Hepatocytes in liver
→ Neurons in CNS

Stromal cells :

→ "Supporting cells w/c supports Paranchymal cells ——."

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ACUTE INFLAMMATION

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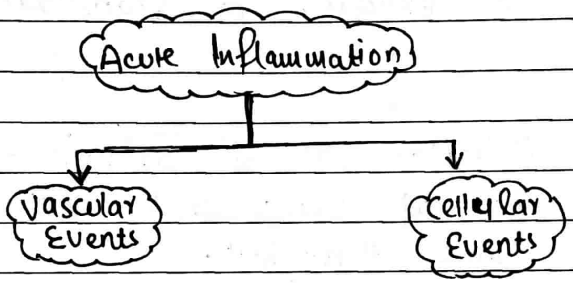
→ When a tissue is injured by any means → Paranchymal & Stromal cells release mediators of Inflammation like Prostaglandin, Leukotriens, tumor Necrotic factor etc.

→ Mast cells are present all over body but they are specially concentrated around the Blood vessels, around the nerves, Around all External & Internal lining of the body.



Vascular Events :

① Vasodialation OF Arterioles :

→ Histamines, PG-E_2, NO etc have receptors on vascular Smooth muscle → due to w/c vasodialation occurs.

② Exudation : ↑↑ Permeability :

→ Loss of Protien-rich fluid from micro circulation to Interstitial fluid of injured tissue → Exudate compartment.

→ Initially there is Neurogenic vasoconstriction w/c is followed by Prolonged vasodialation.

* Exudate has high Specific gravity.

→ Occurs due to Disturbed starling forces, + Disturbed vascular Permeability.

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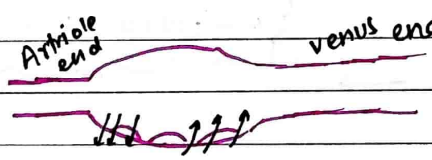
⊛ **Transudate** → Loss of Protien - Poor fluid from vasculature to Interstitial fluid.
→ occurs due to Disturbed starling forces only.
→ have low specific gravity.

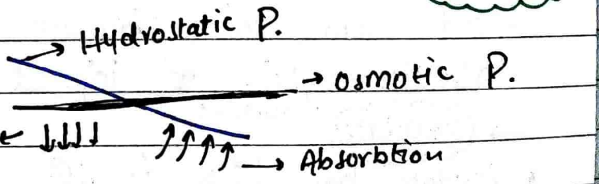
⊛ **Edema** :
↑↑↑ fluid in insterstital fluid ——.
May be due to Exudate or Transudate.

→ Normally at Artriolar side of capillaries → Hydrostatic press. is high & low at venus end But Osmotic colloidal Press. remain same throughout.
so at Artriolar side → Hyd-P. is greater than Osm-P. → so fluid come out of Capillaries but opposite occur at venous end → fluid absorbed into Capillaries.
→ In Inflammation → due to vasodialation → $P_{Hyd.}$ → ↑↑ more and also due to mediators of Inflammation → Permeability of endothelial C-Tissue ↓↓ → thus large amount of fluid & protiens are lost from capillaries to Int-fluid compartment → Exudate.

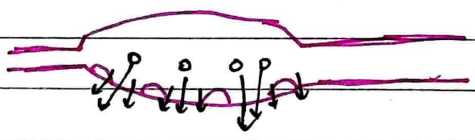
* When Permeability → Same → Only fluid lost → Transudate

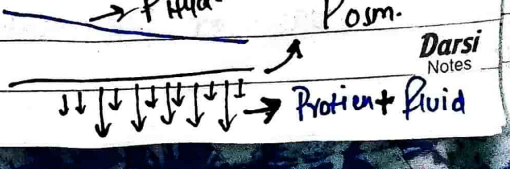
Normal →





Inflammation →





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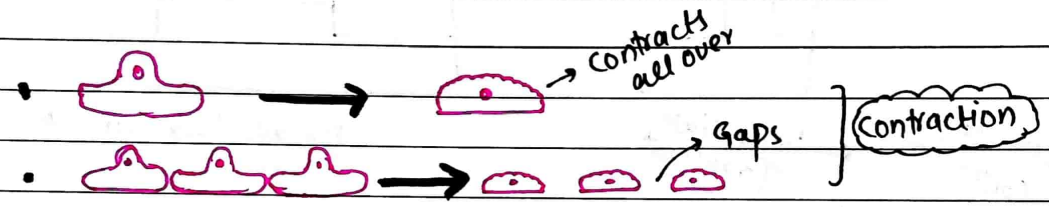
How Permeability of Endothelial Cells Increases ?

* Histamine → By mast cell.
* Brady kinine → By Plasma Protiens.
* Leukotriene → By Injured tissue cell memb.

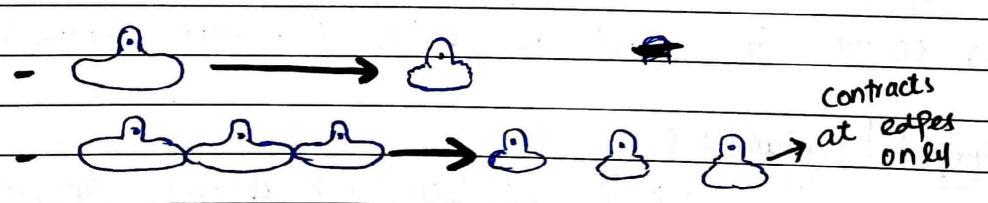
] Vasoactive substance

→ All of them have receptors on Endo-cells → they cause (Contraction) of endoth-cells → inter-endoth-gaps are produced.



→ These mediators are Pre-formed / released rapidly.

→ As Inflammation continues → Cytokines (TNF, IL-2) are produced after some time → w/c cause (Retraction) of end-cell → same gaps are produced.



* Actually These substances binds wd Receptors on endo-cells → w/c activate Intracellular Protien kinases → → Contraction/Retraction occurs.

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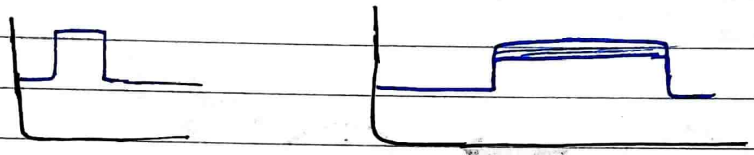
Immediate Transient Response : Increased permeability initially due to Histamine, Brady. L-T → for short Interval.

Prolonged | Delayed Response : ↑ permeability after Transient response → due to Cytokines → for long time



Due to contraction ← Immediate Transient

Delayed → due to Retraction

* ↑ permeability occurs more on venous side of Capillaries | venules → Bcz they have more receptors for chemical mediators of Inflammation.

(Physical Trauma) :

★★★ Injury to tissue → Also directly disrupts endoth. linings → ↑↑↑ vascular permeability.
→ occurs in part of microCirculation equally.

Much
Prolonged | Delayed :
→ In Sun burn → delayed cytokines release →
→ affect appear after many hours.

★★★ ↑ permeability also occurs some times when WBCs gets attached to endo-cell & start destroying them.

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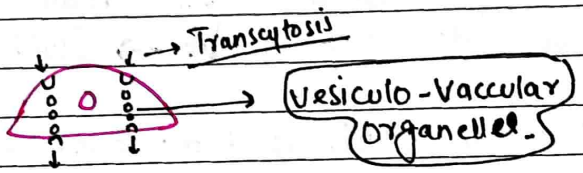
☆☆☆ Leukocytes Mediated Endothelial cells Injury :

→ Commonly occurs in Pulmonry & Glumerular micro-circulation → bcz these ② loves to hold the Leukocytes for Longer duration.

→ Leukocytes cause injury by ①. Oxygen derived free radicals ②. Lysosomal Degradation.

☆☆☆ Transcytosis

→ Histamine & VEGF → ↑↑ transcytosis → can cause endo- injury.



☆☆☆ Excessive leakage of fluid from Newly formed vessels :

→ During Tissue repair → new capillaries are formed → → w/c are immature → don't have tight Junctions b/w endo- cell → leaky → large Gaps.

→ lethal → in Excessive burns → to much fluid exudate → → Hypo volumic shock.

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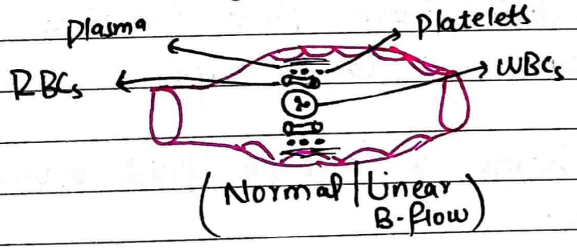
Cellular Events (WBCs Events)

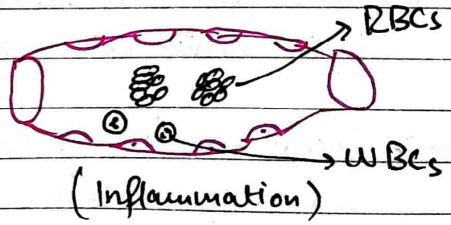
→ The normal blood flow thru B-vessels → Linear Blood Flow → in w/c Big cells i.e WBCs are in center then outer to it are RBCs and outermost are platelets.

→ outer to Platelets → cells free → Plasma → Plasmatic Zone.

→ When there is severe Inflammation → due to vasodialation → → B-flow increases to microcirculation of Inflammed area → → &p also due to ↑ Permeability → Protien rich fluid escapes out of circulation → the blood in vessels become Concentrated due to fluid leakage → (Hemo Concentration) → Its flow doesn't remain Linear → Its viscosity ↑↑ &p its velocity ↓↓ → fluid exit → ↓↓↓ → (Stasis) occ. uvs.

→ Due to Stasis &p Hemo conc. → RBCs starts to clump together → &p their group is bigger than individual WBCs → &p they take central position &p WBCs are Pushed to Periphery → to the margins → this process → (Margination)





→ Now Chemical mediators Histamine, L-T etc acts on vascular Endo-cell &p activate them → i.e → they have pre-formed granules (Weible Palate Bodies) w/c contain (P-T-O)

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→ Adhesion molecule → these granules fuses wd membrane → & sticky / molecular Hooks → P-selectins are expressed on endoth- cells.

→ Also wBCs have Adhesive molec. → all the times present on their surface → Sialated Sugars / sialy Lewis x- oliposacchride

→ These wBCs adheres to endo- cell due to Complementry Adhesion of sialated supar wd P-selectin.

→ These Selectins are first discovered in platelets → so called → P-selectin.

→ Then of due to high B-flow → Adhesion B/w wBCs & Endo-cell breaks & wBc bof become free.

→ Then after some time → Another mediators (IL-1, TNF etc) acts on Endo- cell → & beside P-selectins they also Expresses E-Selectins due to w/c Endo-cell become more sticky & wBCs adhere to it. But again due to high B-flow the bond break & wBCs keep on rolling i.e. attaching & detaching & moving forward → This process → Rolling.

→ Then another mediators (IL-8) → chemokines → & w/c have Receptors on endo-cells → attached wd Endo-cell w/c hold the wBCs strongly → strong Adhesion.
wBCs have Integrins on its surface but they are not active → when Binds wd chemokines on endo-cell surface → → Integrins → Activated & make strong Adhesion wd I-CAM / V-CAM w/c are expressed on endo. cell surface.
(Intercellular Adhesion molecule / Vascular cell Ad. mol-)

(P-T-O)

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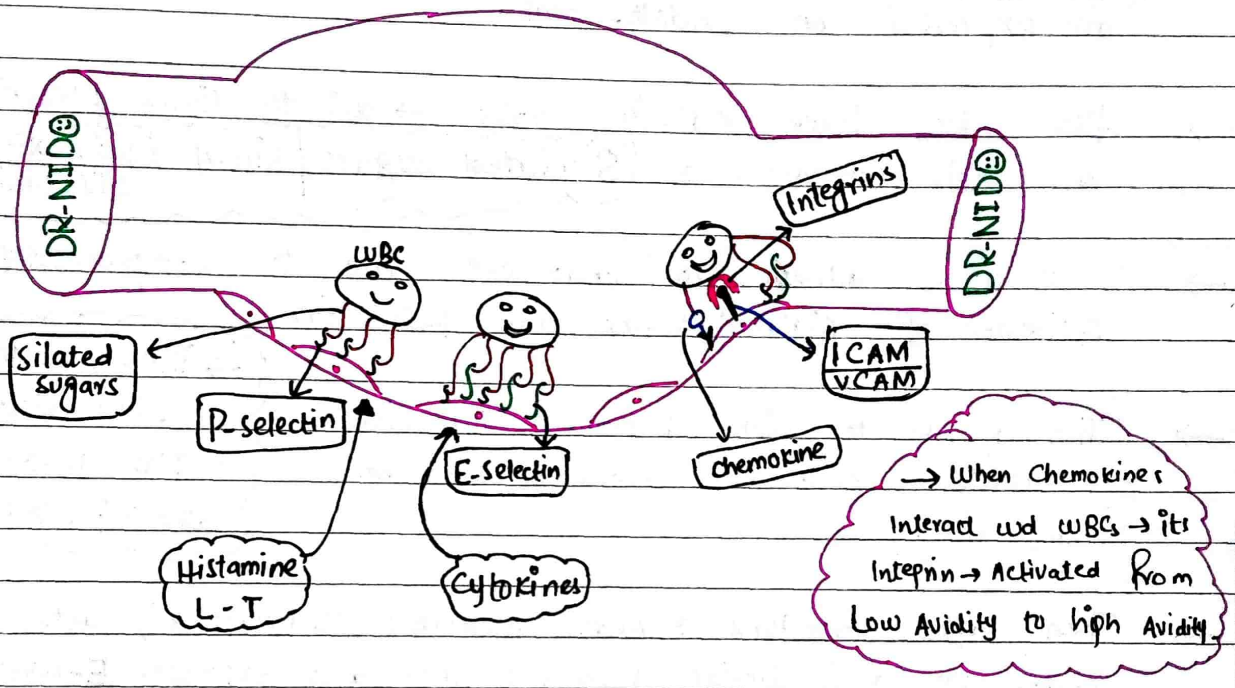
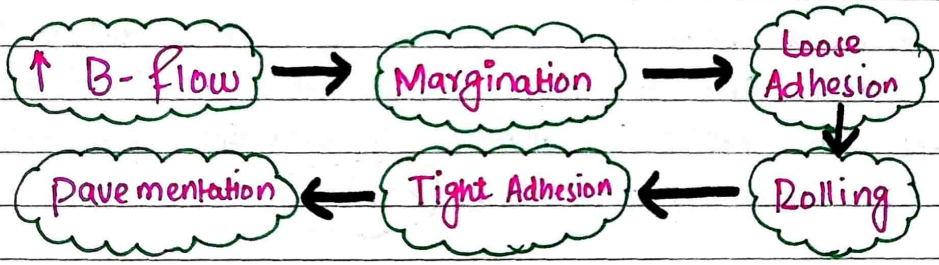
→ Now WBCs are Spread over Endo-cell → as Pavement of WBCs is made over Endo-cell → Process → (Pavementation).





How WBCs get out of Vascular Compartment to Extra-Vascular Comp.

→ Also called "Emigration or Extravasation or Diapedisis."

→ while WBCs are sticked to Endo-cell → other cytokines → → acts on Both WBCs & Endo-cell → & both expresses another adhesion molecules of same type → (P-T-O)

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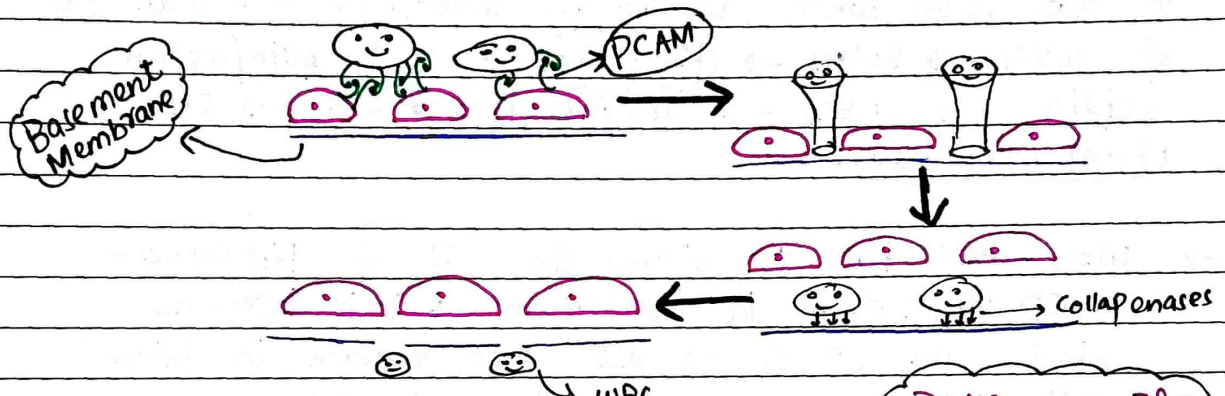
→ Homophilic Adhesion molecule → Platelets Cell Adhesion molecules (PCAMs)

→ through w/c WBCs starts interacting wd adjacent Endo- cells → &p finally WBC squeezes out through gaps b/w Endo- cell &p then WBCs releases Collapenases enzymes w/c digest Collapen of Basement memb- → &p WBCs are extravasated out to Extra Vascular space.



PCAMs are also called CD-31

How WBCs move in a Specific direction toward Injury?

→ Chemotaxis

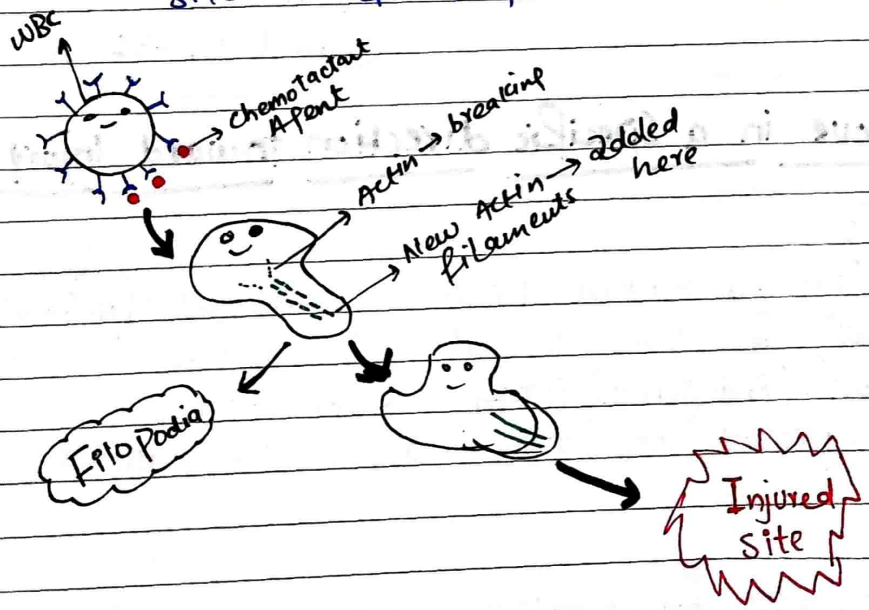
→ At site of injury → Bacteria produces chemotactic Substances (Exogenous) &p also Injured cells produce Chemotactic Substances (Endogenous) (LT-B4) → for w/c receptors are present on WBCs → so they attract WBCs.

(Methionine N-formyl)

→ WBCs have receptor for chemotactic agents all over its surface → But only those receptors are stimulated w/c (P-T-O)

→ are present toward injured site. These receptors are 7-Pass $G_{q\alpha}$ (R) → Phospholipase-C → final IP_3 → formed → w/c cause phosphorylation of Proteins → Actin Filaments are forming in that region where Receptors are stimulated → That Part of WBCs → Bulges → Filopodia → due to Actin/myosin sliding → WBCs → toward injured site → like Front wheel Car.

→ WBCs don't Pass the injured site b/c of Foot Stones → → CD-44 present in interstitium → Their integrins bind wd CD-44 → Thus they remain in injured site → & Perform its Phagocytic Action.



Sr. No.	Date	Topic

Leukocyte Adhesion Difficiency (LAD-2) :

* The disease in w/c WBCs don't have Sialated sugars → so they don't interact wd selectins → don't roll properly → don't helps in inflammation.

Neutrophilic Leukocytosis :

Normally some Neutrophils are sticked to endothelial cells all the time

* When Blood level of Catecholamines, Corticosteroids & Lithium is high → they inhabits endo-cells to express selectins → thus WBCs / Neutrophils → don't stick to endo-cells → → & Apparently Neutrophils level in Blood → high → although total Count may be normal.

Neutropenia :

* Endotoxins → over express selectins → Ntrphils → stick → more → in Blood → less.

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NECROSIS

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→ Always pathological.

→ "Series of morphological changes in a lethally / irreversibly injured cells ——."

* changes occurs due to :
  ** Denaturation of Intracellular structural + Functional Proteins.
  ** Enzymatic digestion of injured cells → Auto + Hetero lysis.
  ** Disruption of cell membrane.
     ↳ Intracellular Components come out to Extracellular compartment → affects Sorrounding cells → Elicit → Inflammation.

→ These changes doesn't occurs suddenly rather they take many hours to occur.

→ If a Person dies early ie. 1-2hrs → there will be no evidance of Necrotic changes (e.g: If a Person → Coronary Artry blockage → dies in (2) hrs → After death → no signs of necrotic changes in his myocardium)
(But due to membrane disruption → Cardiac Specific enzymes may leak out & enter General circulation → & can be detected as early as (2) hrs. These enzymes are C-Troponin-T, C-Troponin-I, CK-MB etc)

* Eosin → Pink (↓ Cytoplasm) * Basophilia / Blue → Hemitoxilin (↓ Nucleus, Ribosome)

★ Cytoplasmic Changes : (Light Microscope)

*→ During Necrosis → cell ↑ becomes more Eosinophilic due to : (cytoplasm)
* cytoplasmic Protiens → denatures → take more Eosin.
* Ribosome dis Integrates → Basophalia → decreases

Darsi Notes

(P-T-O)

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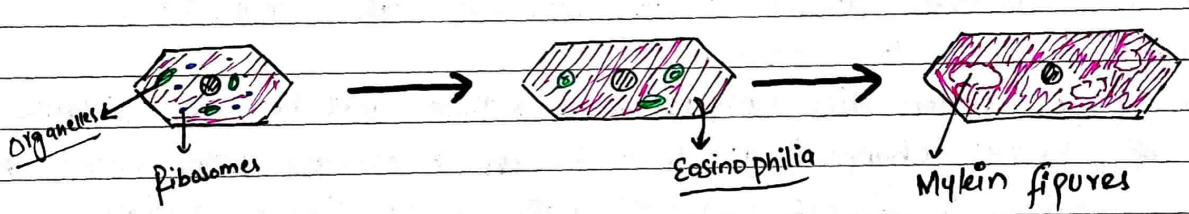
* During stress → Glycogen rapidly converted into Glucose → → Glycogen granules → disappear → So Granular appearance of cytoplasm → vanishes → Glassy / Homogenous appearance.

* Also multiple organelles → disappears from cytoplasm → → empty spaces → Moth Eaten Appearance.

* Cell membrane / organelle's membrane → remain whorl like → → called → Myelin Figures
(Myelin Figures → either engulfed by marcophages or if they remain for long time → calicification occurs → Dystrophic calcification. ← (In T-B) ←)



Ultrastructural Changes: (Under Electron microscope)

* Plasma Memb- → Reptures → Both of cell & organelle's.

* Mitochondria swells up having dense amorphous bodies (Enzymes clumped)

* Organelle's memb- → Small multiple Myelin figures.

* Amphous Bodies in cytoplasm. (Protiens Denatured)

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Nuclear Changes :

1. Nucleus → Fades away → Karyolysis

2. Nucleus → Condenses → Intensly condenses → Pyknosis

3. Nucleus → Condenses initially → Fragments → Karyorrhexis

Types OF NECROSIS

1. Coagulative Necrosis :

→ " When cells → lethally injured → their structural & functional protiens undergo denaturation Simultaneously ".

e.g :

* Myocardial Infaraction

→ Hallmark of Coagulative Necrosis → Cells maintain their Basic Arctiture & outline atleast for few days.

* Severe Ischemia / Hypoxia to many tissues except Brain → → Causes Coagulative Necrosis.

● Ischemia → denaturation of Structural + Functional (enzyme) Protiens → → enzymatic dipestion → doesn't occurs → So cell Arctiture → maintain for few days → Nucleus disappear → ANucleated cells wd Eosinic cytoplasm. Then Neutrophils + Macrophages → Inflammatory Reaction. Fibrocytes → Fibroblast → Collagen formation → Scar → formed.

Darsi Notes

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② Liquifactive Necrosis :

→ "There is denaturation of structural protiens but there is intense Enzymatic Digestion (Autolysis + Heterolysis) ——."

Heterolysis → Leukogenic Microbes → Pus producing / Pyogenic

→ Tissue dissolution → faster than Repair.

* Pus → classical Example.

* In Brain → Liquifactive necrosis occurs → but reason is not sure. (Not wd Associated Mikrobe → but due to Ischemia)

* ③ Suggestions are there:

① . structural Protiens → less in CNS.
② . Lysosomal Enzymes → more Intense in CNS.
③ . Phospholipids → more in CNS.

PUS :

→ "Area of Liquifactive Necrosis w/c consists of: (Alive + Dead + Dying) Local cells + (Alive + dead + dying) microbes + (Alive + Dead + Dying) Neutrophils → All floating in protien-rich Exudate ——."

* Another example of Liqu- Necrosis → **Abcess**

→ Abcess is localized pus in deep tissues

→ Central core → dead Neutrophils + Microbes + cells → Then Layer of Healthy Ntrphils → then Blood vessels → then Proliferating cells + Fibroblasts.

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NEOPLASIA (Nomenclature) M T W T F S

* Neo → New * plasia → Growth

Every new growth is not Neoplasia.

Pre-Molecular Era

→ Neoplasia is Abnormal mass of Tissue w/c :

* Grows in Excessive Manner -
* " " Uncordinater " -
* " is Persistant (Even if you remove the stimulus w/c stimulate it / has initated it.)
* Autonomous (doesn't obey the laws of Growth)

Modern Era

→ "Neoplasia is a Series of Genetic Damages / Mutations in a cell / Prognies of a cell untill they have a tendency to make Abnormal tissue mass w/c grows excessive, Uncordinatedly & is Persistant ——— ."

* Proto Oncho Genes → for Proliferation of cell. (Accelerator)
* Tumor Supressor " → stops over proliferation (Brakes)
* DNA repair " → Repair Mutations.
* Pre-Apoptotic " → For Apoptosis of cell.
* Anti- " " → Prevent Apoptosis.

* If Proto Oncho → over Expressed
* " Tumor Supp. → under "
* " Pre-Apoptotic → " "
* " Anti- " → over "

→ Neoplasia

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→ Neoplasia is like a dangerous Parasite → originate from body at cost of normal Body fonction & also is damaping the body.

Tumor

- Previously → Any swelling in the body → Tumor.
  → Cardinal sign of Inflammation.
- Now → Any swelling → w/c is neoplastic in Nature.

② Basic Components OF Neoplasm | Tumor

Paranchyme

→ Neoplastic cells i.e. Transformed cells.
→ Every tumor has Paranchyme.
* It determines:
  → Nomenclature of Tumor.
  → Biological Behaviour of " .
    ie Malignant / Benign

Stroma

→ Not itself → Neoplastic
→ Supportive & Reactive Component of a tumor.
→ Consists of:
  → Connective Tissue.
  → Blood vessels.
  → Reactive Inflammatory cells.
→ Determines spread of the Tumor.

- Some Tumors → very little stroma → soft + Fleshy.
- " " → a lot of collagen → Desmoplasia.
- " " → Too much collagen → Scirrhous.
  ↳ Stony Hard → Breast Tumor

Darsi Notes

Neoplasia

Benign

→ Those tumors whose microscopic & Macroscopic appearance suggests that they are innocent i.e.

* They are localized.
* They are Non-Invasive.
* They are Non-Metastatic.
* can be removed by Surgery usually.

→ Some Benign Tumors are dangerous like:

→ Ependymoma → In 3rd Ventricle.
→ Meningioma
→ Glioma
→ Atrial Myxoma → In Lt. Atrium.
→ Pheochromocytoma → ↑↑↑ Catecholam.
→ Insulinoma → Severe Hypoglycemia.

Heart Sound → Tumor Plop

Malignant

→ These Tumors are very dangerous as they:

→ Invade the Surrounding str.
→ Metastatizes.
→ Not localized.

Meningioma

Invasive → Malignant

Non-Invasive → Benign

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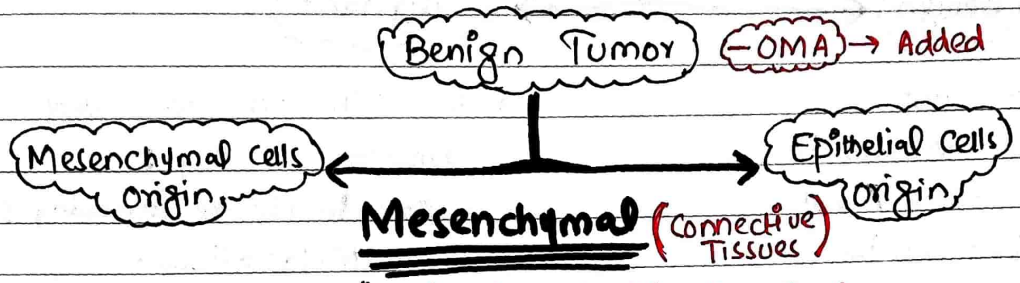
Benign Tumor Nomenclature



→ Usually "-oma" is added at the end.

* From Adipocytes ⟶ Lipoma.
* From Fibrocytes ⟶ Fibroma.
* " Cartilage cells ⟶ Chondroma.
* " Bone cells ⟶ Osteoma.
* " Skelet-Muscle ⟶ Rhabdomyoma.
* " Smooth Muscle ⟶ Leiomyoma ⟶ Most Comon → In Uterus.
* " Blood vessels ⟶ Hemangioma.
* " Lymph vessels ⟶ Lymphangioma.
* " Meninges ⟶ Meningioma. → Non-Invasive

20% of women normally.

Fibroids

Epithelial cell origin

① ADENOMA

→ "Benign Tumors originated from (Glandular Epithelium) or they may originates from (Non-Glandular epithelium)."

→ Those Adenomas w/c are originated from Glandular Epith. may have glandular Pattren or they may have Non-Gland. Pattren.

→ But Adenomas w/c are from Non-gland. epith. must have glandular Pattren.

* Glandular Pattren → Cells → In circle → Acini

Glandular

Glandular Pattren ← → Non-Glandular Pattren

(Acini)

(sheet)

↳ Adenoma of Supra Renal gland.

Non-Glandular

(Glandular Pattren) → Adenoma of Tubular Epith-cell of Kidney.

② Papilloma :

→ "Benign Tumors originating from Surface epithelium → growing in Finger-Like / Papillae Like (Fronds) fashion → Macroscopically or Microscopically".

→ Fronds

→ Classically ② Epitheliums → Stratified Squamous & Urothelium.

* Stratified → Skin + Tongue + Larynx * Urothel. → Urinary Sys.

③ Cyst-Adenoma :

* Cyst → Any fluid filled cavity → lined by epithelium.

→ "Tumors → w/c have fluid filled cavities ——".

→

↳ Cyst-Adenoma

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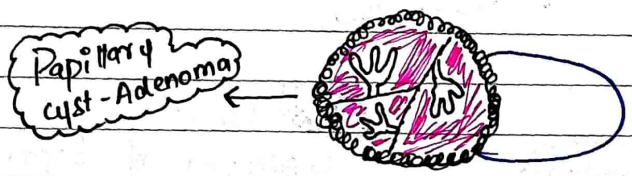
④. Papillary Cyst-Adenoma :

→ "Papillary cyst-Adenomas are those cyst-Adenomas w/c have finger like projection/fronds/papillae ——."

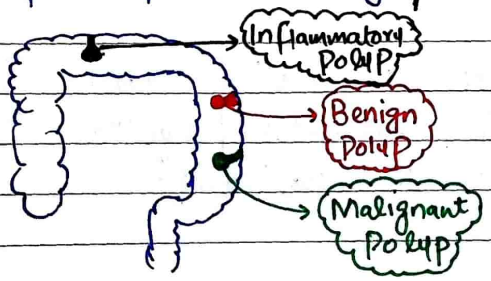


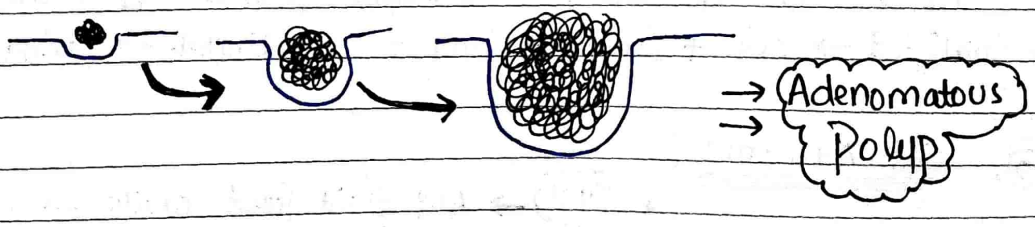
⑤. POLYP :

→ "Any mass → derived from Mucosa → Projecting into the Lumen → Polyp."

→ Polyp may be benign/Malignant/Non-Neoplastic at all.

↳ Inflammatory polyp
↓ ↓
Allergic Polyps in Nose





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MEISNOMERS

→ These have (-OMA) at the end but they aren't Tumors.

* Hematoma
* Granuloma → collection of Immune cells around microbe.
* Christoma → Normal cell, arranged in a normal fashion but placed in a wrong place.
  e.g: * Gastric Mucosa cells in Meckel's Diverticulum.
  * Pancreatic Tissue in Gastric wall.
* Homartoma → Normal cells, At Normal place but Arranged in an abnormal Fashion.
  e.g: Homartomas in Lungs.

(Choristoma):

- ⑤ girls holding Hands wd each other → Enters → Male Toilet

(Homartoma):

- ⑤ girls in girls Toilet → But in uneven Positions.

→ Malignant Tumors having -OMA in their ends:

* Invasive Meningioma
* Glioma
* Melanoma → Malano-Carcinoma of skin.
* Hepatoma → Hepato-Carcinoma.
* Mesothelioma → of Pleura of Lungs.
* Lymphoma
* Seminoma → of Testis.

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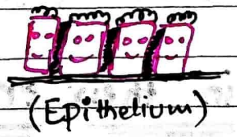
MALIGNANT TUMOR NOMENCLATURE

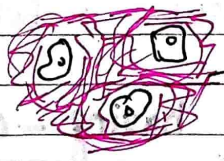
Metastasis: "When Tumor makes secondry growths w/c are discontinuous with Primary mass physically ——."

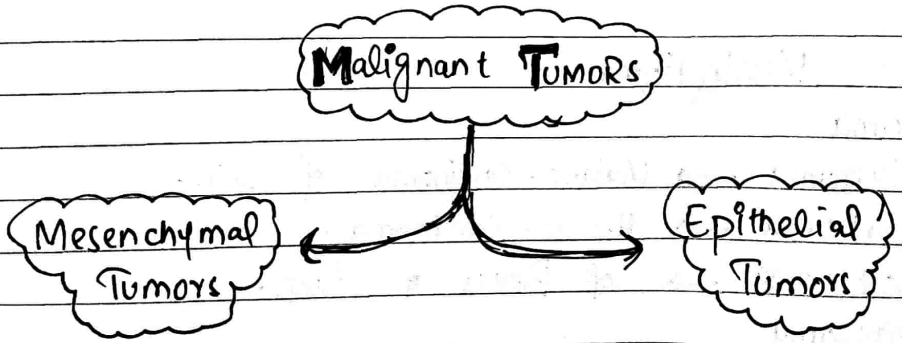
* Malignant Tumors are also called "Cancer".
* Cancer means "CRAB" → stick very tightly to structure like crab.

Epithelium: Connective Tissue in w/c cells are Tightly held to each other & have well defined Basement Membrane & cells shows Polarity (Apical side, Basal side, Lateral side → different)
→ Have No Intercellular Matrix.

Mesenchyme: "Embryonic C-T in w/c cells → no holding → → Away from each other, have large Intercellular matrix in b/w cells & cells → no Polarity."
→ Usually/Almost Mesodermal in Origin.


(Epithelium)


Matrix
(Mesenchyme)



* —Sarcoma
* —Carcinoma

MESENCHYMAL TUMORS

→ Usually have "– SARCOMA" at the end.

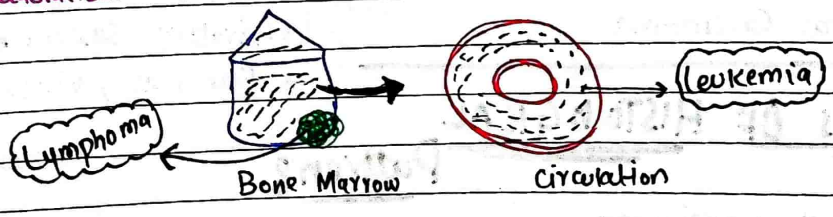
* From Striated Muscle → Rhabdomyo Sarcoma
* From Fibrocytes → Fibro Sarcoma
* From Adipocytes → Lipo sarcoma
* From Cartilage cells → Chondro Sacroma
* " Bone " → Osteo Sarcoma
* " Blood vessel → Angio Sarcoma
* " Lymph vessel → Lymphangio Sarcoma
* " Mesothelium → Mesothelioma*
* " Meninges → Invasive Meningioma*
* " Blood Forming cells (Hematopiotic cells) → Lymphoma* / Leukemia*
* " Smooth Muscles → Leiomyo sarcoma

Lymphoma

* Solid cohesive masses.
* Didn't spill over to Blood Usually.
* Didn't diffuse
→ Like Butter → e.g:
→ Metastatizes → But Metastatic Masses → Also solid

Leukemia

* Diffuses to Bone Marrow.
* Spill over to Blood → Blood Count → ↑↑↑
→ Like Milk → e.g:



* Lymphoma can sometimes shifts in Leukemia & vice versa.
* Mesenchyme of Head & Neck → From Ecto derm.

Darsi Notes

EPITHELIAL MALIGNANCIES

→ Usually have "-CARCINOMA" at the end.

→ Some epith. → derived from Ectoderm, Some → Endo- & Some → from Mesoderm → So Epithel. Malignancies can be of Ectodermal, Mesodermal or Endoderm. Origin.

Ectodermal

→ Cutaneous Squamous Cell Carcinoma
→ Basal Cell Carcinoma
→ Malignant Melanoma* → Neural Crest Cell derivatives.

] → Epidermis derivatives.

Cancer of Melanocytes

MESODERMAL

→ Renal cell Carcinoma.

Epithel. of Renal Tubules is derived from Mesoderm

ENDODERM

→ GIT - Adeno - Carcinomas.
→ Cholo - Rectal Carcinoma

Endoderm → lining of GIT & most of the Respiratory System. → Pancreas, liver etc

On the Basis OF HISTOLOGICAL Pattern:

* Squamous cell Carcinoma.
* Adeno Carcinoma → Glandular
* Papillary Carcinoma → Fronds
* Undifferentiated Carcinoma → cells → undifferentiated.

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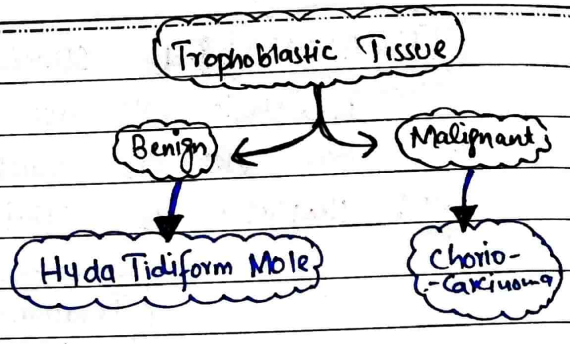
Some other Carcinomas :

* Brocho-Carcinoma → Lungs
* Chorio-Carcinoma → Placenta
* Seminoma* → Testis

Hepatocellular Carcinoma



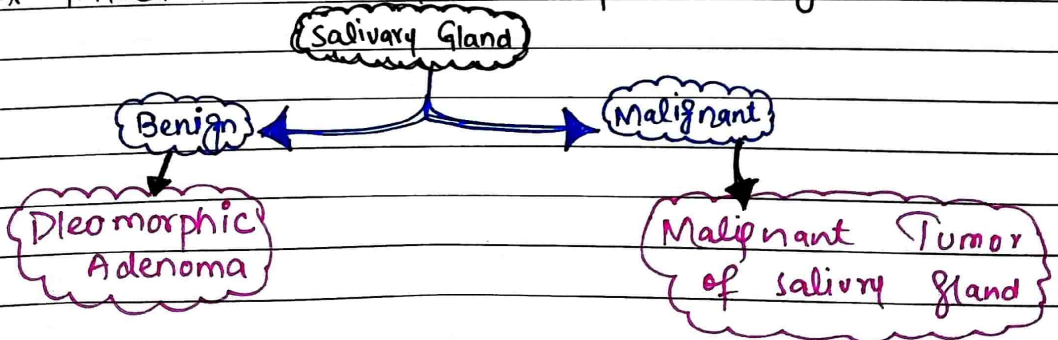
- All the Benign & Malignant Neoplasias → Usually are derived from One Germ Layer & all the Neoplastic cells are usually Closely Resembling to each others.

MIXED TUMORS

→ " Tumors → Derived from one germ layer → then undergo Neoplastic Transformation (Divergent Differentiation) →
→ so tumor contains different populations of cells → But all the cells Types are derivative of one Germ layer →
→ Such Tumors ——— "

e.g. → Tumors of Salivary Gland.

-x Mixed Tumor may be benign or Malignant.



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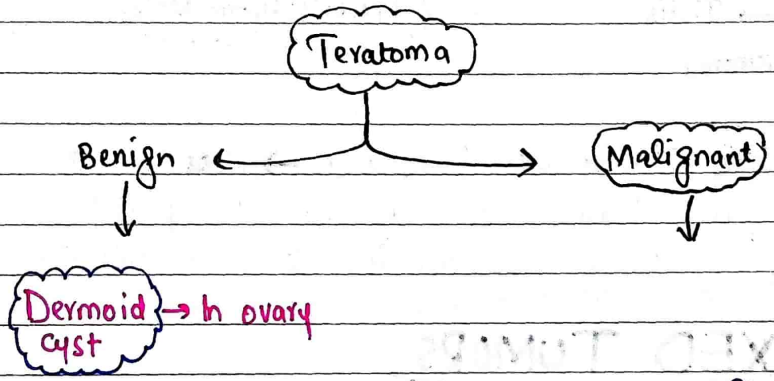
TERATOMA → Special Type of Mixed Tumor in w/c Neoplastic cells are derived from (2) or All (3) Germ cells layers.

e.g: Neoplasia of Toti-potent cell.



* Differentiated Teratoma
* Cystic "
* Mature "

* Undifferentiated Teratoma
* Solid "
* Immature "

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NEOPLASIA

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→ In Neoplastic cells → Non-Lethal damage to DNA.

→ When mutation in (Proto-Oncho) genes → they are converted into (Oncho) genes → start over proliferating uncontrolably.

→ (Mutation): "Permanent Alteration in DNA w/c is heritable to the next Daughter cell ——."

* Every day there are 10,000 injuries to DNA w/c are repaired → so they aren't mutation.

For A Cell to Be Neoplastic :

* It should be self Sufficient to Proliferate. (oncho genes → Activated)
* It should be Insensitive to Anti-Proliferative Signals. (Tumor Suppresor genes → Deactivated)
* Its repair System → Not functional - (DNA repair Genes → Not-functional)
* Its Apoptotic System → Not functional - (Pro-Apoptotic Genes → " ")
  (Evasion of Apoptotic System) (Anti-Apoptic Genes → Gain of function)
* Limitless Replicative Capicity - (Telomerase Producing Gene → Gain of function)
* Sustained Angiogenisis -
* Invasion + Metastasis - (Malignant)
* Escape from Immunity.

→ Normally during each replication → Ends of chromosome (Telomeres) shortens → A stage come that Telemers → so much short → No further Replication.

→ Some cells → high Repl-Power/Capicity → → (Telomerase) → More Active.

→ But Cancerous Cells → → Telomerase → Over Expressed → Keep on adding Nucleotides at Telomeres → cell keep on Proliferating → Replicating.

Darsi Notes

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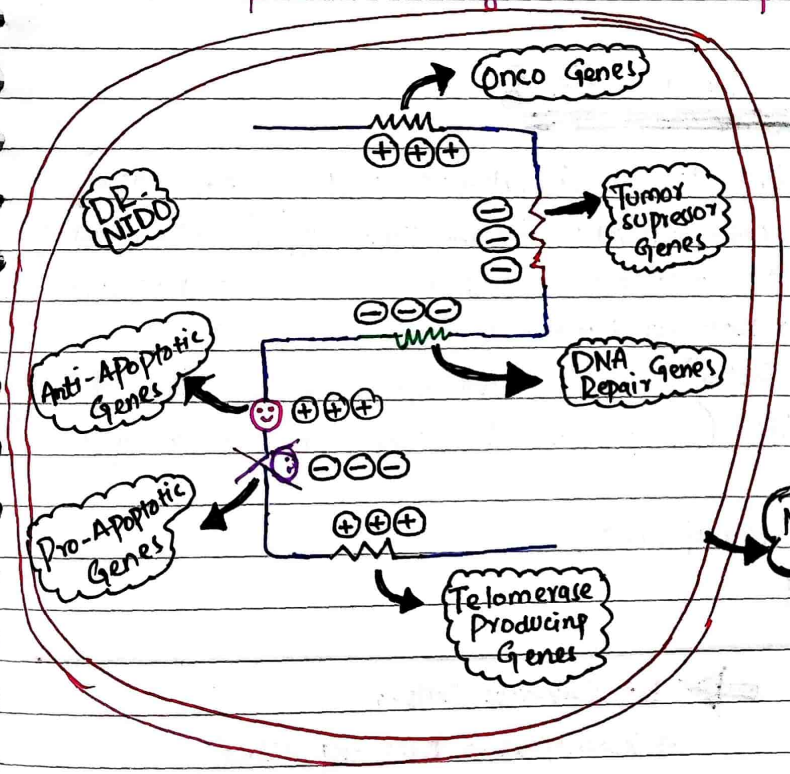
Metastasis :

→ Normal cells → Well Differentiated → can Only survive in its own micro Environment → i.e Liver cell cannot grow in Brain.

But Malignant cells → So much mutated → that some Embryonic genes → Activated → Undifferentied characteristics → → can grow in any Tissue micro Environment → → i.e can spread Throughout the body & can replicate throughout the body.



- ⊕ → Gain of Function.
- ⊖ → Loss of Function.

GENETICS OF NORMAL CELL CYCLE

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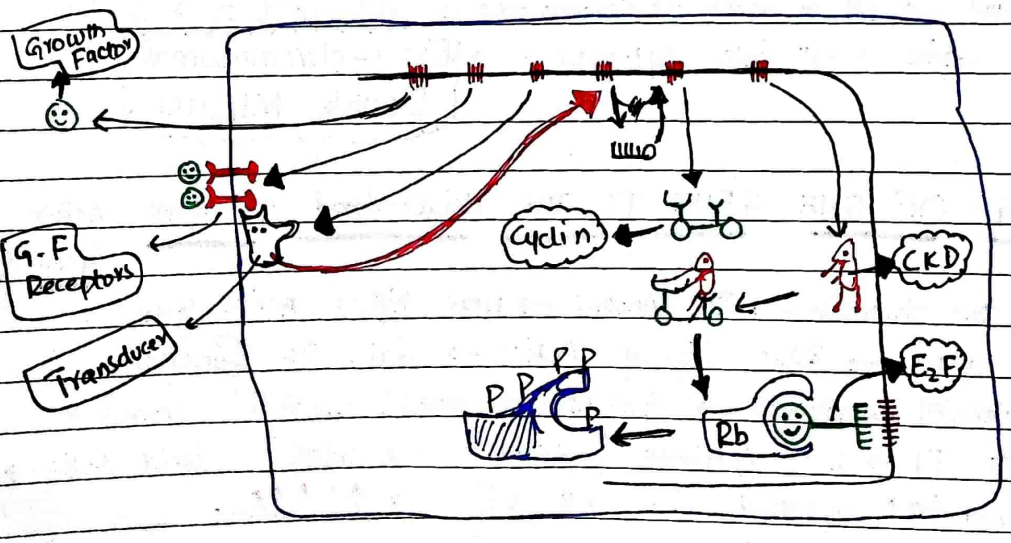
→ When Cell is resting / Normal state → It is in (Go-phase).

→ When it is about to Proliferate → It is in (G1-phase).

→ In G1-phase → 1st gene → Activated → make Protien → (Growth Factor).
→ Then another gene → Activated → another protien → (Growth Factor Receptor).
→ Growth Factor binds wd G-Factor Receptor → Dimerization occurs →
→ Tyrosine kinase Activity.
→ Then another gene → protien → (Signals Transducers) → All time sticking wd membrane. → signal back to DNA. → Activate another Gene → (Responder Gene) → w/c make protien →
→ w/c act on other gene → activated → Produces
→ (CYCLINS) → w/c activate (Cyclin-dependant kinases) → (CDK) w/c in turn phosphorylates (Rb-Protien) w/c become inhabited & (E2F-Protien) become free from it → cell Synthesis genes → Activated → (S-phase)

* Production of Cyclins → G1 → (S-phase).
* (Rb) → Also called (Retinoblastoma) → b/c first discovered in Retinoblastoma But Actually → they are present in every cell of body.



Darsi Notes

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Genetics OF CACEROUS CELL

① GAIN OF FUNCTION (ONCHO-GENE) or Proto Oncho

Point Mutation In Proto Oncho Gene / Chromosome :

→ Due to this gain of function of Genes may occur.

e.g:

* Gene for Growth Factor → gain of function → Growth Fac. → become too much sticky → didn't detach from Receptors → → so Continuous Signals to cell Synthesis.

* Gene for G-F Receptors → gain of function → Dimerization occur even in absence of G-Factors → so Continuos Signls—.

GENE - AMPLIFICATION :

→ During Replication → Many copies of One Gene is made. So Every copy → produce normal protiens → But Total no. of Protien → Too much bcz of many copies of Gene → → so Gain of function of that Gene occurs.

** Too Many Copies of Gene → Chromosome → Can't hold it → So some copies → fall into Cytoplasm → Extra-chromosomal Double Minutes

SHIFTING OF ONE GENE TO THE Neighbourhood of highly Active Gene :

→ Gene from one chromose → To Another → Near highly Active gene → → so this gene → also highly Active → Gain Of function.

e.g: In Follicular Cell Lymphoma → Anti-Apoptotic Gene (Bcl2) → shift from Chromo-18 to 14 → Near Antibody Producing gene w/c is highly Active → → So Bcl-2 → ↑↑↑ Expressed → Cell life → ↑↑↑↑↑.

Darsi Notes

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* Proto-Oncho Genes → Dominant Genes → If one Allele of Copy → Mutated → Cell over proliferates.

* Tumor Suppresser Genes (Rb etc) → ~~Dominant~~ Recessive Genes.

→ Proto-Oncho → Gain of function → Oncho-Genes.

* Tumor Supresser → If one copy → Mutated → still the other Allele → Sufficient to prevent cell from over-Proliferation.

PROTO-ONCHO-GENES

1. Growth Factor Genes :
   - → Platelets Derived Growth Factor Gene.
   - → Epithelial G-F. Gene. etc.

2. G.F. Receptor Genes :
   - → PDGF-R Gene
   - → EGF-R Gene etc.

3. TRANSDUCER GENES : (Most Common Mutation in Proto-Oncho- is Mutation of Transducer gene)
   - → Ras-Gene

* Normally Ras has GDP & is inactive → when It is stimulated → It looses GDP & Acquire GTP & Give Signal to Nucleus through Raf-Map etc pathway.
But once it give signal → It has Intrinsic GTPase activity w/c Breaks its GTP to GDP again & become inactivated.
→ Also Tumor Suppresor Gene produce protien w/c stimulate it GTPase activity.

(P-T-O)

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* Now Ras is Mutated → when become active → GTPase activity is lost → so given signal again & again.

→ Also some times Tumor supressor → Mutated → cannot stimulate GTPase activity → so again → signal → again & again.

(4) Transducer Gene :

* ABL-Gene / Tyrosine kinase → usually inhabited by Tumor supressor.

But in Chronic Myloid Leukemia (CML) → ABL gene → translocated from Gene-22 to Gene-9 near Bcr-gene.

bcr & ABL → fuses → make Hybrid gene → Hybrid protien → w/c is not inhabited by Tumor Suppressor → so cell keep on proliferating.

● IMATINIB MESYLATE Drug → selectively inhabit mutant-ABL → & also this drug has least side effects.

* myc, cyclin genes etc → same gain of function → → over proliferation of cell.

→ Cyclins → Not all the times present → One type of cyclin produced when cell cycle move from one phase to another. Then Another type of cyclins → produced → cell cycle → Another phase

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2. TUMOR SUPPRESSOR GENES (LOSS OF FUNCTION)

→ Actually these genes stops over proliferation of cells when cell is normally Proliferating → But their absence → cell over proliferation → Tumor.

★ **Rb-gene** → Present in all cells.
→ Physiological Brake.
* Retinoblastoma - Gene

* **Rb-protein** → Present in all the cells w/c is not Proliferating.

Retino Blastoma

Sporadic
→ 60 %
→ Old Age
→ Unilateral
→ Both Alleles → normal → mutation → in one then in another → so will occur in old age.
→ Cannot Pass it to offsprings.

Heriditory
→ 40 %
→ Young Age
→ Bilateral
→ defected Allele from Parents & mutation in 2nd Allele → → chances → more → Young age.
→ can Pass defective Allele to offspring.

* For Retinoblastoma to develop → both Allele should be disfunctional.

→ On chromosome # 13 → Rb.

Knudson 2-HIT HYPOTHESIS :
→ "To develop Retinoblastoma → Both the Alleles of Rb-gene must be hit by mutation ——."
→ Later on this hypothesis → True in All Tumor Suppressor Genes.

→ Those People who have one mutated Rb-gene/Allele → Also have risk of developing **Osteo Sarcoma** & some other tumors as well.

(45)

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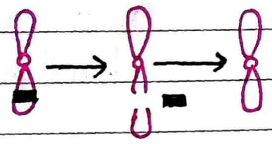
HOW LOSS OF FUNCTION MUTATION OCCURS :

① Interstitial Deletion :
→ " A piece of chromose / gene → deleted & remaing chromosome fused again ——."



② Missing Chromosome :
→ whole chromosome is missing ——.

③ Point Mutation :
→ Point mutation occur in gene → produce products → w/c can not Perform its normal function.

⇒ Loss of Function → Must be in Both Alleles.

★ **Rb-gene** → Recessive
★ But Heridatory Retinoblastoma → inherited in Autosomal Dominant Fashion?
→ This is bc2 Patient has already inherited one Mutated Allele through Germ line & need Just one Hit from Environment.
→ Although gene → Recessive bc2 Retinoblastoma only develops when both Alleles are defective.
→ But the Carriers (one defected Allele) → is so much valnurable to Environmental Hit. → easily get defective.

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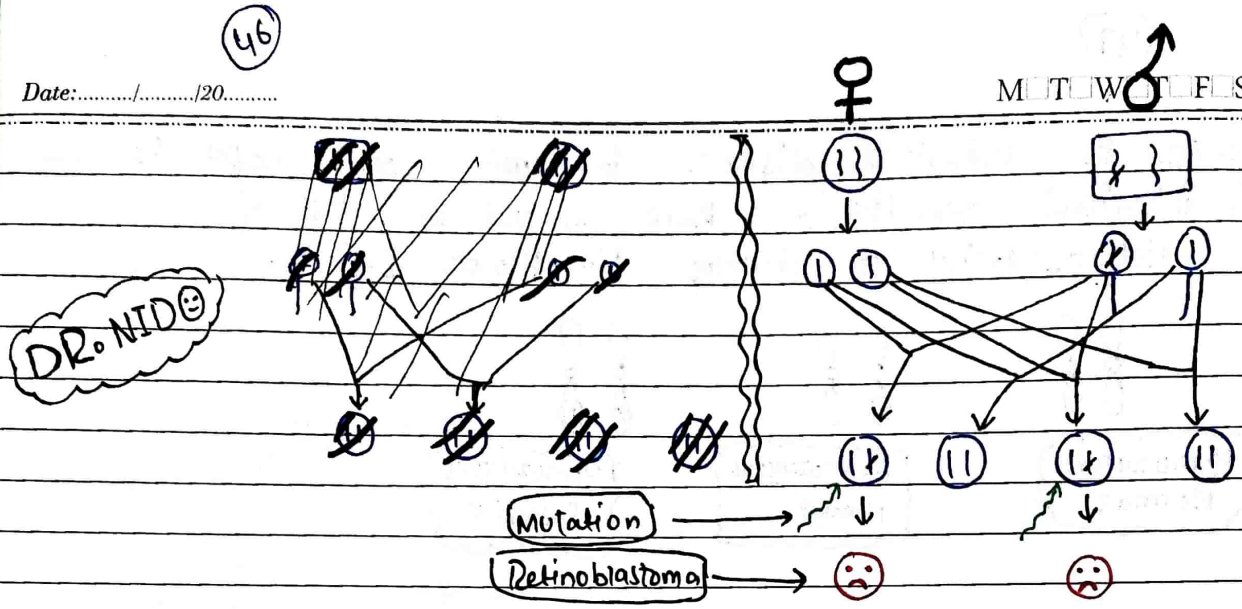

- All the Growth Factors → Stimulatory Except Transforming Growth Factor-β (TGF-β) → inhabitory.
→ Normally TGF-β-Gene produces TGF-β. & other gene produces TGF-β-Receptor.
→ TGF-β binds wd TGF-β (R) → w/c will stimulate CDK-Inhabitor gene → w/c produces (CDK-inhabitor).
→ CDK-I → inhabits CDK-cyclin complex → thus phosphorylation of Rb-protien → inhabited → cell over-proliferation → inhabited.

★ So In (Neoplasia) → TGF-β gene → Both Alleles → Mutated → → loss of function.

Also Normally → After cell cycle → Phosphatases → remove phosphates from rb-protien & it became Active again.

- HUMAN PAPILOMA VIRUS (HPV) → increases → risk of (Cancer. Cervical)
→ HPV-16 → produces protien → (E-7) → These protiens gets attached to rb-gene → so rb cannot hold E_2-F → so cell cycle → continues → over proliferation → Cervical Cancer.

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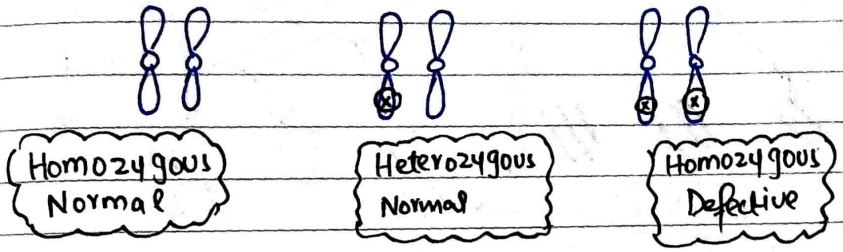
- All the inherited diseases in w/c one copy is inherited defective → there should be loss of Heterozygocity to develop Full-Blown Defect.



- **P53** (Important Tumor Supressor Gene) & (Guardian of Genome)

→ Not Active all the time but become activated when there is some Serious damage to DNA.

→ When DNA is synthesizing normally → If any abnormality occurs → ATM-gene (DNA Proofreader gene) → signals P53 w/c become Activated → make product → w/c activate another gene → w/c make CDK-Inhabitor → thus Cell cycle is stopped Immediately. (P-16)

→ P53 also Activates {DNA-repair gene} w/c make Protiens/Enzyme → repair the Abnormality in DNA.

→ when repair → done → No more signals from Proofreaders to P53 → so P53 switched off.

(P-T-O)

* A → Ataxia
* T → Telangiectasia
* M → Mutated

→ First discovered in this condition or ATM → Mutated in this condition.

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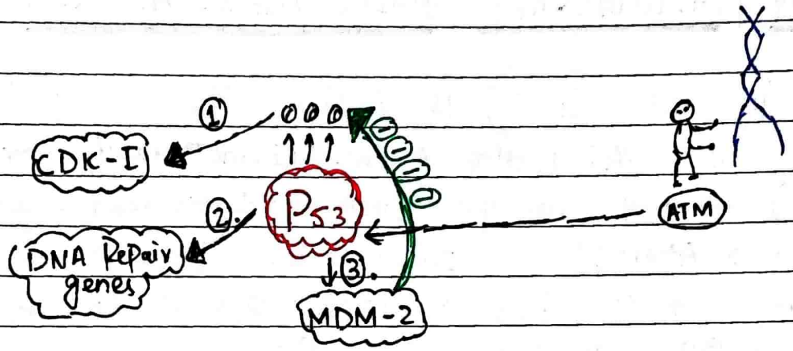
→ But Before switching off → P53 Activates another gene (MDM-2) w/c destroy P53-Proteins → so CDK-I → ↓↓↓ → cell cycle → Continues again.



→ IF DNA → Severly damaged → that (P53) cannot repair it by activating DNA repair genes → then P53 directs the cell to Apoptosis so that this damaged DNA cannot Pass to next generation.

→ So P53 → Pro-Apoptotic genes → BAX → neutrilize effect of Bcl-2 on Mitochondrial channels → cyt-C → come out → → Activates Caspases → Apoptosis.

● In (Cancer) → Both Alleles of P53 → Mutated + loss of function.

★ P53 → on chromosome # (17)

→ Most Common Proto Oncho / Dominant gene affected in Cancer → (Ras)

→ " " Tumor Supr- / Recessive " " " " → (P53)

★ Li-Fraumani Syndrome :

→ One Copy of P53 → inherited thru germ line.

→ 25% of more chances to develop multiple type of cancer at age of 50 yrs.

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- **HPV**: Produces **E-6** → Binds wd **P53** → Stops it function.

WHY SOME CANCERS ARE RESPONSIVE TO CHEMOTHERAPY / RADIOTHERAPY WHILE OTHERS ARE NOT ?

★ Those cancers in w/c **P53** is Active are responsive bc2 when we use Alkylating Agents (Chemotherapy) or Radiations (Radio-) → they damage DNA → Proof reader genes signals P53 → Attempt to repair → But Damage to DNA → severe → so P53 → Directs → cell to → → Apoptosis → thus Cancer → Responsive.

★ Those cancers → **P53** → In Active → Not-Responsive → → No P53 → No Apoptosis.

β-Catenin & APC System :

→ **Normally** β-Catenin binds wd ~~Receptor~~ Transcriptional Factor of **MYC-gene** w/c in turn activate MYC → Trancriptional factors → cyclin-gene → cyclins → Cell cycle → Move forward.

→ **APC-gene** → Produce products → w/c destroy β-Catenin → → then β-Cat- can't stimulate Proto-Oncho → cell → → over proliferation → Stops.

→ **WNT** → Stimulate its receptors → w/c in turn → → destroy APC-proteins → thus β-Cat- → free → cycle → ↑↑↑.

★ So WNT & β-Catenin Sym → Stimulatory to Cell cycle.

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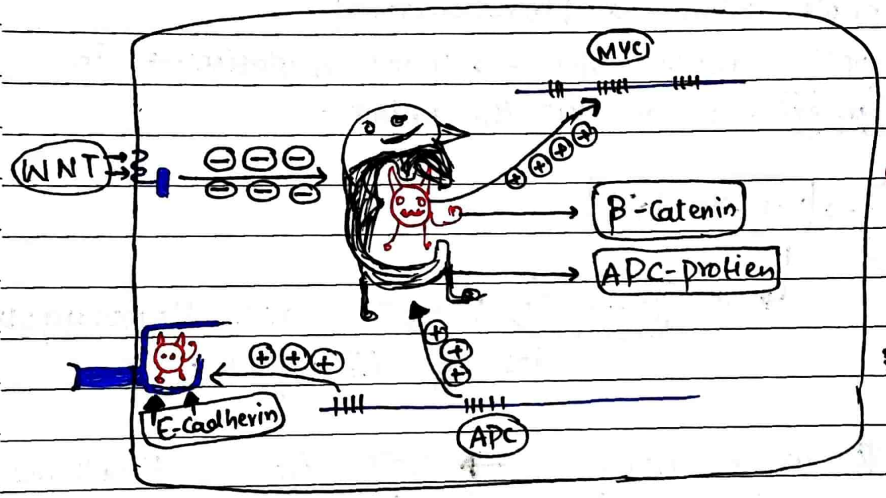
→ Another gene produces (E-cadherens) → w/c are present on cell membrane → hold β-catenin wd itself & didn't allow it to stimulate Proto Oncho genes.

- E-cadherens also help the two cells to bind wd each other → cell → inhabited → (Contact Inhabition).

★ APC + E-cadherins → Tumor Supressors.



* A → Adenomatous
* P → Polyposis
* C → coli

* Actually APC-system inhabits Proto-Oncho genes system.

IN CANCER :

- **Loss OF E-CADHERINS :**

→ Both Alleles → loss of fonction.

→ Commonly Seen in Gastric Carcinoma + Esophageal Carcinoma.

→ Also E-Cadherins → lost → cell to cell Contact → lost → → cancerous cell → detaches from Primary mass → Metastasis will also occur.

E-Cadherin → ↓↓↓

① * Cells → over proliferate

② * Metastasis

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Problem Wd APC-genes

→ Those who have inherited one copy of mutated APC → → more chances → other Allele → Mutated → At the age → of 20yrs → Thousand Adenomas → Polyps → in their colon.
→ This condition → (Heriditory Polyposis Coli).

★ Treatment:
→ Removal of whole colon → Pan-colectomy
→ bcz if you don't remove colon → Many mutations → in Adenomas → (Cancer) → can kill the patient.

★ In (Colo-Rectal Carcinomas) → Non-Heridary
↳ still (70-80%) Patients have Homozygous loss of APC-gene.

→ For a cell to work normally → Both APC & E-cadherins are required i.e Half of β-catenin is controlled by APC & half of β-catenin → by E-cadherins.
So if any of these (2) → lost → cell → over proliferate → → cz → Cannot be controlled by one Alone.

★ Also when β-catenin is (mutant) & both APC & E-cadherin are present → still there will be no effect of these (2) on this mutant β-Catenin & cell will over proliferate.

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★ NF-1 (Neuro Fibromin-1) Gene :

→ Normally NF-1 increases GTPase activity of Ras-Protien thus preventing the cell from over proliferation by inhabiting proto-Ocho genes.

→ But in Cancer NF-1 → loss of Function → Ras → GTPase-activity → down → signaling proto oncho genes → cell → over proliferating.

★ NF-1 → Also Called GTPase Activating Protien (GAP).

● NeuroFibromatosis Type-1 : (Von-Recklinghausen Disease)

→ When someone inherits one defected copy of (NF-1 gene) & then there is strong chances of defect in other copy → defected → patient develops hundered of Adenomas all over his body w/c may later develop into cancers.

* NF-1 gene → On Chromosome #17.
* Also in Von-Recklinghausen → (17) Alphabets.

★ NF-2 Gene :

→ Normally NF-2 produces Merlin-protien w/c on one side binds wd CD-44 & on other side binds wd Actin.

→ CD-44 → helps the cell to keep stabilized relationship wd Extracellular matrix & neighbouring cells.

→ So CD-44 + Merlin + Actin → Contact inhabition.

(P-T-O)

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→ In Malignancy → NF-2 → defective / loss of function → no Merein → no Contact inhabition → Cells over proliferate.

★ Neuro Fibromatosis - II :

● Patients → develops → Schwanomas → Bilateral → on 8th Cranial Nerve / Vestibulo Cochlear Nerve.

→ One Copy → inherited. → 2nd → easily mutated.

→ These patients also have risk of developing other Tumors / Meningiomas of CNS.

★ Von Hipple Lindau Gene :

→ Normally when there is Hypoxia in body → It stimulates a gene w/c produces Hypoxia Inducible Factor (HIF).

→ HIF stimulates (2) genes Vascular Endoth. Growth Factor (VEGF) & platelets derived Growth Factor (PDGF) → w/c causes Blood vessels formation → So that Blood Supply to that Ischemic part is increased.

→ But After Production → HIF needs to be destroyed →

→ w/c is done by Ubiquitin.

★ Ubiquitin - Ligase → causes ligation / binding b/w HIF & Ubiquitin.

→ This Ub-ligase is Produced by "Von Hipple Lindau Gene".

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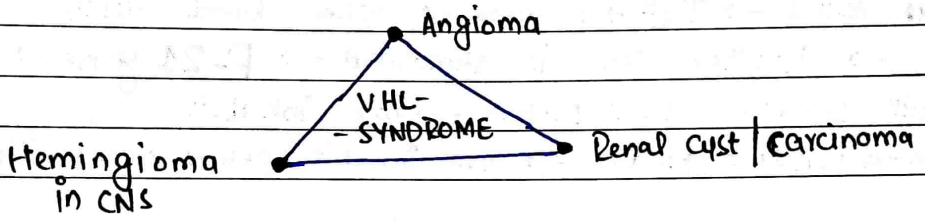
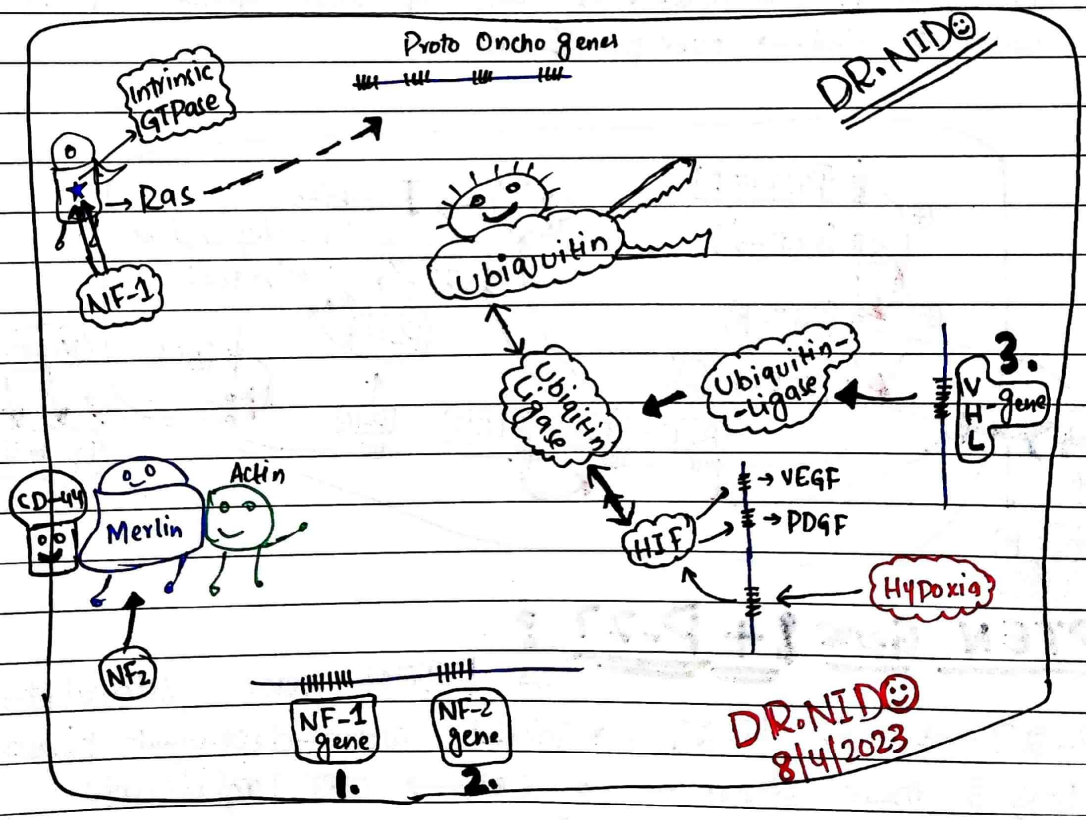
VON HIPPLE LINDAU SYNDROME :

→ VHL-gene → defective → patients → develops (Vascular Tumors) in the body.

★ Patients develops → Angioma in Retina + Hemingioma in the cerebellum + Renal cysts / Renal cell carcinoma.





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★ TGF-β Gene :

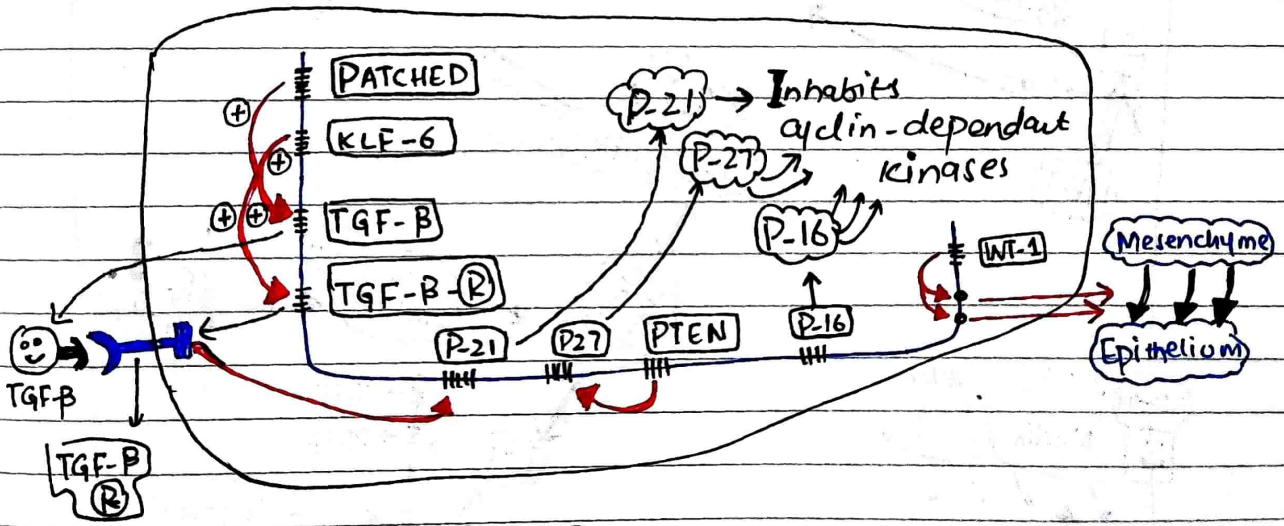
→ TGF-β gene produces TGF-Protien.

→ & TGF-β Receptor gene → produces TGF-β-Ⓡ for TGF-β protien.

→ Genes called PATCHED Gene & KLF-6 → Both have stimulatory effect on TGF-β & TGF-β-Ⓡ genes.

→ Thus PATCHED & KLF → stimulate TGF-β & TGF-β Ⓡ genes → → as a result → TGF → produced → when binds with TGF-Ⓡ → Another gene is stimulated → P-21 gene → w/c will produce P-21 protien → w/c inhabits cyclin-dependant kinases → thus inhabit cell → over proliferation.

★ Any loss in both Alleles of any of these Genes → P-21 → lost → Cell → over proliferate.



★ PTEN Gene & P-27 :

→ P-TEN gene stimulates P-27 → & P-27 → inhabit cyclin-dependant kinases.

* Loss in these Genes → Cell → over proliferate.

★ (P-16) → same like P-21, P-27.

Sr. No.	Date	Topic
		★ **Willm's Tumor-1 (WT-1) Gene :**
		Willim's Tumors : → Most Comon Renal Tumors of children :- → Sometimes → so massive → whole Abdomen → Protruberant.
→	Normally	WT-1 gene stimulates ② genes → w/c in turn produces Differentiation Factors → w/c Differentiate Mesodermal cells into Epithelial cells in Kidneys. (Mesenchymal)
→	Loss in	WT-1 → no Epithelial differentiation → Tumor develops in Kidney w/c may contain bone, cartilage, Muscle etc (Derivatives of mesoderm/ Mesenchyme) → → Willim's Tumor.

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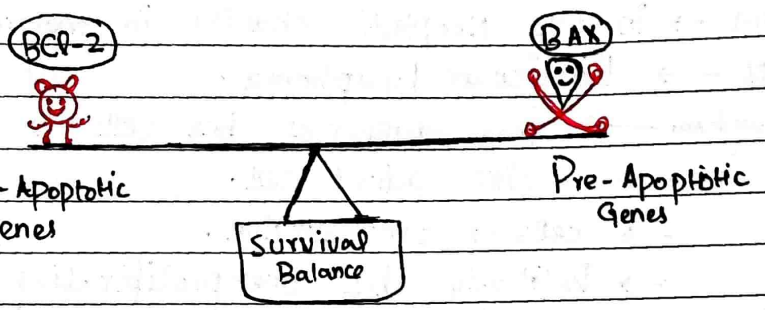
(3). Cancerous cells → Anti-Apoptotic ⁰⁄₀ (Evasion Of Apotosis)



* In Normal cell → there is balance b/w Pro-Apoptic & Anti-Apopt-
  → If Pro-Apoptotic → ↑↑↑ → cell → Apoptosis → Dies.
  → " Anti- " → " → " → survives.

* But In Neoplasia → Anti-Apoptotic → ↑↑↑ & Pro-Apoptotic → ↓↓↓ →
  → cell → survives → for long time.

☆ BCl-2 → Gain of function
☆ BAX → Loss of function
→ Neoplasia

★ Gain OF Function OF Anti-Apoptotic Genes ⁰⁄₀

* Normally → BCl-2 → inhabs the exit of cyct-c from mitochondria & thus preventing → Activation of Caspases → inhabiting → Apoptosis.

★ B-Cell Lymphoma (Follicular Type) ⁰⁄₀ (18-14 Translocation)

(translocated)

→ BCl gene on chromosome # 18 → shifted to chromosome # 14 near highly active Immunoglobulin (Ig-Gene). Thus BCl → also become highly active → BCl-2 ↑↑↑ → Apoptosis → ↓↓↓ → cell → live longer. cell → living longer → Chances of mutation → ↑↑↑ → Also Restisting →
→ Apoptosis → Neoplasia.

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→ Normally mature B-Lymphocytes → (Tendancy) make follicles in Lymph Node.

→ So Lymphoma → in w/c Neoplastic changes in Mature/well differen-tiated B-lymphocytes → Follicular Lymphoma.

→ Follicular Lymphom → less danperous bc2 cells → some what like adult cells.

→ " → cells → over survive.

→ " → Relatively less over proliferating.

→ Indolent lymphoma.

Diffused Lymphoma | Burkitt Lymphoma : (8→14 Translocation)

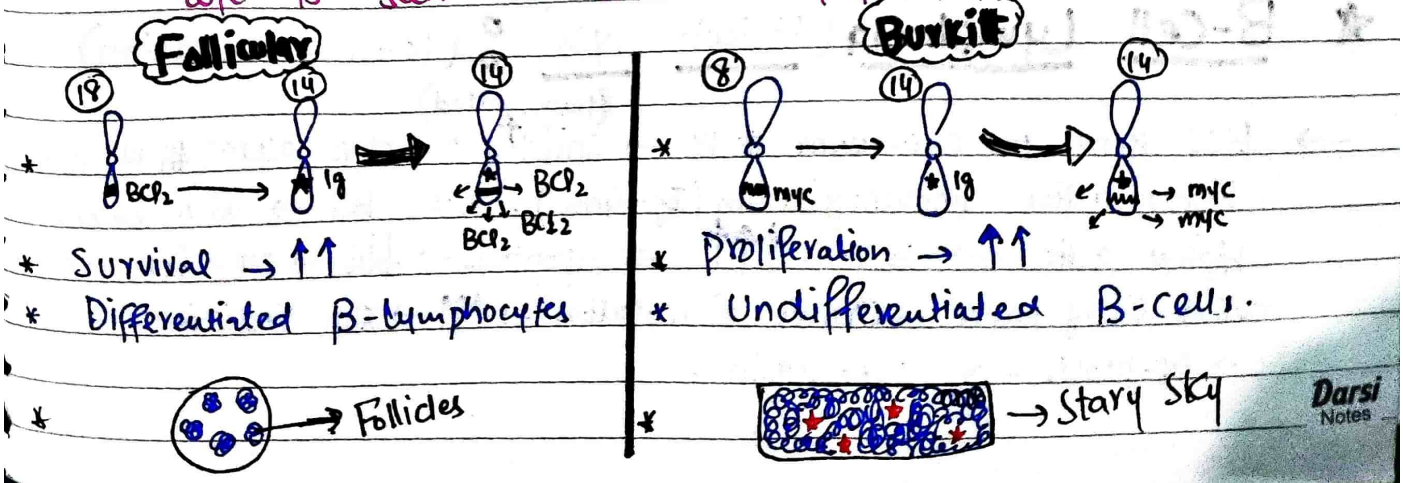
→ On chromosome # 8 → myc-gene → mutated → over proliferating → shifted to chromosome # 14 → B-cells → over proliferate → but less/not-differentiated → no follicles.

→ Danperous → bc2 → Rapidly proliferating.

→ Aggressive lymphoma.

● Some times Follicular Lymphoma way get Converted into Diffused Lymphoma.

→ Histologically → sheets of B-lymphocytes in b/w w/c star like Necrotic cell/Macrophages are present → Stary-Sky Appearance w/c is seen in Burkitt's lymphoma.



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* 18 → 14 → 18 yrs. old boy → 14 yrs old girl → → Mature → well differentiated → Follicles / Follicular Lymphoma.

* 8 → 14 → 8 yrs old boy → 14 yrs old girl → Immature → or Girl is like his mother → ∴ Mothers are (برکت) Barkat for children → Burkitt's Lymphoma.

★ Loss of Pro-Apoptotic Genes :

→ Either → BAX → loss of function.
→ or → P53 → loss of function. (bcz P53 stimulates BAX)
→ or → MDM-2 → Gain of function. (bcz MDM-2 inhabits P53)

★ In All such situations → Apoptosis → inhabited ∴ cell will survive more.

X X X

④. DNA Repair Mechanism

→ Every day → DNA encounter 5000 – 10,000 injuries / damages ∴ most of them → repaired for survival of organism.

→ Failure of DNA repair sym → doesn't directly produces Neoplasia but it play a vital role in it by allowing alot of mutation in proto Oncho genes, Tumor supressor genes etc.

→ Some People → born wd heridatory defect in DNA repair Mechanism → → high risk of developing Neoplasia → These People → Suffering from → "Genomic Instability Syndrome".

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(1). DNA Mismatch Repair System :

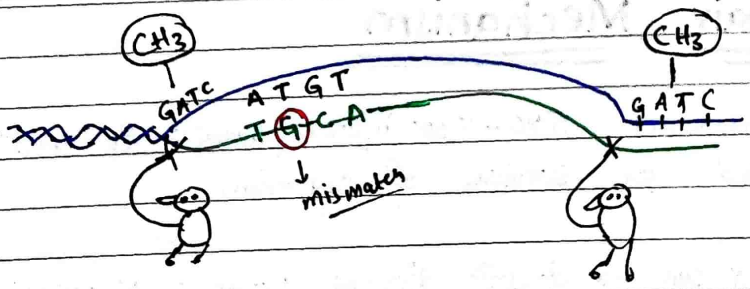
→ Normally Newly synthesized DNA is double checked i.e while synthesis → polymerases first read parental Nucleotides sequence then add complimentary base pairs.

→ 2ndly when DNA is synthesized → it is wholy scanned again → proofreader → read both strands & find mismatch.

How Enzymes know which strand is Parental & wfc is Newly Synthesized ?

→ Actually Parental DNA → at G.A.T.C region is Methylated & newly formed DNA → no methylation.

* So when Proofreaders finds mismatch they makes cuts at methylated points in Daughter DNA & then another polymerases remove bases one by one & insert correct bases & finally ligation occurs at cuts points.



Heridatory Non-Poly Posis Colon Carcinoma : (HNPCC)

→ DNA mismatched sym → defected → bcz one allele → defected heridatorily & other → thru Environmental etc.

→ so chances of mutation → move & not repaired.

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→ Most commonly affects cecum & Proximal colon.
→ Runs in families.
→ Usually MSH-2 gene → defective.
→ In females → there is also increased risk of Endometrial & ovarian carcinoma as well.

● **Tandem Repeats / Micro satellites :**
→ A sequence of 2-6 Nucleotides in DNA w/c are repeated again & again.
→ They remain same for one individual i.e everyone have same Paternal & maternal micro satellites in their each cell.
→ Vary from person to Person.
→ Used for identification of individual → DNA Finger printing.

→ To keep the micro satellites in place generation after generation → DNA repair system should be Normal.
→ If DNA repair sys → mismatched → micro satelites → not in correct position / Inbalanced → so in patient wd (HNPCC) will have different microsatelites in colon than rest of body.

● **Replicative Error Phenotype :**
→ "Change / variability in micro satellite from cell to cell or tissue to tissue within the same individual ——— ."

→ Those People who have familial / Heridatory colon carcinoma will develop carcinoma at younger age usually while those who have Sporadic type → develop it at Older age bc2 in familial → One Gene → defective already through Germ line.

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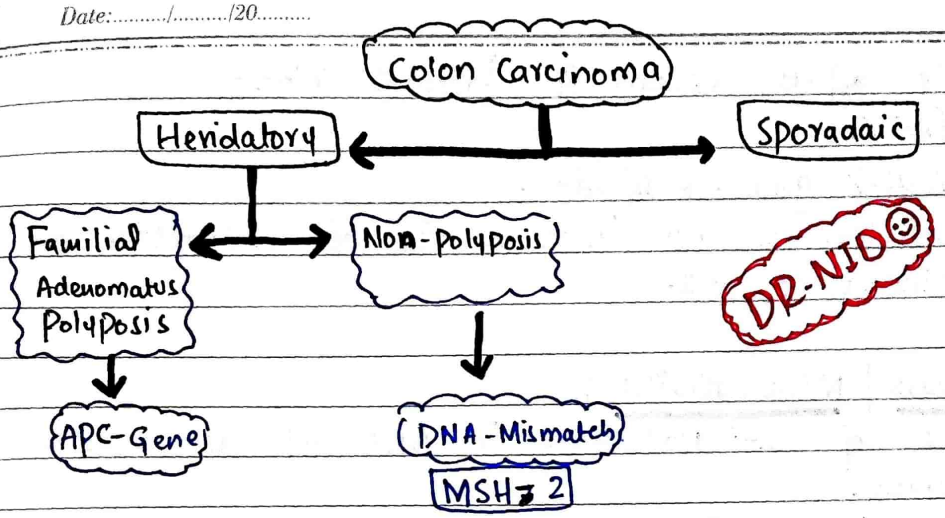

②. Nucleotide Excision Repair (NER) :

→ Causes a disease → Xeroderma Pigmentosa.

→ This system involves when damage to DNA is more severe.

→ Caused by Ultra voilet light classically. (* UV-B (280-320 nm))

→ UV causes cross linking b/w pyramidines esp. Thymine → T-T dimers are formed.

→ Normally when dimers are formed → Same ultra voilet activates another enzyme UV-specific Endo Nuclease w/c will repair it in the following sequence.

* It will Recognize it first & then will make nicks/cuts at 5' & 3' ends of dimer → Endo Nuclease Activity.
* Then this segment is Removed & New bases are added → Polymerase.
* Then ends are ligated.

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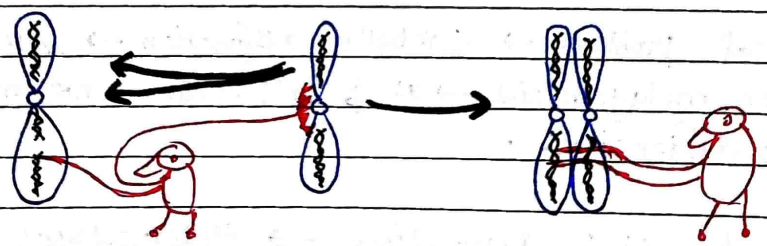
→ In Xeroderma Pigmentosa → one Allele of UV-specific Endonuclease enzyme is defective → DNA repair → not working properly & wd time → other Allele also defective → so Repair mechanisms → → stops → Mutations accomolates in skin cells → Carcinogenisis.
→ Risk of developing skin Carcinomas → 1000 times more than normal.
→ Chances → more in white People of European origin → → Setteled near Equator → even if Genes normal → still sun light → too much → Can cause the System to be over whelmed.

③. Homologous Recombination Repair :

→ When there is very much severe damage to DNA ie. both the strands are broken down then this repair system come into action.
→ When the enzymes find broken pieces → they bring Homologous chromosome to that defected chromosome & then repair it accordingly.



* On (2) occations → Homologous chromosome come near to each other → (1). during meosis (2). During sever DNA damge repair.
* Alkylating agents & Radiation → Causes sever damage.

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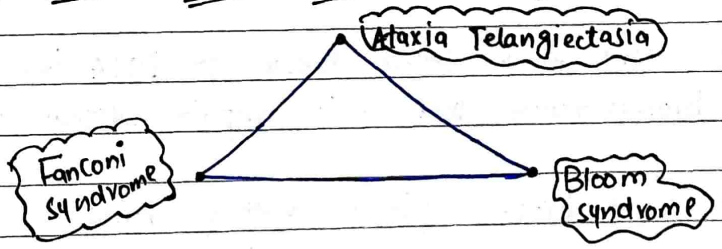
* Following genes are required to repair Double strand repair:
  1. Ataxia Telangiectasia gene/Protien
  2. ~~BRCA~~ BRCA-1 gene/Protien
  3. BRCA-2 gene/Protien
  4. RAD-51 protien
  5. Fanconi Anemia Protien Complex.

→ First A-T protien & F.A-P-Complex (Double stranded DNA repair Sensors) will locate the damage then they will phosphorylate BRCA-1 & (2) w/c along wd RAD-51 → will repair the defect.

→ If these Repair System is dificient:



ATAXIA TELANGIECTASIA: (By Ionizing Radiation)

* Neurological problems → Cerebellar dysfunction → Purkinji cell → damaged.
* Lymphoid melagnancies → as B & T-cells → not matured properly.
* Immuno difiencient.

→ (1%) of U-S population → Heterozygous for this gene → so high risk of developing melagnancies even by slight radiation.

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Bloom Syndrome : (By Ionizating Radiation)

* Rare → multiple developmental + conginital defects.
* Tendancies to develop cancers due to impaired DNA repair system.

FANCONI ANEMIA : (By Alkylating Agents)

* Anemia → bcz → Hematopiotic cells → defective.
* Impaired Double Stranded DNA repair.

BRCA-1 & BRCA-2 Gene Defects :

→ When one copy of Defective BRCA-1 & or BRCA-2 →
→ there is high risk of developing Breast Cancers.

BRCA-1 only :

→ Females → Affected
* Breast Carciuoma
* Ovarian Cancer

BRCA-2 only :

→ Both Male + Female
* Breast cancer in both Male + Female.

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⑤. Limitless Replicative Capicity Of Cancerous cells:

→ Normal cells → limited replicative capicity → bcz ends of chromosome (Telomeres) → shortens after every replication → → when significantly shortened → $P53$ → activated → BAX-gene → → Apoptosis → cell dies.

→ But In cancer cells → an enzyme (Telomerase) keep on elangating the telomeres → so cancer cell → limitless replicative capicity.

● Physiologically → high telomerase activity → In stem cells.
* Also in Gemetes → zygote → high telomerase → so too much replication → untill make Complete Human being.

* Sometimes Telomerase → not defective but (P53) → defective → → so chromosome shortning → signal P53 but P53 is not there to start Apoptosis → so cell → keep on proliferating & shortning Chromosome → dangerous mutations.