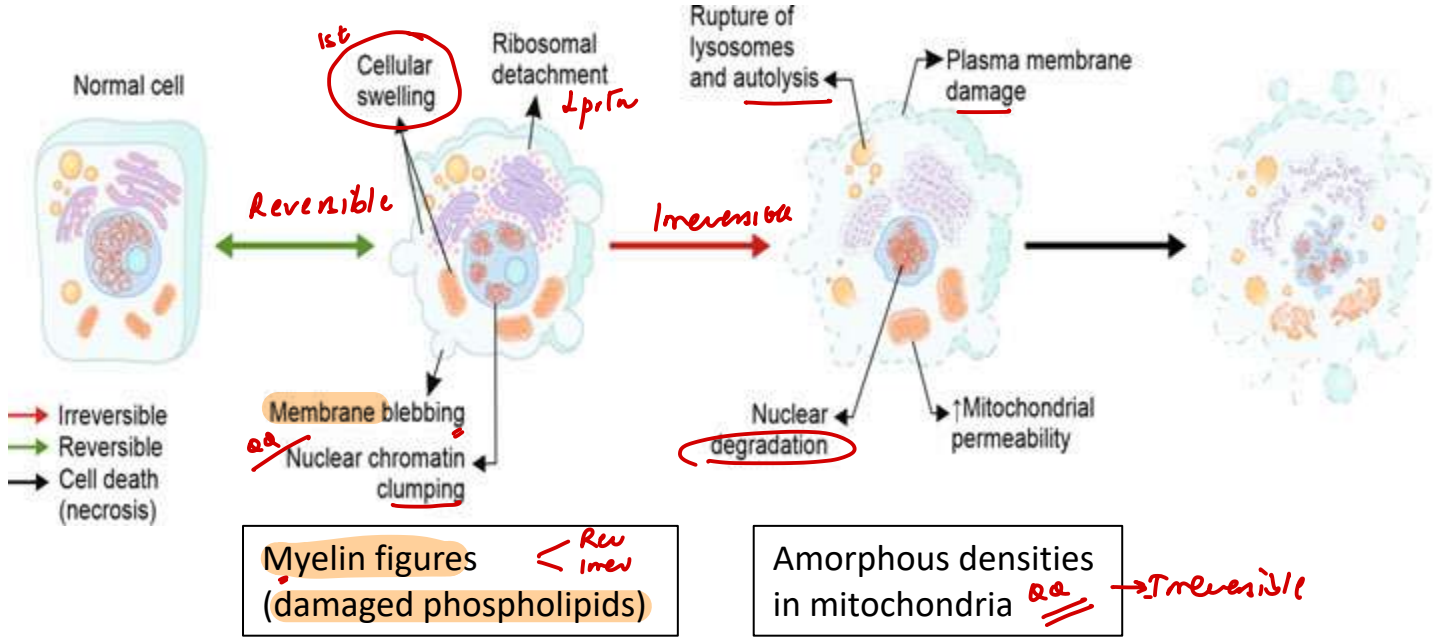
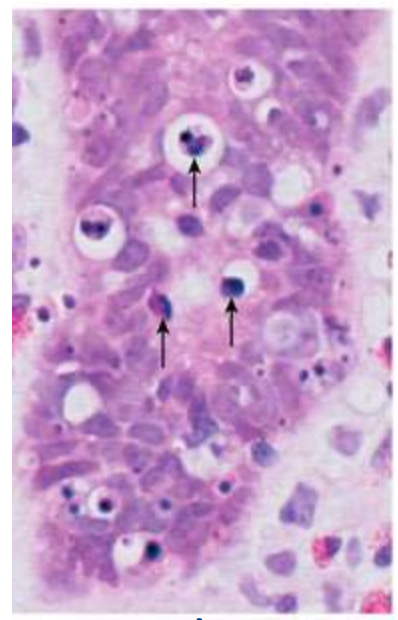
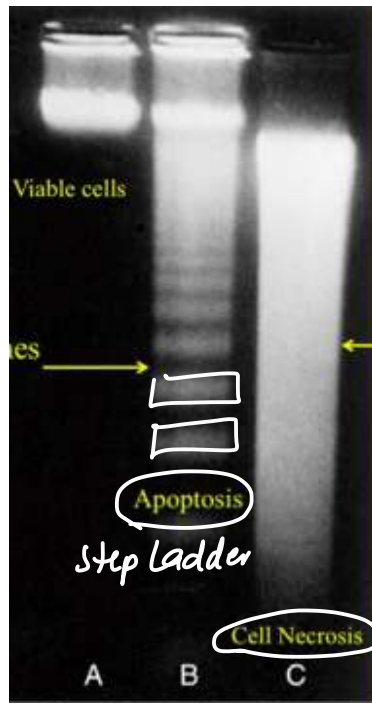


GENERAL PATHOLOGY

Cell injury

Feature	Necrosis	Apoptosis = PCD
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized fragments
Plasma membrane	Disrupted	Intact; altered lipid orientation
Cellular contents	Enzymatic digestion	Intact
Inflammation	Frequent	Absent
Role	Invariably pathologic	Often physiologic



PCD with RIPK-1 and MLKL (caspase-independent)- Necroptosis (↑inflammation)

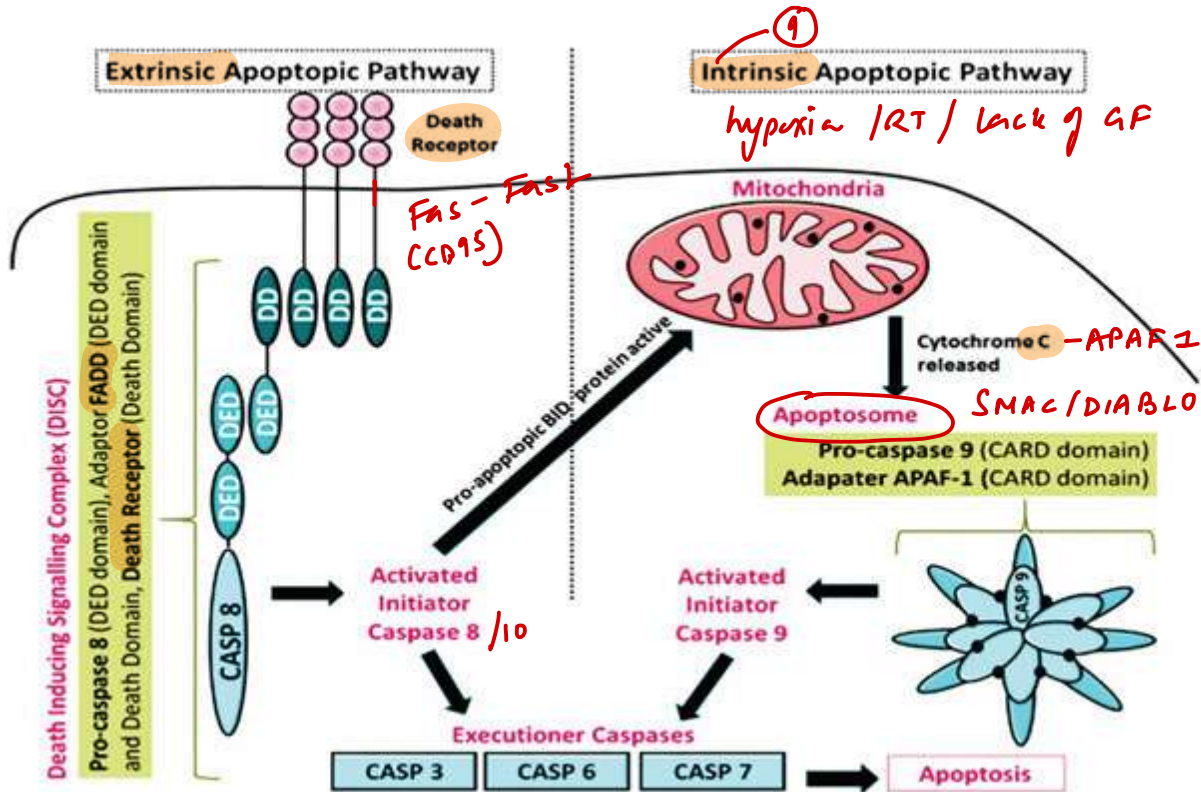
PCD with Caspase 1,4,5,11 (NOD-2)- Pyroptosis

PCD with iron- Ferritinosis (fenton reaction/lipid peroxidation)

Efferocytosis- phagocytosis of apoptotic cells

Autophagy- kill itself (nutrient deprived)

LC3, ATG16L1 (marker)



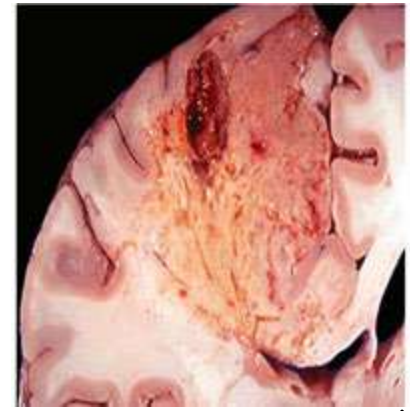
Pro-apoptotic Genes (BH1-3)	Anti-apoptotic Genes L-anti	Apoptosis Initiators/Sensors
BAK gene	BCL-2 gene (most important)	BIM gene
BAX gene	BCL-XL gene	BAD gene
p53 gene	MCL1 gene	PUMA gene
Glucocorticoids	Sex (Love) steroids	NOXA gene

Phosphatidyl serine flipping-Annexin V: "Eat me"
 TUNEL stain

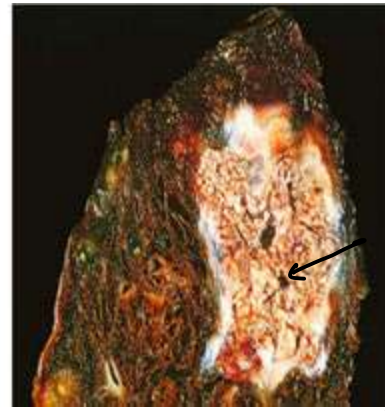
AI Lymphoproliferative syndrome CD95 / Fas x x
 ↑ Lymphocytes + LN + HSM

MCC of cell injury: Hypoxia
 Most sensitive cells: Neurons - Hippocampus CA1
 Most resistant cells: Fibroblasts

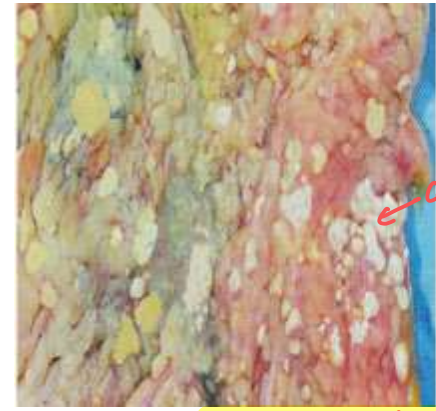
Coagulative necrosis
 ↓
 "ghost cells"
 outlines maintained
 eosinophilic



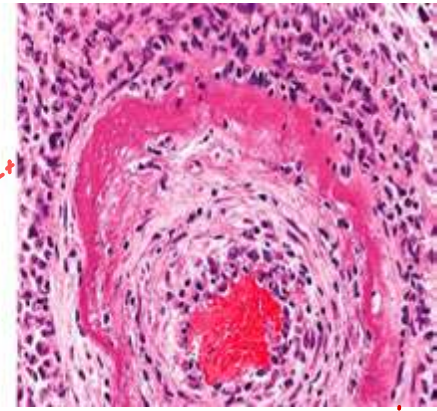
Liquefactive necrosis
 L brain
 L outlines (R) maintained



Caseous necrosis
 TB
 Histoplasma (occidionycosis)

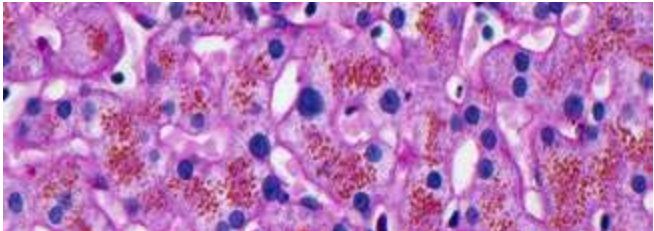


FAT NECROSIS
 omental
 pancreatitis
 Breast - trauma - D/D - cancer (↑Ca²⁺)



Fibrinoid necrosis
 ANS
 malignant hypertension
 Aschoff bodies

High-yield



Lipofuscin - lipid peroxidation
 "wear & tear"
 perinuclear intralysosomal



NET Neutrophil extracellular trap
 "beneficial suicide"
 - arginine
 - pathogen - SLE
 (x) mitochondrial DNA
 (x) phagocytes

Aging: Free radical mediated damage/Telomere shortening
 TTAGGG - stem cells / Cancer cells / telomerase
Sirtuins → NAD dep deacetylase
Histone deacetylase } = calorie restriction +/- red wine
Lonafarnib - farnesyl transferase ⊖
Hutchison-Gilford Sx - Lamin A (vs) - childhood Werner Sx - mid-age DNA helicase

Dystrophic calcification: Ca²⁺ + dead tissue
 eg. TB LN-Ca²⁺ / Psammoma bodies / Fat necrosis / Monckeberg medial sclerosis → Ca²⁺ wall + pulses (x)
 DM / CKD
Metastatic calcification: (T) serum Ca²⁺ eg. Hyper PTH
 P - medullary nephrocalcinosis / PA / stomach

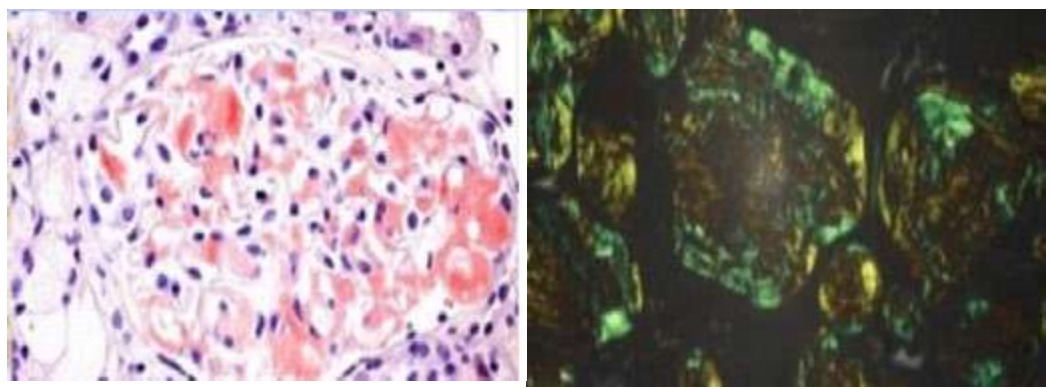
HLA B27: seroneg spondylo A - ank spnd Reactive A
B57: Abacavir hyen
B51: Behcets
DQ2 / DQ8: Celiac
DR2: MS / Goodpasture / Narcolepsy
DR3: SLE
DR4: Rheumatoid A } DM type 1 (4-3=1)
Cw6: Psoriasis
A3: Hemochromatosis

Cell adaptation
Hypertrophy: size ↑
Hyperplasia: no. ↑
Muscles during weight lifting (T)
LVH - (T)
Breast during puberty (P)
BPH (P)
Endometrium after estrogen (P)
Uterus during pregnancy → T + P
Metaplasia: Reversible? ✓
Barretts: squamous → intestinal columnar (Goblet cells)
Smoking: ciliated pseudo columnar → squamous
Myositis ossificans muscle → bone

Dysplasia: reversible [abn prolifer of tissue limited by BM = CIS
Anaplasia: irreversible - lack of differentiation
 TN/c } mitotic figures
Hamartoma: Haphazard prolifer of native tissue
 Lipom chondroma (x) abn tissue at (N) site
Choristoma: (N) tissue at abn site
 eg. Meckel's ← gastric / pancreatic

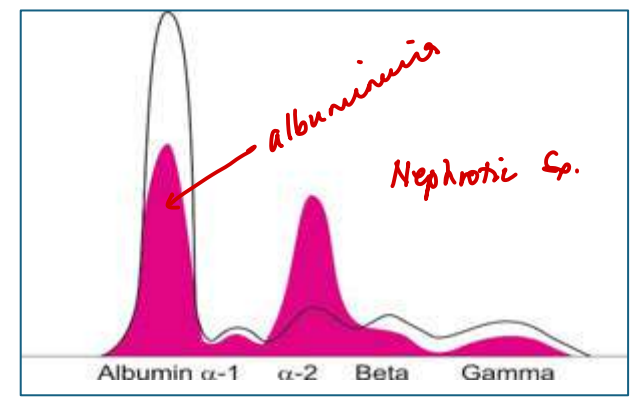
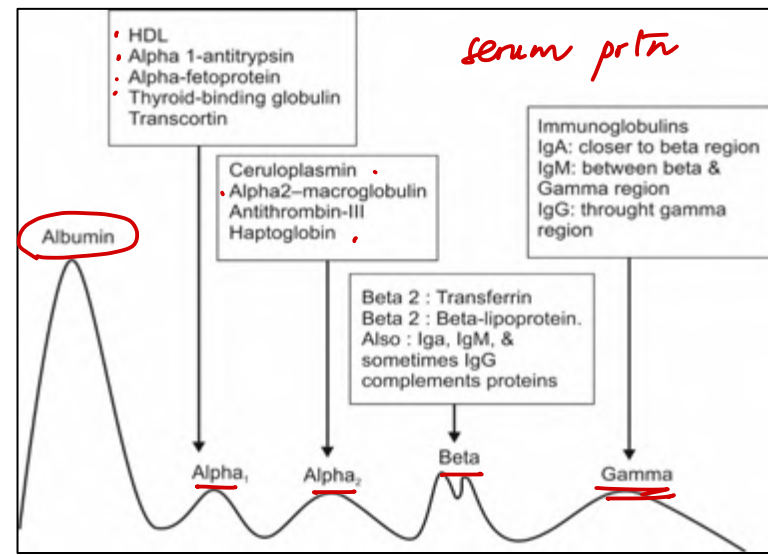
Amyloidosis

- extracellular eosinophilic amorphous



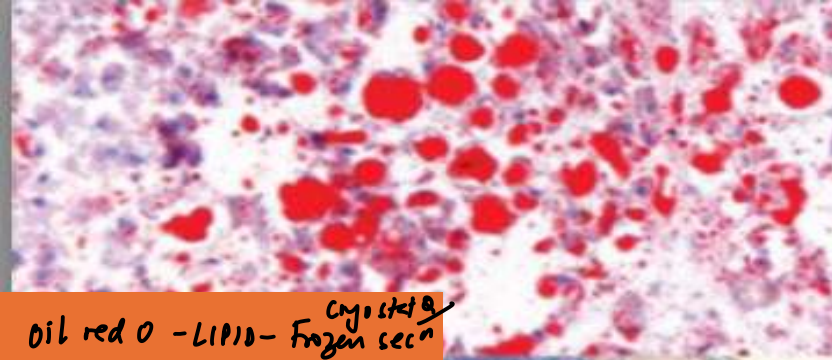
IOC: *Abdo fast aspirⁿ > Rectal bx*
 E/M: Non-branching fibrils
 7.5-10nm
 Xray crystallography-
 B pleated sheets

Congo red - salmon pink *pol μ → apple green birefringence*

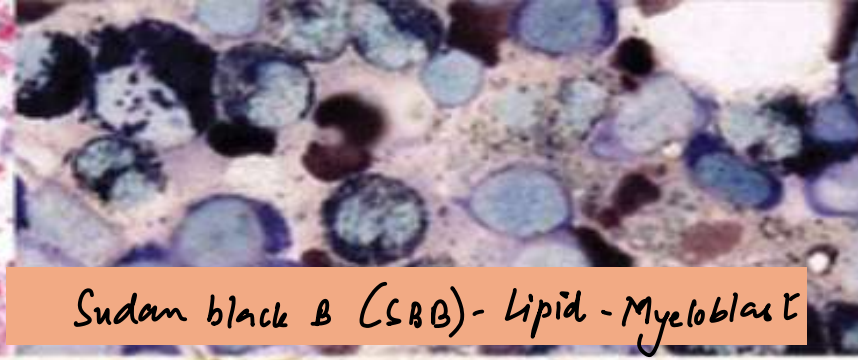


Amyloidosis	Fibril protein
Primary amyloidosis (MM)	- AL - mc: C most sp: RCM \heartsuit
Secondary amyloidosis (AA)	chr inflam ⁿ except chr bronchitis
Dialysis-related → Carpal tunnel Sx	A-B2 uglobulin
Alzheimer disease	AB \leftarrow AB40 \rightarrow CAA \rightarrow lobar hge AB42 \rightarrow Neuritic plaques
Type 2 diabetes mellitus	IAPP
Medullary thyroid cancer	A-calcitonin
Isolated atrial amyloidosis	A-ANP
Systemic senile amyloidosis	wild - TTR
Amyloid polyneuropathy	mutated - abN TTR

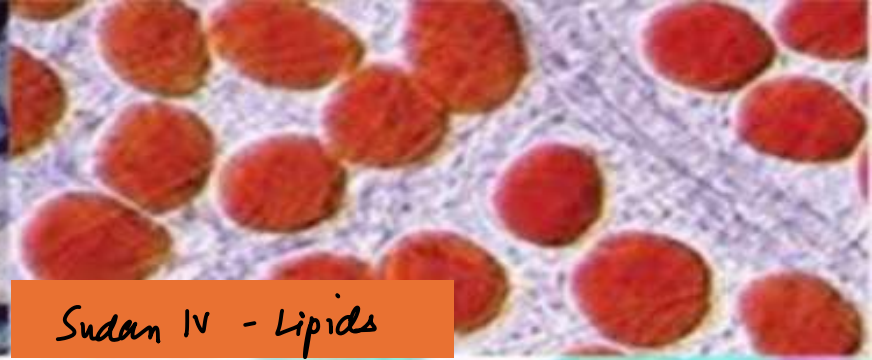
Negative APR: *inflamm* \downarrow
 Albumin, Antithrombin, Transferrin,
 Transthyretin, Transcortin
"A/T"
TIBC



oil red O - LIPID - Frozen secⁿ



Sudan black B (SBB) - Lipid - Myeloblasts



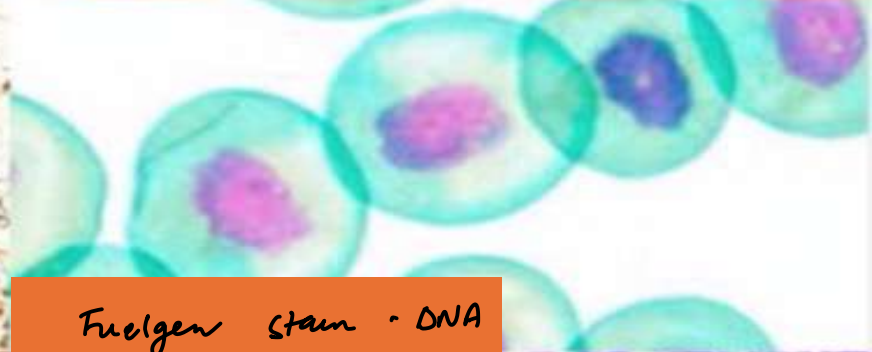
Sudan IV - Lipids



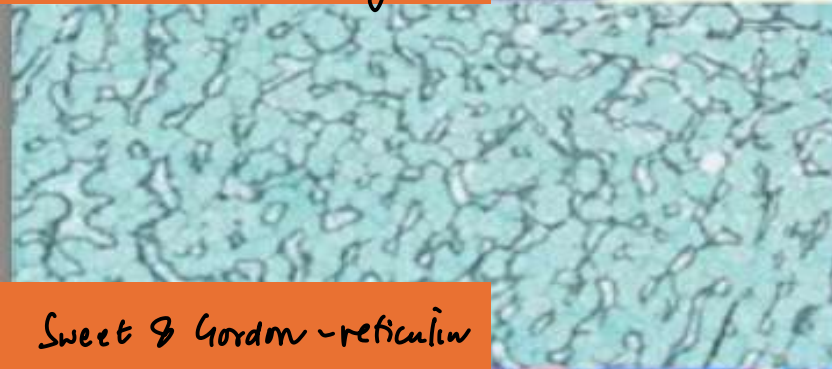
Luxol blue - myelin



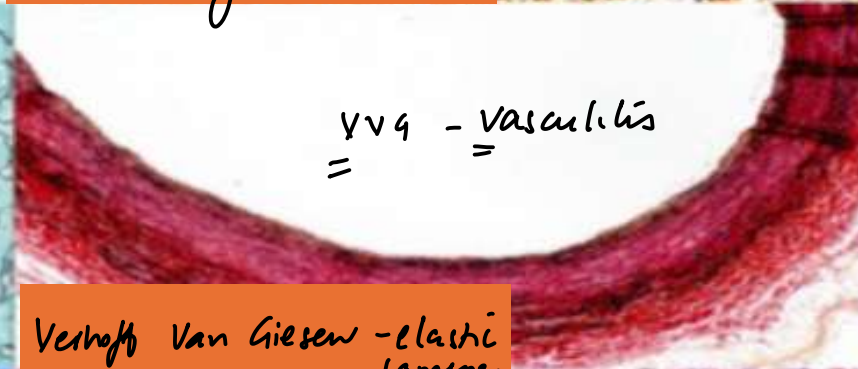
Bielschowsky - neurons



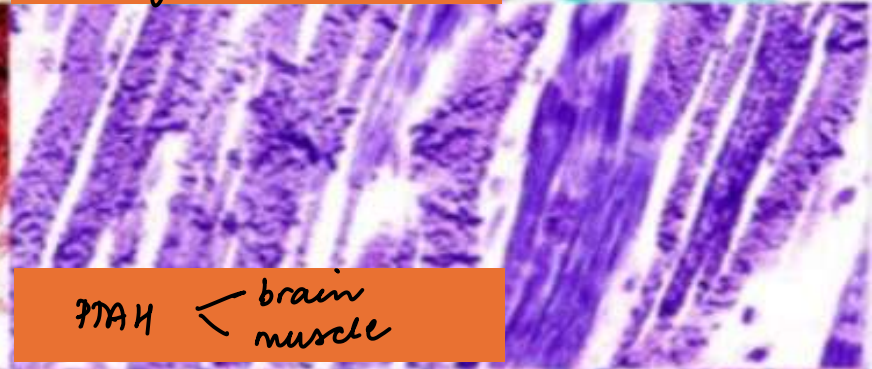
Feulgen stain - DNA



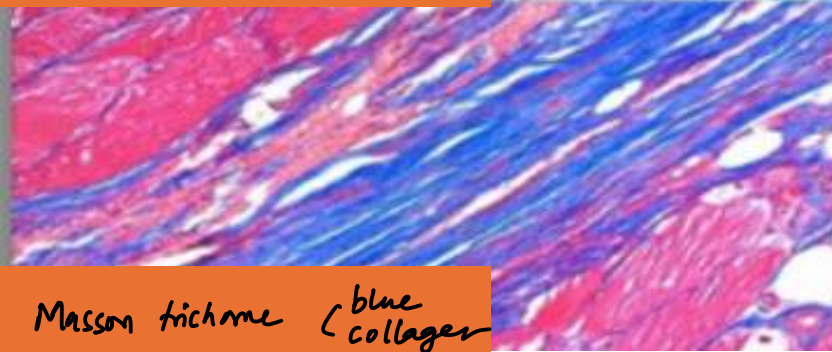
Sweet & Gordon - reticulin



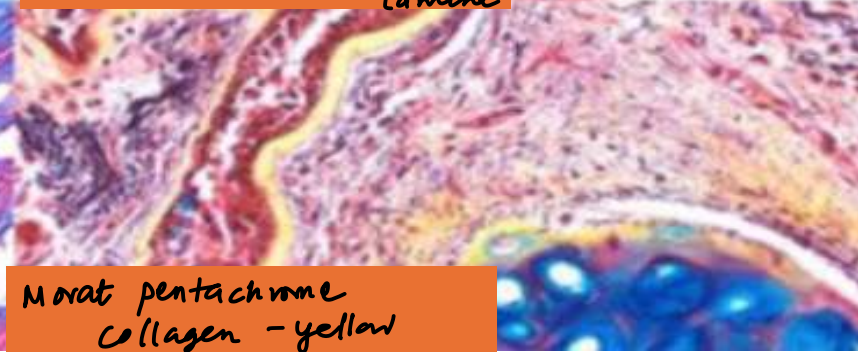
VVG - vasculitis
= =
Verhoeff Van Gieson - elastic lamina



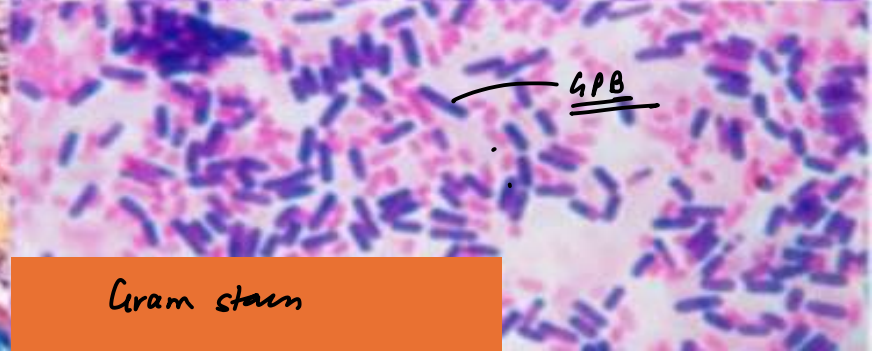
PTAH - brain muscle



Masson trichrome (blue collagen)

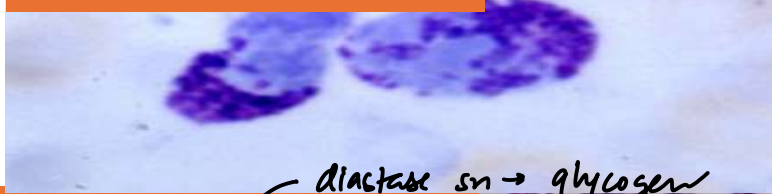


Morat pentachrome collagen - yellow



Gram stain
GPB

Toluidine blue - mast cell



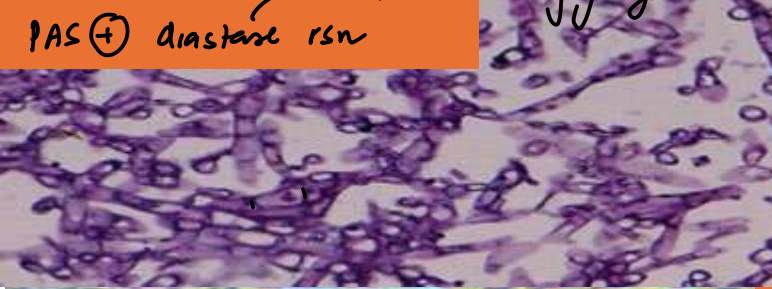
ZN - cold - Kinyoun's



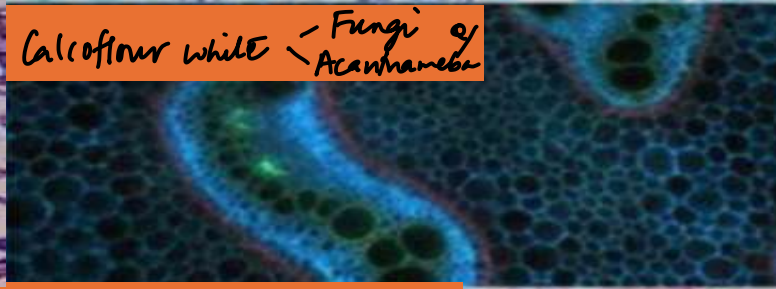
GMS - Fungi / PCP



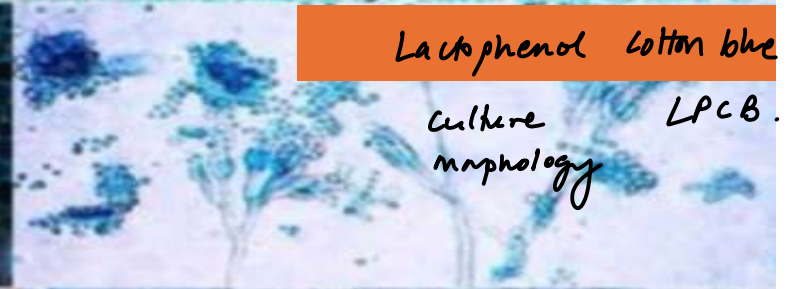
PAS (+) diastase rxn
diastase rxn → glycogen



Calcofluor white - Fungi & Acanthameba



Lactophenol cotton blue



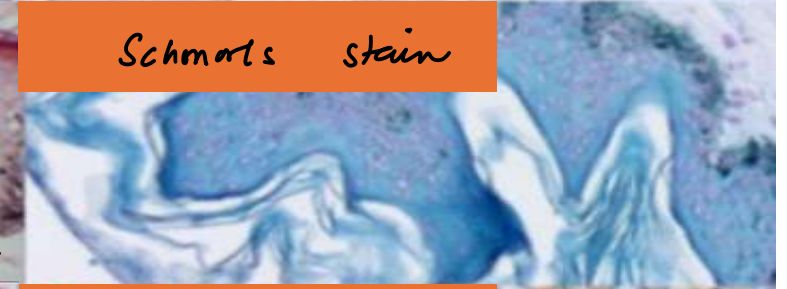
Warthin Stain - H. pylori Whipple's



Masson - Fontana



Schmaltz stain



DOPA oxidase



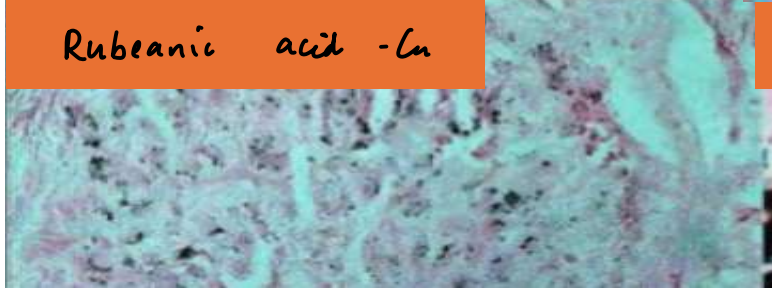
Alcian blue - acidic mucin



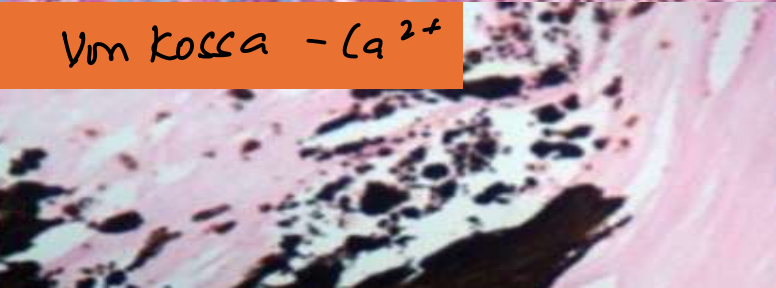
Rhodanine - Cu



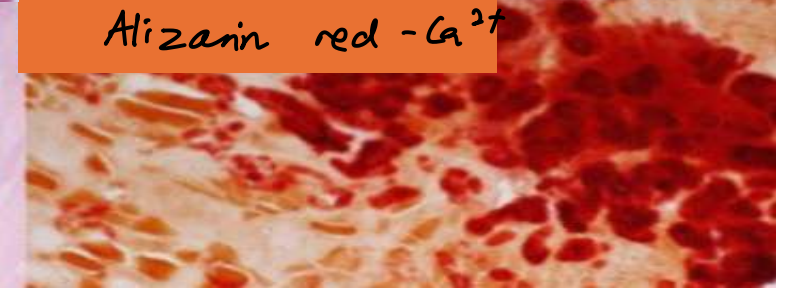
Rubeanic acid - Cu



Von Kossa - Ca²⁺



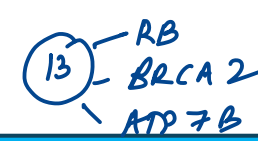
Alizarin red - Ca²⁺



melanin Talaromyces +

Barnett's

NEOPLASIA-GENES



Proto-oncogenes activation (one mutation)

- KRAS** - adenoca - colon / lung / pancreas
- HRAS** - UB ca
- NRAS** - melanoma / AML
- GNAQ** → Sturge Weber Sx, uveal melanoma
- GNAS** → toxic adenoma / pit adenoma
- C MYC** - Burkitt lymphoma
- L MYC** - small cell ca lung
- N MYC** - NB
- ALK** - anaplastic large cell / adenoca lung / lipi myofibr tumor / NB
- RET** MEN 2a / 2b (chr 10)
- ABL** → TK ↑ → ALL (CML) CML
- C-KIT** ^{or} - Gut Mastocytosis / seminoma / AML / melanoma / GIST
- NOTCH** - ALL
- FLT3** - AML
- ERBB1=EGFR** - adenoca lung / colon / pancreas
- ERBB2=HER** - breast ca
- BRAF** LCN / HCL pilocytic / pap ca GIST / ca colon melanoma
- CYCLIN D1** - Mantle cell

Tumor-suppressor genes - two hit - inactivation - one germline "LOH"

- P53** ¹⁷ → **P21** (Inhibits G1-S) → Li Fraumeni Sx
- RB** ¹³ (inhibits G1-S) → RB / O/S / pinealoblastoma
- APC** ⁵ - FAP
- NFI** ¹⁷
- NF2** ²² (XD)
- PTCH** (inhibits SHH) - Gorlin Goltz Sx → BCC
- PTEN** ¹⁰ - Cowden Sx - B E T
- SMAD2, SMAD4** - Juvenile polyposis Sx
- VHL (HIF)** 3p - clear cell RCC / pheo / cerebellar HB
- STK11** - Peutz Jeghers Sx
- SDH** - paraganglioma / pheo
- CDH1** - E-cadherin - CDH12 (chr 16)
 () diffuse ca stomach
 () Lobular ca breast
- BRCA1** → Breast / ovarian ca
- BRCA2** → Male breast / prostate / pancreatic ca
- MSH2 / MLH1** - HNPCC / Lynch Sx
- WT1** - 11 - WT
- MEN1** - 11

NEOPLASIA

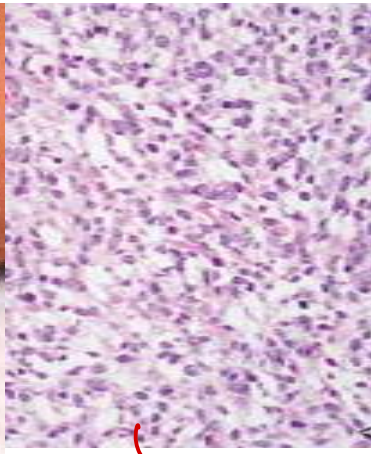
Tumor markers

- AFP - HCC / Hepatoblastoma / Endodermal sinus = YST / Mixed GCT / ATM chr11 / NTD / Abdominal wall defect - MSAFP ↑
- CA-125 - ovary → serous cystadenoc
- CA 15-3, CA 27-9 - ca breast
- CA-19-9 - Pancreas / mucinous ca ovary.
- CA 72-4 - stomach
- CK7 - CK20 + → ca colon / merkel cell ca
- CK7 + CK 20 + → Bladder ca / stomach ca
- Cell-Free DNA Markers
- EGFR in serum ca lung.
- TP53, APC, RAS in stool and serum ca colon
- TP53, RAS in stool and serum ca pancreas
- TP53, RAS in sputum and serum ca lung
- TP53 in urine ca bladder

Chemical Carcinogens:

- Aflatoxin- HCC
- Arsenic - ca lung / skin / HCC
- Vinyl chloride = neurotoxic → hepatic angiosarcoma
- Aromatic dyes (Benzidine)- UB ca
- Benzene- AML

Field cancerization:
 Head and neck
 Skin ca
 Bladder ca



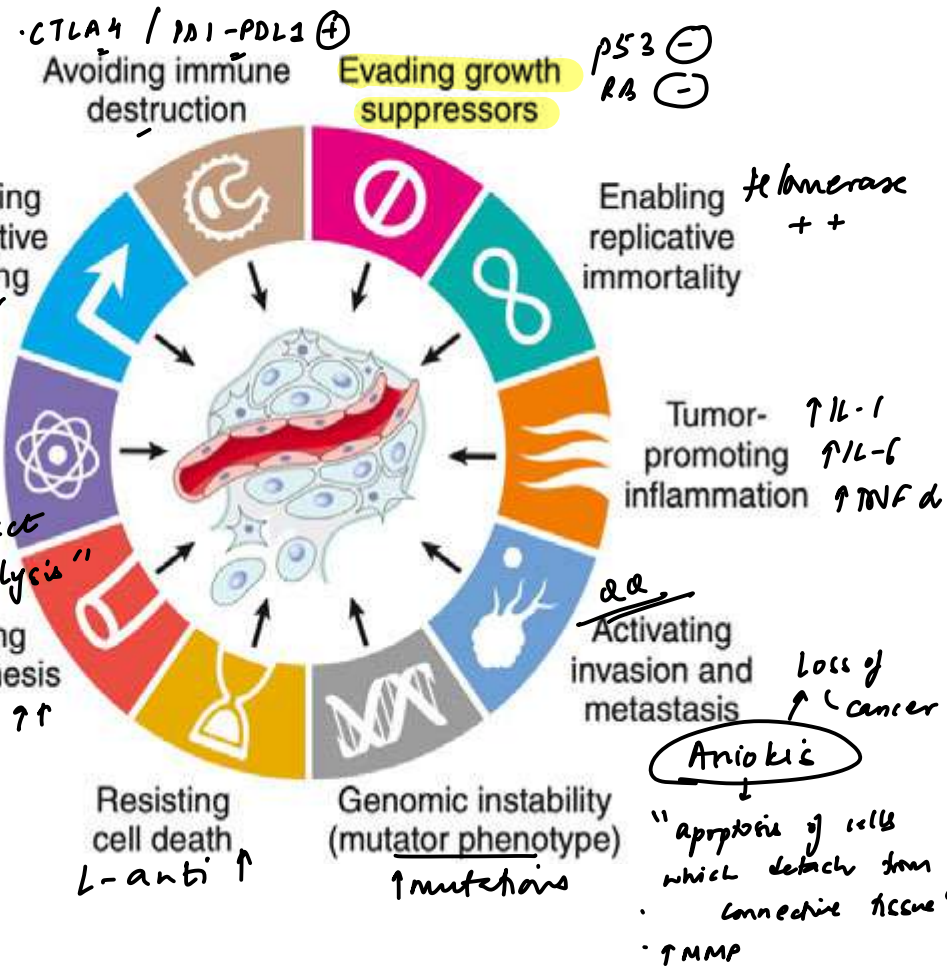
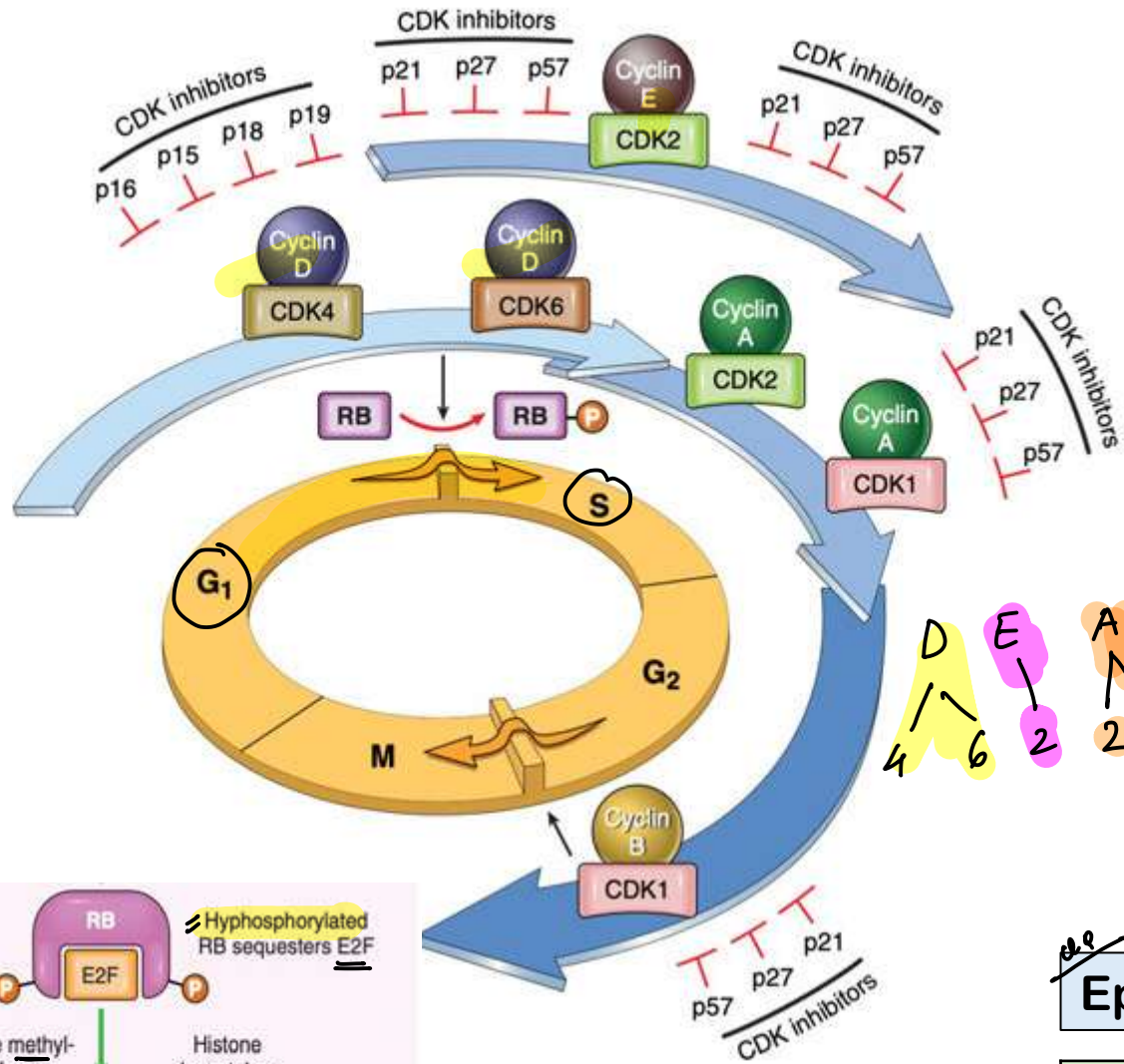
- syncytious - 2 in 6mm
 - metachromas - > 6mm

"botryoides sarcoma"

tadpole cells.

grapes - Embryonal RMS

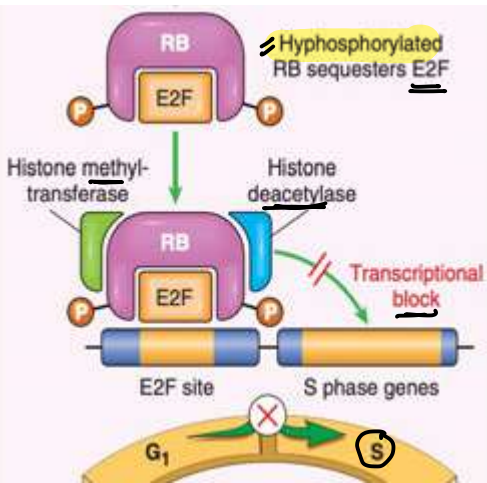
Soft tissue sarcoma	Translocation gene	Chromosomes
Ewing sarcoma	EWSR1-FLI1	t(11;22)
Desmoplastic small round cell tumor	EWSR1-WT1	t(11;22)
Synovial sarcoma ^{al}	SYT-SSX1	t(X;18)
Alveolar rhabdomyosarcoma	PAX3-FOXO1	t(2;13)
Clear cell sarcoma	EWSR1-ATF1	t(12;22)



Epithelial to mesenchymal transition: SNAIL / TWIST

Metastases: Carcinoma: lymphatic mets except clear cell RCC, Follicular in thyroid, CCA

Sarcoma: hematogenous mets except RMS, clear cell sar, synovial sarcoma } lymphatic mets



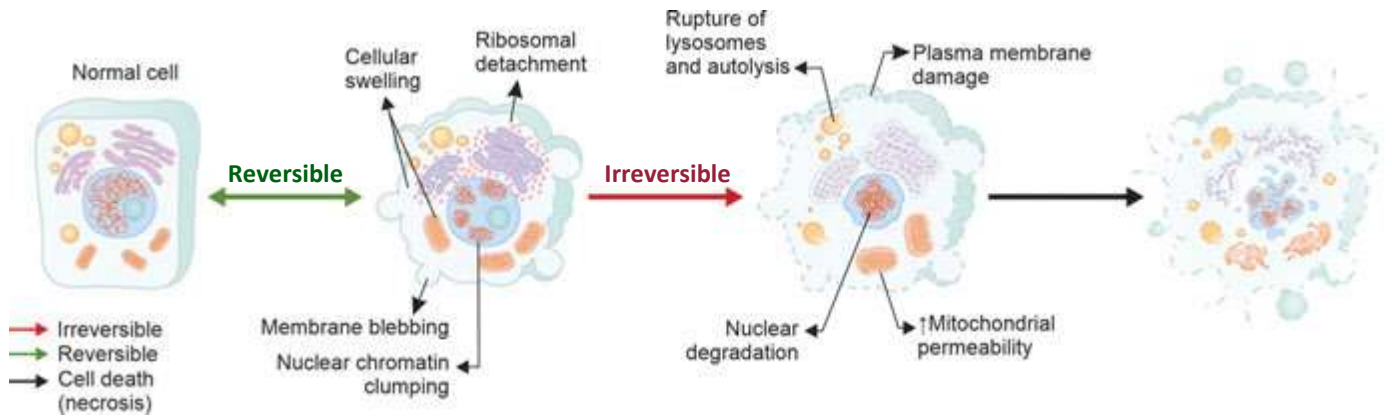


GENERAL PATHOLOGY

BTR 3.0



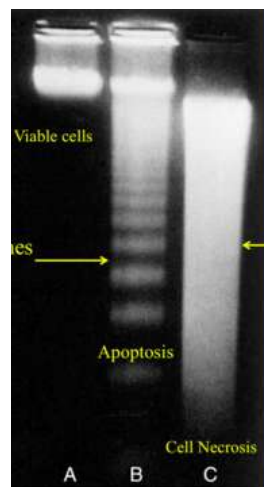
Cell Injury



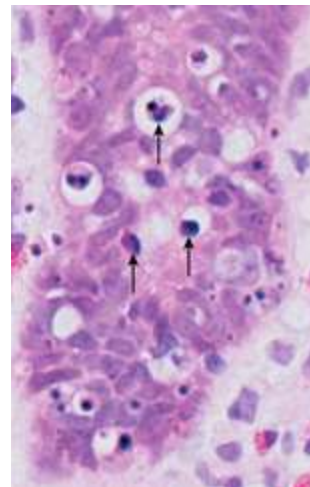
Mechanisms of cell injury
1st step : Hydropic change (reversible) <i>In ischemia, ATP pumps stop functioning due to low ATP causing cellular swelling (cytotoxic edema)</i>
2nd step : Ribosomal detachment (reversible) <i>reduced protein production.</i>
3rd step : Myelin figures (can be seen in both) <i>aggregation of damaged phospholipids from membranes</i>
4th step : Mitochondrial permeability increased (irreversible) <i>Amorphous densities on EM</i>
5th step : Plasma membrane damage (irreversible)
6th step : Nuclear degradation (irreversible) <ul style="list-style-type: none"> • Chromatin condensation : <i>Pyknosis</i> • Nuclear fragmentation : <i>Karyorrhexis</i> • Nuclear lysis : <i>Karyolysis</i>

- MCC of cell injury : **Hypoxia** (*ischemic*)
- Cells **most sensitive** to hypoxia : **Neurons** (*hippocampus CA1*)
- Cells **most resistant** to hypoxia : **Fibroblasts**

Feature	Necrosis	Apoptosis
Cell size	Enlarged (<i>swelling</i>)	Reduced (<i>shrinkage</i>)
Nucleus	<ul style="list-style-type: none"> • Pyknosis • Karyorrhexis • Karyolysis 	Fragmentation into nucleosome-sized fragments
Plasma membrane	Disrupted	Intact ; altered lipid orientation
Cellular contents	Enzymatic digestion	Intact
Inflammation	Frequent	<u>Absent</u>
Role	Invariably pathologic	Often physiologic

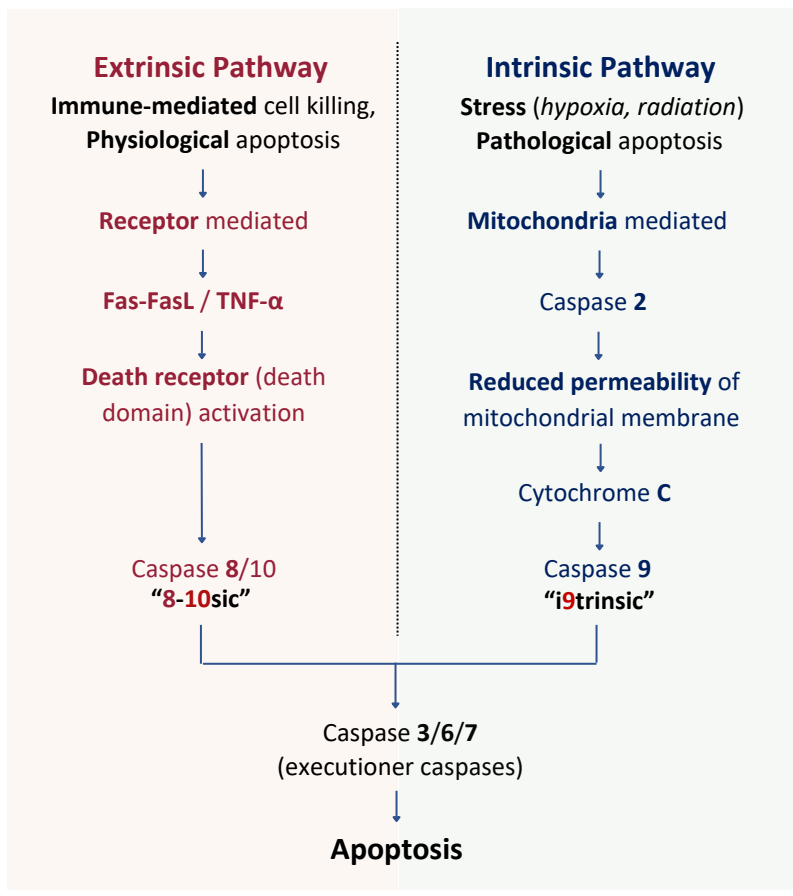
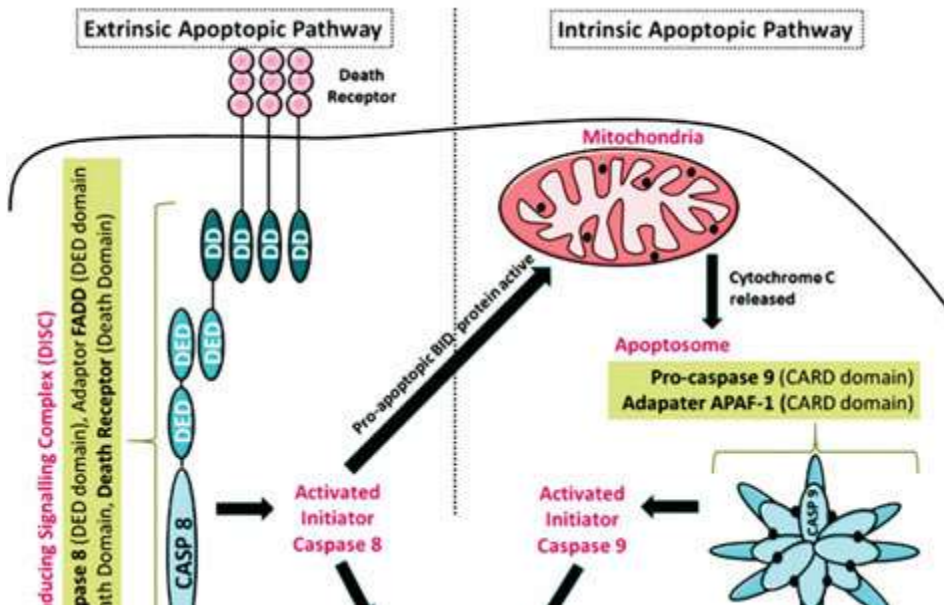


Apoptosis : **Step ladder pattern**
 Necrosis : **Smear pattern**



Apoptotic bodies
 (Membrane-bound cell fragments)

Cell Injury - Apoptosis



Pro-apoptotic genes (BH1-3)

- BAX, BAK, p53
- Cause mitochondrial **membrane permeabilization**
- Effect pronounced with **glucocorticoids**

Anti-apoptotic genes

1. BCL-2 (most important)
 2. BCL-XL
 3. MCL-1
- **Stabilize** mitochondrial membrane
 - Prevent cytochrome-c release
 - Effect pronounced with **sex steroids**

Apoptosis initiators/sensors (BH3-only)

- BIM, BAD, PUMA, NOXA
- Inhibit BCL-2/BCL-XL (*anti-apoptotic genes*)
- Activate BAX/BAK and trigger apoptosis

Variants of Apoptosis (Programmed Cell Death)

1. **Necroptosis** : Apoptosis with **inflammation**
 - RIPK-1 and MLKL (caspase-independent)
2. **Pyroptosis** : Apoptosis with **fever**
 - Caspase 1, 4, 5, 11 (*inflammasome*)
3. **Ferroptosis** : **Iron dependent** apoptosis
 - Fenton reaction (*lipid peroxidation*)
4. **Efferocytosis** : **Phagocytosis** of apoptotic cells
5. **Autophagy** : Nutrient-deprived cell **kills itself**
 - Markers : LC3, ATG16L1

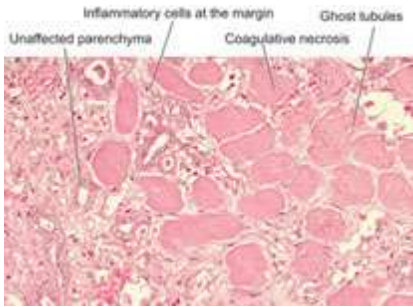
- **Fas - FasL defect** : *Auto-immune lymphoproliferative syndrome*
 - Lymphocytosis + Lymphadenopathy + Hepatosplenomegaly (HSM)
- **Apoptosis markers**
 - a. **Annexin V** (Stains Phosphatidylserine)
 - b. **TUNEL stain**

- Protein present in caspases : **Cysteine**
- **Hallmark feature** of apoptosis : **Chromatin condensation** (*pyknosis*)
- **Physiological apoptosis** : Embryogenesis, Breast/endometrium involution
- **Pathological apoptosis** : DNA damage, Viral hepatitis (*councilman bodies*)

Over expression of BCL - 2 : **B cell lymphomas**

Under expression of P-53 : **Li Fraumani Sx**

Cell Injury - Necrosis



Coagulative necrosis

- M/c type of necrosis
- **Architecture** preserved : "ghost cells" (cell outlines maintained)
- Due to **protein denaturation** (classically in ischemia except brain) eg. MI, Renal infarcts
- **Dry gangrene** : Coagulative necrosis
- **Wet gangrene** : Liquefactive necrosis



Liquefactive necrosis

- Cell outlines not maintained
- Seen in **brain ischemia** (aka wet gangrene)
- Also seen in **abscess** (pus formation)



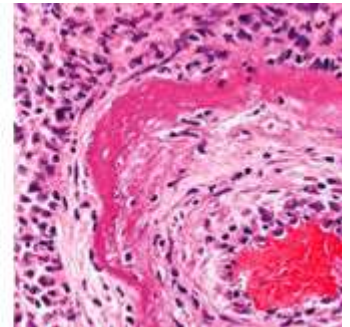
Caseous necrosis

- **TB** (*mycolic acid* in cell wall)
- **Histoplasma, Coccidiomycosis**
- Also seen with **Nocardia**



Fat necrosis

- **Saponification** of fat
- **Calcium deposits**
- Seen in **pancreatitis, breast trauma** (can mimic BIRADS 5)



Fibrinoid necrosis

- **Vasculitis** (PAN, HSP)
- **Malignant hypertension**
- **Aschoff nodules** (in rheumatic fever)

Ageing

Mechanisms of Aging

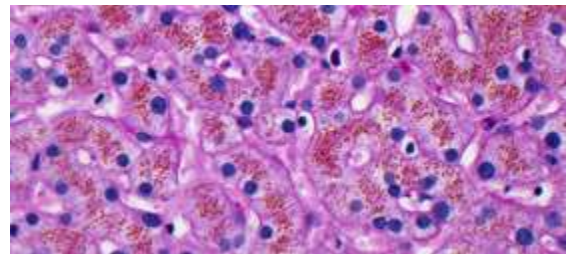
1. Free radical damage
2. Telomere shortening

Telomerase : Adds DNA sequences and prevents telomere shortening

- Present in : **Stem cells & Cancer cells**
- Absent in most somatic cells
- **Hayflick limit** : Telomere can replicate **40-60** times before shortening

Sirtuins : NAD⁺ dependent deacetylases

- Promote longevity
- Activated by **calorie restriction**



Lipofuscin (Golden-brown pigment)

- Due to **lipid peroxidation**
- Seen in **aging / chronic wear & tear**
- Location: **Perinuclear, intra-lysosomal**
- Common in **heart, liver**

Premature Aging Syndromes

Hutchinson-Gilford Progeria Syndrome

- **Lamin A** mutation
- **Childhood** onset
- Drug: **Lonafarnib** (*farnesyltransferase inhibitor*)

Werner syndrome

- **DNA helicase** defect (WRN gene - AR transmission)
- **Adult** onset



Progeria



WS patient age 15 yrs

WS patient age 48 yrs

Werner Syndrome

Cellular Adaptations

Hypertrophy (↑ size)

- **Skeletal muscle** (exercise)
- **Left ventricular hypertrophy (LVH)**



Hyperplasia (↑ number)

- **Breast** (puberty)
- **BPH**
- **Endometrium** (estrogen)

Muscle | Size | Trophy

Both Hypertrophy + Hyperplasia

- Uterus in pregnancy

Dysplasia vs Anaplasia

Dysplasia

- **Reversible** change
- *Disordered growth*
- Confined by **basement membrane**
- Severe dysplasia = **carcinoma in situ**

Anaplasia

- **Irreversible**
- *Loss of differentiation*
- ↑ **N:C ratio**, **atypical mitoses**

Tumor-like Lesions

Hamartoma

- **Disorganized growth** of native tissue
- Example: **Pulmonary chondroma** ("popcorn" calcification)

Choristoma

- **Normal tissue** in **abnormal location**
- Often **congenital**
- Example: **Gastric/pancreatic tissue** in **Meckel's diverticulum**

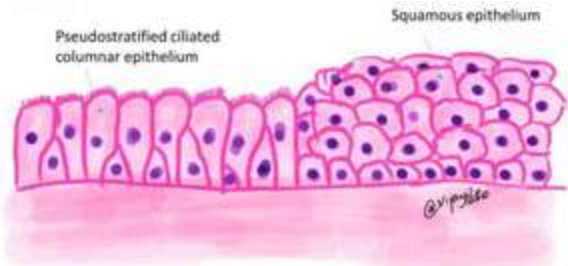
Features of malignant transformation

1. **Anaplasia** (lack of differentiation)
2. **Pleomorphism**
3. Increased **N/C ratio**
4. **Hyperchromasia**
5. Increased **mitosis**
6. **Loss of polarity**

Metaplasia (Reversible change)

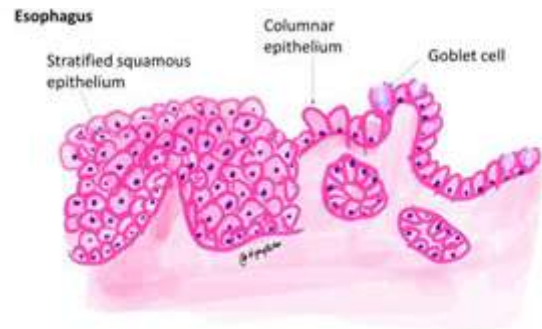
Squamous Metaplasia

1. **Airways** : Chronic smoking
2. **Urinary bladder** : Bladder stones, chronic irritation
3. **Cervix** : Low vaginal pH



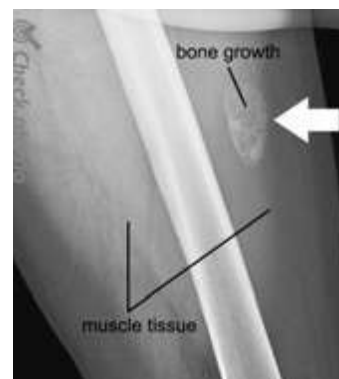
Columnar Metaplasia

1. **Barrett's esophagus** - Due to chronic GERD
 - aka **Intestinal metaplasia** (with goblet cells)
 - Premalignant → **adenocarcinoma**



Connective Tissue Metaplasia

1. **Myositis ossificans** (bone formation inside muscle tissue after trauma)



Pathologic Calcification

Pathologic Calcification

Dystrophic calcification

- Occurs in **dead** or **damaged** tissues
- Serum calcium: **NORMAL**
- **Localized** calcification
- **Psammoma bodies** present

Examples:

1. **TB lymph nodes**
2. **Atherosclerosis**
3. **Monckeberg medial sclerosis**
 - Calcification of **tunica media**
 - *Does not cause luminal narrowing*
 - **Pulse is normal**
 - Seen in **Diabetes, CKD**

Metastatic calcification

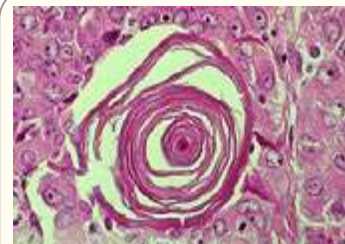
- Occurs in **normal tissues**
- Due to **hypercalcemia**
- Typically **diffuse deposition**

Common Sites:

1. **Lungs** (m/c site)
2. **Kidneys** (medullary nephrocalcinosis)
3. **Gastric mucosa**

Causes of hypercalcemia:

- Hyperparathyroidism
- Vitamin D excess, Sarcoidosis
- Bone destruction (metastasis, myeloma)
- Milk-alkali syndrome



Psammoma bodies

(PSM)²

- P** Papillary carcinoma
- P** Prolactinoma
- S** Somatostatinoma
- S** Serous ovarian tumors
- M** Mesothelioma
- M** Meningioma

High-Yield

HLA Associations

- **HLA-B27** : Seronegative spondyloarthropathies
 - Ankylosing spondylitis
 - Reactive arthritis
 - IBD-associated arthritis
 - Psoriatic arthritis
- **HLA-B57** : Abacavir hypersensitivity
- **HLA-B51** : Behçet disease
- **HLA-DQ2 / DQ8** : Celiac disease
- **HLA-DR2** :
 - a. Multiple sclerosis
 - b. Goodpasture syndrome
 - c. Narcolepsy
- **HLA-DR3** : Systemic lupus erythematosus (SLE)
- **HLA-DR4** : Rheumatoid arthritis
- **HLA-DR3 + DR4** : Type 1 diabetes mellitus
- **HLA-Cw6** : Psoriasis "Psoria6"
- **HLA-A3** : Hemochromatosis



Neutrophil Extracellular Traps (NETs)

- **Web-like structures** that trap microbes
- Mechanism: "**Beneficial suicide**" (NETosis)
- Composed of: Nuclear DNA + histones + granule proteins
- Key points:
 - **No phagocytosis** involved
 - **Not mitochondrial DNA** (mainly nuclear DNA)
- Involved in **SLE pathophysiology**
- **Arginine metabolism** plays a role

Amyloidosis

Features of Amyloid

- Extracellular, eosinophilic, amorphous deposits
- Light microscopy : **pink amorphous material**
- Electron microscopy : **non-branching fibrils** (7.5–10 nm)
- X-ray crystallography : **β -pleated sheet** structure

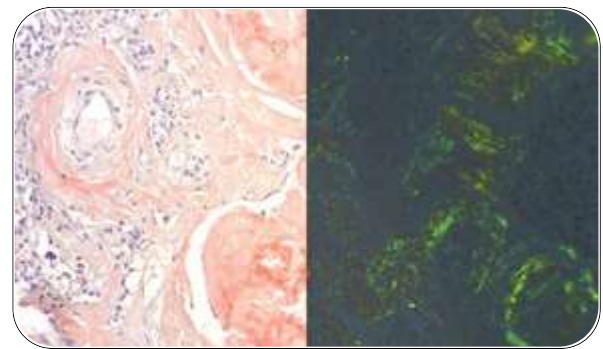
Staining

- Congo red : **salmon pink/red**
- Polarized light : **apple-green birefringence**

Investigation:

- IOC : **Abdominal fat pad aspiration**
- Alternative : **Rectal biopsy**

Congo red stain



Stains amyloid,
Salmon pink

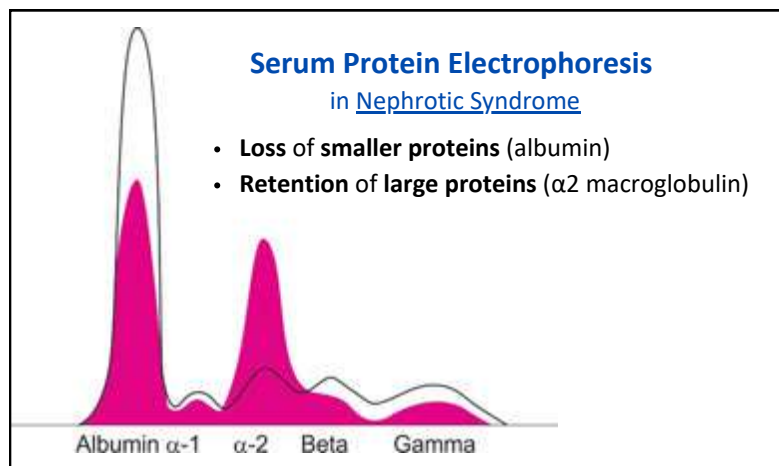
Under **polarized light** shows
apple green birefringence

Type of Amyloidosis	Fibril Protein	Cause / Association	Key Organs / Features
Primary	AL (<i>light chains</i>)	Plasma cell dyscrasia (e.g. multiple myeloma)	Kidney (most common) Heart (most specific, RCM)
Secondary	AA	Chronic inflammation (TB, RA, IBD, bronchiectasis) <i>Not seen with chronic bronchitis</i>	Kidney, liver, spleen
Dialysis-related	β2-microglobulin	Long-term dialysis	Joints : carpal tunnel syndrome
Alzheimer disease	Aβ (amyloid beta)	Neurodegenerative	A β 40 : CAA (<i>Lobar hemorrhage</i>) A β 42 : neuritic plaques
Type 2 Diabetes Mellitus	Islet amyloid polypeptide (<i>amylin</i>)	Insulin resistance	Pancreatic islets
Medullary thyroid carcinoma	Calcitonin-derived	C-cell tumor	Thyroid
Isolated atrial amyloidosis	ANP	Aging	Atria of heart
Senile systemic amyloidosis	Wild-type transthyretin (TTR)	Aging	Heart (restrictive cardiomyopathy)
Familial amyloid polyneuropathy	Mutant transthyretin (TTR)	Genetic	Peripheral nerves

Serum Protein Electrophoresis

in Nephrotic Syndrome

- **Loss of smaller proteins** (albumin)
- **Retention of large proteins** (α 2 macroglobulin)



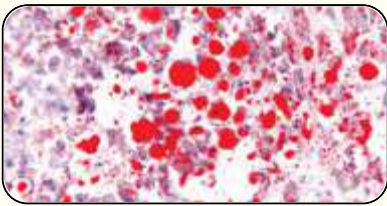
Negative Acute Phase Reactants

Decrease in inflammation:

1. **Albumin**
2. **Antithrombin**
3. **Transferrin** (\downarrow TIBC in A OCD)
4. **Transthyretin** (pre-albumin)
5. **Transcortin**

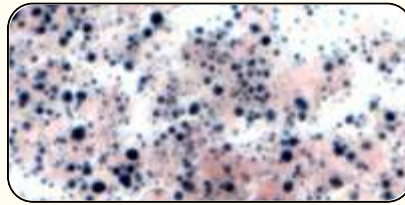
Special Stains

Lipid/fat stains



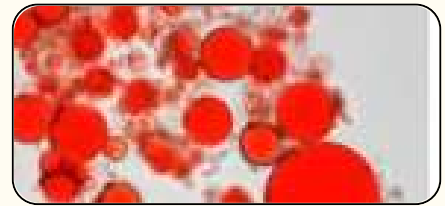
Oil-Red-O stain

Stains lipids in **frozen section / cryostat**



Sudan Black B

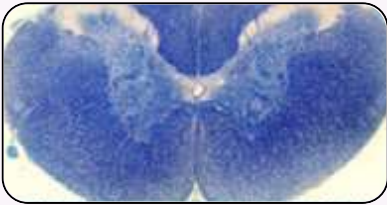
Stains lipids + **myeloblasts (AML)**



Sudan IV

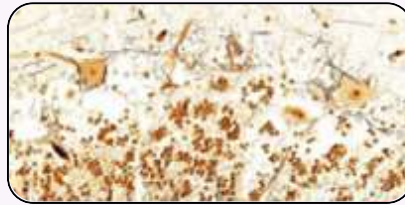
Stains lipids

Neuro stains



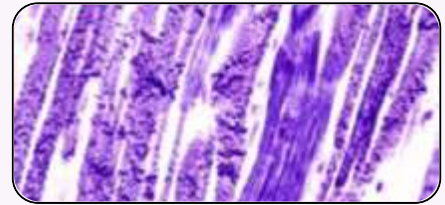
Luxol Fast Blue

Stains **myelin**



Bielschowsky stain

Stains **neurons, neurofibrillary tangles**



PTAH stain

Stains **glial fibers (brain) + Muscles**

Connective tissue / fibers stains



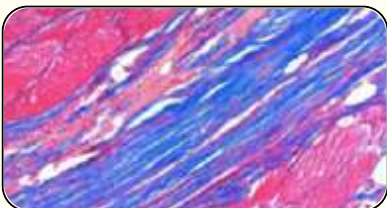
Gordon & Sweet stain

Stains **reticulin fibers**



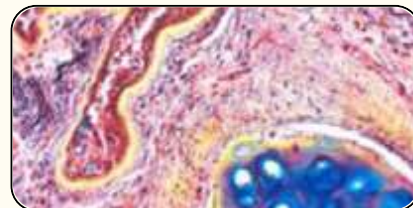
Verhoeff-Van Gieson (VVG)

Stains **elastic fibers** of vessel wall
(used in **giant cell arteritis**)



Masson trichrome

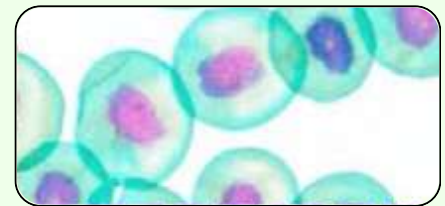
Stains **Collagen = blue (scarring, fibrosis)**



Movat pentachrome

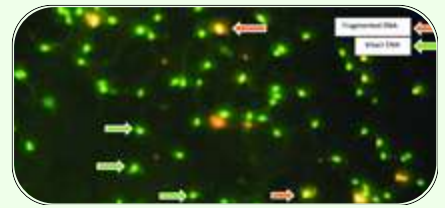
Stains **Collagen = yellow**

Nuclear stains



Feulgen stain

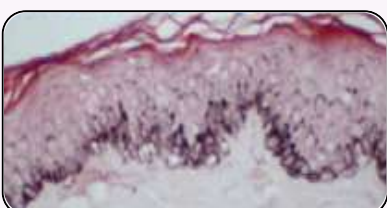
DNA (specific)



Acridine orange (fluorescent)

Stains **DNA and RNA**

Pigments (Melanin)



Masson Fontana

Stains **melanin**



Schmorl stain

Stains **melanin**

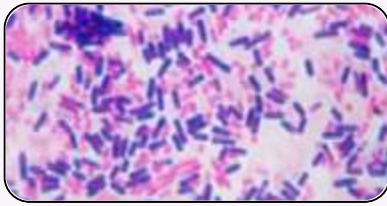


DOPA oxidase reaction

Melanin synthesis

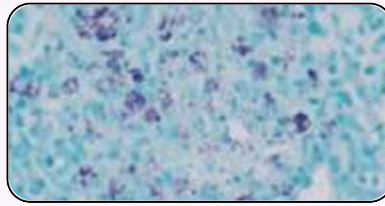
Special Stains continued

Microbiology stains

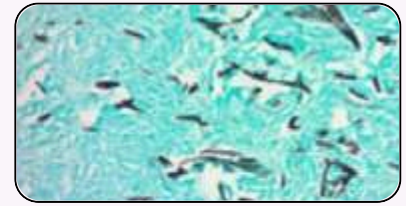


Gram stain

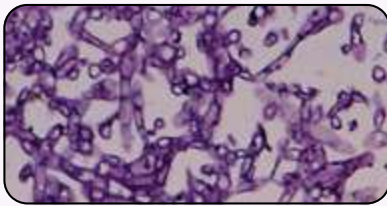
Gram(+) = blue, Gram(-) = pink



Ziehl-Neelsen (ZN) / Kinyoun modification
Acid-fast bacilli (TB), Coccidian parasites in HIV

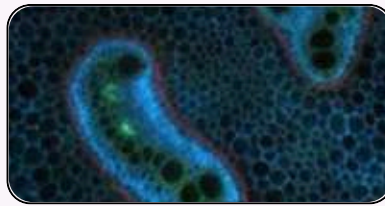


GMS (Gomori methenamine silver)
Fungi + *Pneumocystis jirovecii*



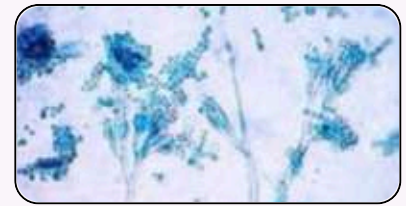
PAS stain

- **Fungi** (septations, e.g., *Aspergillus*)
- **Glycogen** - diastase sensitive
(Everything else which is PAS positive is diastase resistant)



Calcofluor white

Fluorescent stain for
fungi + *Acanthamoeba*



Lactophenol cotton blue

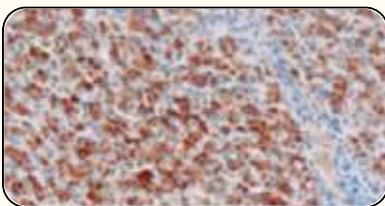
Fungal culture morphology



Warthin-Starry stain

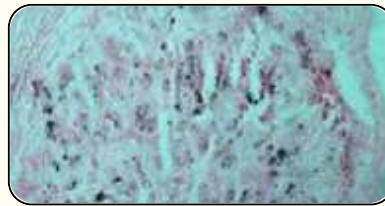
- **Helicobacter pylori**
- **Whipple disease** (*Tropheryma whippeli*)

Metal stains



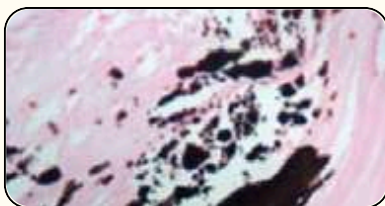
RhodaNine* stain

Stains copper



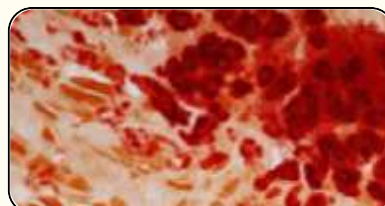
Rubenic acid

Stains copper



Von Kossa

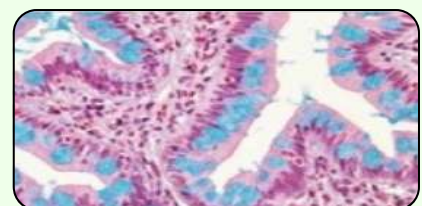
Stains calcium salts



Alizarin Red

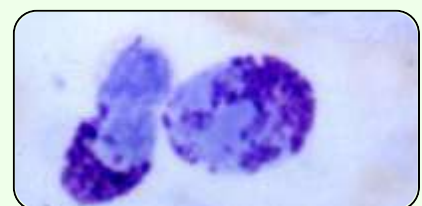
Stains calcium

Other stains



Alcian blue

Stains mucin (in Barrett esophagus)



Toluidine blue

Stains Mast cells (histamine granules)

*RhodaMine : used to stain acid fast bacilli

Neoplasia - Genes

PROTO-ONCOGENES (Gain of function)	TUMOR SUPPRESSOR GENES (Loss of function)
<p>RAS pathway (MAPK signaling)</p> <ul style="list-style-type: none"> • K-RAS : Adenocarcinoma - colon, pancreas, lung • H-RAS : Bladder cancer • N-RAS : Melanoma, AML 	<p>Loss of heterozygosity (LOH) Based on Knudson two-hit hypothesis</p>
<p>G-protein signaling</p> <p>GNAQ (Gq)</p> <ul style="list-style-type: none"> • Sturge-Weber syndrome • Uveal melanoma (<i>MC intraocular tumor in adults</i>) <p>GNAS (Gs) - Adenomas</p> <ul style="list-style-type: none"> • Toxic adenoma (thyroid) • Pituitary adenoma 	<p>Cell cycle regulators - inhibits G1 to S</p> <ul style="list-style-type: none"> • p53 (acts via p21) : Li-Fraumeni syndrome • RB : Retinoblastoma, Osteosarcoma
<p>MYC family (transcription factors)</p> <ul style="list-style-type: none"> • c-MYC : Burkitt lymphoma t(8;14) • L-MYC : Small cell Lung carcinoma • N-MYC : Neuroblastoma 	<p>APC (Chr 5) : FAP (Autosomal Dominant)</p>
<p>Tyrosine kinase / receptor genes</p> <p>ALK</p> <ul style="list-style-type: none"> • Anaplastic large cell lymphoma • Lung adenocarcinoma • Inflammatory myofibroblastic tumor • Neuroblastoma <p>RET - MEN2A, MEN2B</p> <p>ABL (BCR-ABL fusion) - CML, ALL, CNL</p>	<p>Neurocutaneous</p> <ul style="list-style-type: none"> • NF1 (Chr 17) • NF2 (Chr 22)
<p>c-KIT (CD117)</p> <ul style="list-style-type: none"> • GIST (<i>strong association</i>) • Cutaneous Mastocytosis • AML, Seminoma, Melanoma 	<p>PTCH : Gorlin - Goltz syndrome (inhibits Sonic hedgehog gene and causes basal cell carcinoma)</p>
<p>NOTCH : T-ALL</p> <p>FLT3 : AML (<i>poor prognosis</i>)</p>	<p>PTEN (Chr 10)</p> <ul style="list-style-type: none"> • Cowden syndrome • Breast, Endometrial, Thyroid cancers
<p>EGFR family</p> <ul style="list-style-type: none"> • ERBB1 (EGFR) : Adenocarcinoma - colon, pancreas, lung • ERBB2 (HER2/neu) : breast carcinoma 	<p>SMAD2, SMAD4 : Juvenile polyposis Sx</p>
<p>BRAF (MAPK pathway)</p> <ul style="list-style-type: none"> • Hairy cell leukemia, Langerhans cell histiocytosis • Papillary thyroid ca., Pilocytic astrocytoma • Colon cancer, GIST, Melanoma 	<p>VHL (↑ Hypoxia inducible factor)</p> <ul style="list-style-type: none"> • Clear cell RCC • Cerebellar hemangioblastoma • Pheochromocytoma
<p>Cell cycle</p> <ul style="list-style-type: none"> • Cyclin D1 : Mantle cell lymphoma t(11;14) 	<p>STK11 (LKB1) : Peutz-Jeghers syndrome</p> <p>SDH : Familial paraganglioma Sx</p>
	<p>CDH1 (E-cadherin, Chr 16)</p> <ul style="list-style-type: none"> • Lobular breast carcinoma • Diffuse gastric carcinoma
	<p>DNA repair genes</p> <ul style="list-style-type: none"> • BRCA1 : breast cancer, ovarian cancer • BRCA2 : Male breast cancer, Prostate ca, Pancreatic cancer • MSH2, MLH1 : Lynch syndrome (HNPCC)
	<p>WT1 (Chr 11) : Wilms tumor</p>
	<p>MEN1 (Chr 11) : <i>Wermer syndrome</i></p> <ul style="list-style-type: none"> • Pituitary tumors • Parathyroid tumors • Pancreatic endocrine tumors

Neoplasia continued

Tumor Markers

AFP (Alpha-fetoprotein) "HEMAN"

H - Hepatocellular carcinoma, Hepatoblastoma

E - Endodermal sinus tumor (*yolk sac tumor*)

M - Mixed germ cell tumor

A - Ataxia telangiectasia

N - Neural tube defects / abdominal wall defects (\uparrow maternal serum AFP)

CA markers

- **CA-125** : Ovarian carcinoma (*serous*)
- **CA 15-3, CA 27-29** : Breast carcinoma (*used for monitoring, not diagnosis*)
- **CA 19-9** : Pancreatic cancer, Mucinous ovarian tumors
- **CA 72-4** : Gastric carcinoma

Cytokeratin patterns

- **CK7- / CK20+** : Merkel cell carcinoma, Colorectal carcinoma
- **CK7+ / CK20+** : Bladder carcinoma, Gastric carcinoma



Field cancerization :

- Due to **diffuse epithelial exposure** to carcinogen - Entire field becomes **preneoplastic**
- High risk of **multiple primary tumors**
- Tumors arise independently
- Seen in:
 - a. **Head & neck** cancers (oral cavity)
 - b. **Skin** cancers (UV exposure)
 - c. **Bladder** cancer
- The multiple primary tumors can be
 1. **Synchronous** : within **6** months
 2. **Metachronous** : after **6** months

Cell-free DNA markers

- **EGFR** in serum : Lung cancer
- **APC, RAS, TP53** in stool & serum : Colon cancer
- **RAS, TP53** in stool & serum : Pancreatic cancer
- **RAS, TP53** in sputum & serum : Lung cancer
- **TP53** in urine : Bladder cancer

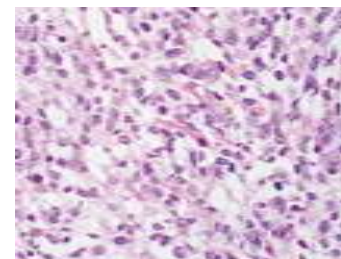
Chemical carcinogens

- **Aflatoxin** : Hepatocellular carcinoma
- **Arsenic** : Carcinoma of Skin, lung, liver
- **Vinyl chloride / Thorotrast** : Hepatic angiosarcoma
- **Aromatic amines (benzidine)** : Bladder cancer "*Larger name*"
- **Benzene** : AML "*smaller name*"



Embryonal Rhabdomyosarcoma
(sarcoma botryoides)

- **Grapelike** mass projecting into lumen
- **Vagina** (infants) is a common site
- **Tadpole / strap cells** on h/p



Tadpole / strap cells (rhabdomyoblasts)

Soft tissue sarcoma	Translocation gene	Chromosomes
Ewing sarcoma	EWSR1-FLI1	t(11;22)
Desmoplastic - small round cell tumor	EWSR1-WT1	
Synovial sarcoma	SYT-SSX1	t(X;18)
Alveolar rhabdomyosarcoma	PAX3-FOXO1	t(2;13)
Clear cell sarcoma	EWSR1-ATF1	t(12;22)

Neoplasia continued

Metastasis

(defines malignant vs benign tumors)

Exceptions : Cancers that don't metastasize

- a. Gliomas
- b. Basal cell carcinoma

Route of metastasis

1. **Carcinomas** : Lymphatic spread (better prog.)

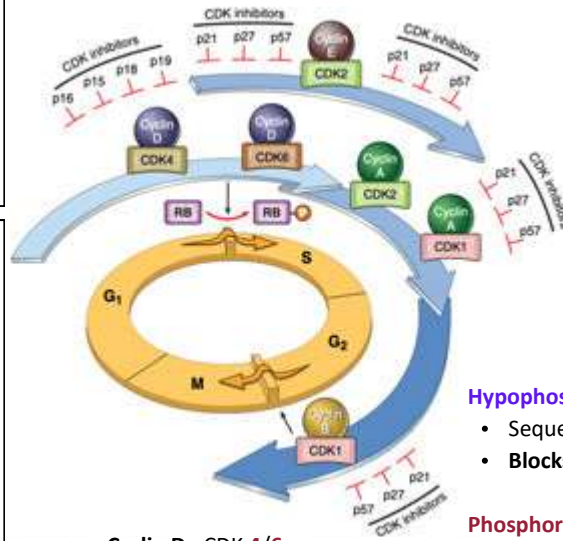
Exceptions (hematogenous spread):

- a. Clear cell RCC
- b. Follicular carcinoma thyroid
- c. Choriocarcinoma

2. **Sarcomas** : Hematogenous spread

Exceptions (lymphatic spread):

- a. Clear cell sarcoma
- b. Synovial sarcoma
- c. Rhabdomyosarcoma (RMS)



Hypophosphorylated Rb = ACTIVE

- Sequesters E2F
- Blocks entry into S phase

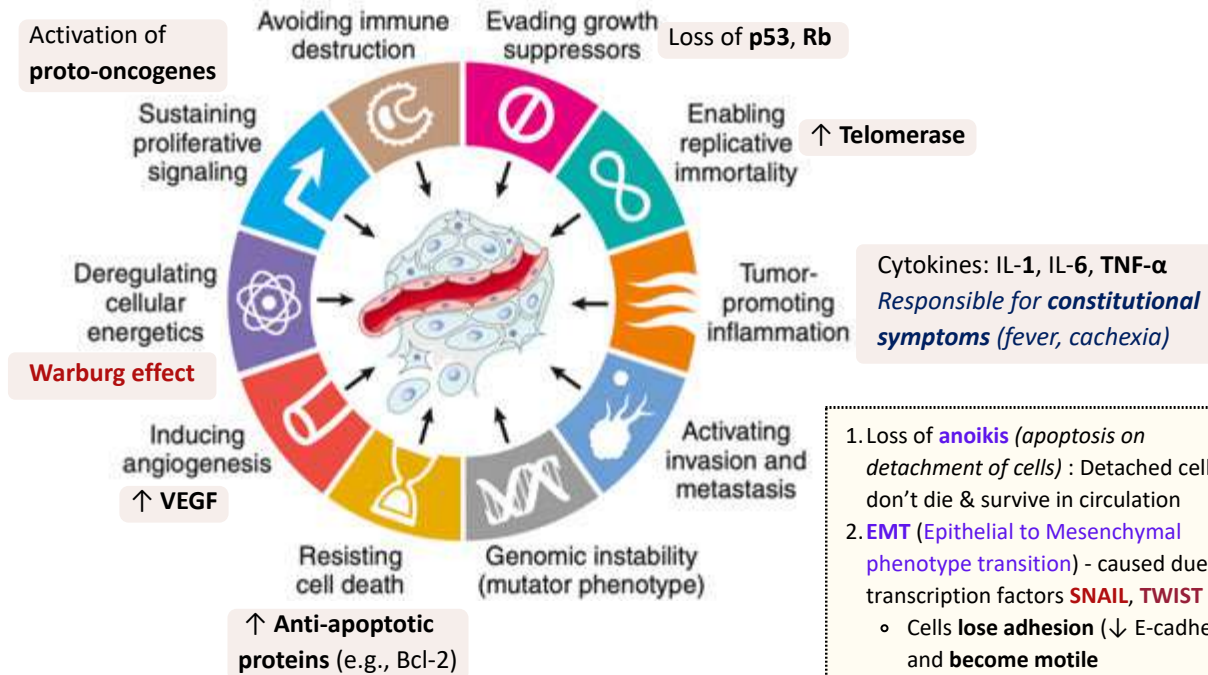
Phosphorylated Rb = INACTIVE

- Releases E2F : Entry to S phase

- Cyclin D : CDK 4/6
- Cyclin E : CDK 2
- Cyclin A : CDK 2, CDK 1
- Cyclin B : CDK 1

Activating **inhibitory immune checkpoint** pathways
(CTLA-4, PD-1/PD-L1)

Hallmarks of Cancer cells



Cytokines: IL-1, IL-6, TNF- α
Responsible for **constitutional symptoms** (fever, cachexia)

1. Loss of **anoikis** (apoptosis on detachment of cells) : Detached cells don't die & survive in circulation
2. **EMT** (Epithelial to Mesenchymal phenotype transition) - caused due to transcription factors **SNAIL, TWIST**
 - Cells **lose adhesion** (\downarrow E-cadherin) and **become motile**
3. \uparrow **Matrix Metalloproteinases** (MMPs) : Helps in breakdown of **basement membrane** - tumor cells invade surrounding tissue & vessels

Warburg effect : aerobic glycolysis

- Cancer cells **preferentially use glycolysis** even in presence of oxygen
- Cells show **Increased glucose uptake**
- Basis of **18-FDG PET** imaging (detects metabolically active tumors)