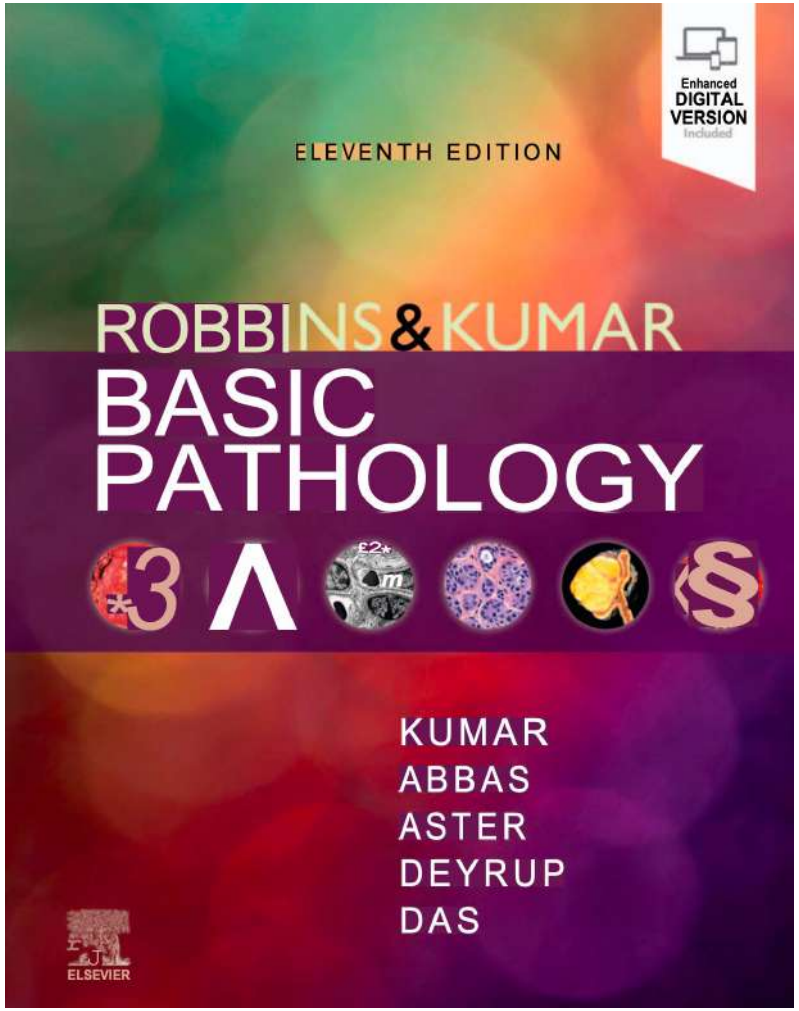
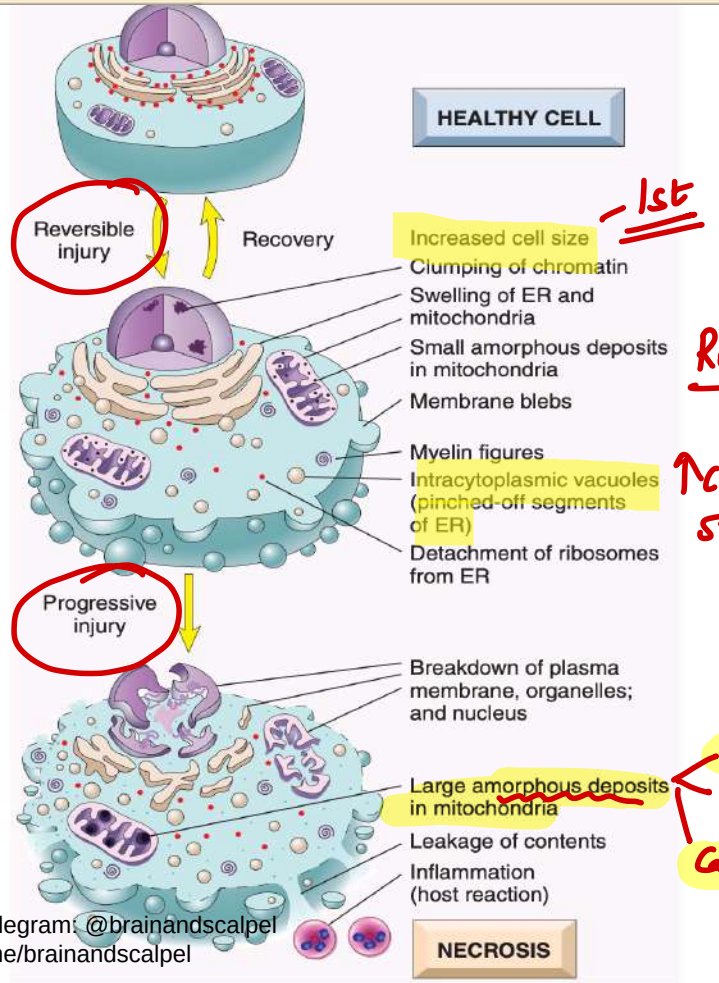
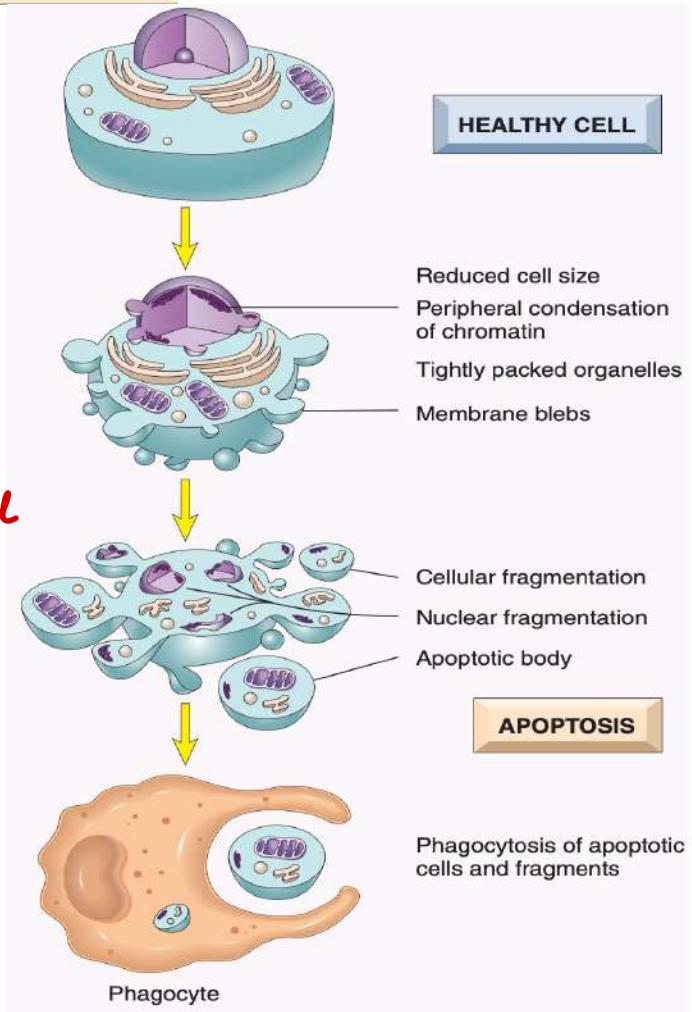
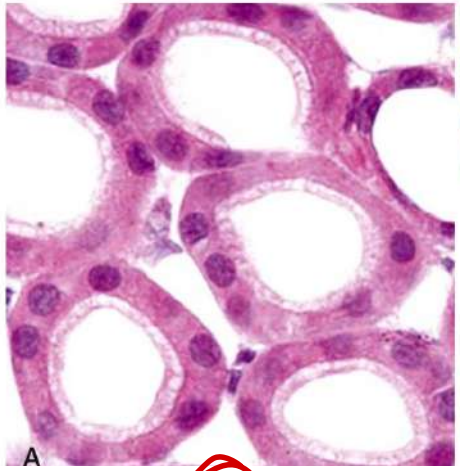
COMPILED MODULE: ROBBINS SPECIAL

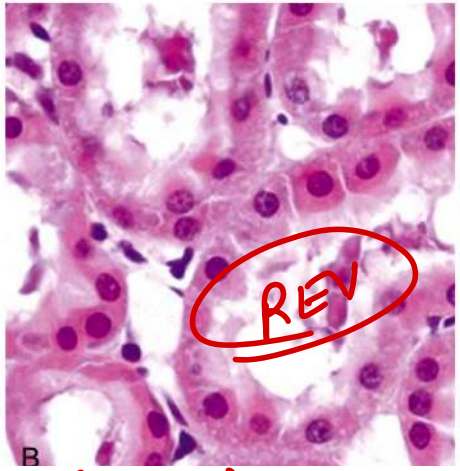


Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	Absent
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic; means of eliminating unnecessary cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

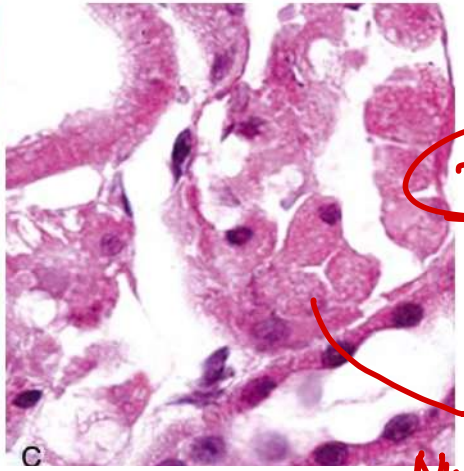






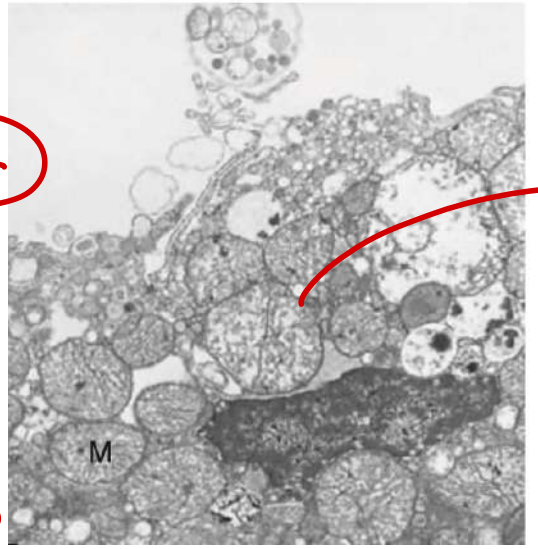


REV



-IRR

Nucleus disapp



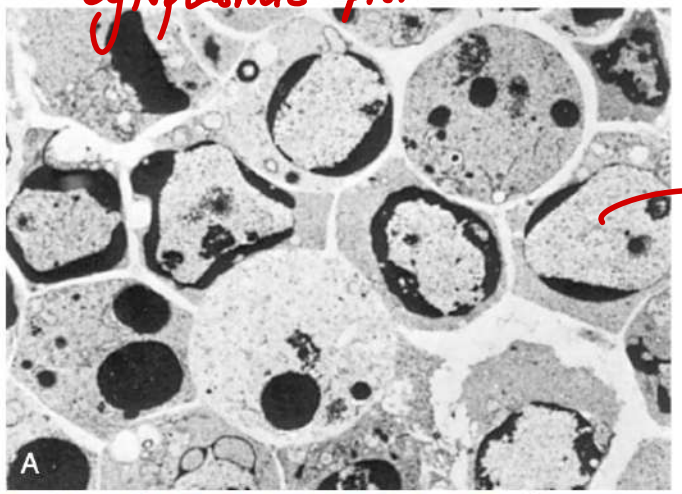
E/M

Amorphous density

N

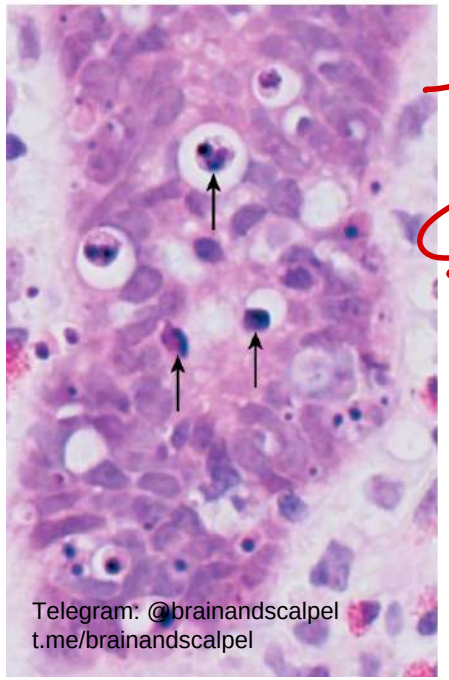
Necrosis

↑ cell size
↑ eosinophilic - eosin - denatured cytoplasmic prtn



E/M

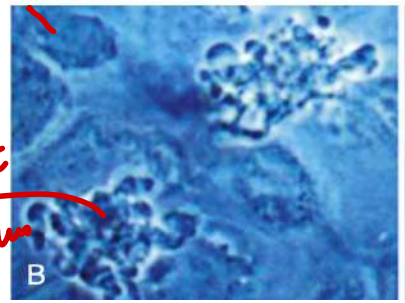
apoptosis



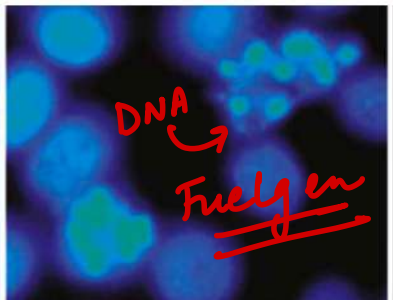
cell size ↓
fragmentn

Apoptosis

Phase contrast microscopy



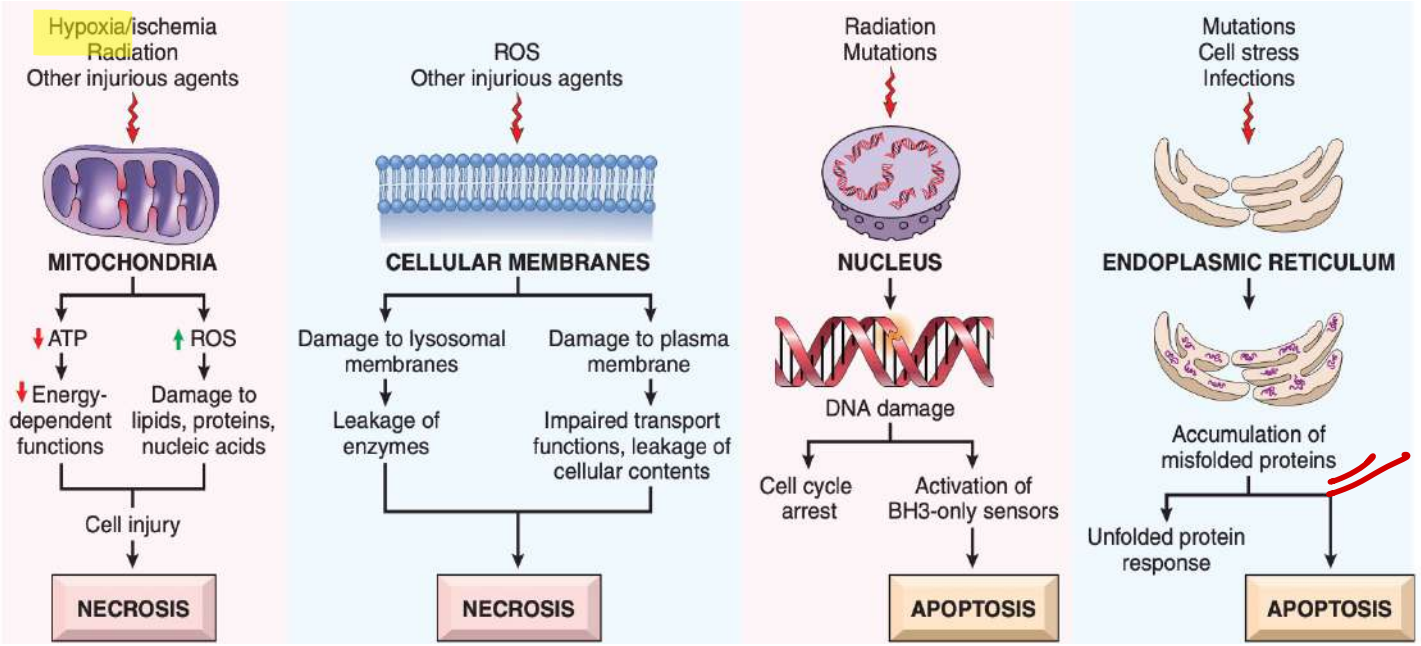
Compact chromatin



DNA → Fuelgen

Caspase

+



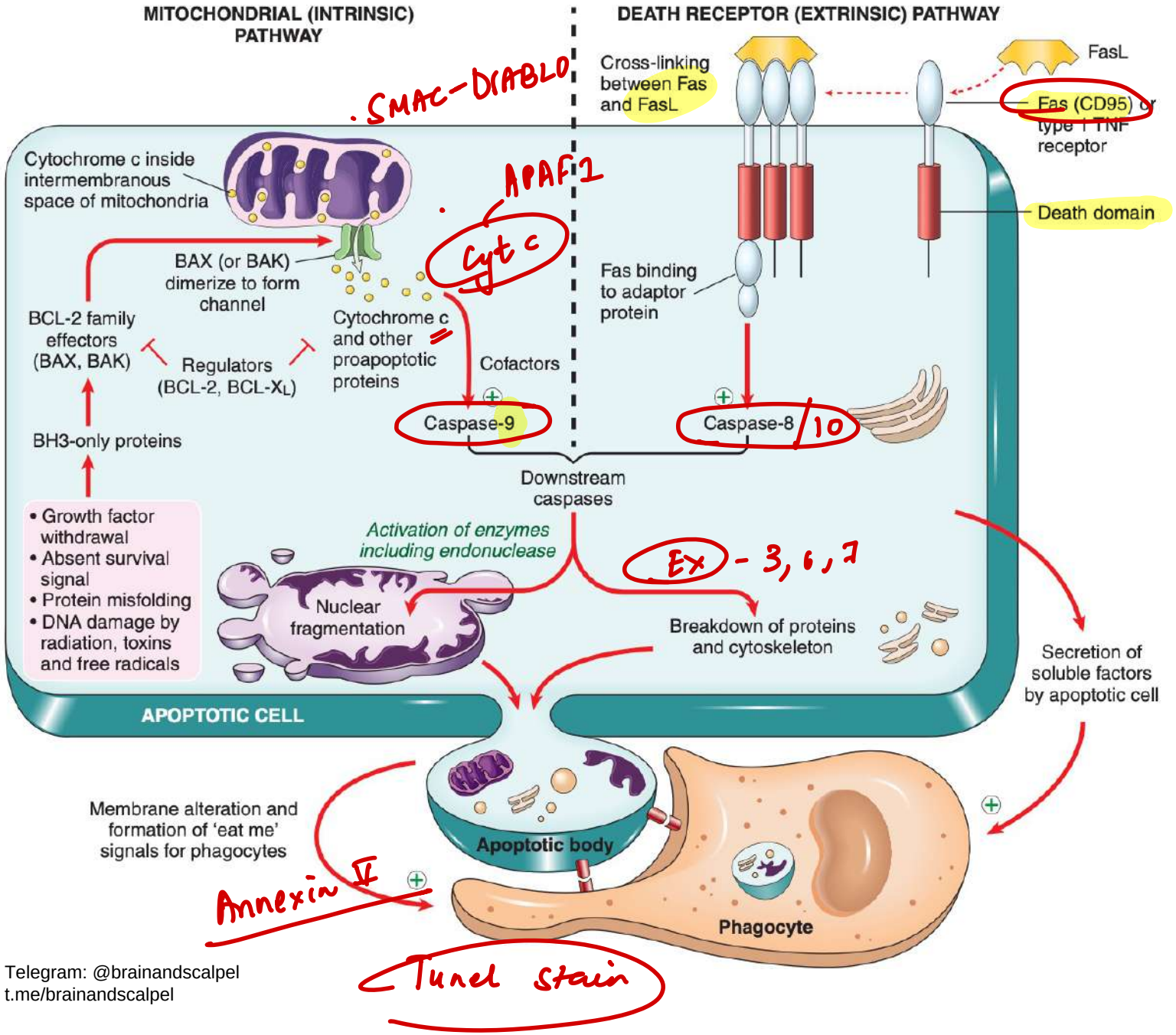
MCC of cell injury: Hypoxia
Most sensitive cells: Neurons
Most resistant cells: Fibroblasts

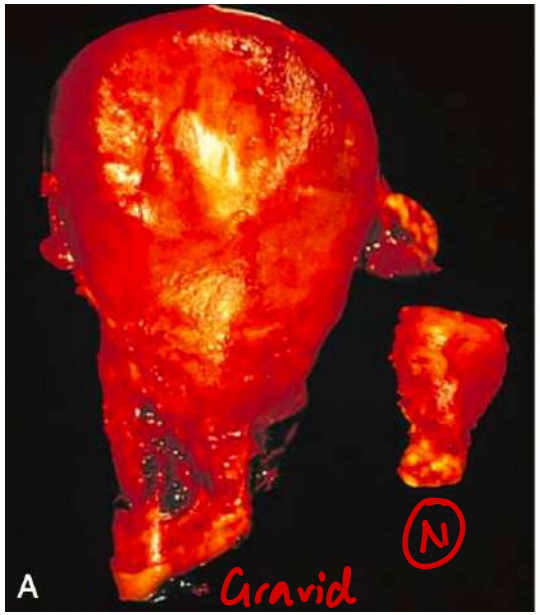
Table 1.4 Diseases Caused by Misfolded Proteins

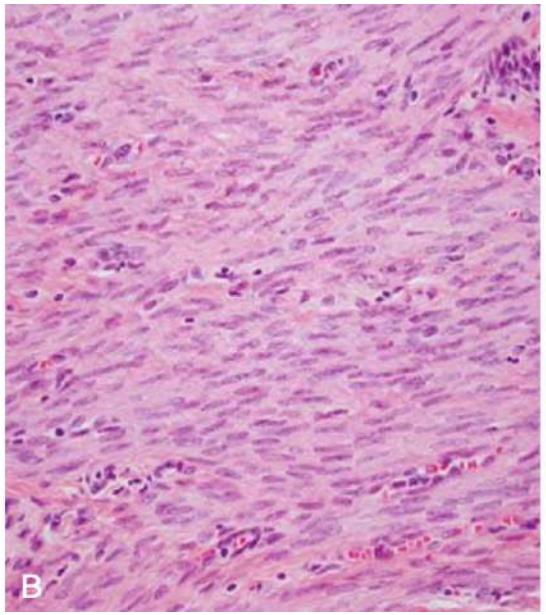
Disease	Affected Protein	Pathogenesis
Diseases Caused by Mutant Proteins That Are Degraded, Leading to Their Deficiency		
Cystic fibrosis[a]	Cystic fibrosis transmembrane conductance regulator (CFTR)	Loss of CFTR leads to defects in ion transport
Familial hypercholesterolemia[a]	LDL receptor	Loss of LDL receptor leading to hypercholesterolemia
Tay-Sachs disease[a]	Hexosaminidase α-subunit	Lack of the lysosomal enzyme leads to storage of GM_2 gangliosides in neurons
Diseases Caused by Misfolded Proteins That Result in ER Stress-Induced Cell Loss		
Retinitis pigmentosa[a]	Rhodopsin	Abnormal folding of rhodopsin causes photoreceptor loss and blindness
Creutzfeldt-Jakob disease	Prions	Abnormal folding of PrP^{sc} causes neuronal cell death
Diseases Caused by Misfolded Proteins That Result From Both ER Stress-Induced Cell Loss and Functional Deficiency of the Protein		
α-1-antitrypsin deficiency	α-1 antitrypsin	Storage of nonfunctional protein in hepatocytes causes apoptosis; absence of enzymatic activity in lungs causes destruction of elastic tissue, giving rise to emphysema

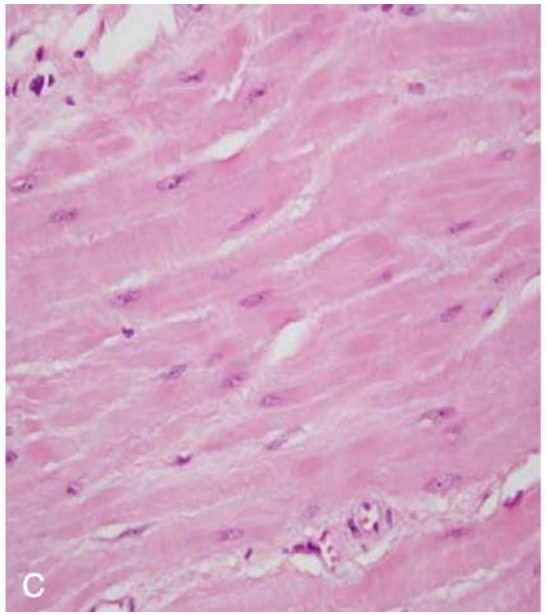
Chaperone-mediated autophagy (HSP-70)
LAMP2a-Lysosomal associated membrane protein

CSF: 14-3-3









Hypertrophy > Hyperplasia

Size ↑

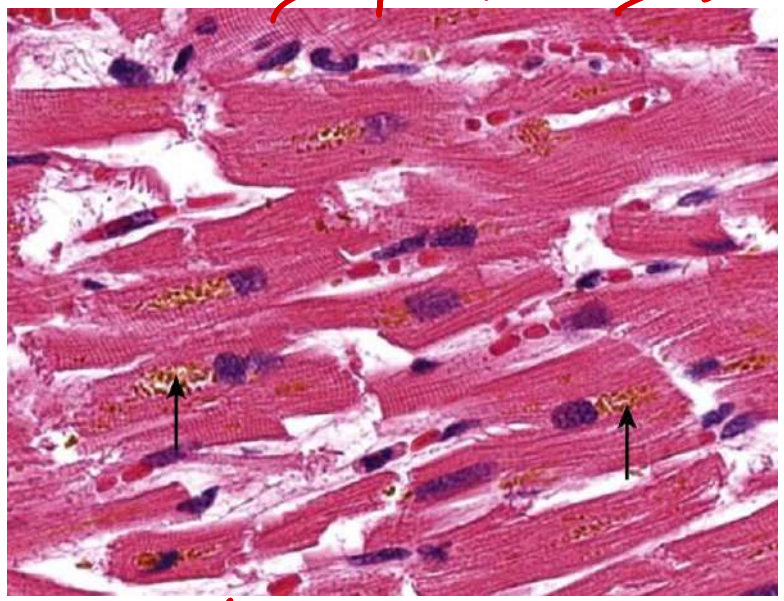
Smoking

ciliated pseq

Sq

Metaplasia → protective

Dysplasia - irreversible

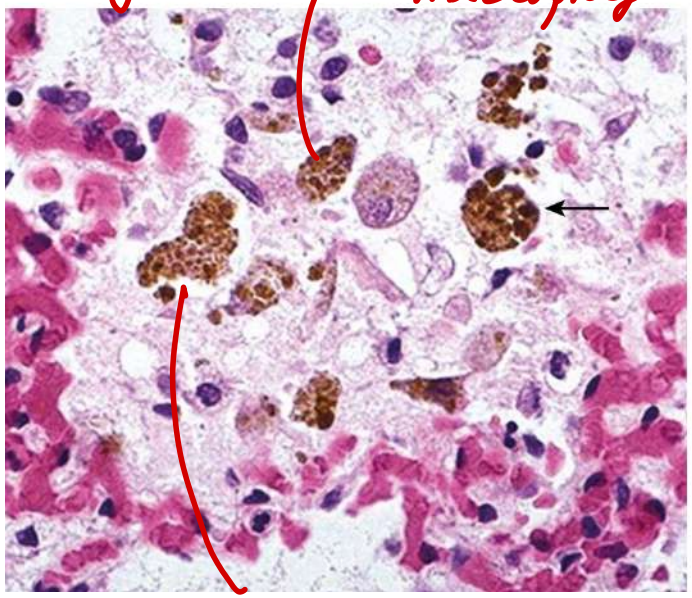


Lipid peroxidation

brown atrophy

Lipofuscin

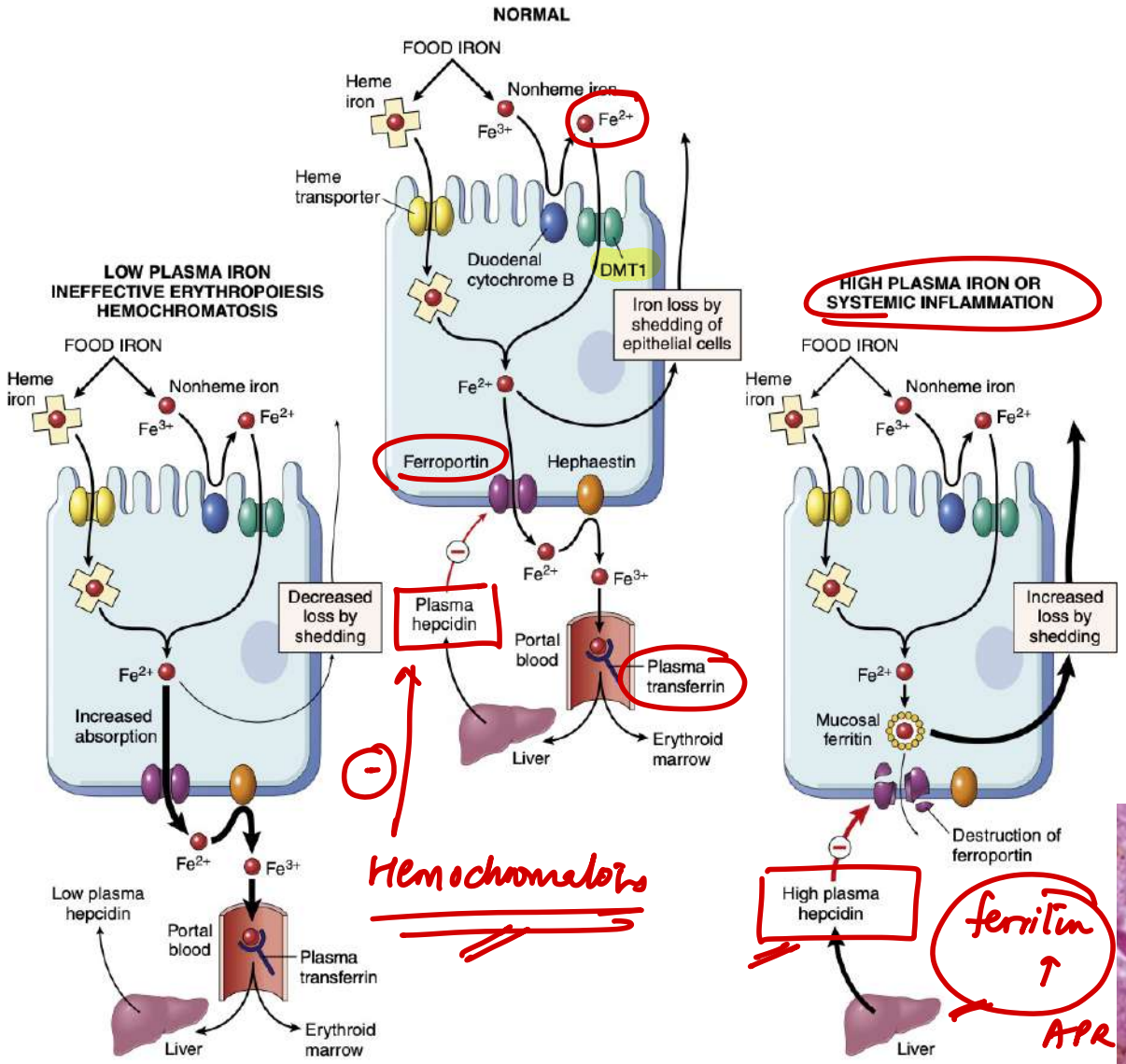
- perinuclear
- intralysosomal



Hemosiderin (macrophages)

↳ failure cells

~~Reversible?~~ YES



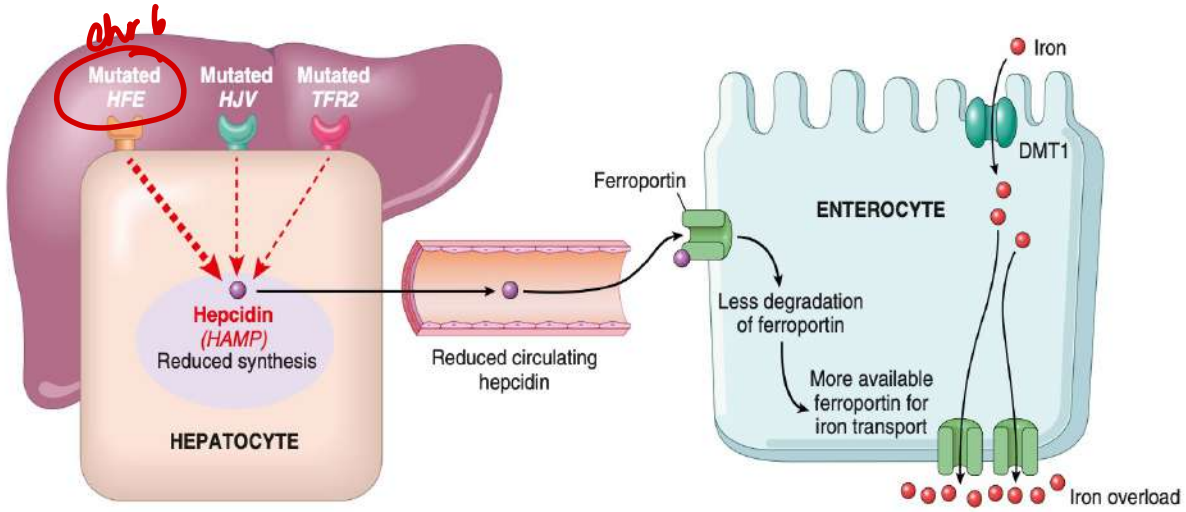
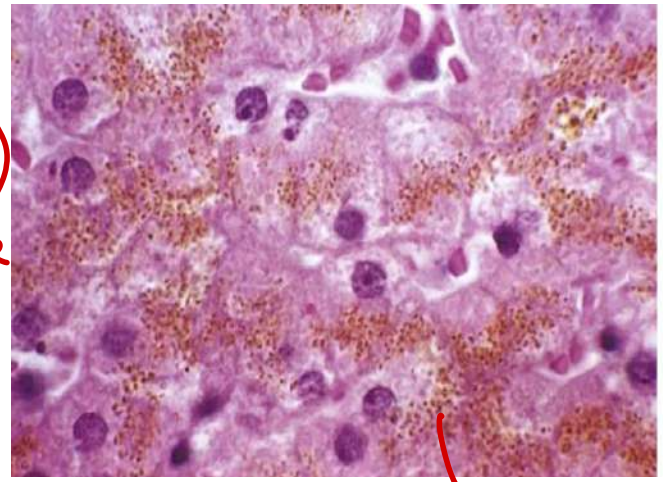
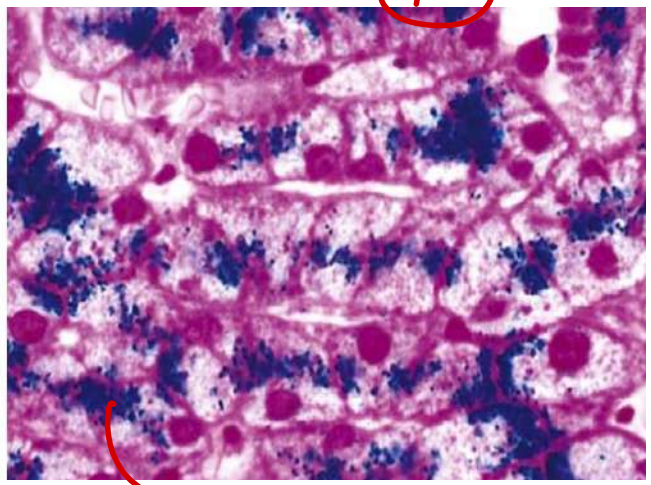


FIG. 14.20 Pathogenesis of hemochromatosis. Following iron uptake into enterocytes mediated by divalent metal transporter 1 (DMT1), iron secretion into the plasma depends on a second transporter, ferroportin. Hepcidin negatively regulates this process by binding ferroportin and stimulating its proteolytic degradation. Hepcidin production is regulated by an "iron sensor" in the liver that requires multiple factors, including HFE, HJV, and TFR2. Defects in any of these factors or hepcidin itself (encoded by the *HAMP* gene) result in increased iron uptake and hemochromatosis. *DMT1*, Divalent metal transporter 1; *HAMP*, hepcidin antimicrobial peptide; *HFE*, high Fe; *HJV*, hemojuvelin; *TFR2*, transferrin receptor 2.

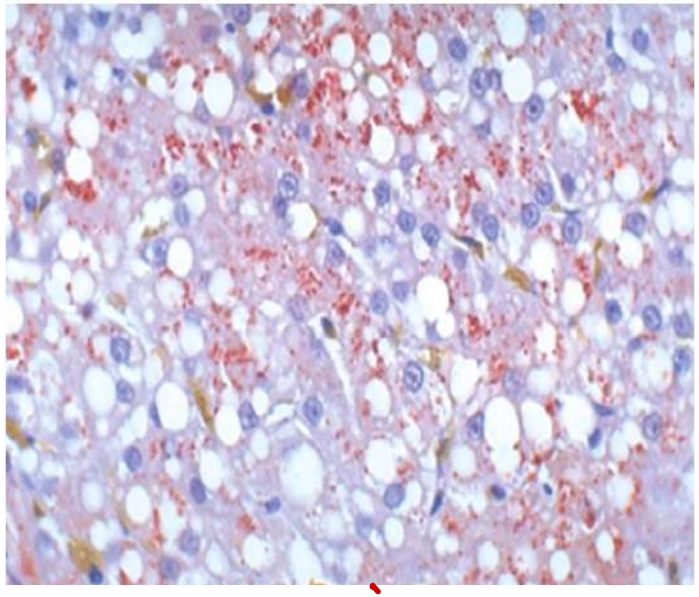
MC: HFE C282Y



Hemosiderin



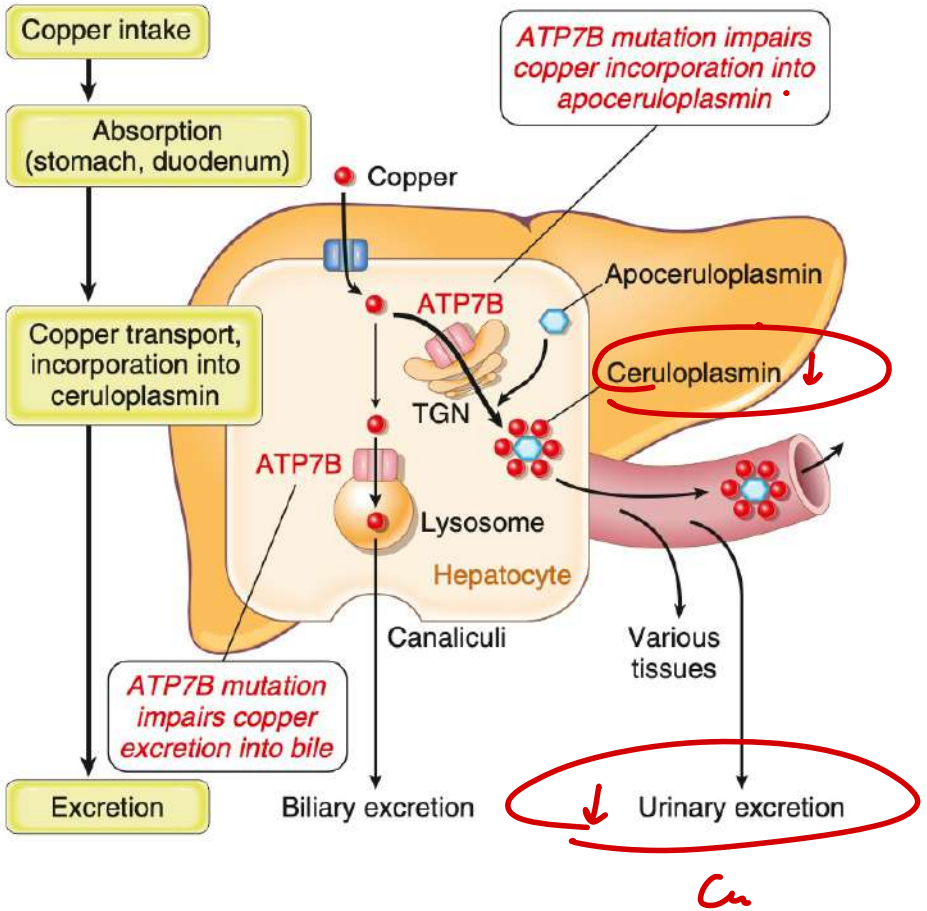
Perls' / Prussian blue

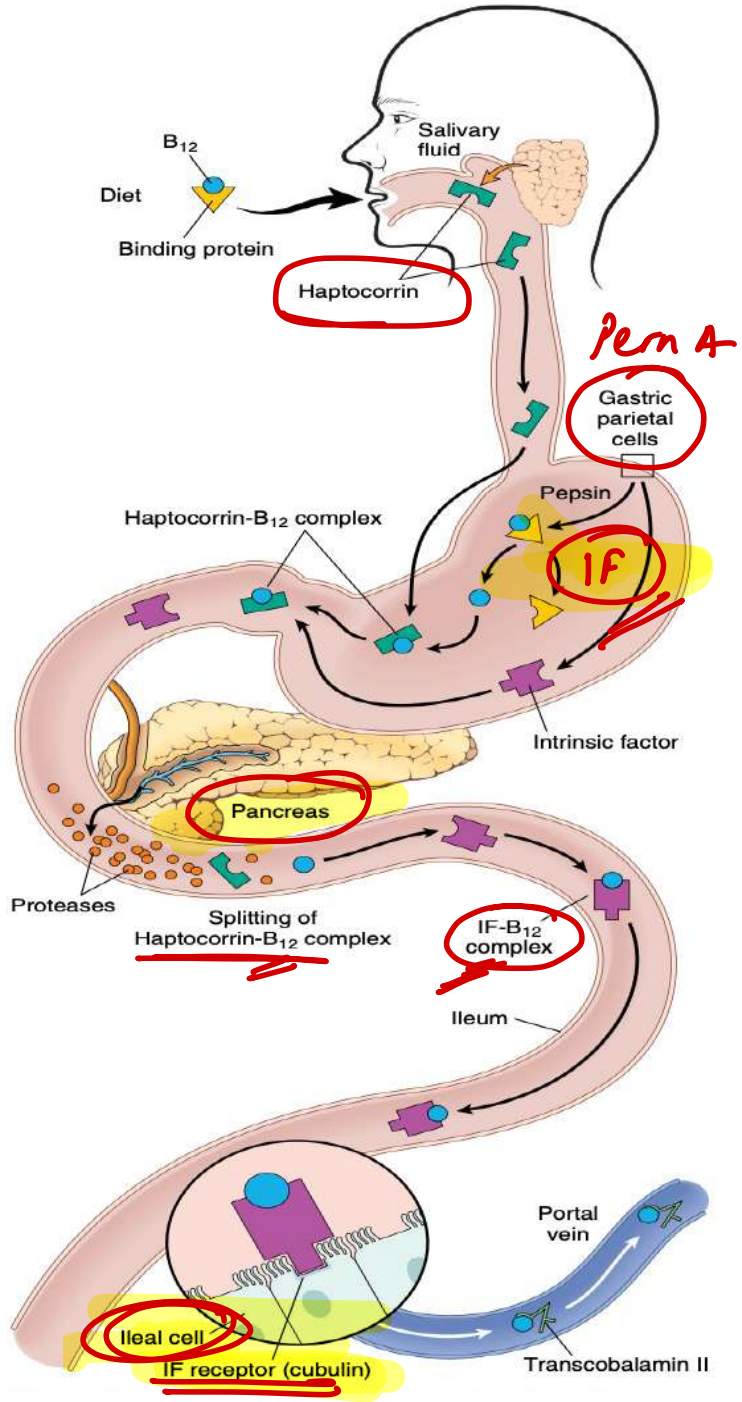


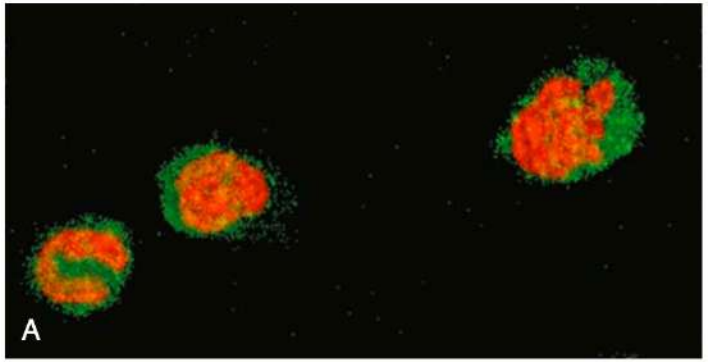
Rhodanine

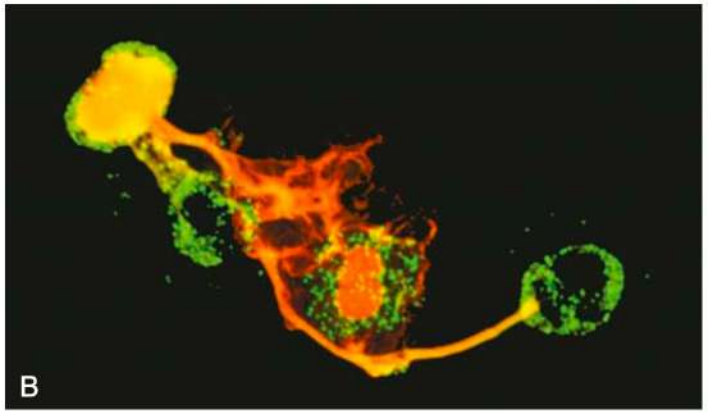
Rubeanic acid

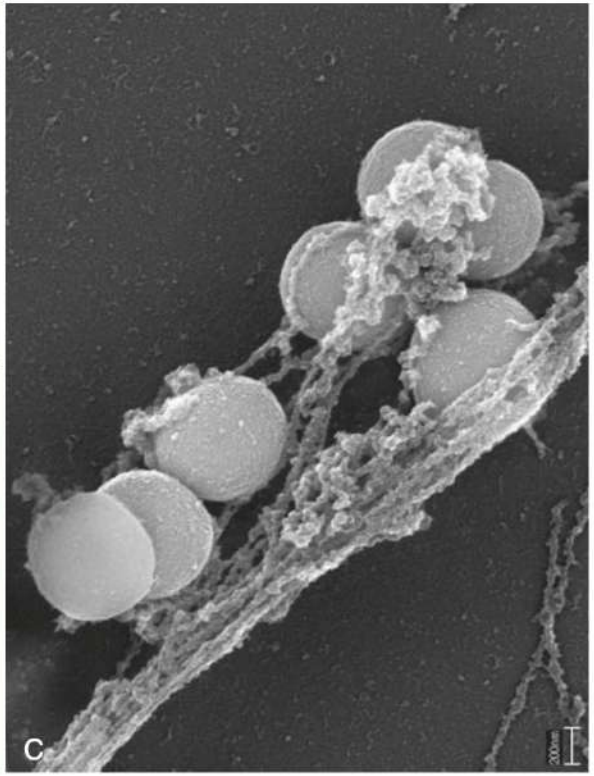
Wilson











NET

- arginine
- ⊗ mitochondrial
- SLE
- sepsis ++

beneficial suicide

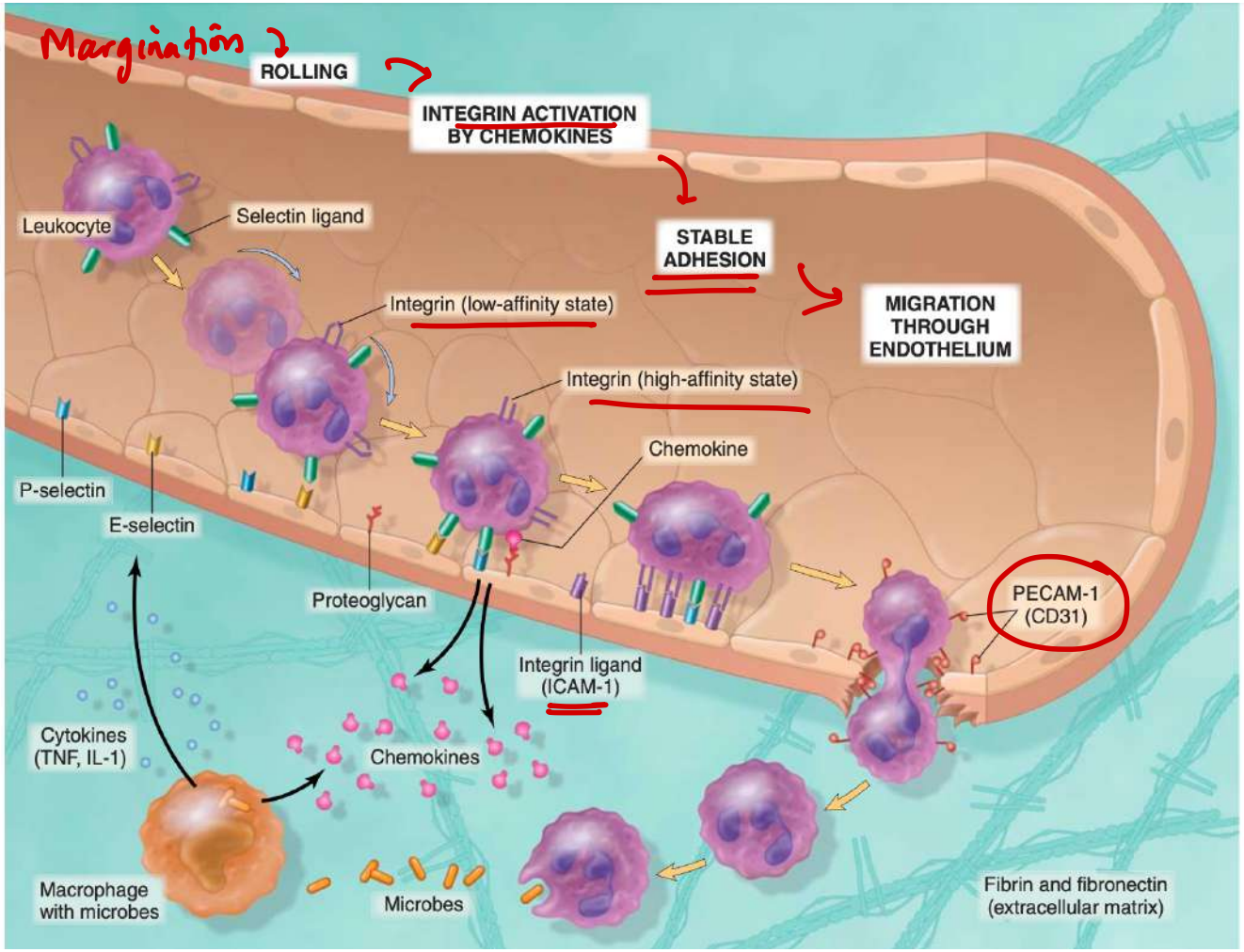


Table 2.3 Endothelial and Leukocyte Adhesion Molecules

Family	Adhesion Molecule	Major Cell Type	Principal Ligands
Selectin	L-selectin	Leukocytes	Sialyl-Lewis X on various glycoproteins expressed on endothelium
	E-selectin	Activated endothelium	Sialyl-Lewis X on glycoproteins expressed on neutrophils, monocytes, T lymphocytes
	P-selectin	Activated endothelium	Sialyl-Lewis X on glycoproteins expressed on neutrophils, monocytes, T lymphocytes
Integrin	LFA-1	T lymphocytes, other leukocytes	ICAM-1 expressed on activated endothelium
	MAC-1	Monocytes, other leukocytes	ICAM-1 expressed on activated endothelium
	VLA-4	T lymphocytes, other leukocytes	VCAM-1 expressed on activated endothelium
	α4β7	Lymphocytes, monocytes	MAdCAM-1 expressed on endothelium in gut and gut-associated lymphoid tissues

Table 2.7 Cytokines in Inflammation

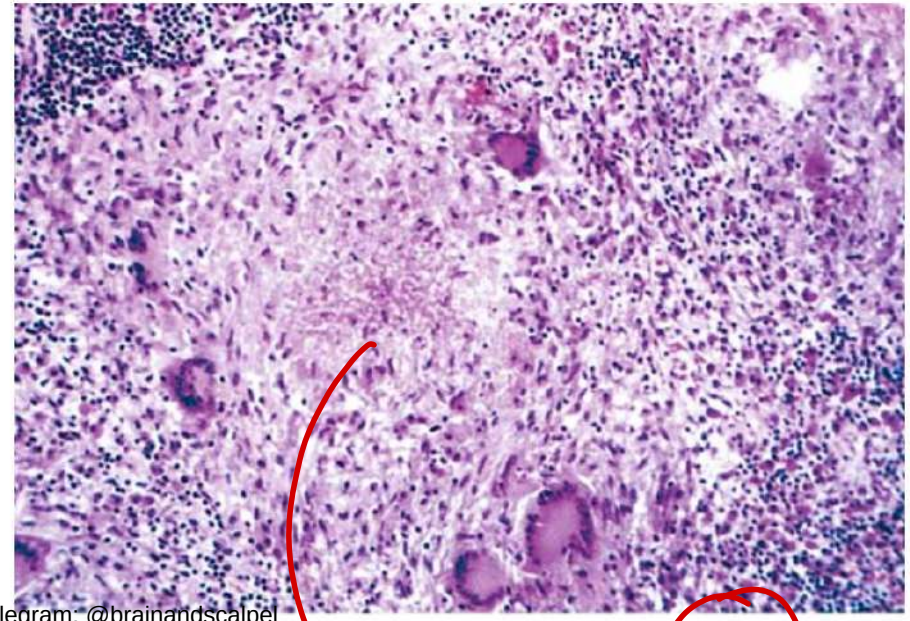
Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute-phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in healthy tissues
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

Chemokines

- **C**: Contains only two cysteines, and lymphotactin α and β are examples of C chemokines
- **CC**: Contains four cysteines, and most chemokines are in this class (Eotaxin / Rantes / MIP 1 α)
- **CXC**: Contains four cysteines, and there are more than 15 CXC chemokines in humans (IL-8)
- **CX3C**: Contains four cysteines, and fractalkine is an example of a CX3C chemokine

Table 2.9 Examples of Diseases With Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis* infection	Caseating granulomas (tubercles): foci of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes; occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae* infection	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum* infection	Gumma: microscopic to grossly visible lesion; surrounding wall of macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	*Bartonella henselae* (gram-negative bacillus) infection	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, possibly self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate



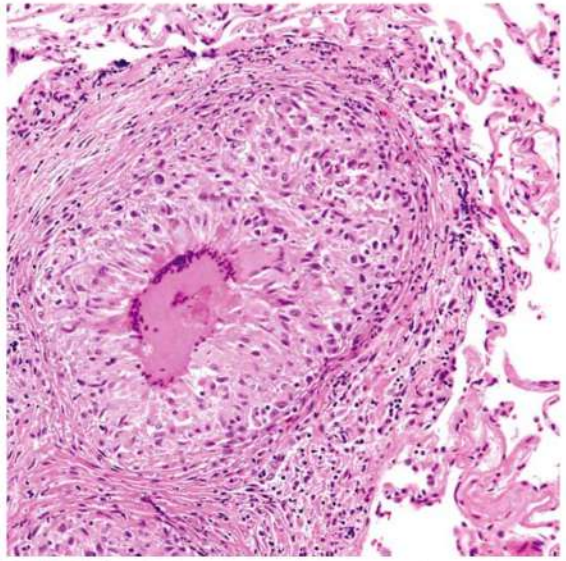


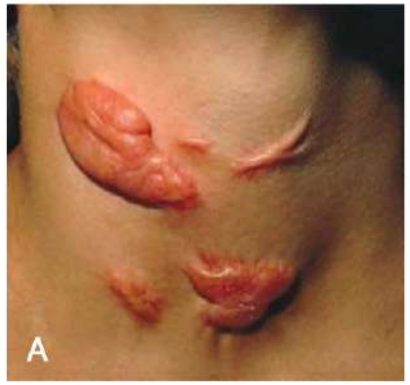
FIG. 11.21 Sarcoidosis. A characteristic noncaseating granuloma with a large central multinucleated giant cell is present. (From Diagnostic Pathology: Thoracic and ExpertPath. Copyright Elsevier 2022.)

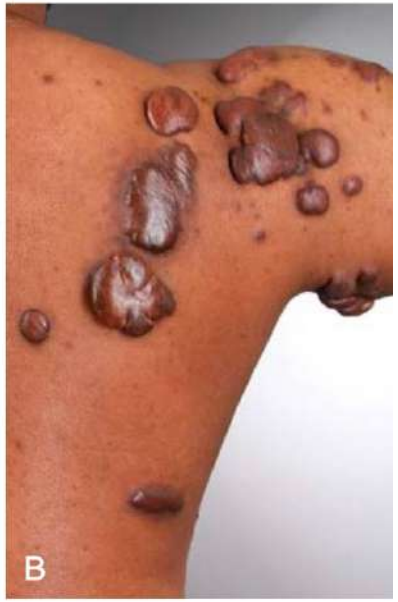
Table 2.10 Growth Factors

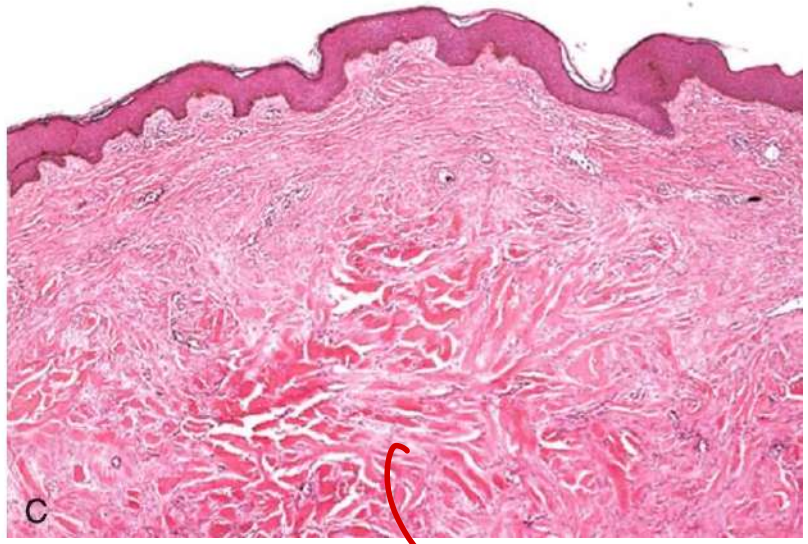
Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
Vascular endothelial growth factor (VEGF)	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

ECM, Extracellular matrix.

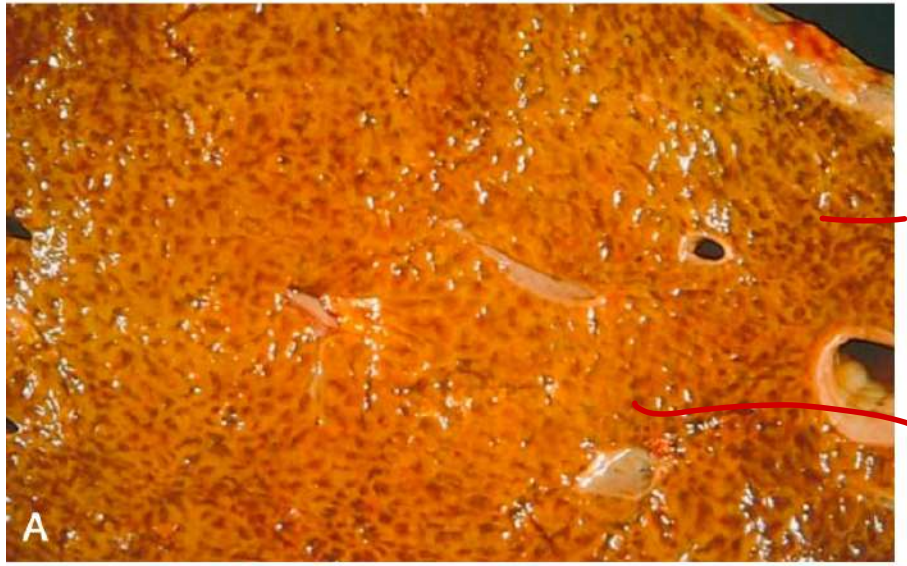
Keloid







haphazard collagen

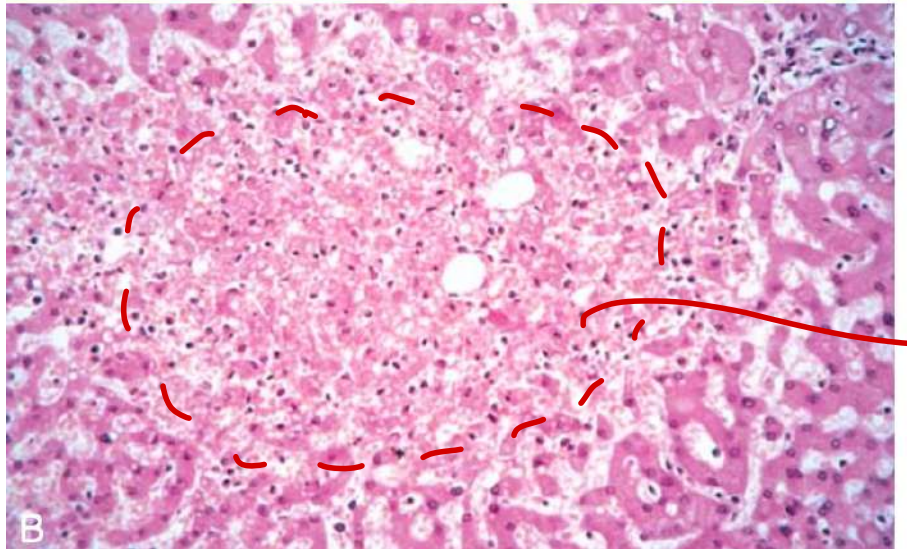


Nutmeg liver

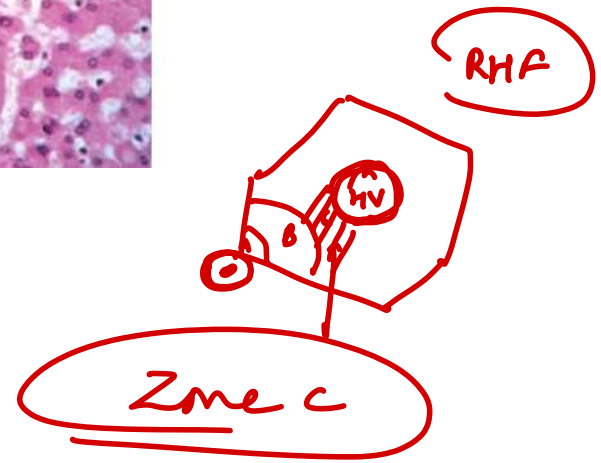
brown

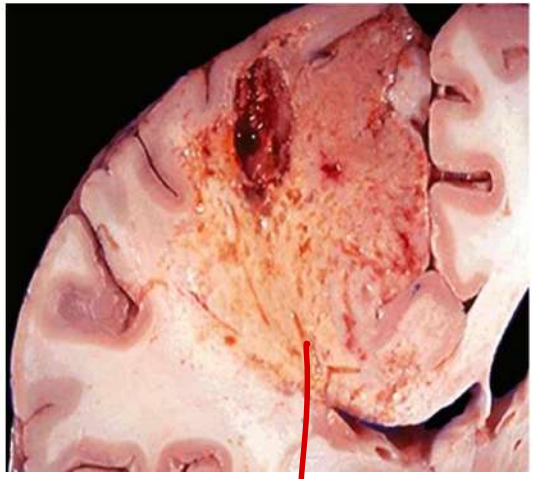
hemosiderin

venous Congestion

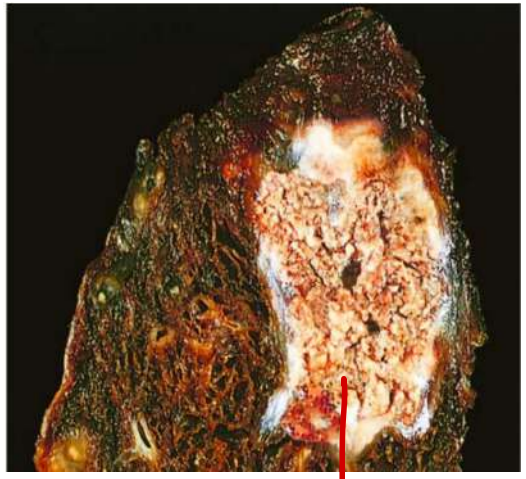


Centrilobular Congestion

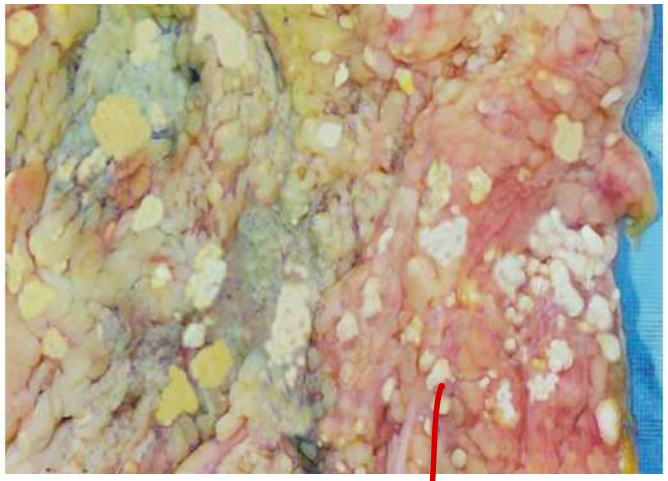




Liquefactive



Caseous

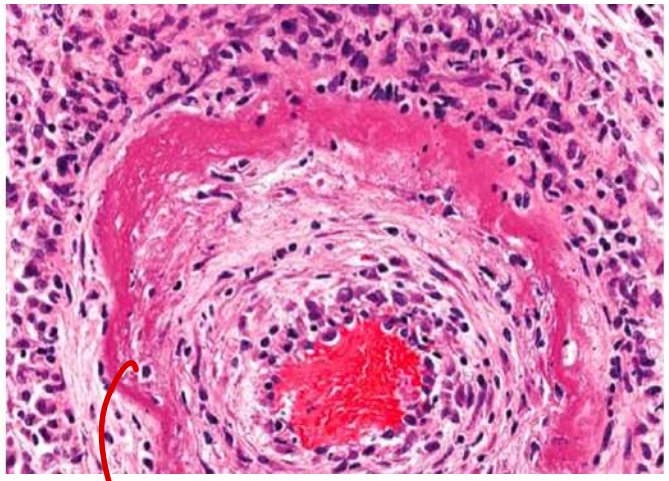


Fat Necrosis

Breast

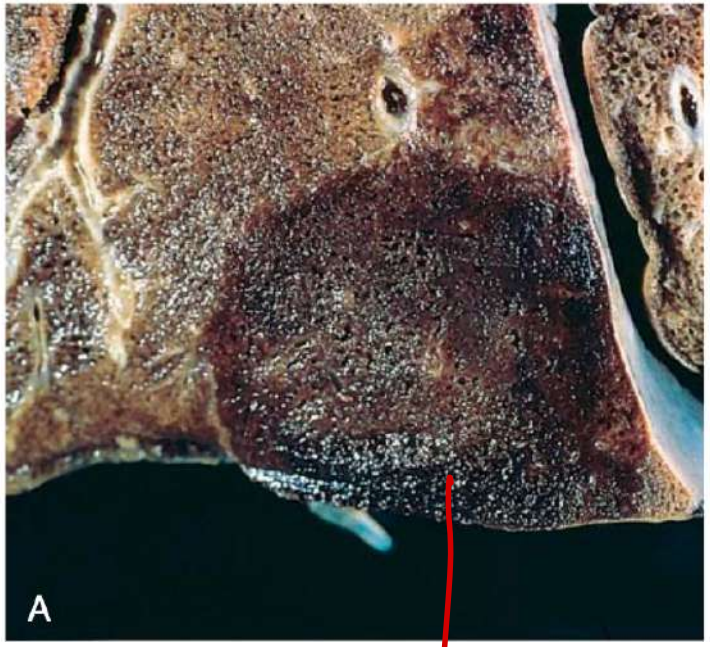
Omentum

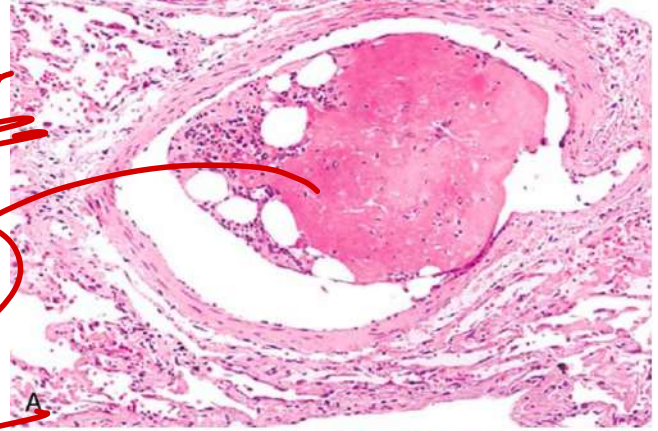
+ pancreatitis

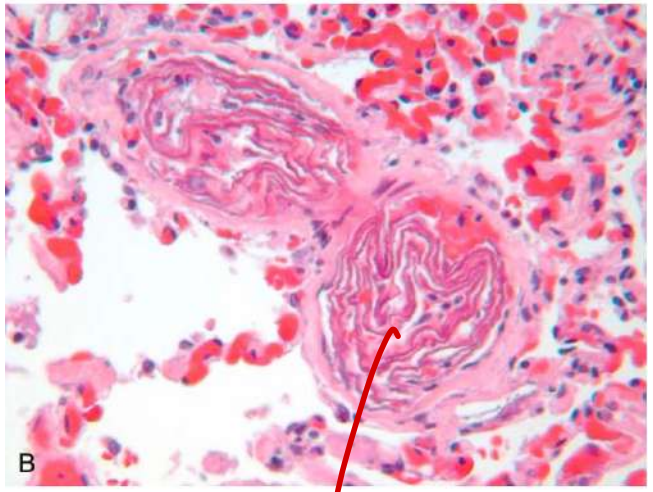


Fibrinoid

PAN







femur

FAT emboli

Red Infarct White

dual / collateral

- Lung
- Intestine

torsion

venous

end-organ

- Spleen
- kidney
- ♡

Amniotic fluid emboism

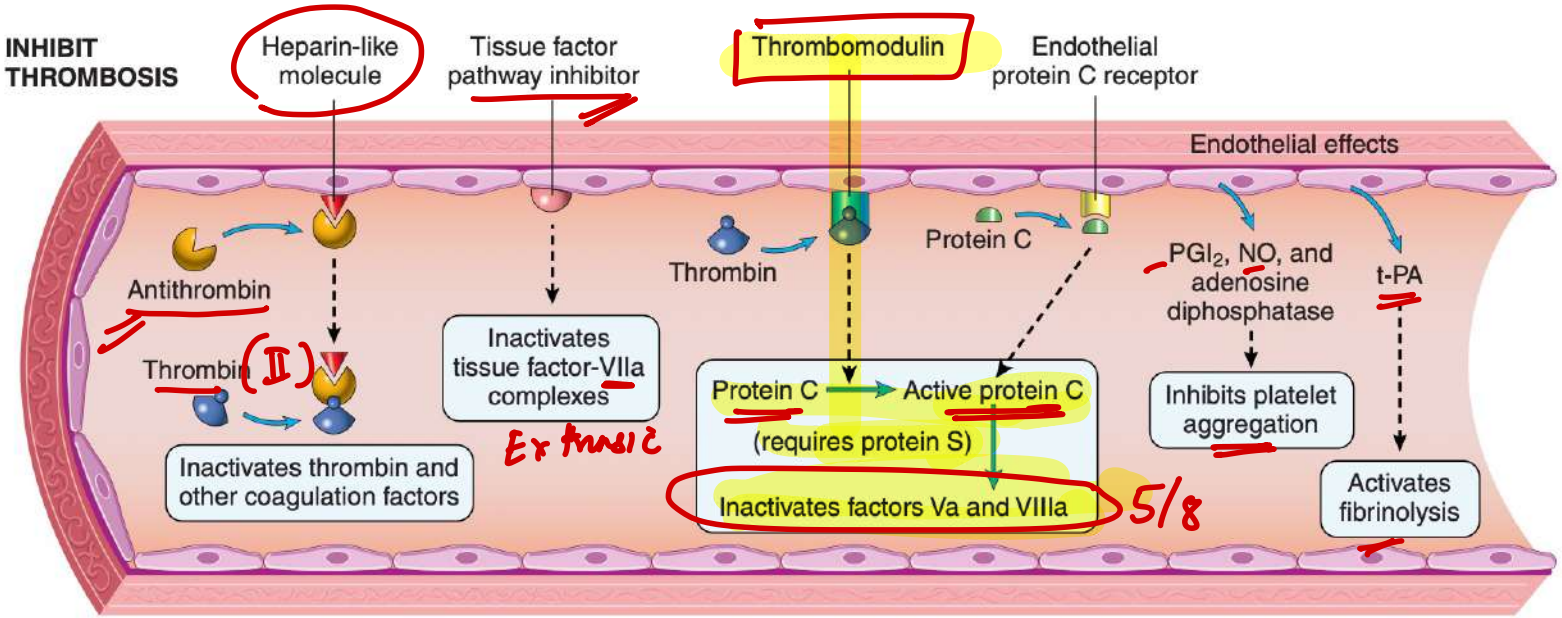
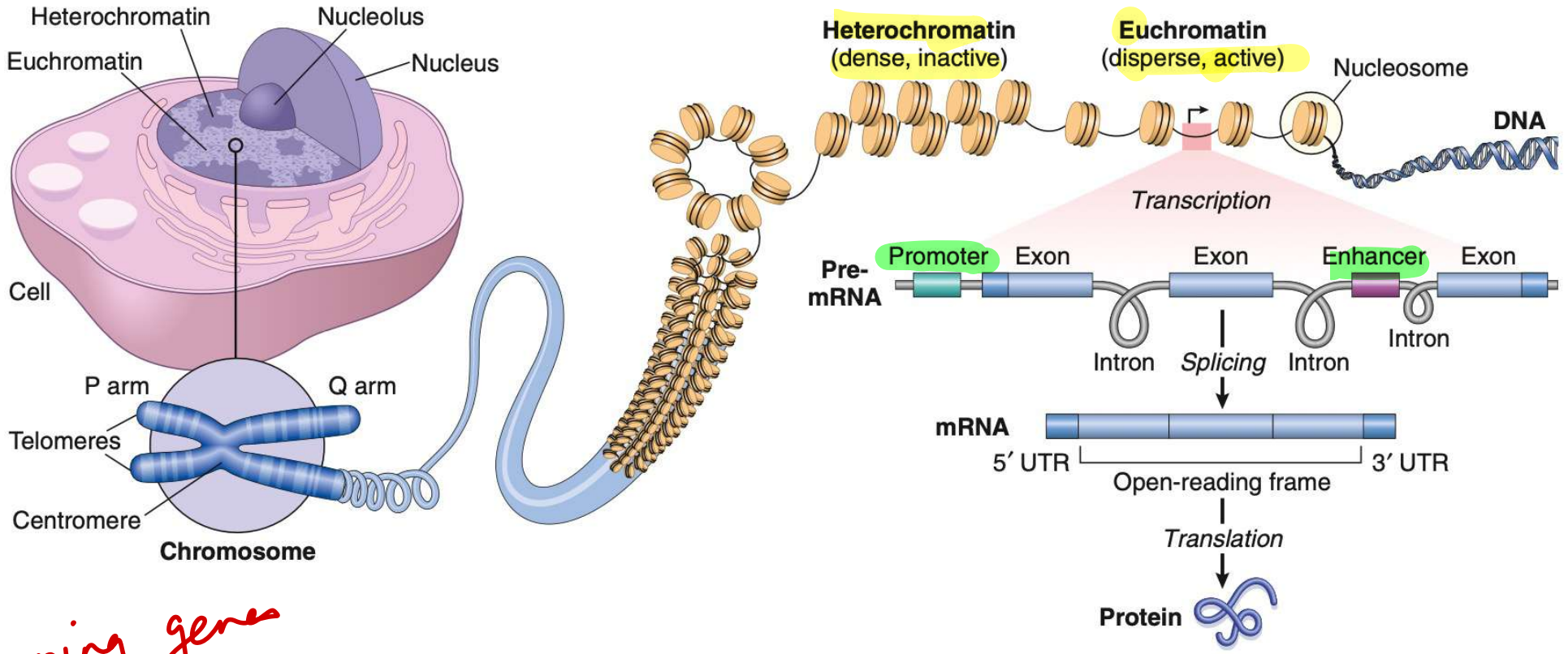


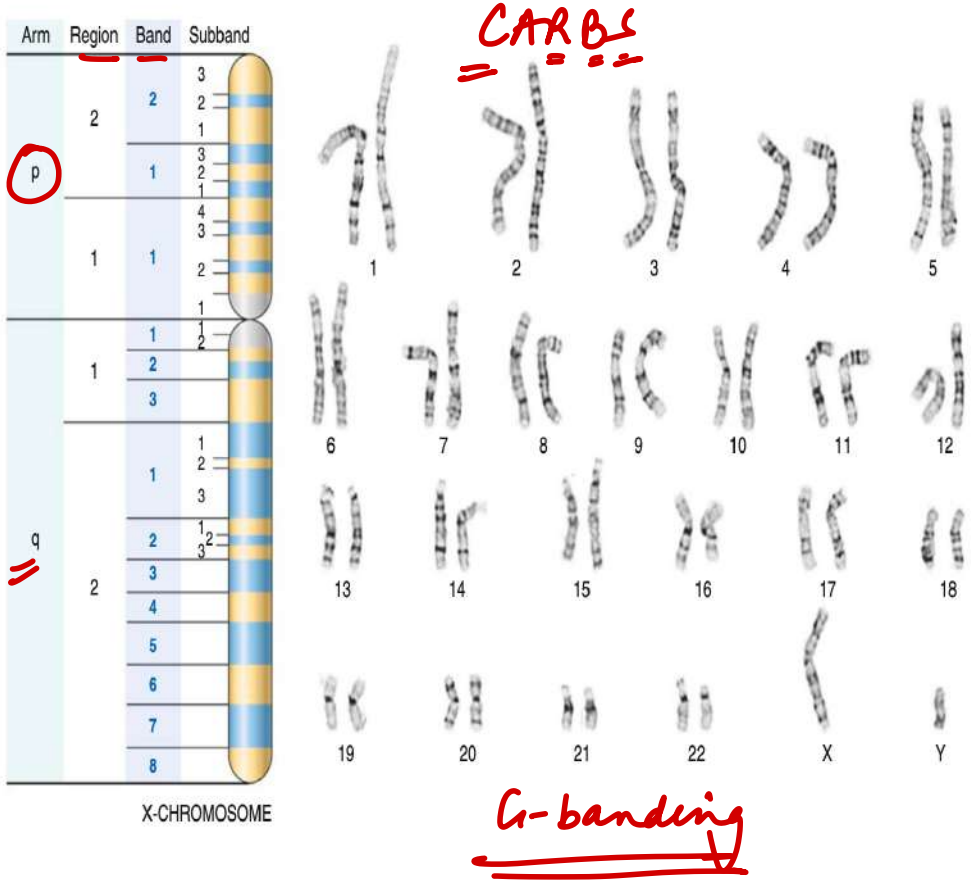
FIG. 3.11 Antithrombotic effects of normal endothelium. See text for details.

Lines of Zahn: antemortem thrombus



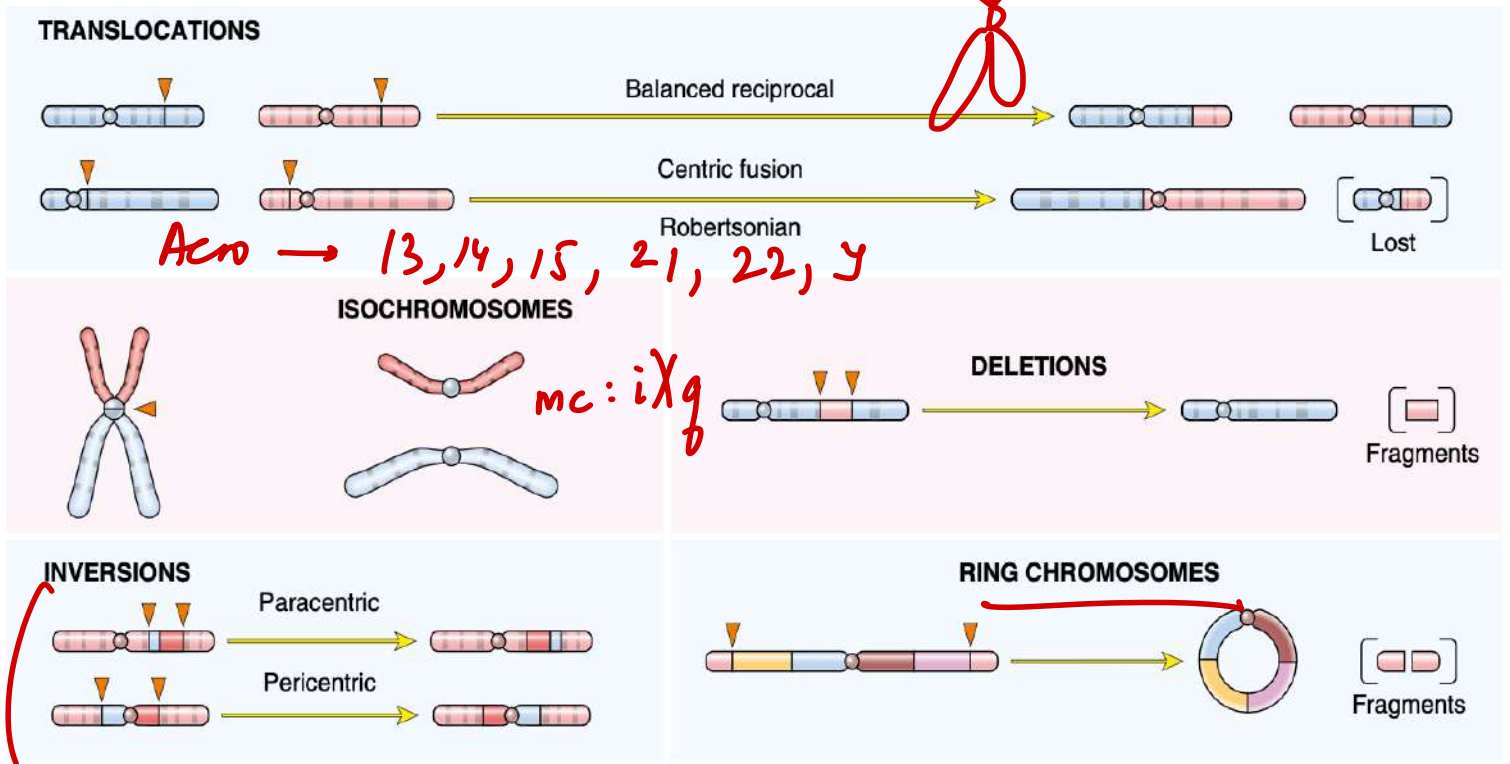
jumping gene

DNA linkers. *Promoters* are noncoding regions of DNA that initiate gene transcription; they are on the same strand and upstream of their associated gene. *Enhancers* are regulatory elements that can modulate gene expression across distances of 100 kB or more by looping back onto promoters and recruiting additional factors that are needed to drive the transcription of pre-messenger RNA (mRNA) species. The intronic sequences are subsequently spliced out of the pre-mRNA to produce mature mRNA, which includes exons that are translated into protein and 5′- and 3′-untranslated regions (UTR) that may have regulatory functions. In addition to the enhancer, promoter, and UTR sequences, noncoding elements are found throughout the genome; these include short repeats, regulatory factor binding regions, noncoding regulatory RNAs, and transposons.



CARBS

G-banding



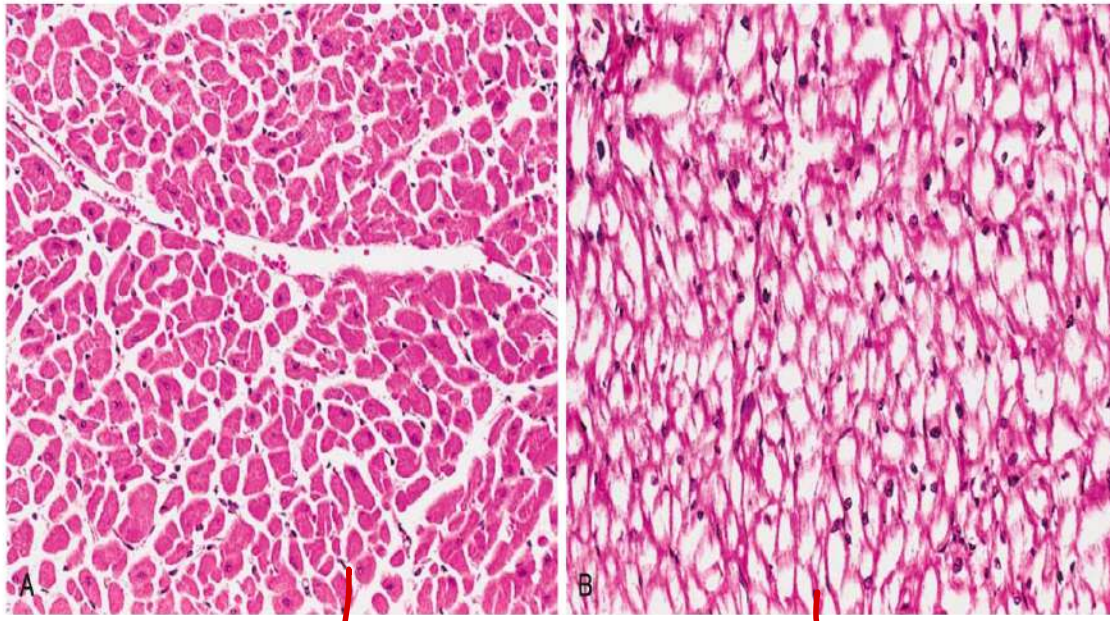
Acro → 13, 14, 15, 21, 22, Y

mc: i(X)q

Inv(16) → M4

AML

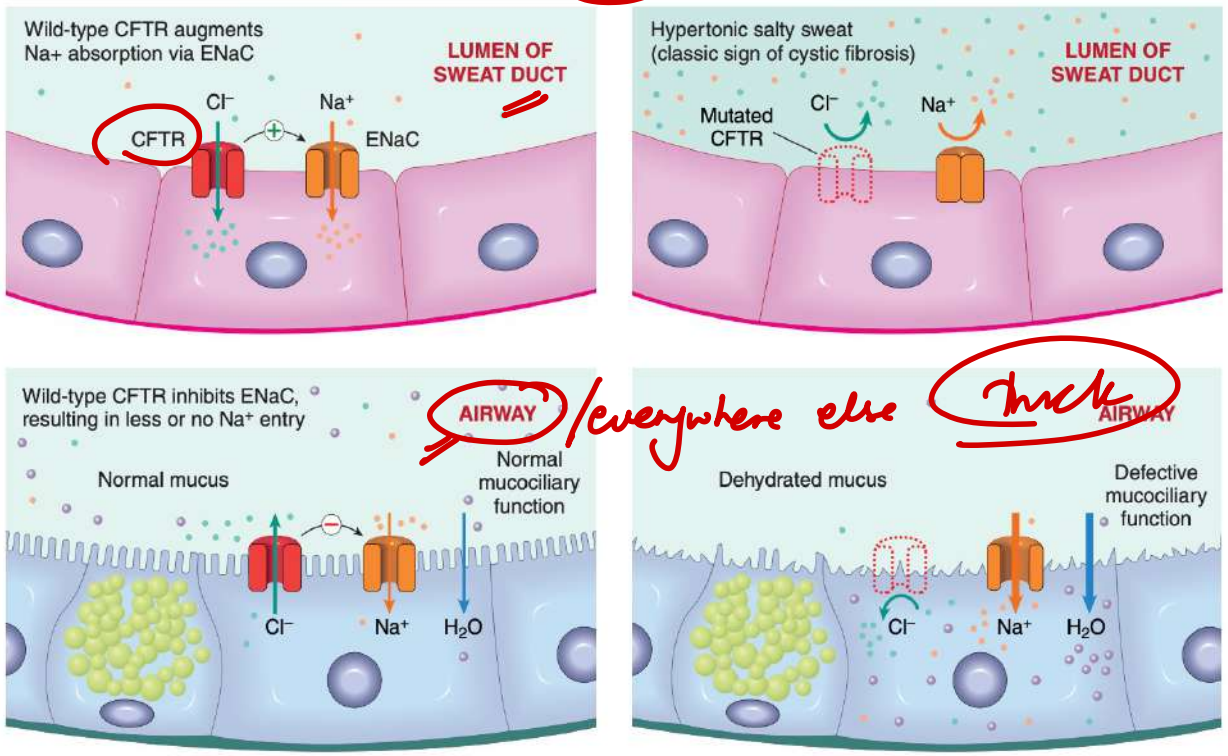
FIG. 4.18 Types of chromosomal rearrangements.



N

Pompe's

CF



AIRWAY / everywhere else

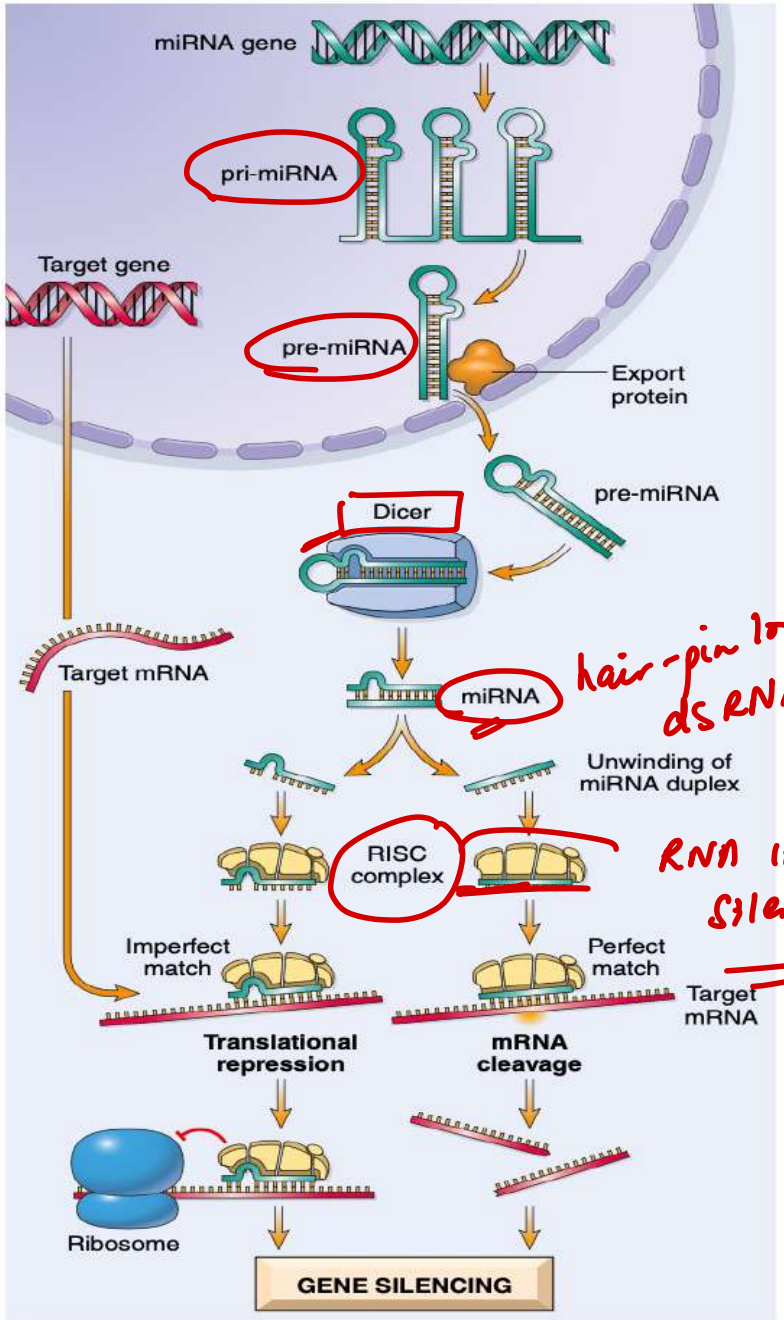
Duct

sweat → ↑

Cl⁻ levels in CF

other ducts — ↓

Cl⁻ transport in CF — everywhere ↓



RNA interference

knock down

Supression

PTGS

post-transcriptional gene silencing

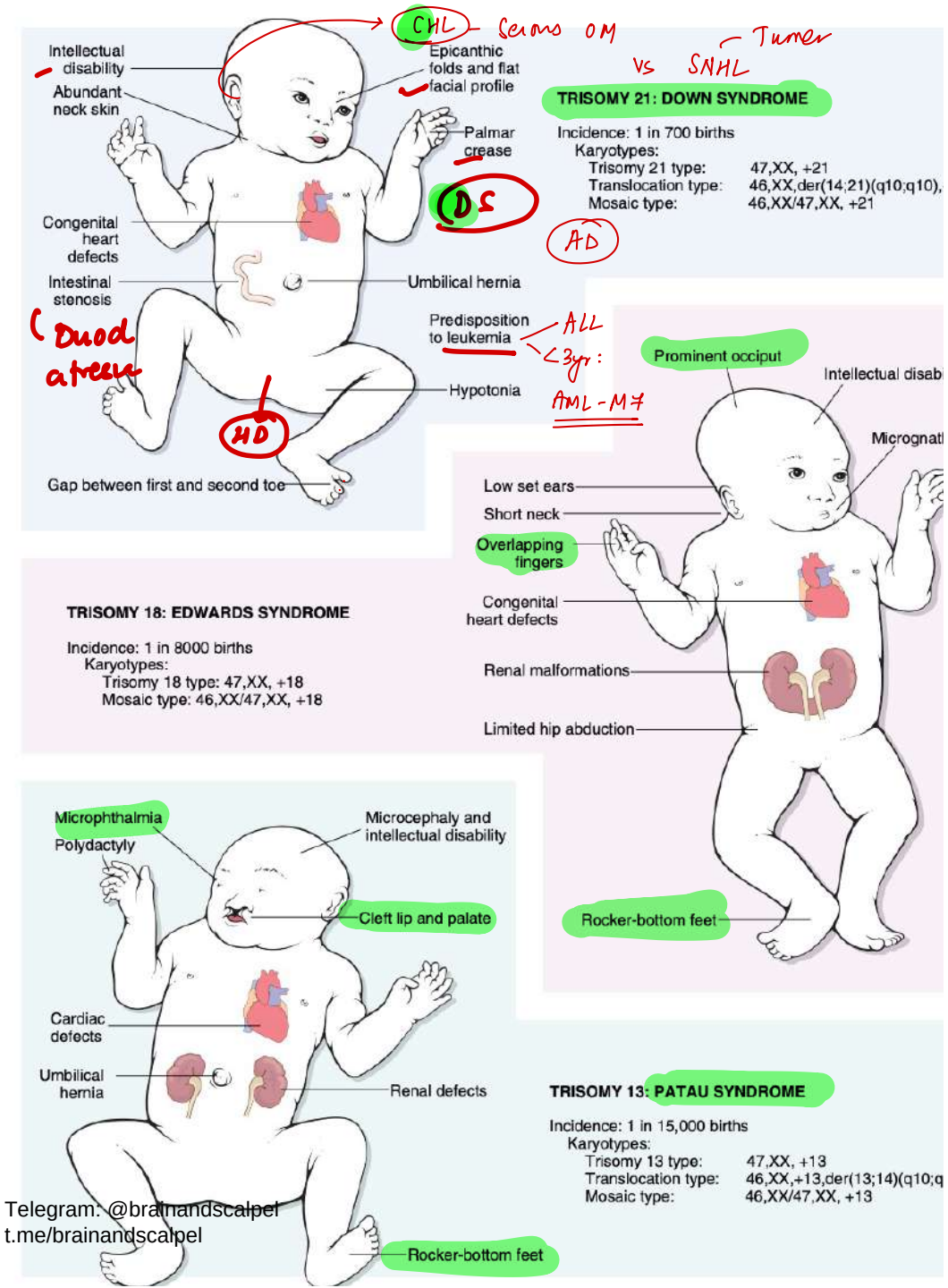
hair-pin loop dsRNA

RNA induced Silencing complex

mRNA

(−)

miRNA



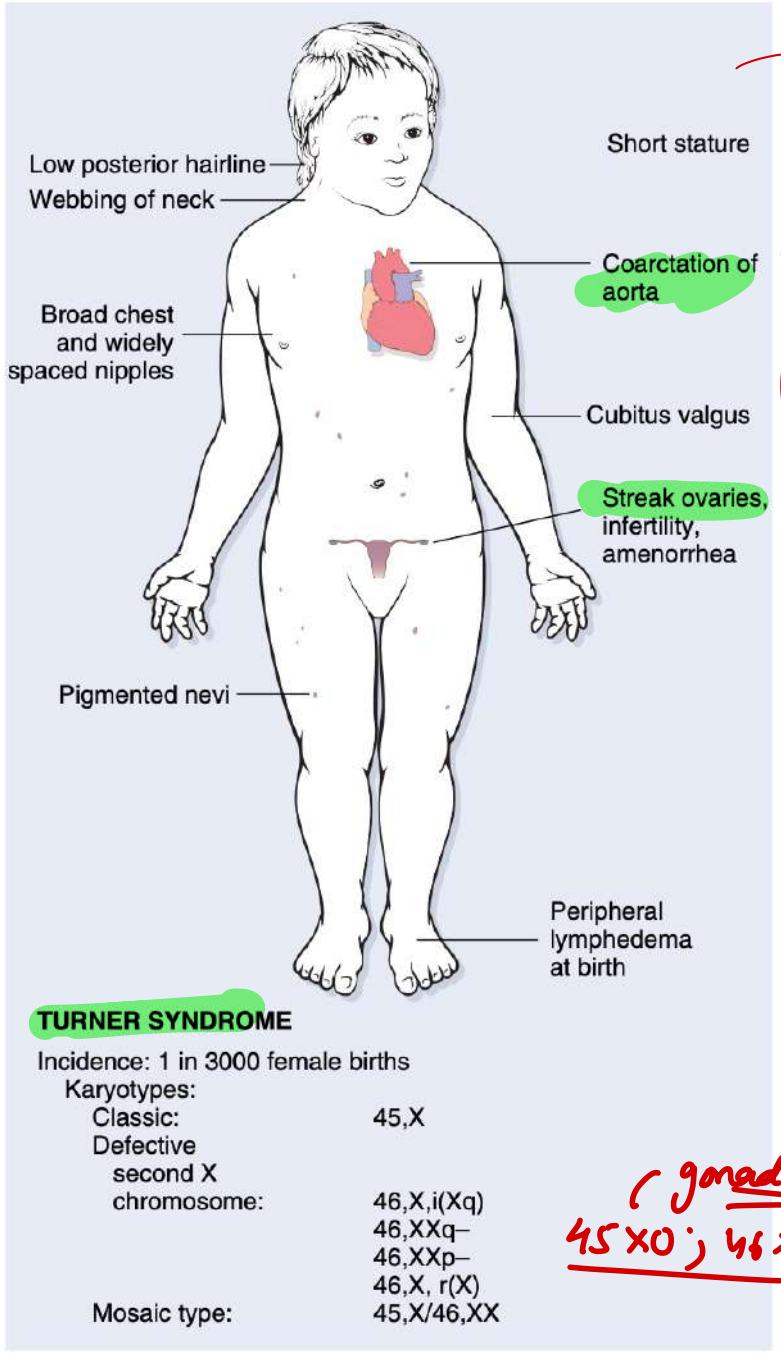
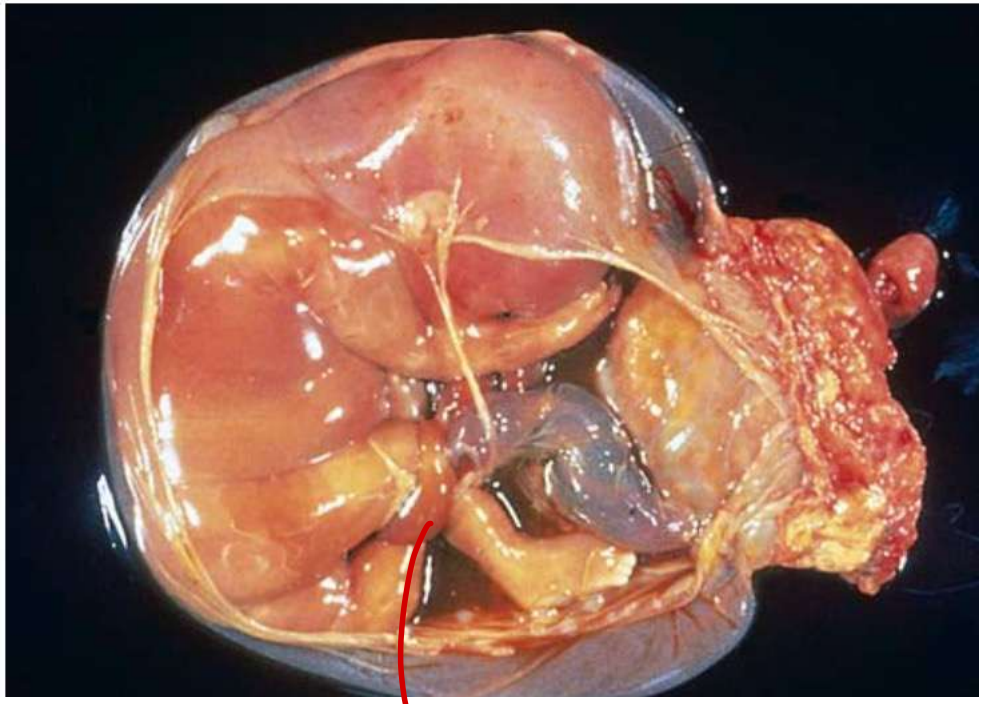
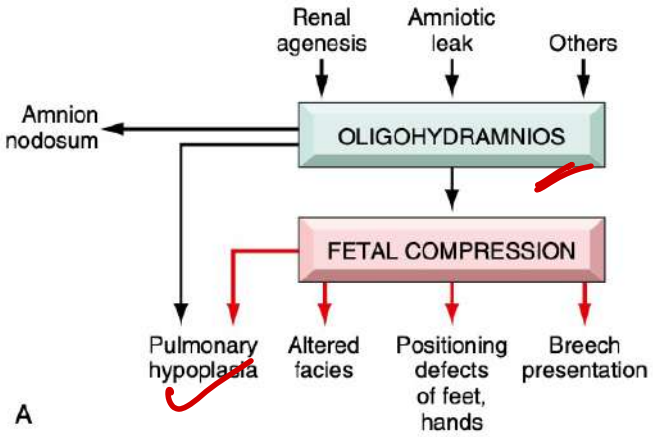


FIG. 4.20 Clinical features and karyotypes of Turner syndrome.

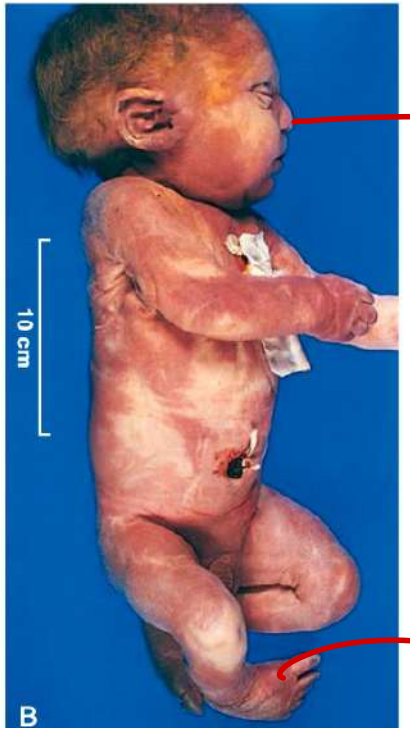


Amniotic band Sx

DISRUPTION



Potter sequence

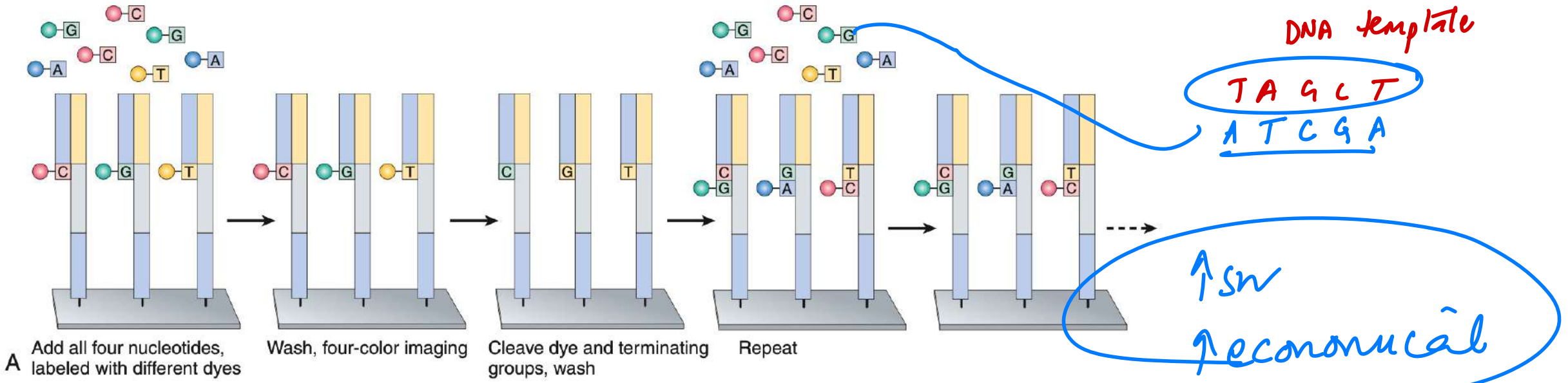


Flattened facies

CTEV

Table 4.9 Testing Modalities for Genetic Disorders

Test Type	Applications and Examples
Biochemical Assays	
Quantitative assays for metabolites or electrolytes	Detection of abnormal metabolite levels in metabolic disorders (e.g., phenylketonuria); detection of high chloride levels in sweat (cystic fibrosis)
Assay of enzyme activity	Detection of enzyme deficiencies (e.g., acid maltase in Pompe disease; G6PD deficiency)
Hemoglobin electrophoresis	Detection of abnormal hemoglobins (e.g., sickle hemoglobin)
Cytogenetic Assays	
Karyotyping	Grossly evident structural changes in chromosomes (e.g., trisomy 21 in Down syndrome)
Fluorescence in situ hybridization (FISH)	Subtle/submicroscopic structural changes in chromosomes (e.g., 22.q11.2 del syndrome)
"Molecular" Cytogenetic Assays	
Multiplex ligation-dependent probe amplification	Small deletions and insertions (e.g., partial deletion of *BRCA1* in familial breast cancer)
Array-based genomic hybridization	Copy number changes (e.g., trisomy 21 in Down syndrome)
Next-generation sequencing (NGS)	Copy number changes, translocations (mainly used clinically to identify somatic copy number changes and translocations in cancer cells)
Genetic Assays	
Allele-specific PCR and related techniques	Specific base pair changes (single, e.g., sickle hemoglobin mutation, or multiple, e.g., *CFTR* mutations in cystic fibrosis)
Sanger DNA sequencing	Mutations in individual genes (e.g., glucose-6-phosphatase mutations in von Gierke disease)
Next-generation sequencing (NGS)	Mutations in many genes and/or in noncoding regions (used clinically to identify somatic mutations in cancer cells and in research to discover mutations responsible for unusual phenotypes)



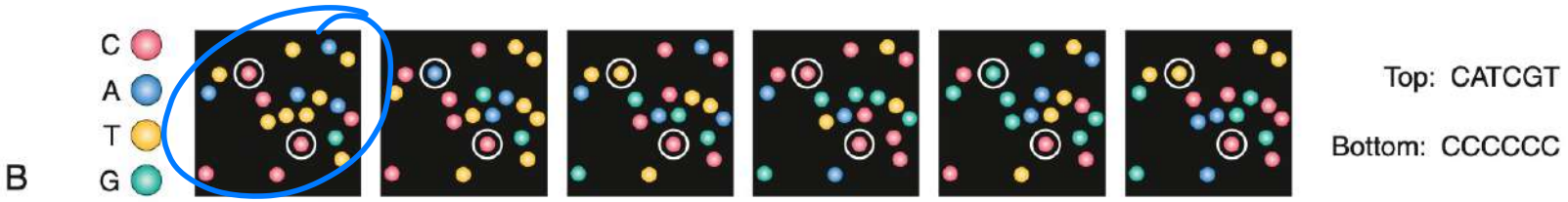
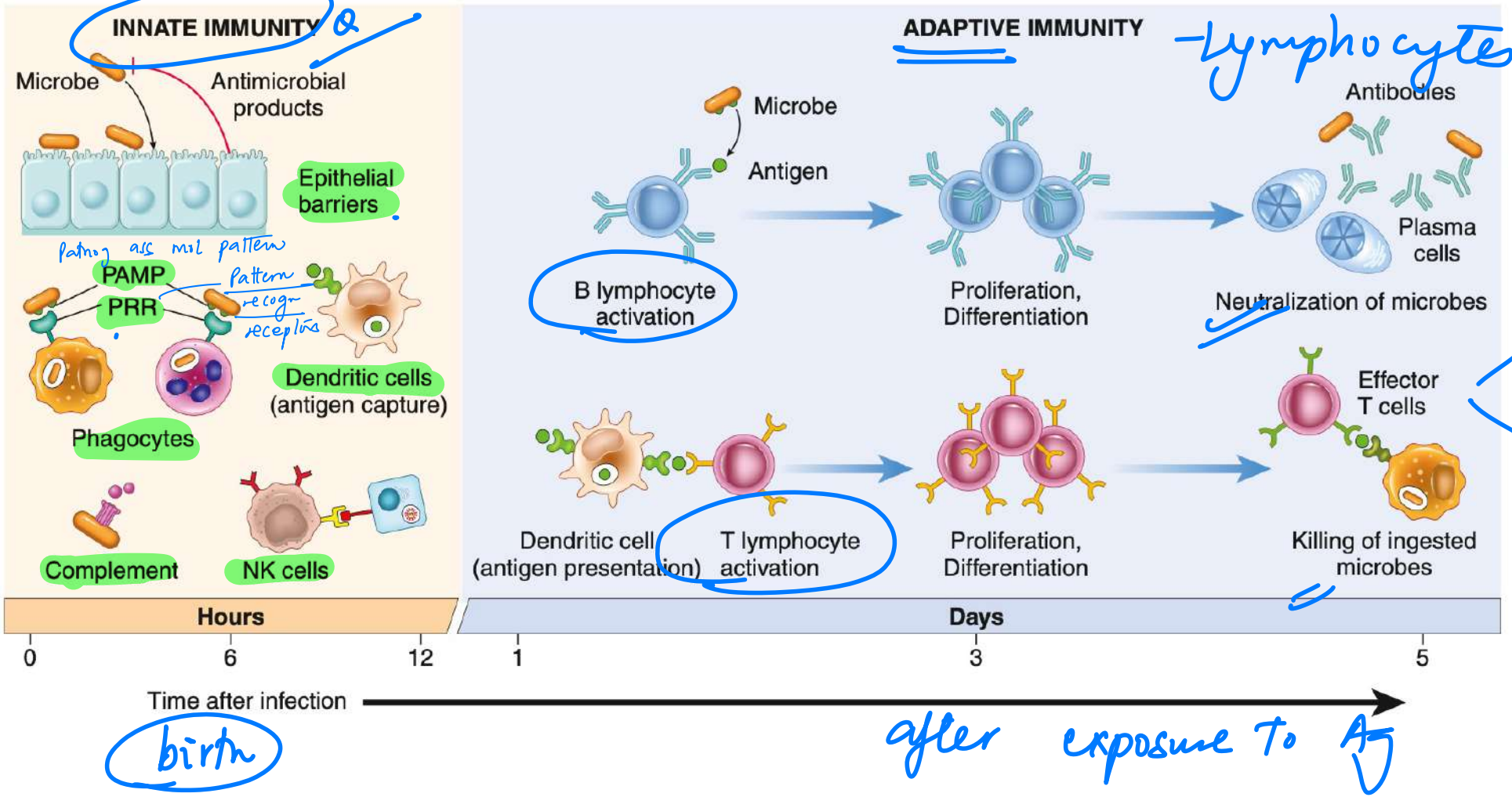


FIG. 4.43 Principle of next-generation sequencing. Several alternative approaches are currently available for "Next generation" sequencing, and one of the more commonly used platforms is illustrated. (A) Short fragments of genomic DNA ("template") between 100 and 500 base pairs in length are immobilized on a solid phase platform such as a glass slide, using universal capture primers that are complementary to adapters that have previously been added to ends of the template fragments. The addition of fluorescently labeled complementary nucleotides, one per template DNA per cycle, occurs in a "massively parallel" fashion, at millions of templates immobilized on the solid phase at the same time. A four-color imaging camera captures the fluorescence emanating from each template location (corresponding to the specific incorporated nucleotide), following which the fluorescent dye is cleaved and washed away, and the entire cycle is repeated. (B) Powerful computational programs can decipher the images to generate sequences complementary to the template DNA at the end of one "run," and these sequences are then mapped back to the reference genomic sequence, to identify alterations. (Reproduced with permission from Metzker M: Sequencing

Pyroseq - contaminated samples



Natural killer (NK) cells kill cells that are infected by some microbes or are stressed and damaged beyond repair. NK cells express inhibitory receptors that recognize MHC molecules that are normally expressed on healthy cells and are thus prevented from killing normal cells.

Toll-like Rc: Bacterial
C-type Rc: Fungi (chitin)
RIG Rc: RIG-STING-IFNgamma
NOD like Rc: Periodic fever/ CD

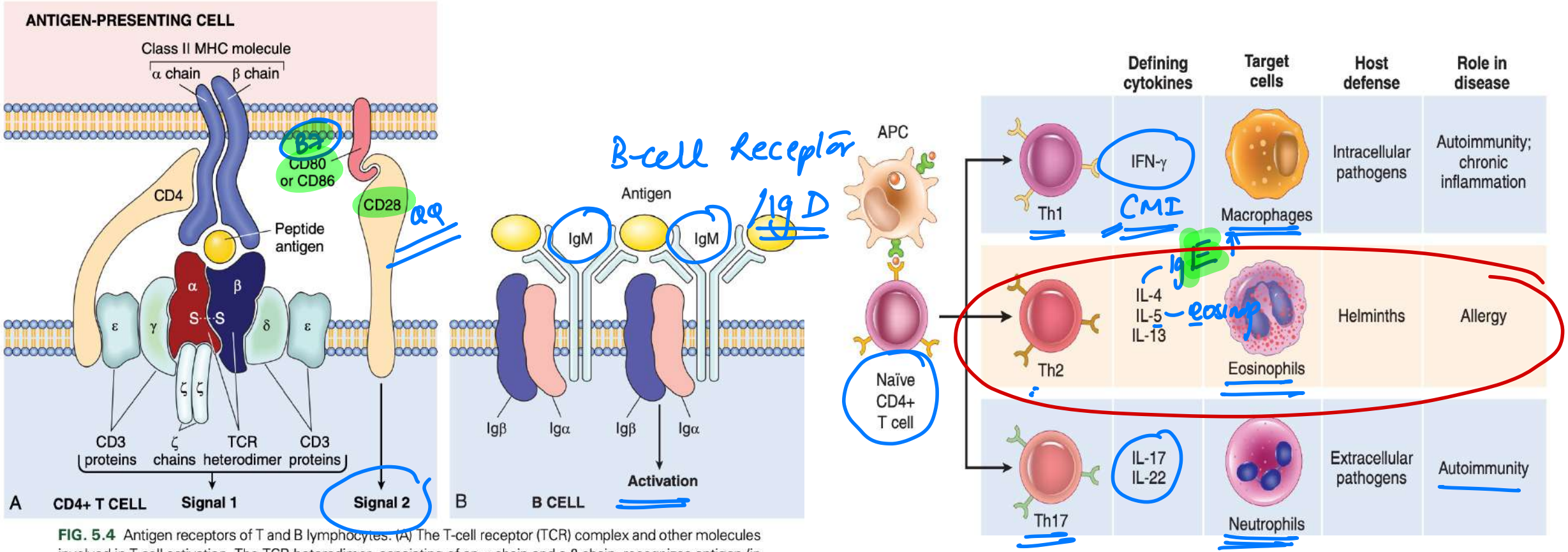
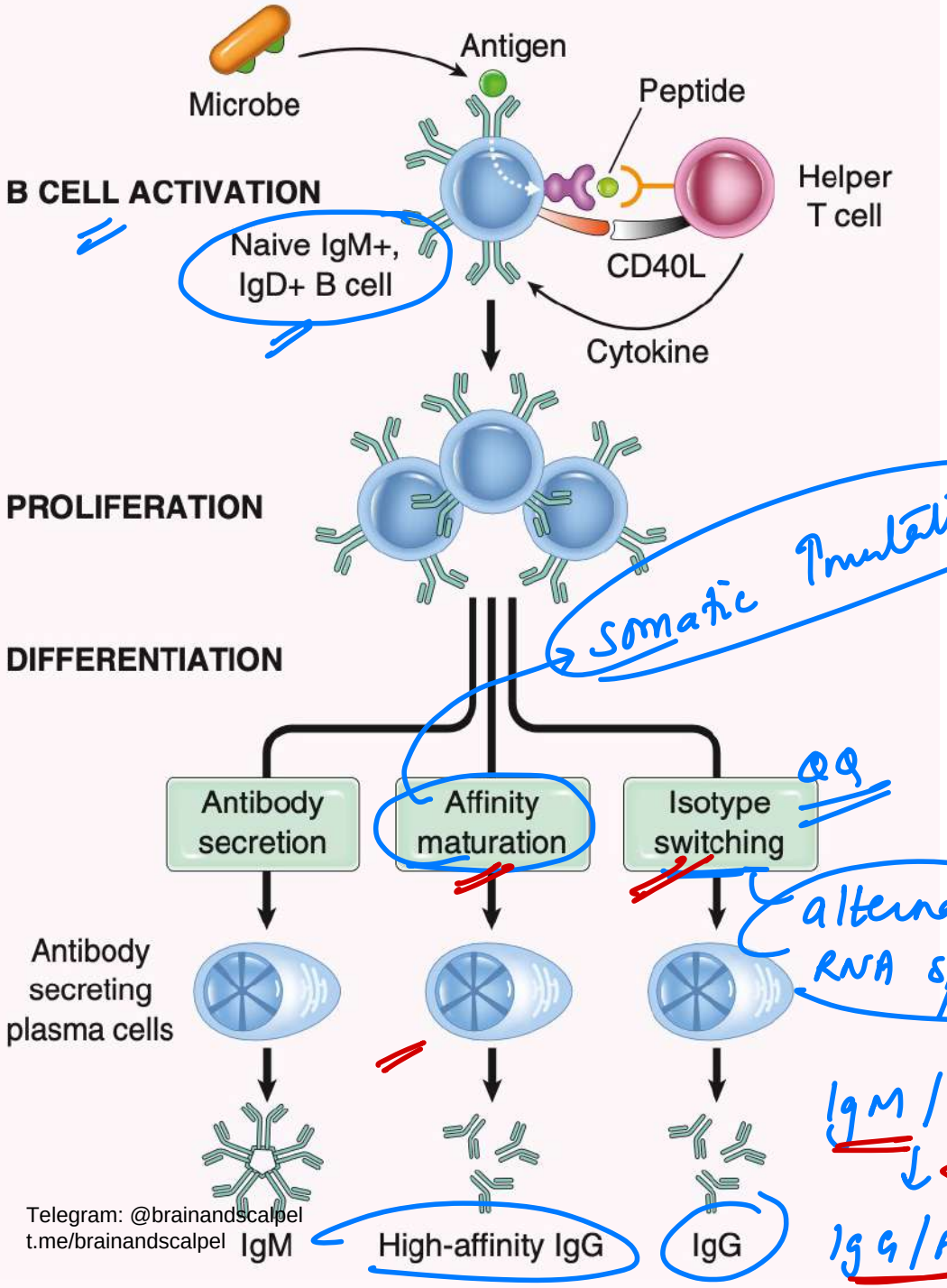


FIG. 5.4 Antigen receptors of T and B lymphocytes. (A) The T-cell receptor (TCR) complex and other molecules involved in T-cell activation. The TCR heterodimer, consisting of an α chain and a β chain, recognizes antigen (in the form of peptide-MHC complexes expressed on antigen-presenting cells), and the linked CD3 complex and ζ chains initiate activating signals. CD4 and CD28 are also involved in T-cell activation; CD28 recognizes the costimulators CD80 and CD86 (also called B7 molecules). (Note that some T cells express CD8 and not CD4; these molecules serve analogous roles.) The sizes of the molecules are not drawn to scale. (B) The B-cell antigen receptor complex is composed of membrane immunoglobulin M (IgM; or IgD, *not shown*), which recognizes antigens, and the associated signaling proteins Igα and Igβ. *MHC,* Major histocompatibility complex.



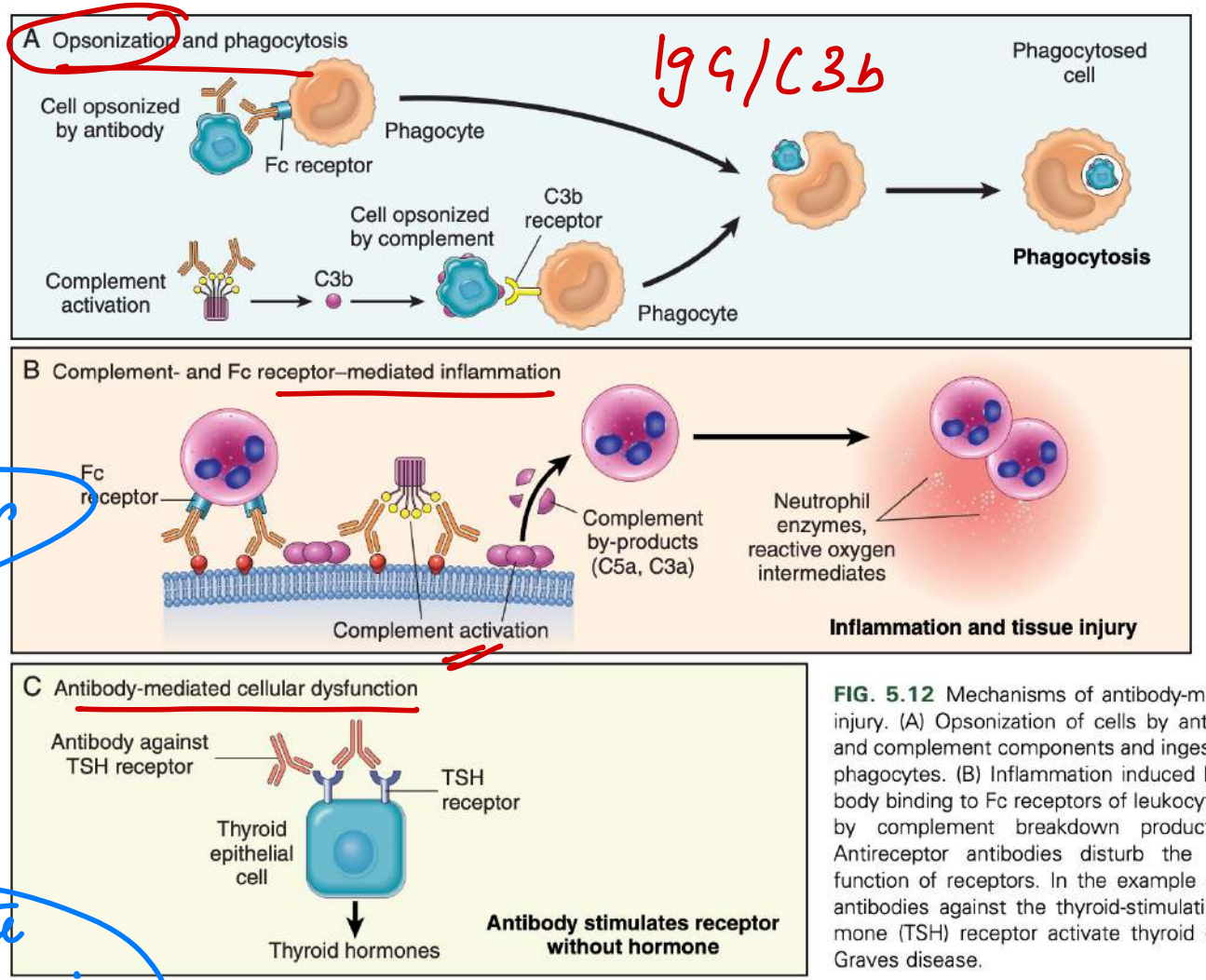
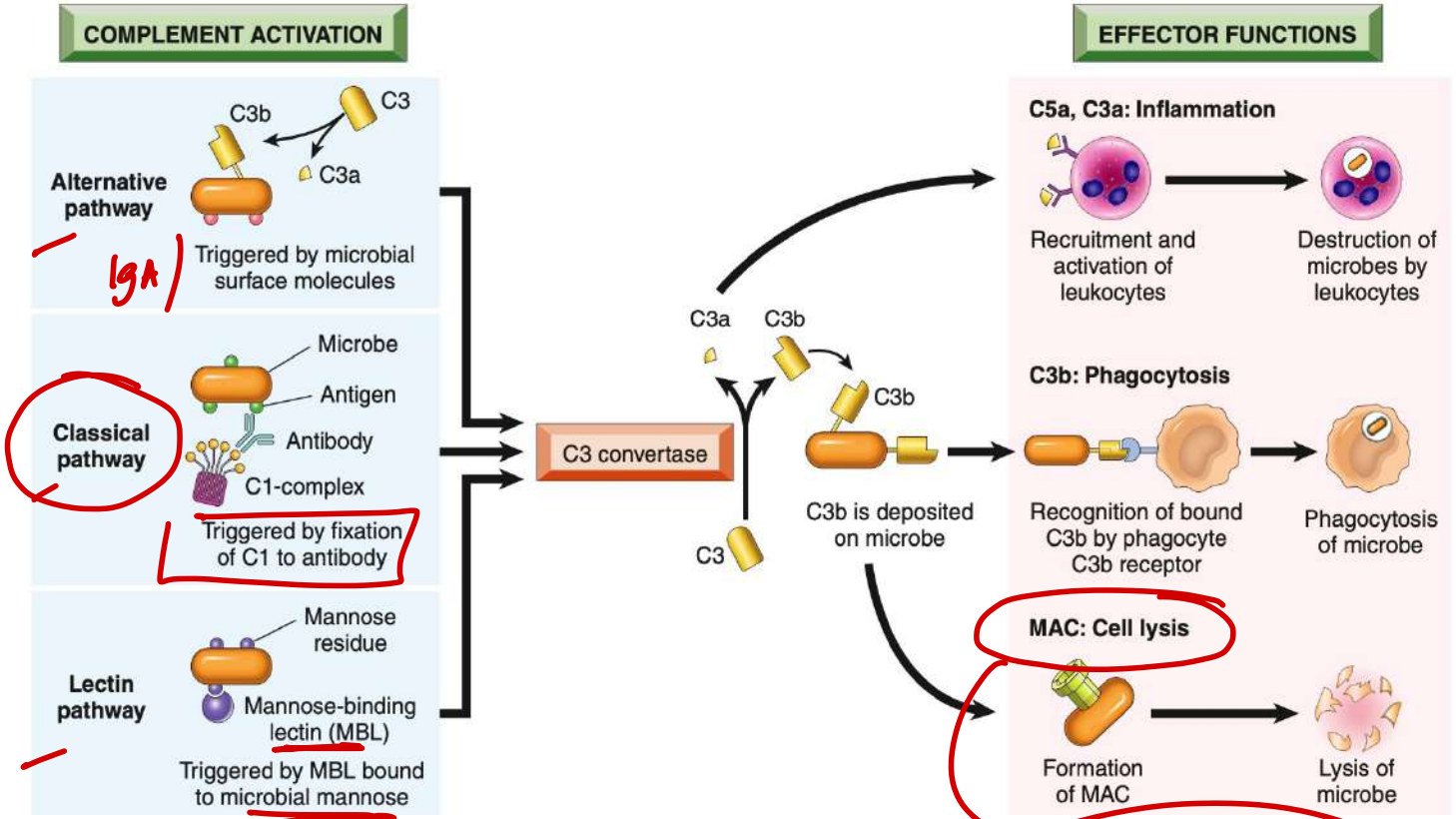
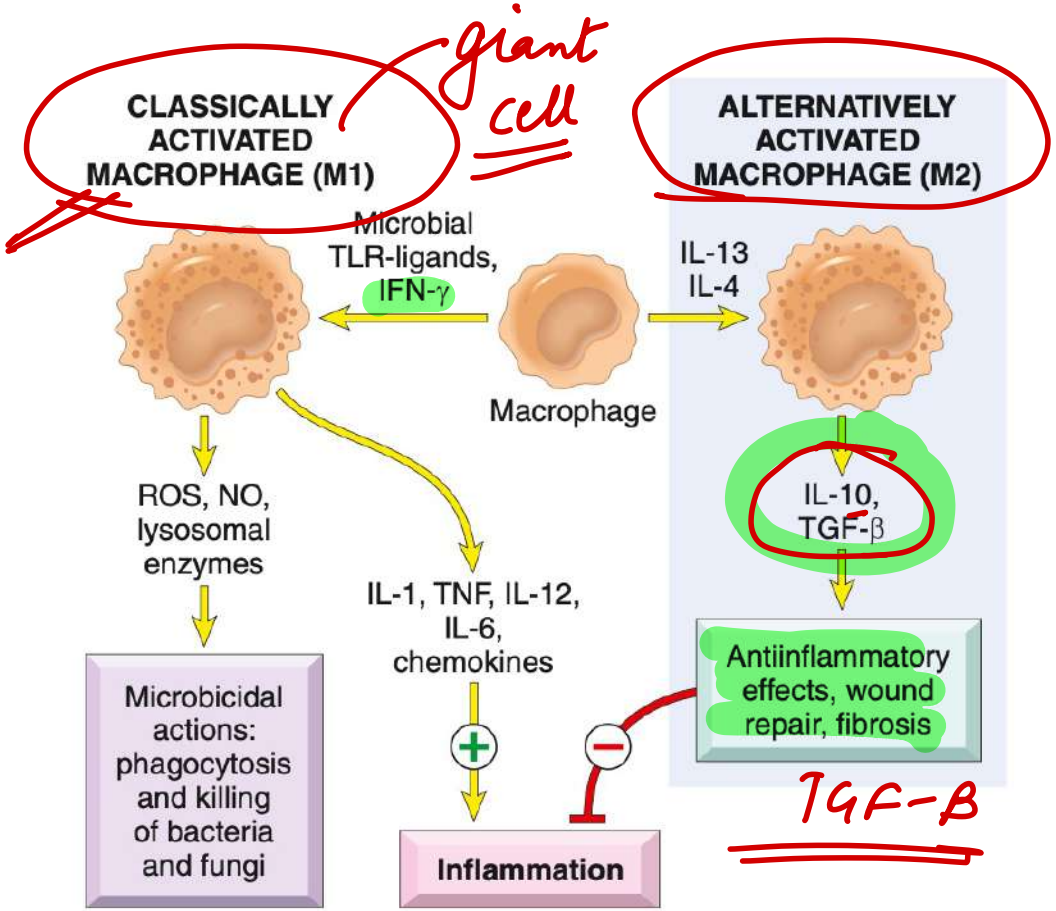


FIG. 5.12 Mechanisms of antibody-mediated injury. (A) Opsonization of cells by antibodies and complement components and ingestion by phagocytes. (B) Inflammation induced by antibody binding to Fc receptors of leukocytes and by complement breakdown products. (C) Antireceptor antibodies disturb the normal function of receptors. In the example shown, antibodies against the thyroid-stimulating hormone (TSH) receptor activate thyroid cells in Graves disease.

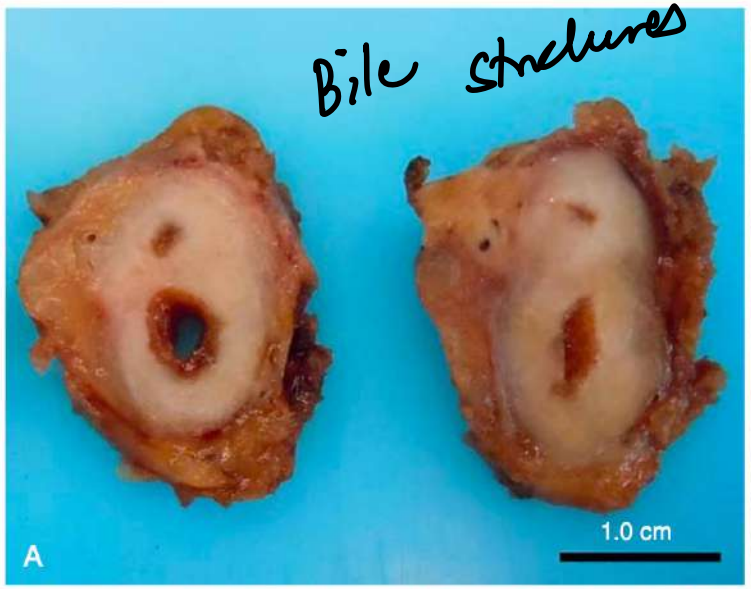




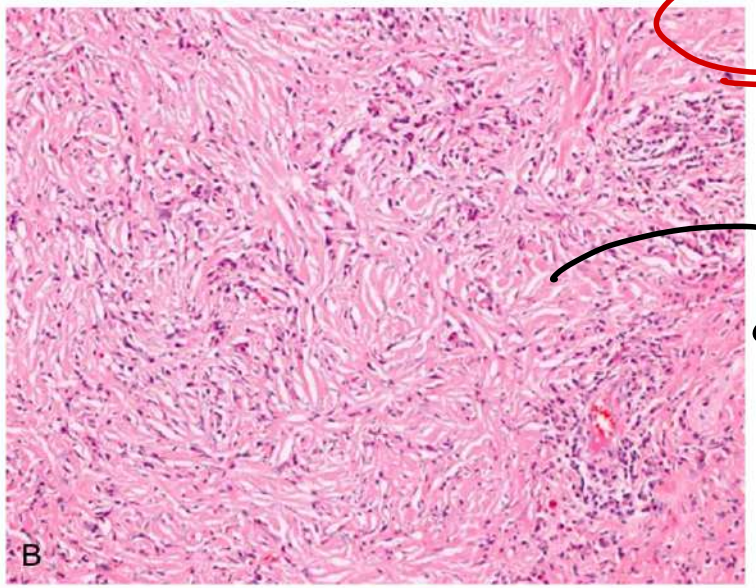
defective: Neisseria

type III hyper → Immune complex ↓ Complement

type IV hyper – CMI ↺ T_{H_1} IFN γ

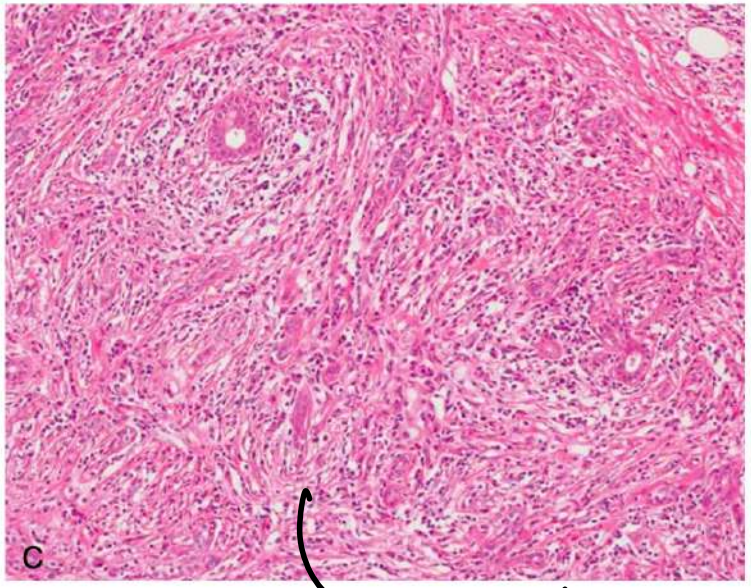


Bile stictures

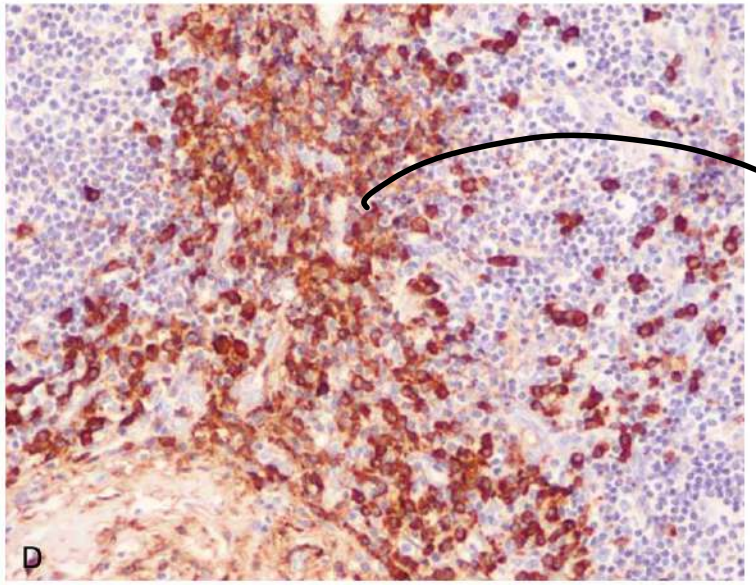


IgG4 RD

Storiform fibrosis



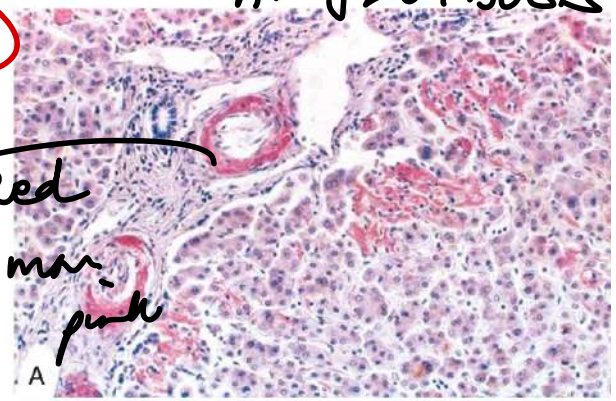
Plasma cells



IgG4

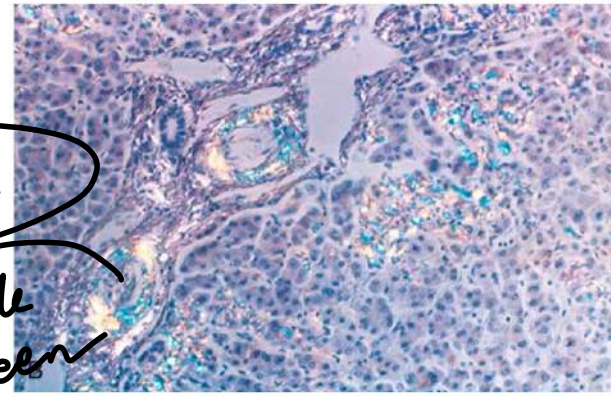
IHC +

AMYLOIDOSIS



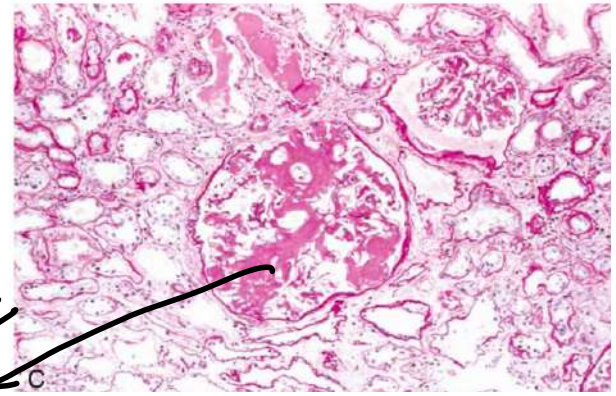
Congo Red

salmon pink



pol H

apple green



- fibrils
- starch

acellular

extracellular

cosinp

Amyloidosis- Pinch purpura-Due to fX inhibition

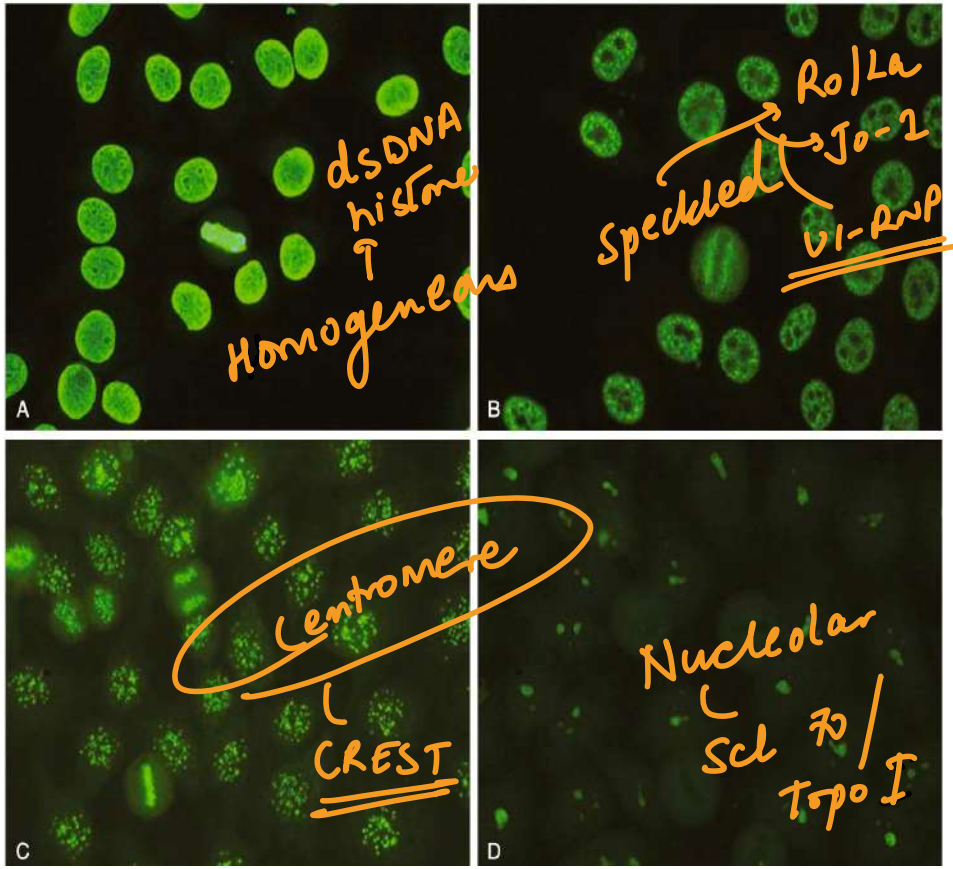
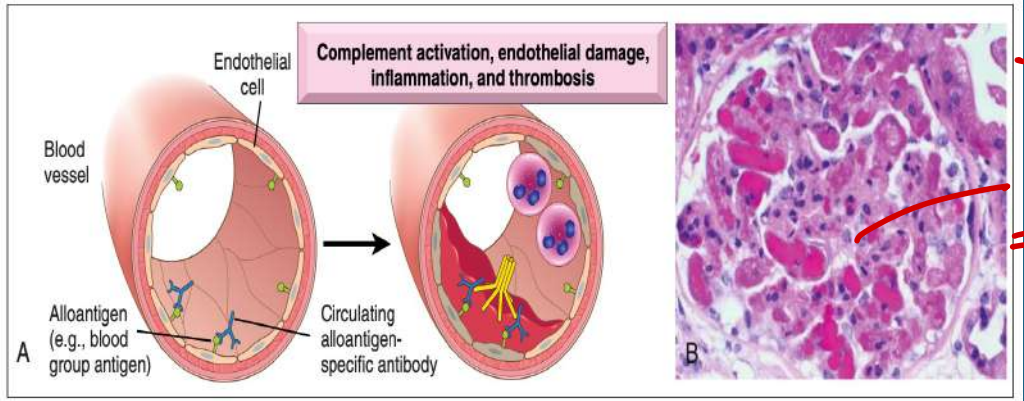


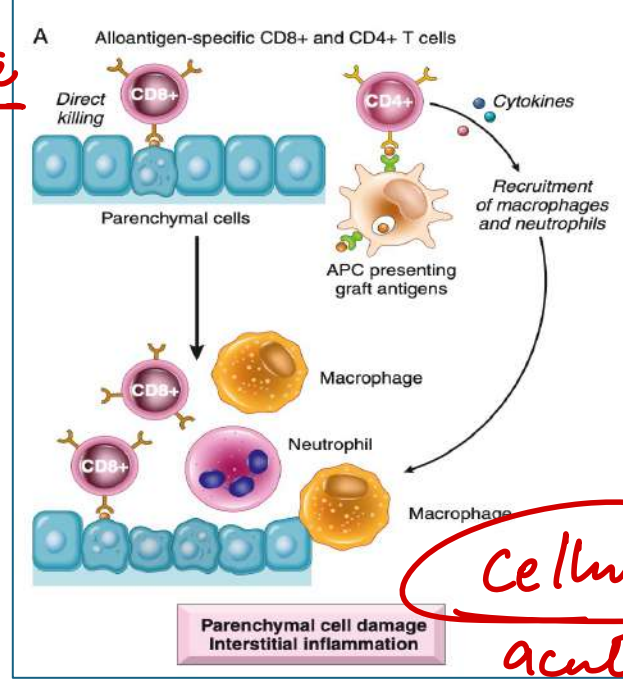
Table 5.8 Autoantibodies in Systemic Autoimmune Diseases

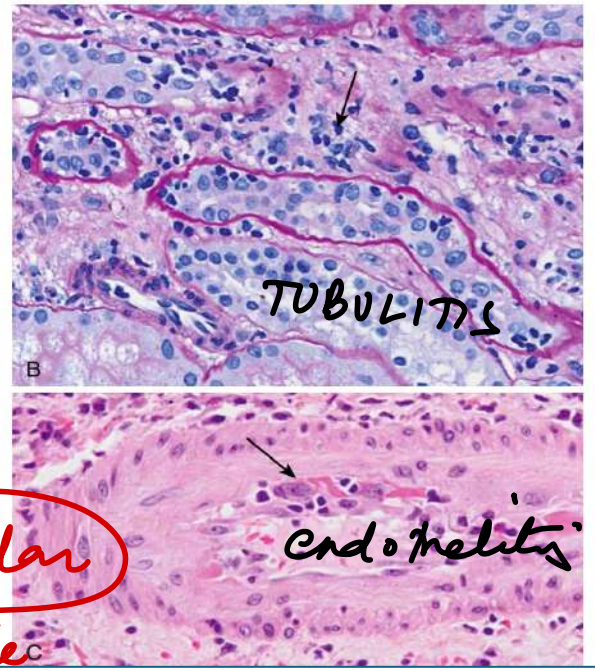
Disease	Specificity of Autoantibody	% Positive	Disease Associations
Systemic lupus erythematosus (SLE)	Double-stranded DNA	40–60	Nephritis; specific for SLE
	U1-RNP	30–40	
	Smith (Sm) antigen (core protein of small RNP particles)	20–30	Specific for SLE
	Ro (SS-A) nucleoprotein	30–50	Congenital heart block; neonatal lupus
	Phospholipid-protein complexes (anti-PL)	30–40	Antiphospholipid syndrome (in ~10% of patients with SLE)
	Multiple nuclear antigens ("generic ANAs")	95–100	Found in other autoimmune diseases, not specific
Systemic sclerosis	DNA topoisomerase 1	30–70	Diffuse skin disease, lung disease; specific for systemic sclerosis
	Centromeric proteins (CENPs) A, B, C	20–40	Limited skin disease, ischemic digital loss, pulmonary hypertension
	RNA polymerase III	15–20	Acute onset, scleroderma renal crisis, cancer
Sjögren syndrome	Ro/SS-A	75	More sensitive for Sjogren syndrome
	La/SS-B	50	More specific for Sjogren syndrome
Autoimmune myositis	Histidyl aminoacyl-tRNA synthetase, Jo1	25	Interstitial lung disease, Raynaud phenomenon
	Mi-2 nuclear antigen	5–10	Dermatomyositis, skin rash
	MDA5 (cytoplasmic receptor for viral RNA)	20–35 (Japanese)	Vascular skin lesions, interstitial lung disease
	TIF1γ nuclear protein	15–20	Dermatomyositis, cancer
Rheumatoid arthritis	Peptides from various citrullinated proteins	60–80	Specific for rheumatoid arthritis
	Rheumatoid factor	60–70	Not specific



Hyperacute

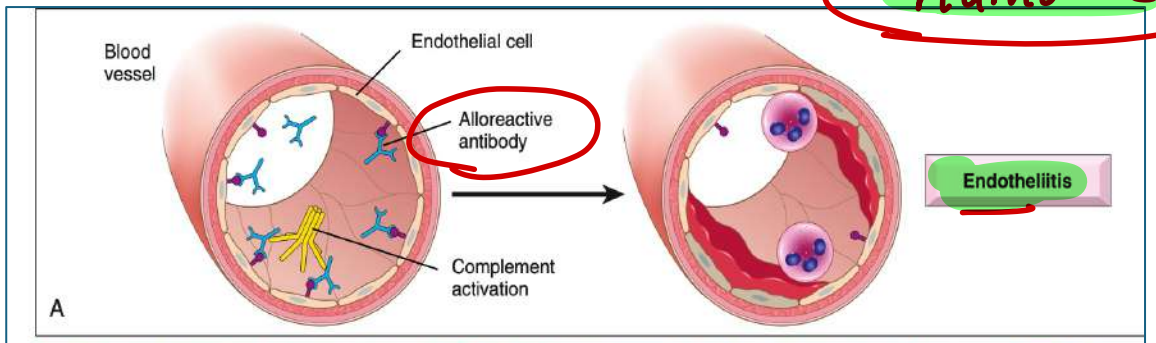
Necrosis

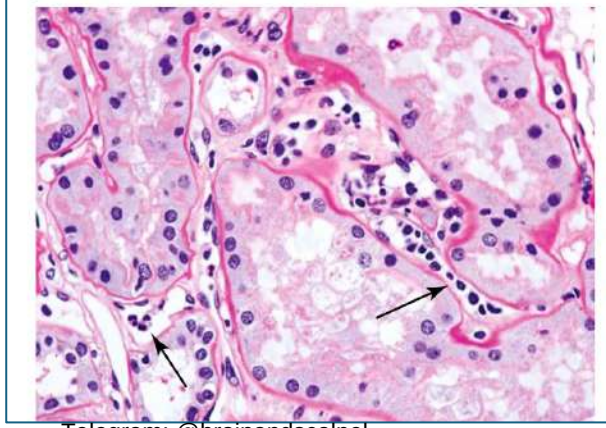


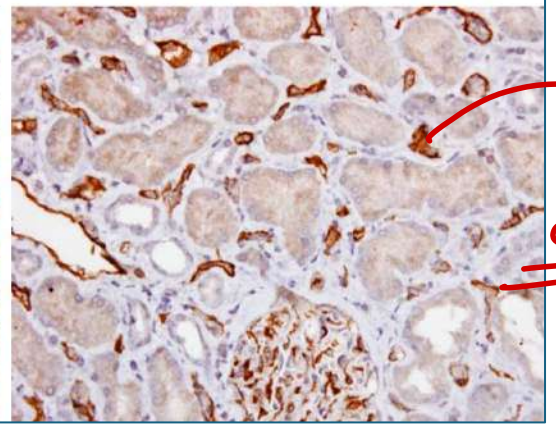


Cellular acute

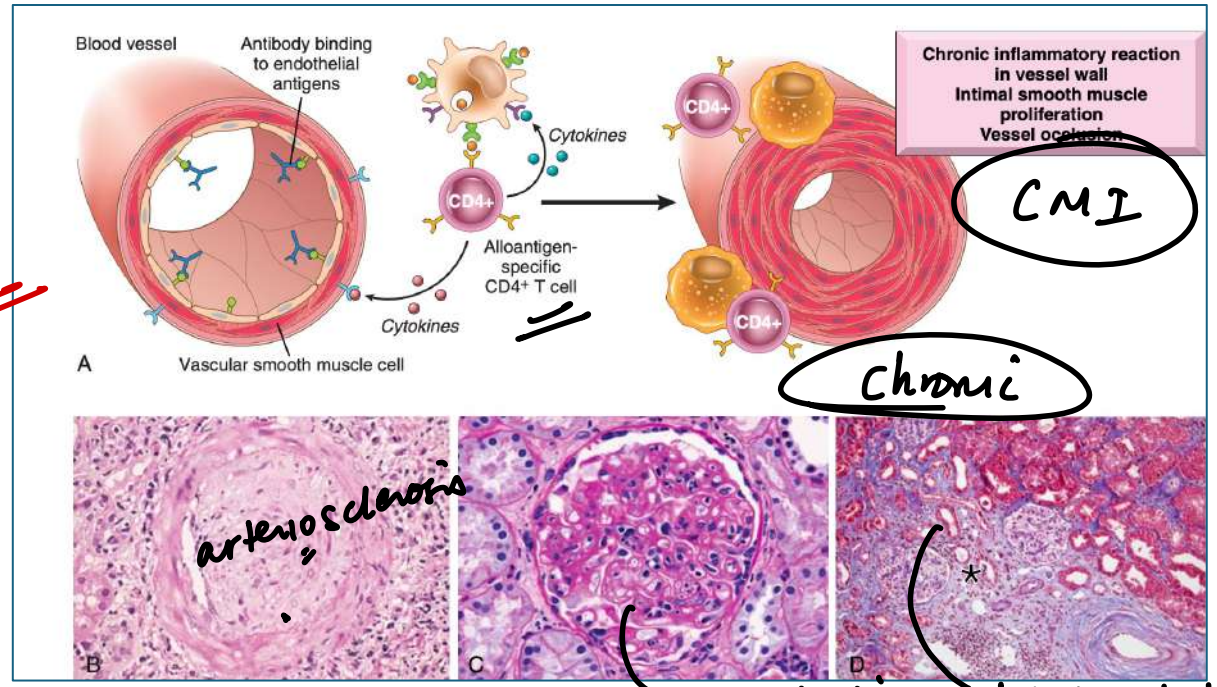
Acute Humoral

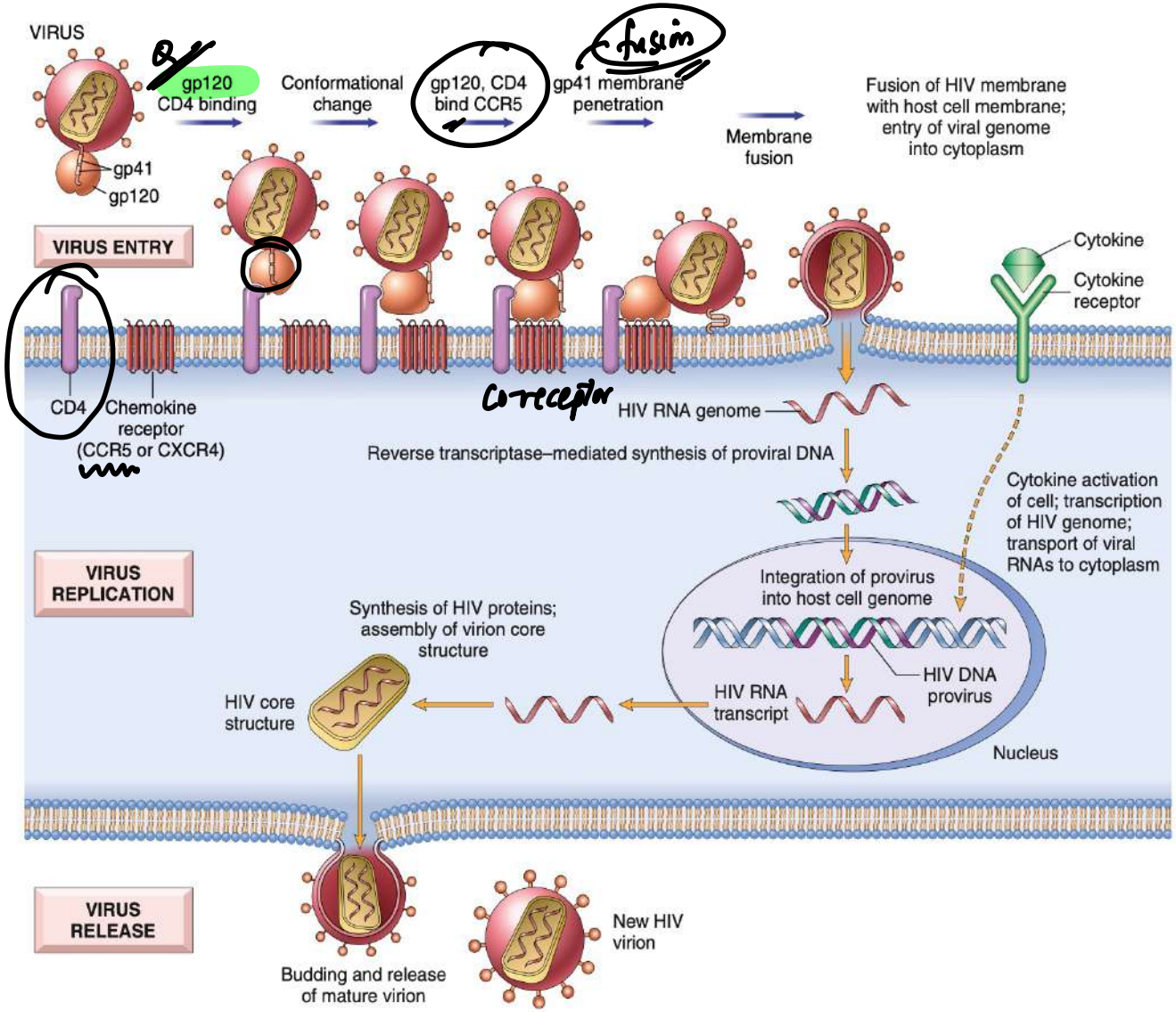


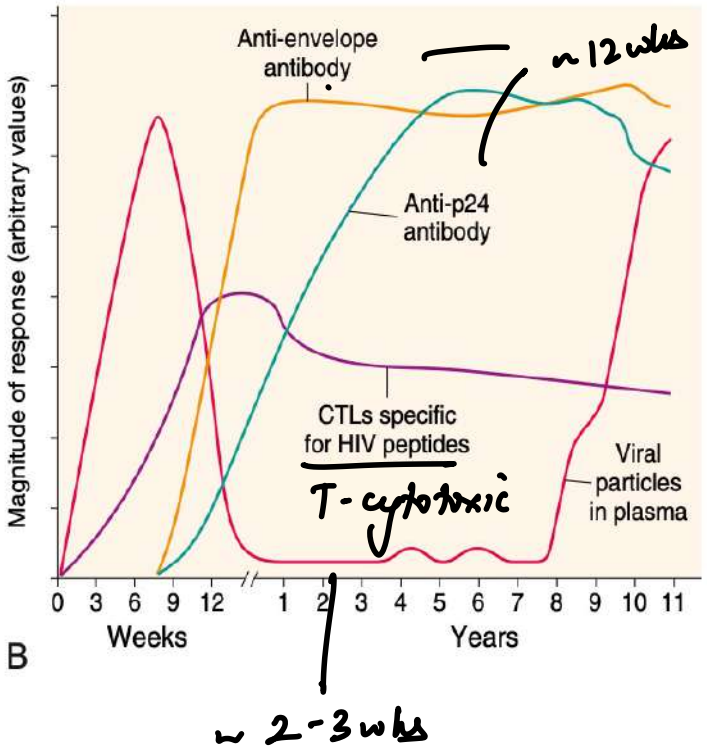


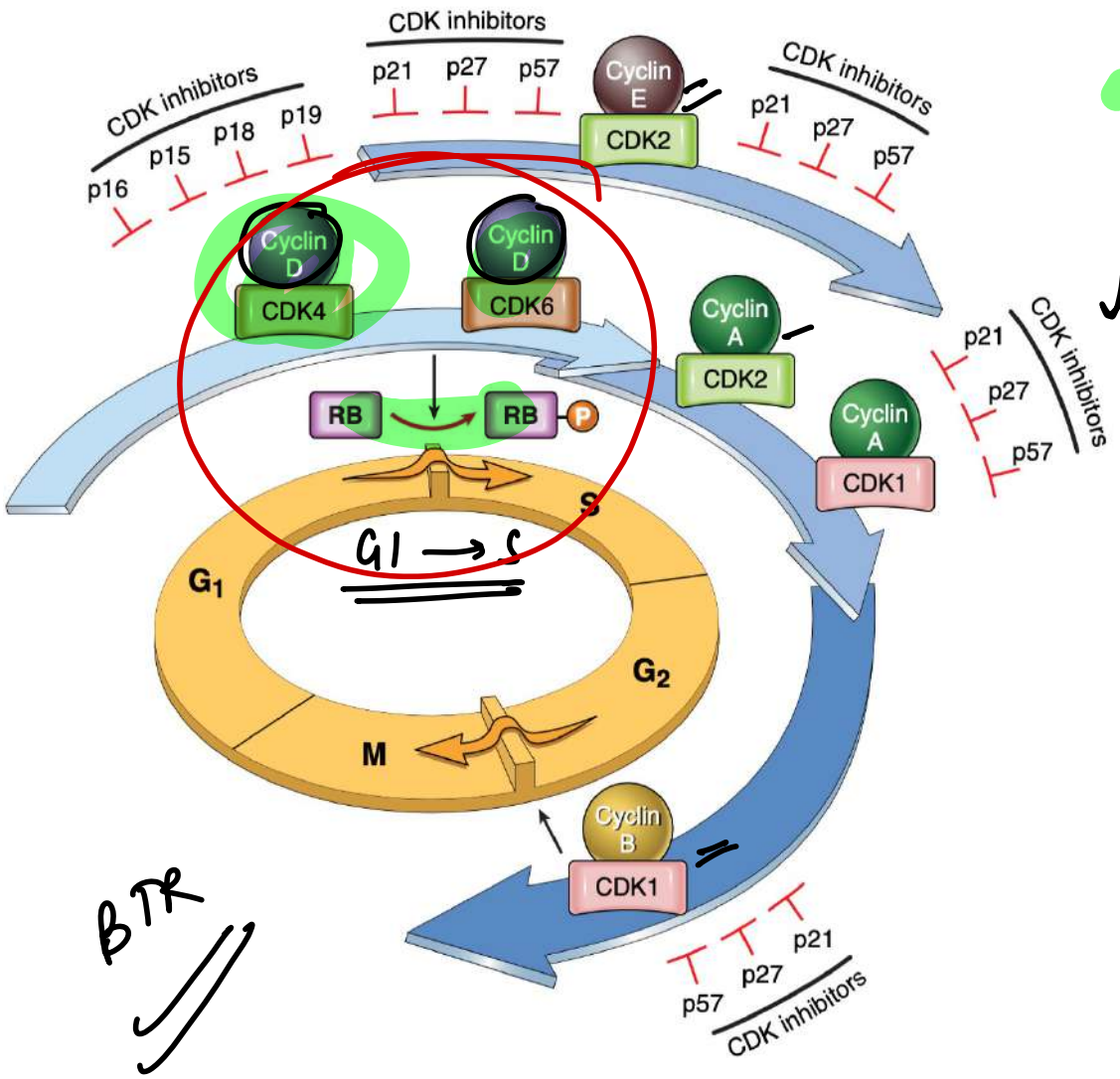


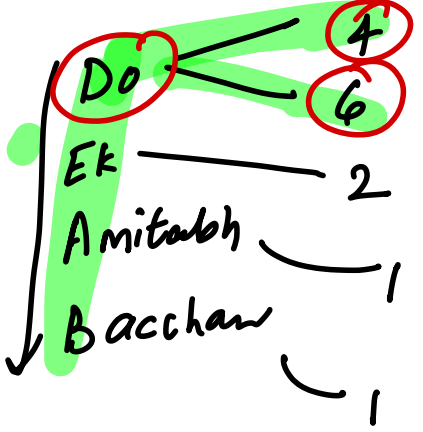
QQ C4d stain

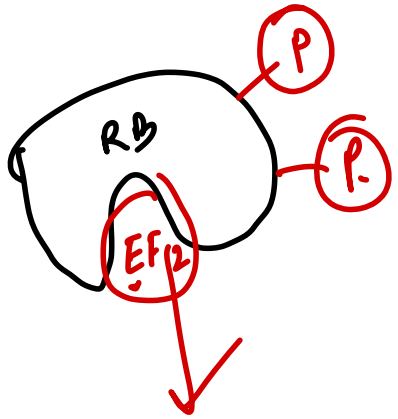


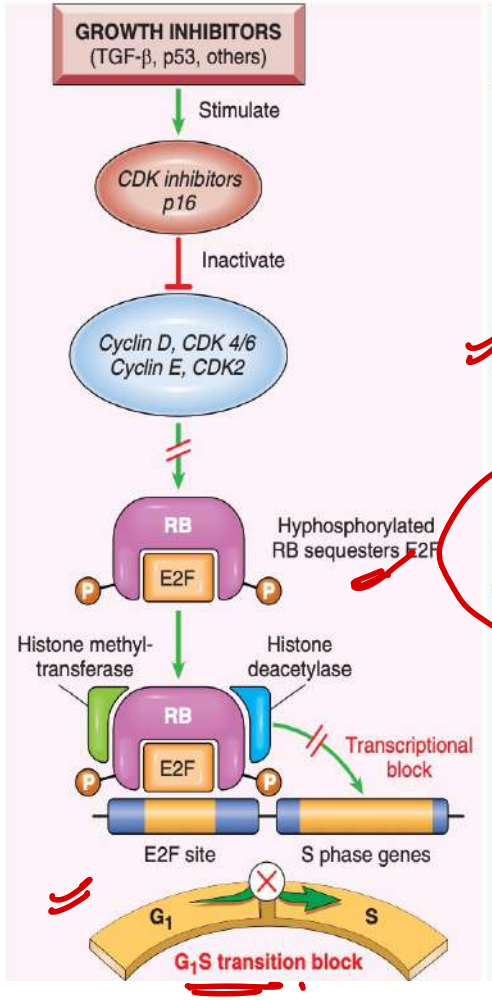


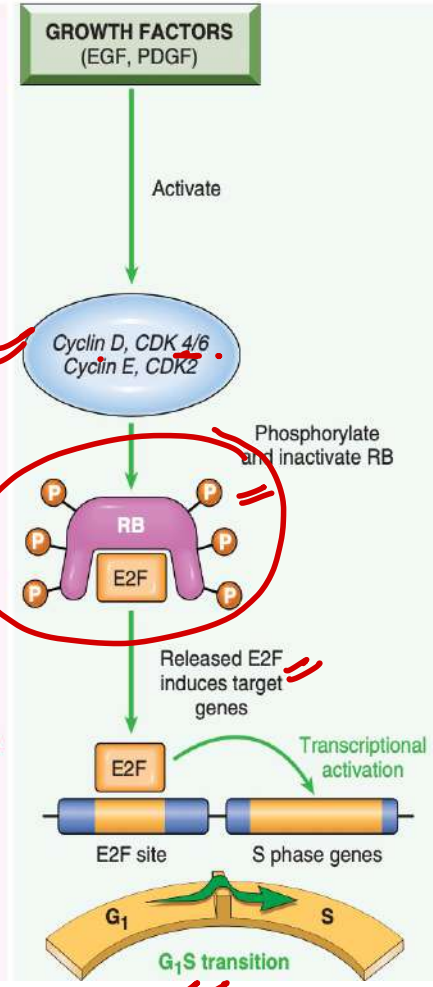


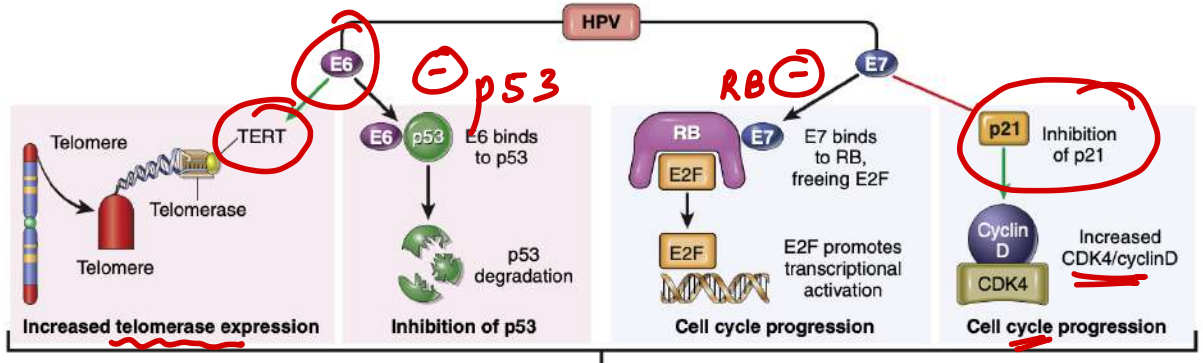












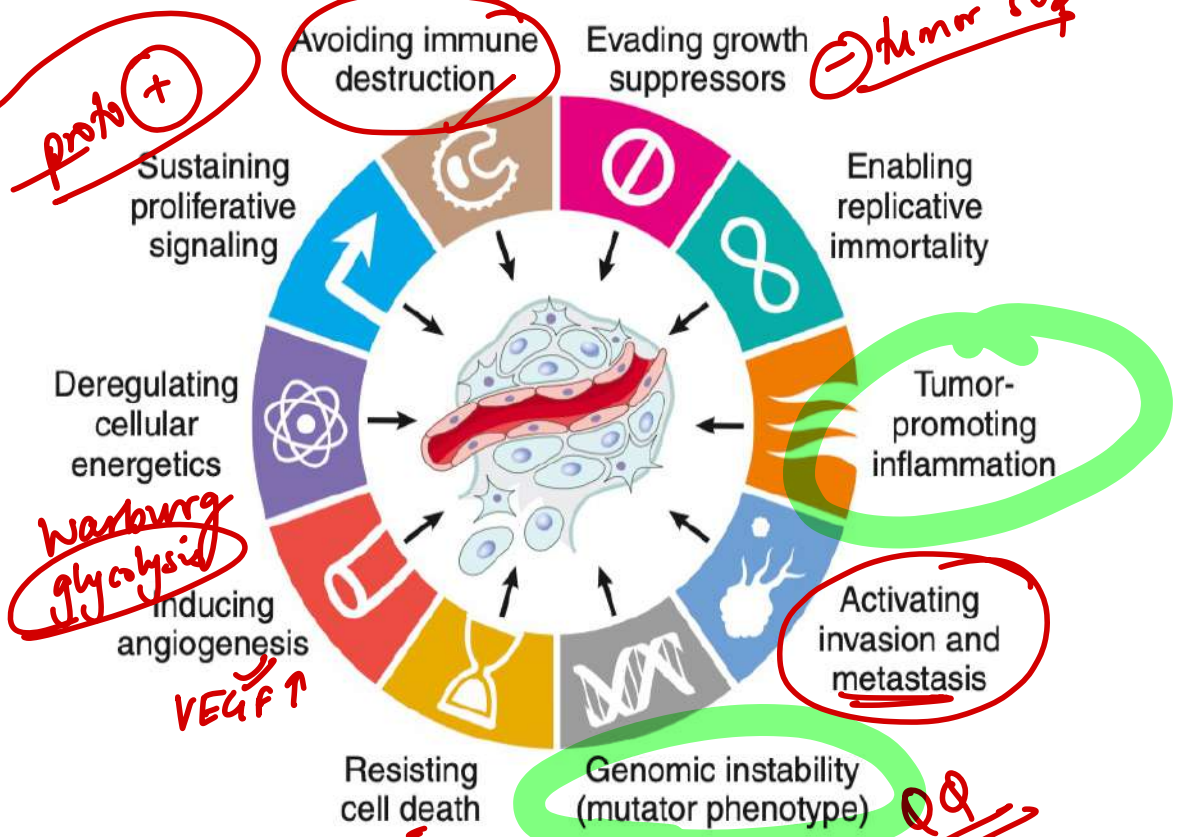
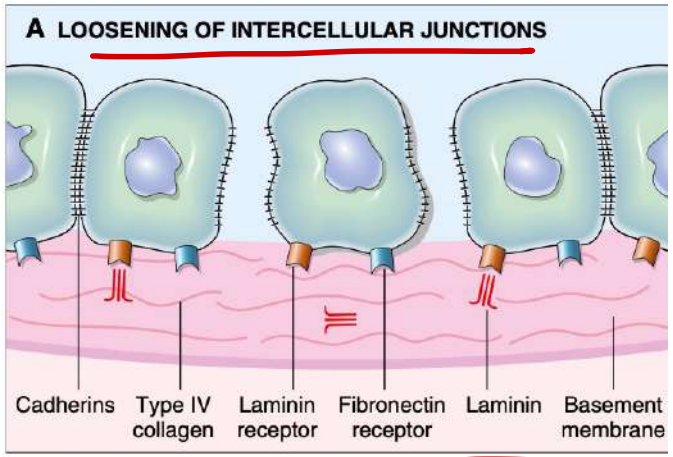
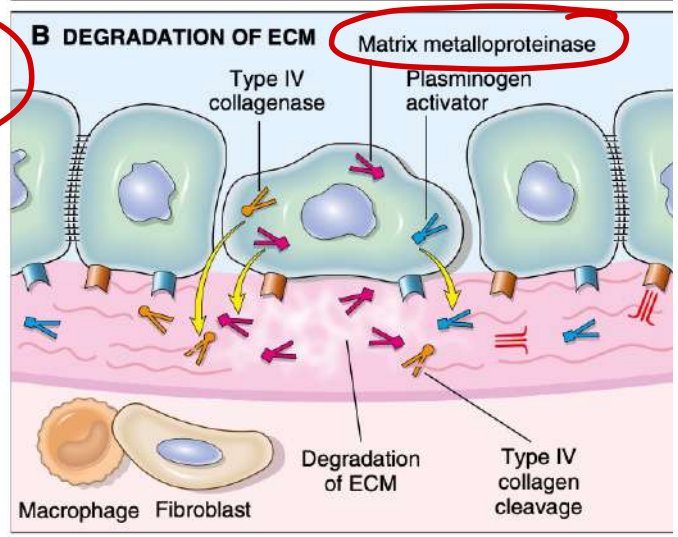


FIG. 6.15 Eight cancer hallmarks and two enabling factors (genomic instability and tumor-promoting inflammation). Most cancer cells acquire these properties during their development, typically due to mutations in critical genes. (From Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. *Cell* 144:646, 2011.)

Evasion often involves loss of p53 (a proapoptotic transcription factor) or overexpression of p53 inhibitors (e.g., MDM2).

Other evasion mechanisms involve overexpression of antiapoptotic members of the BCL2 family (e.g., BCL2, BCL-XL).





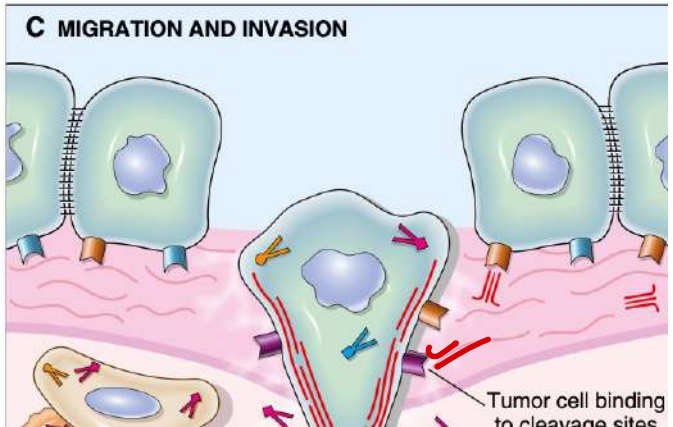
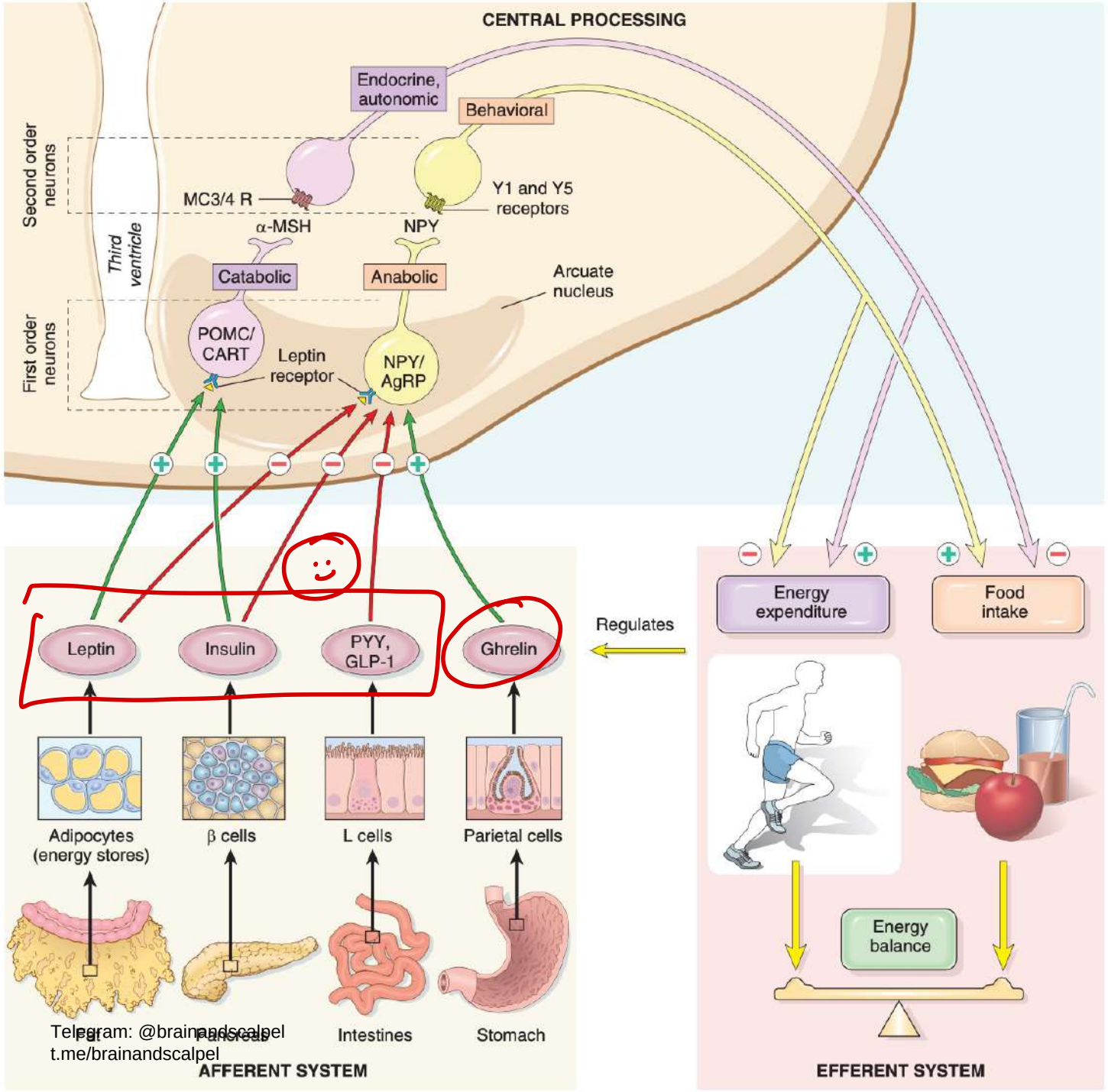


Table 6.5 Paraneoplastic Syndromes

Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small cell carcinoma of lung Intracranial neoplasms	Antidiuretic hormone
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal cell carcinoma Adult T-cell leukemia/lymphoma	Parathyroid hormone–related protein, TGF-α
Hypoglycemia	Fibrosarcoma Other sarcomas Ovarian carcinoma	Insulin or insulin-like substance
Polycythemia	Renal cell carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	Immunologic
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Secretion of epidermal growth factor or other growth factors
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Osseous, Articular, and Soft-Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Lung carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Red cell aplasia	Thymoma	Immunologic
Other		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes



Adiponectin

Adiponectin is produced in adipose tissue and has been called a "fat-burning molecule," as it directs fatty acids to muscle for oxidative metabolism. Adiponectin also decreases glucose production in the liver and increases insulin sensitivity, protecting against the metabolic syndrome. In addition to its metabolic effects, adiponectin has anti-inflammatory, antiatherogenic, antiproliferative, and cardioprotective effects. Its serum levels are lower in obese than in lean individuals, a factor that contributes to obesity-associated insulin resistance, type 2 diabetes (Chapter 18), nonalcoholic fatty liver disease (Chapter 14), and possibly increased risk of certain cancers, discussed later.

Table 7.8 Effects of Whole-Body Ionizing Radiation

	0–1 Sv	1–2 Sv	2–10 Sv	10–20 Sv	>50 Sv
Main site of injury	None	Lymphocytes	Bone marrow	Small bowel	Brain
Main signs and symptoms	—	Moderate leukopenia	Leukopenia, hemorrhage, epilation, vomiting	Diarrhea, fever, electrolyte imbalance, vomiting	Ataxia, coma, convulsions, vomiting
Timing	—	1 day–1 week	2–6 weeks	5–14 days	1–4 hours
Lethality	—	None	Variable (0–80%)	100%	100%

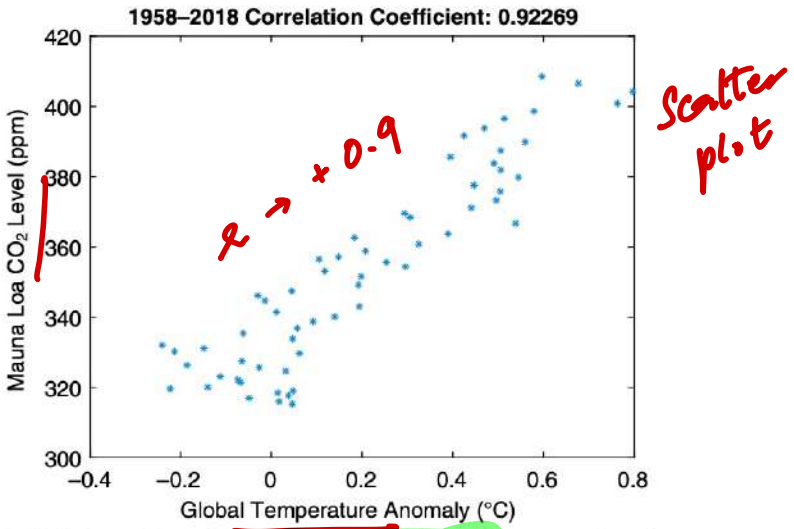
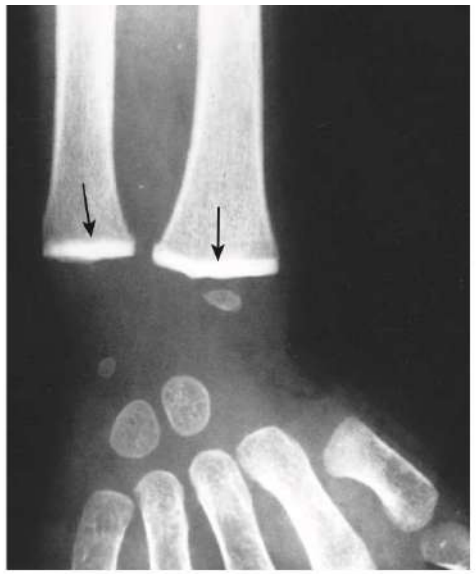
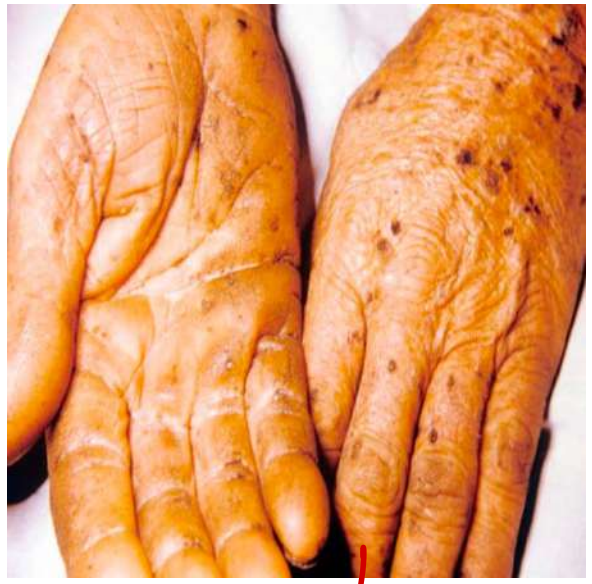


FIG. 7.2 Correlation of carbon dioxide (CO_2) levels measured at the Mauna Loa Observatory in Hawaii with average global temperature trends over the past 60 years. Global temperature in any given year was deduced at the Hadley Center (United Kingdom) from measurements taken at more than 3000 weather stations located around the globe. (Courtesy of Dr. Richard Aster, Department of Geosciences, Colorado State University, Fort Collins, Colorado.)



where it remains a significant cause of toxicity. Blood levels of lead in children living in older homes containing lead-based paint or lead-contaminated dust often exceed 5 µg/dL, the level at which the Centers for Disease Control and Prevention (CDC) recommends intervention to limit further exposure. Lead exposure is related to



Arsenic

Cellular Aging

- Results from combination of multiple and progressive cellular alterations
- Accumulation of DNA damage and mutations
- Replicative senescence: reduced capacity of cells to divide secondary to progressive shortening of chromosomal ends (telomeres)
- Defective protein homeostasis: loss of normal proteins and accumulation of misfolded proteins
- Exacerbated by chronic diseases, especially those associated with prolonged inflammation, and by stress; slowed down by calorie restriction and exercise / red wine — sirtuins ↑

Healing of skin wounds can be classified into *healing by first intention (primary union)*, referring to epithelial regeneration with minimal scarring, as in well apposed surgical incisions, and *healing by second intention (secondary union)*, referring to larger wounds that heal by a combination of regeneration and scarring. The key

- In the healthy population, there are about 29 to 55 CGG repeats in the *FMR1* gene. The genomes of carrier males and females contain premutations with 55 to 200 CGG repeats that can expand up to 4000 repeats (full mutations) during oogenesis. When full mutations are transmitted to progeny, FXS occurs.
- Carriers of premutations develop fragile X–associated tremor/ataxia (males) and fragile X–associated primary ovarian failure (females) due to toxic gain of function by the abnormal *FMR1* mRNA.

Sudden Infant Death Syndrome

- SIDS is a disorder of unknown cause, defined as the sudden death of an infant younger than 1 year of age that remains unexplained after a thorough case investigation including performance of an autopsy. Most SIDS deaths occur between the ages of 2 and 4 months.
- The most likely basis for SIDS is a delayed development of arousal reflexes and cardiorespiratory control.
- Numerous environmental risk factors have been proposed, of which the prone sleeping position is best recognized—hence the success of the "Back to Sleep" program in reducing the incidence of SIDS.

Lead, blood (venous)	Children <3.5 µg/dL (see explanation) Adults: ≤70 µg/dL (occupational)	Most lead is absorbed via the gastrointestinal tract and is distributed throughout the body, predominantly in developing teeth and bone. Adults absorb about 15% of ingested lead while children absorb up to 50%, particularly if they have coexistent nutritional deficiencies. Lead forms covalent bonds with protein cysteine sulfhydryl groups, which contributes to renal toxicity. Lead decreases heme biosynthesis and acts as a mitochondrial toxin. No safe blood lead level has been established for children. At levels above 3.5 µg/dL, the CDC provides a series of recommendations; chelation therapy may be indicated in children with blood levels >45 µg/dL. Blood lead levels are monitored to ensure occupational exposures meet established federal standards.

Another open question is whether there are genes whose principal or sole contribution is to control the expression of proteins that promote metastasis. Among candidates for such "metastasis oncogenes" are those encoding SNAIL and TWIST, transcription factors whose primary function is to promote epithelial-to-mesenchymal transition (EMT). In EMT, carcinoma cells downregulate certain epithelial markers (e.g., E-cadherin) and upregulate certain mesenchymal markers (e.g., vimentin, smooth muscle actin). These molecular changes are accompanied by phenotypic alterations such as morphologic change from a polygonal epithelioid cell shape to a spindly mesenchymal shape, along with increased production of proteolytic enzymes that promote migration and invasion. These changes are believed to favor the development of a promigratory phenotype that is essential for metastasis. Loss of E-cadherin expression seems to be a key event in EMT, and SNAIL and TWIST are transcriptional repressors that downregulate E-cadherin expression. How expression of these master transcriptional regulators is stimulated in tumors is not clear.

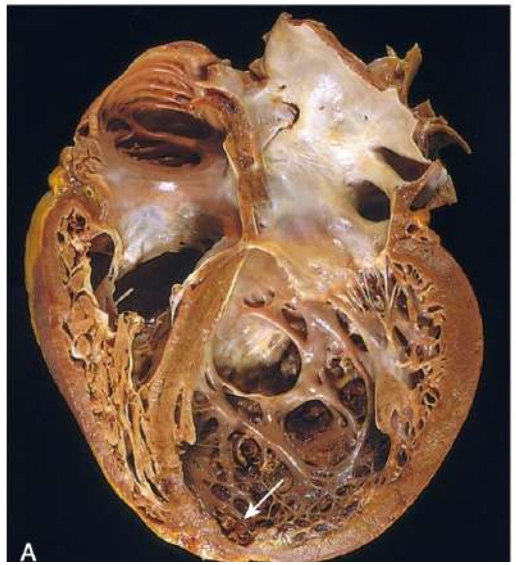
Lonafarnib: Uses, Interactions, Mechanism of Action - DrugBank

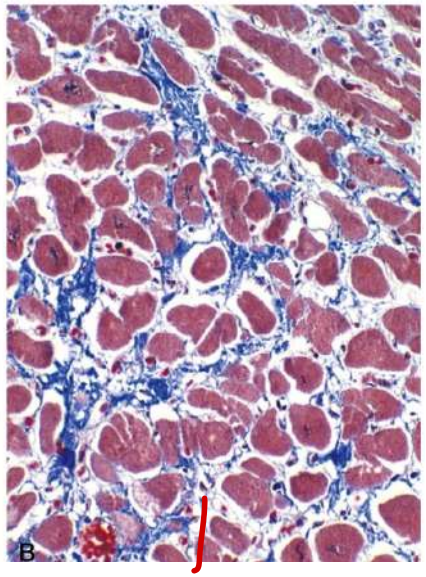
Lonafarnib is a potent farnesyl transferase inhibitor used to reduce mortality associated with Hutchinson-Gilford progeria syndrome (HGPS) and other progeroid ...

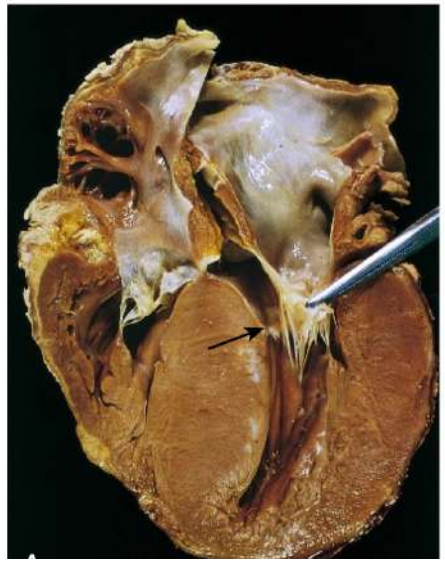
Lamin A

Table 9.5 Cardiomyopathies: Functional Patterns, Causes

Functional Pattern	Left Ventricular Ejection Fraction[a]	Mechanisms of Heart Failure	Causes	Secondary Myocardial Dysfunction (Mimicking Cardiomyopathy)
Dilated	<40%	Impairment of contractility (systolic dysfunction)	Genetic; alcohol; peripartum; myocarditis; hemochromatosis; chronic anemia; doxorubicin; sarcoidosis; idiopathic	Ischemic heart disease; valvular heart disease; hypertensive heart disease; congenital heart disease
Hypertrophic	50%–80%	Impairment of compliance (diastolic dysfunction)	Genetic; Friedreich ataxia; storage diseases; infants of mothers with diabetes	Hypertensive heart disease; aortic stenosis
Restrictive	25%–50%	Impairment of compliance (diastolic dysfunction)	Amyloidosis; radiation-induced fibrosis; idiopathic	Pericardial constriction







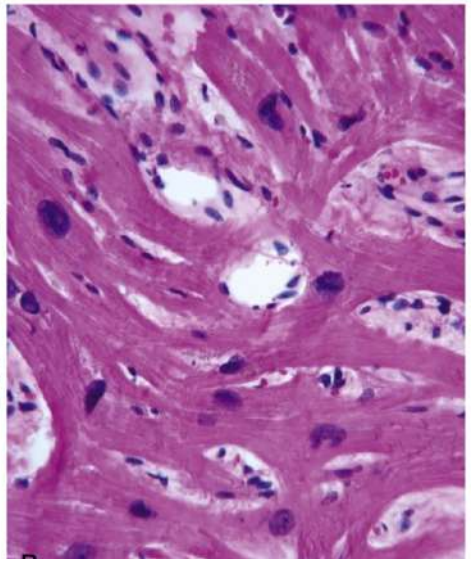


Table 9.2 Evolution of Morphologic Changes in Myocardial Infarction

Time Frame	Gross Features	Light Microscopic Findings
Reversible Injury		
0–½ hour	None	None
Irreversible Injury		
½–4 hours	None	Usually none; variable waviness of fibers at border
4–12 hours	Occasionally dark mottling	Onset coagulation necrosis; edema; hemorrhage
12–24 hours	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; hypereosinophilic appearance of myocytes; marginal contraction band necrosis; early neutrophilic infiltrate
1–3 days	Mottling with yellow-tan infarct center	Coagulation necrosis with loss of nuclei and striations; increased infiltrate of neutrophils
3–7 days	Hyperemic border; central yellow-tan softening	Initial disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border
7–10 days	Maximally yellow-tan and soft, with depressed red-tan margins	Well-developed phagocytosis of dead cells; early formation of granulation tissue at margins
10–14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition
2–8 weeks	Gray-white scar, progressing from border toward core of infarct	Increased collagen deposition, with decreased cellularity
>2 months	Scarring complete	Dense collagenous scar

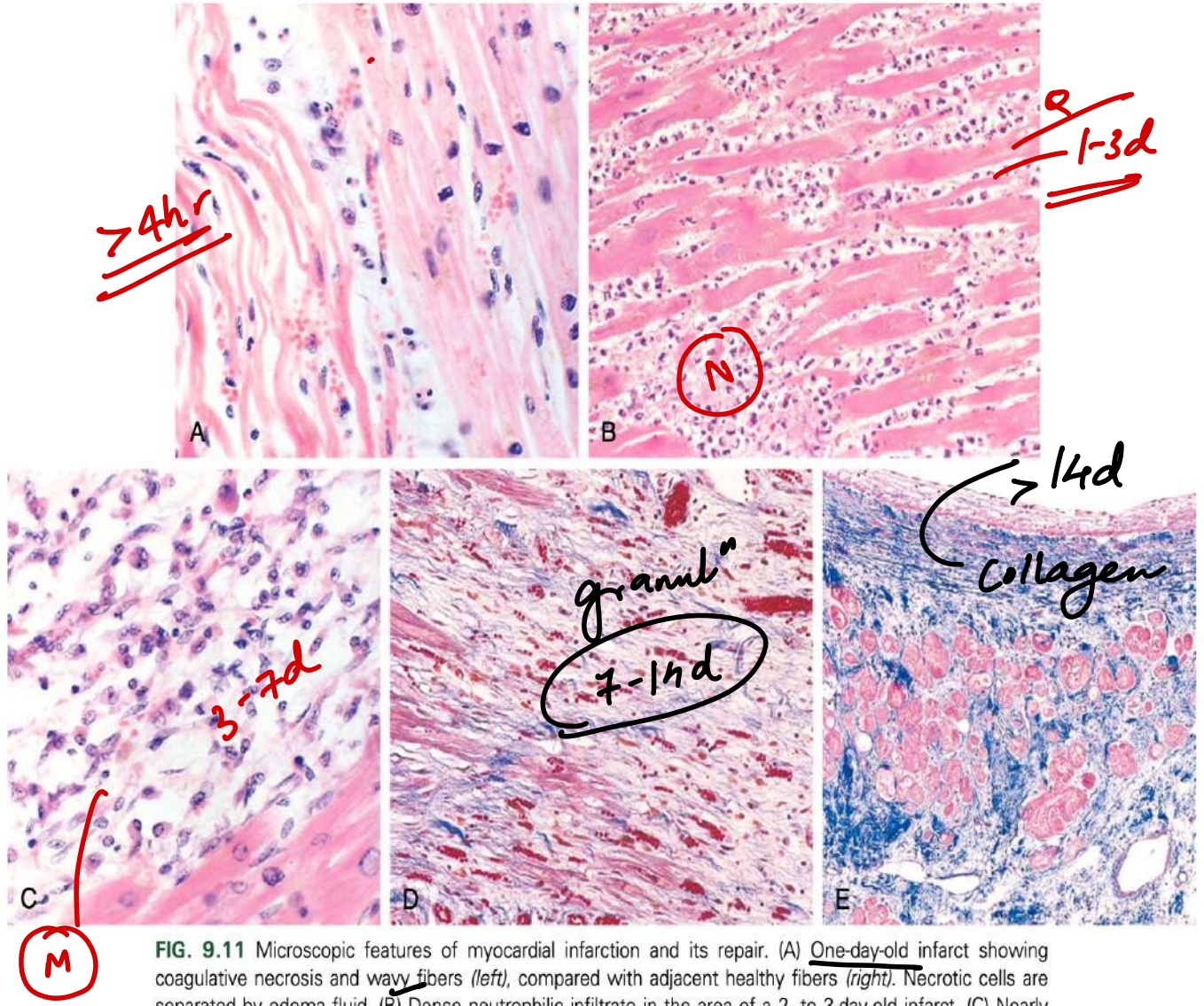
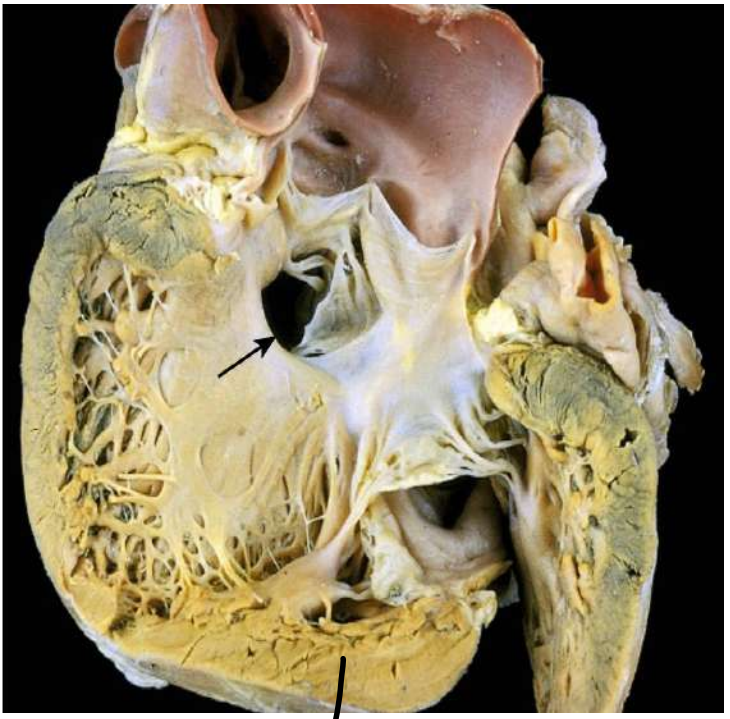
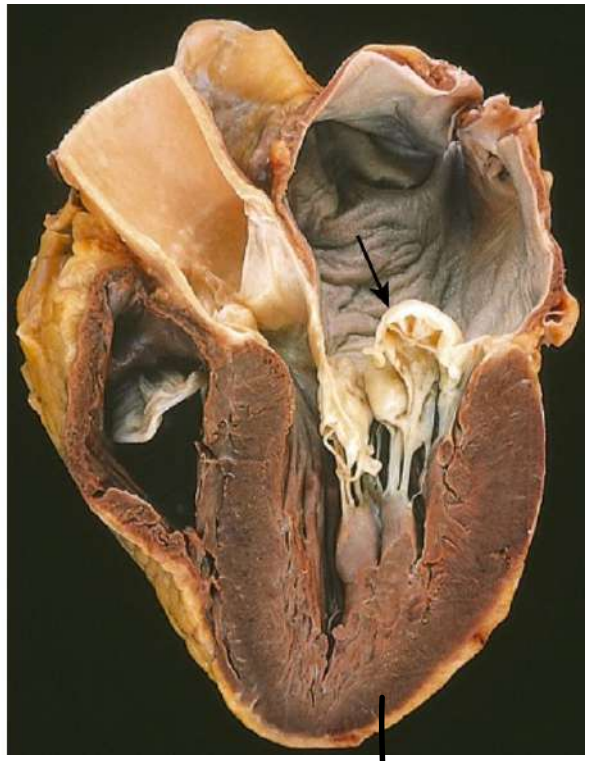
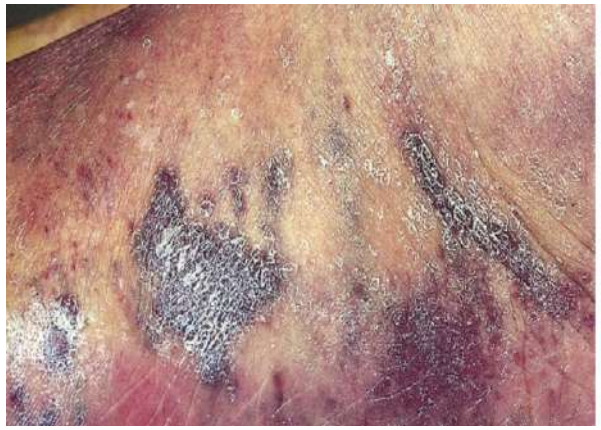
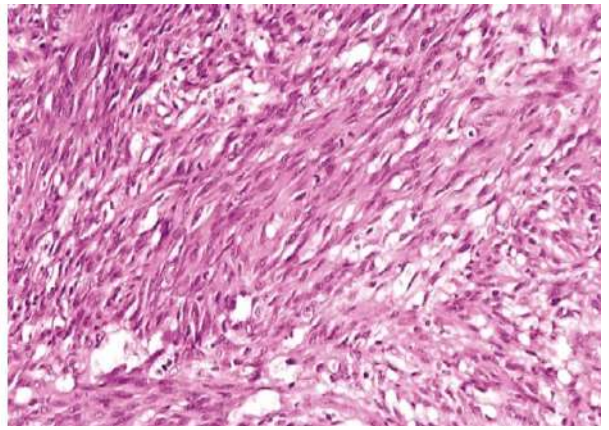


FIG. 9.11 Microscopic features of myocardial infarction and its repair. (A) One-day-old infarct showing coagulative necrosis and wavy fibers *(left)*, compared with adjacent healthy fibers *(right)*. Necrotic cells are separated by edema fluid. (B) Dense neutrophilic infiltrate in the area of a 2- to 3-day-old infarct. (C) Nearly complete removal of necrotic myocytes by phagocytic macrophages (7 to 10 days). (D) Granulation tissue characterized by loose connective tissue and abundant capillaries. (E) Healed myocardial infarct consisting of a dense collagenous scar. A few residual cardiac muscle cells are present. (D) and (E) are Masson trichrome stain, which stains collagen blue.









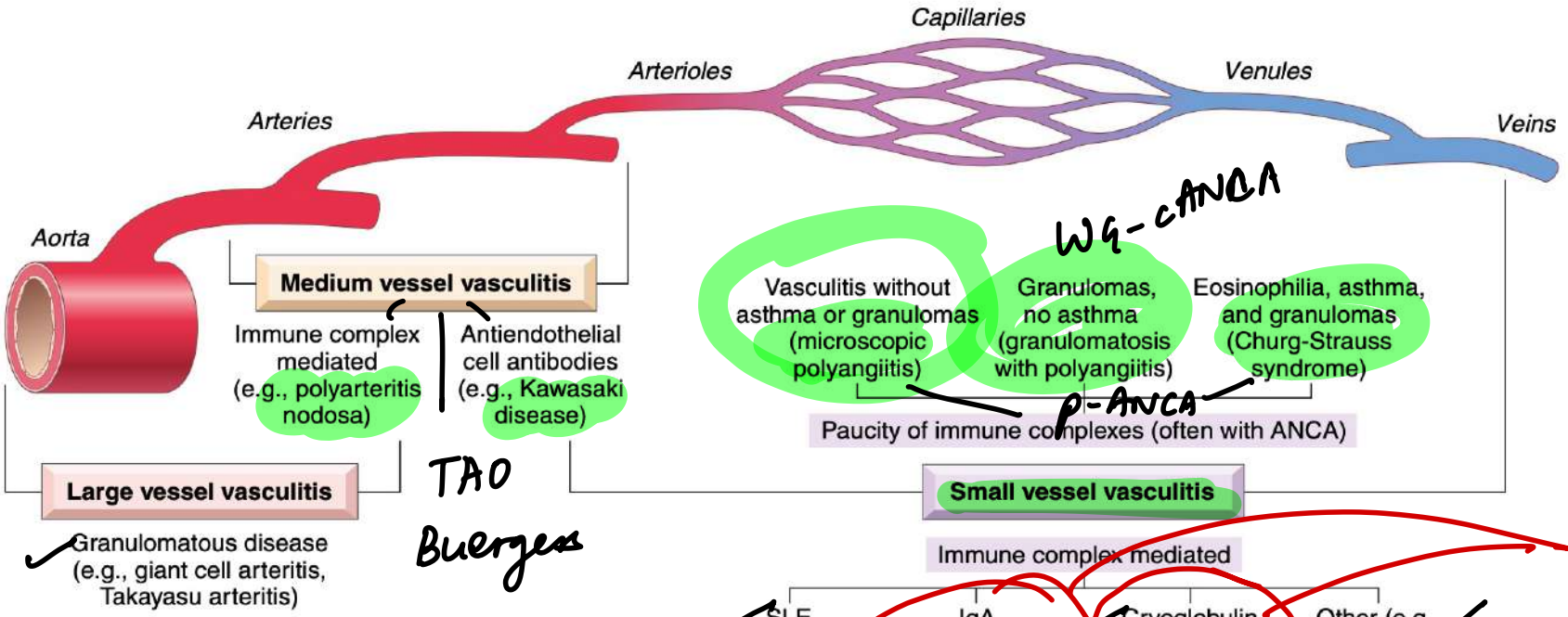
HIV(+)

Kaposi sarcoma

VSD

member (NCC → endo cushing)

MVP



WG-cANCA

P-ANCA

TAO

Buerger

Leukoclastic vasculitis

No glomeruli

No PA

Hep B

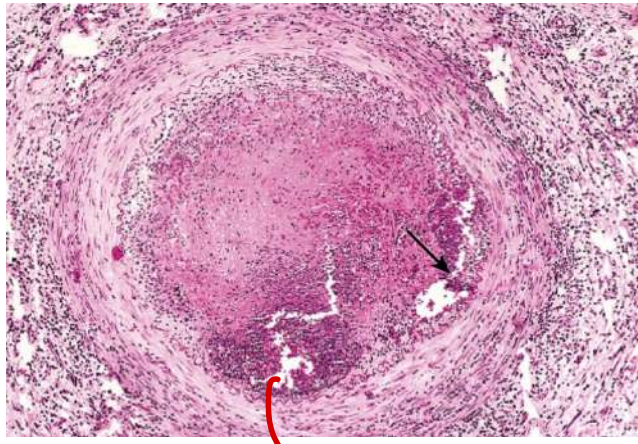
PAN

Fibrinoid

Transmural segmental

glomeruli & alveoli

MPA

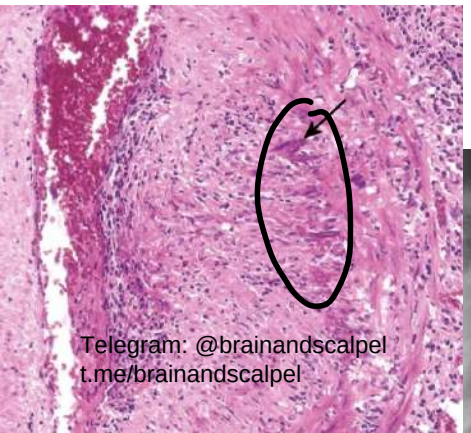


Smoker

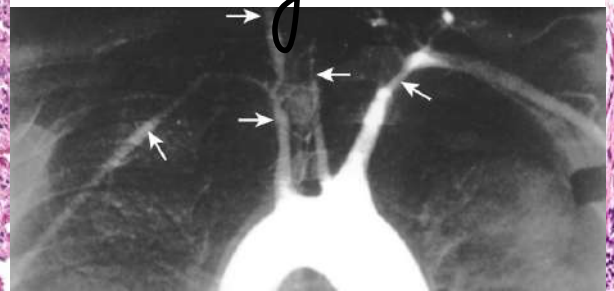
Abscess

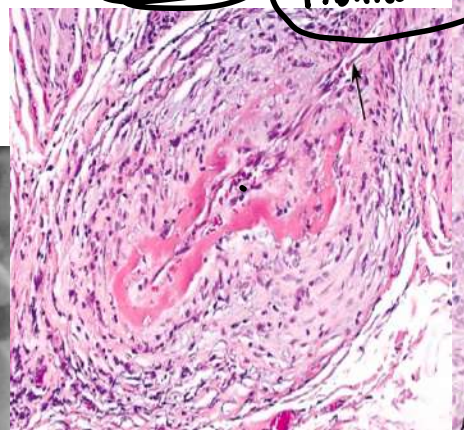
TAO

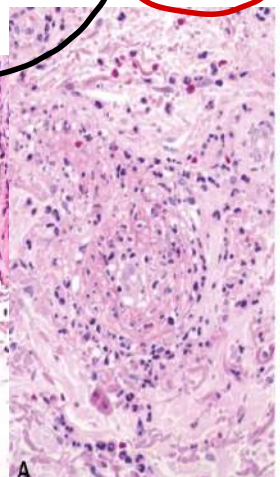
Giant cells



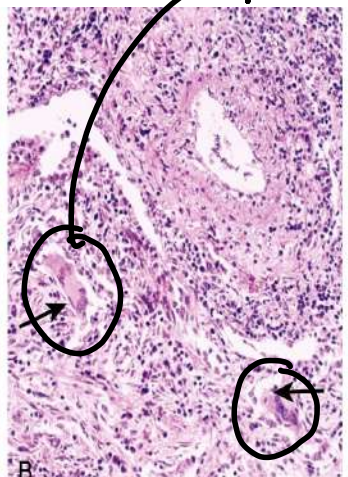
Takayasu





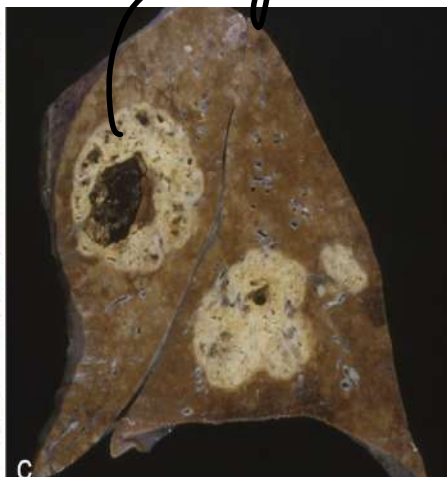


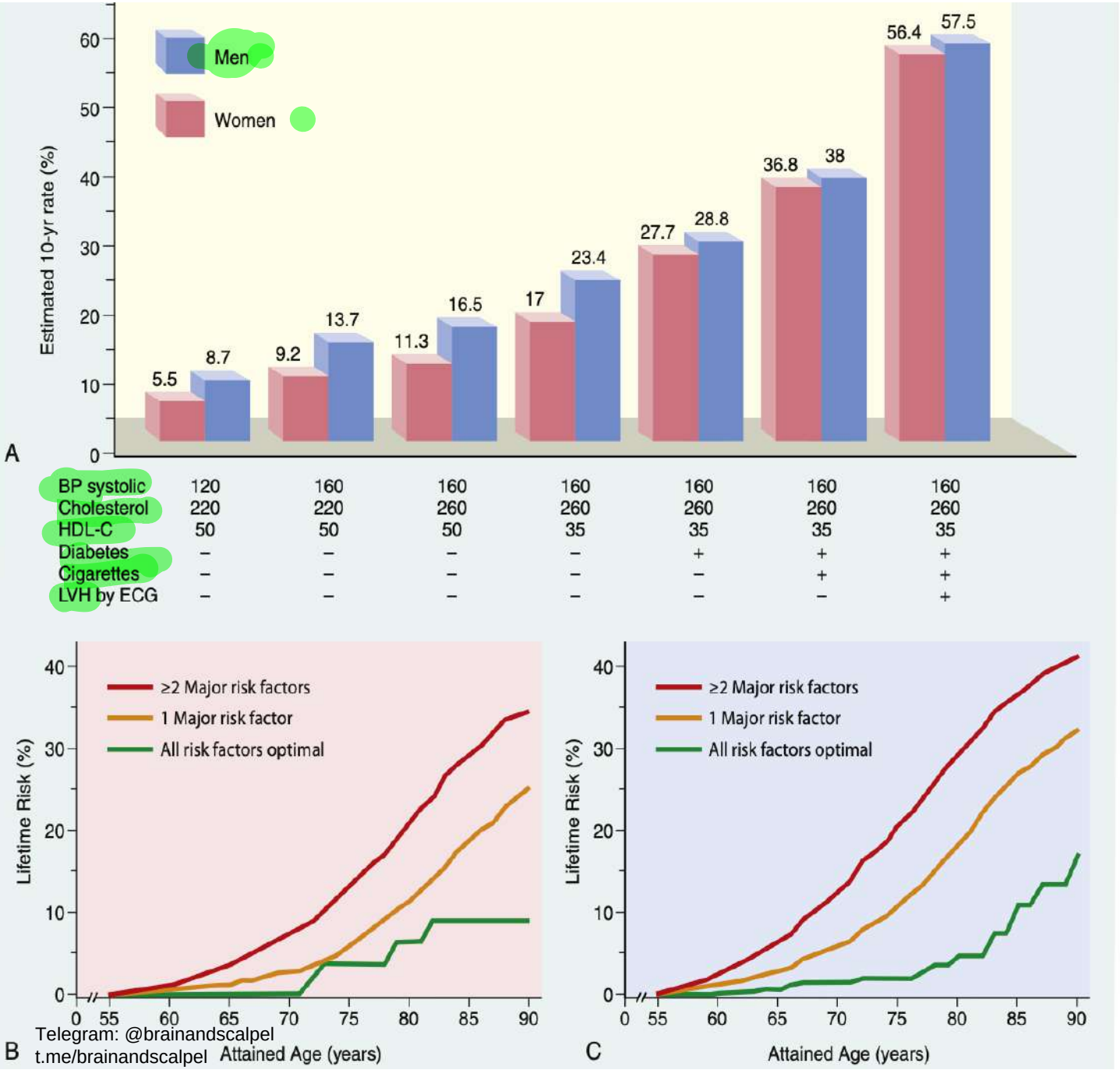
Giant cells



WG

Cavity





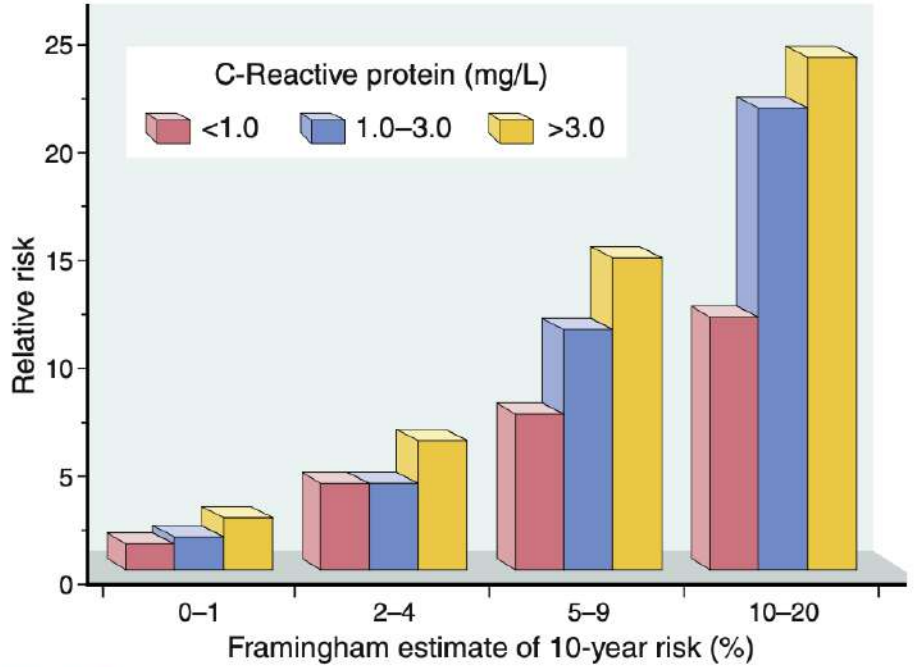
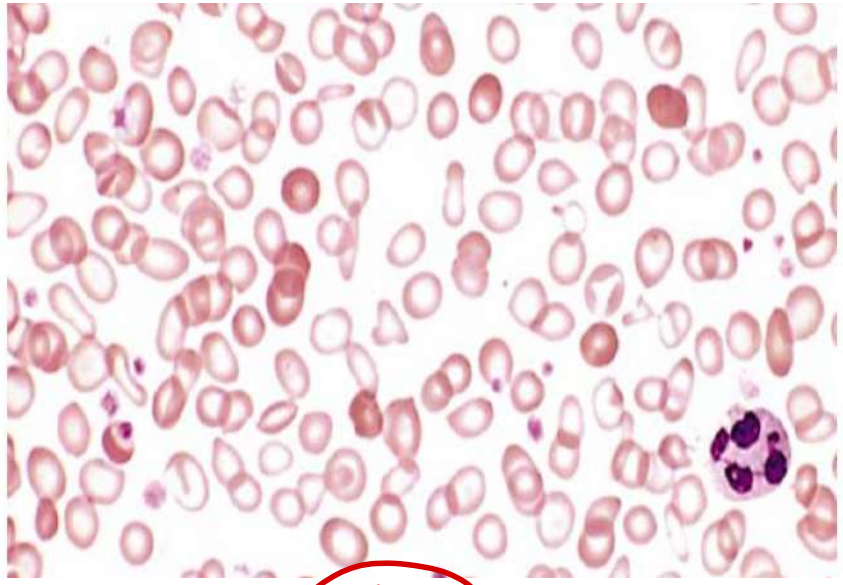
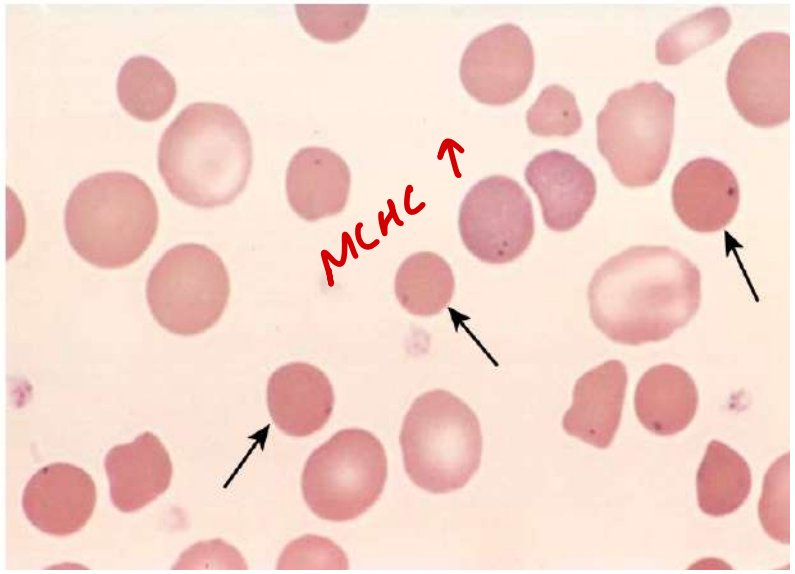


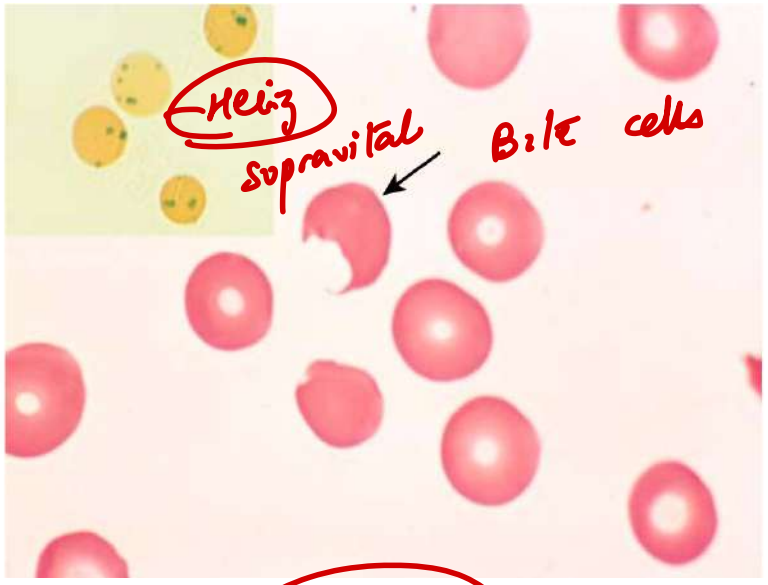
FIG. 8.7 Prognostic value of C-reactive protein (CRP) in coronary artery disease. Relative risk (y-axis) reflects the risk for a cardiovascular event (e.g., myocardial infarction). The x-axis shows the 10-year risk for a cardiovascular event calculated from the traditional risk factors identified in the Framingham Study. In each risk group, CRP levels further stratify the patients. (Data from Ridker PM, et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347:1557, 2002.)



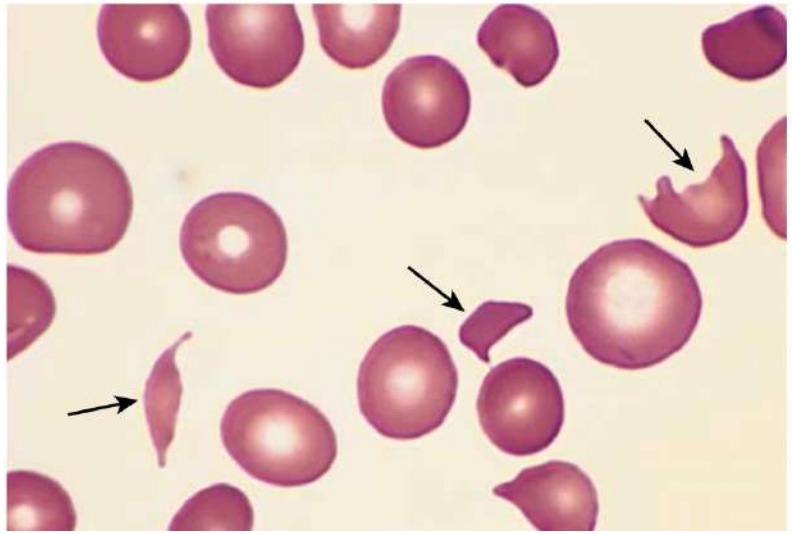
IDA + recent BT



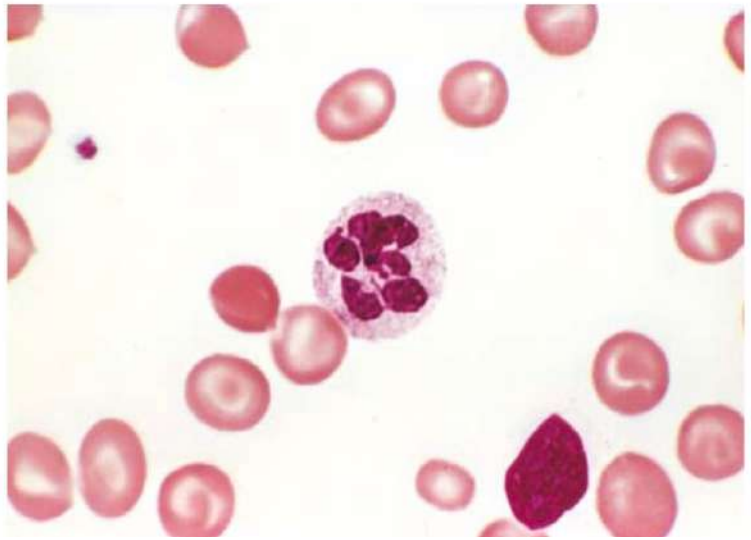
HS + Howel Jolly bodies
(splenectomy



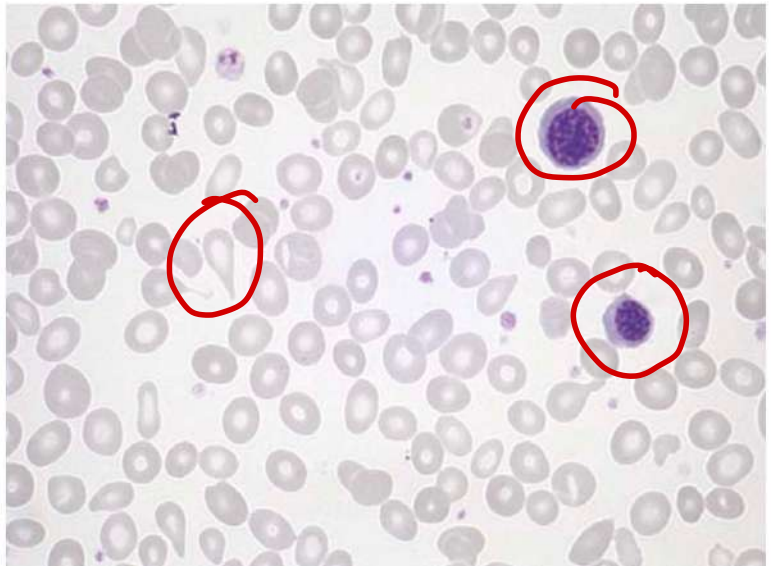
G6PD



Schistocytes - MAHA

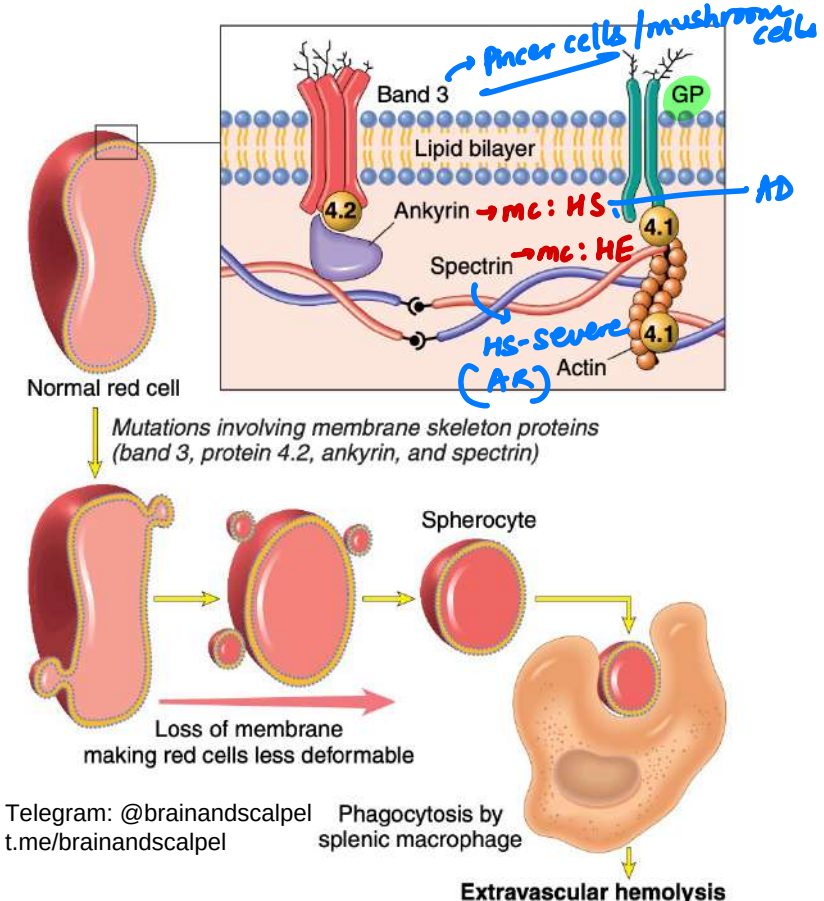


megaloblastic



Myelofibrosis

	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.2–16.6	11.6–15.0
Hematocrit (Hct)	%	38–49	35–45
Red cell count	$\times 10^6/\mu L$	4.4–5.6	3.9–5.1
Reticulocyte count	%	0.6–2.7	0.6–2.7
Mean cell volume (MCV)	fL	78–98	78–98
Mean cell Hb (MCH)	pg	26–34	26–34
Mean cell Hb concentration (MCHC)	g/dL	32–36	31–36
Red cell distribution width (RDW)		11.8–14.5	12.2–16.1



Clinical Syndrome	Genotype	Clinical Features
β-Thalassemias		
β-Thalassemia major	Homozygous β-thalassemia (β^0/β^0, β^+/β^+, β^0/β^+)	Severe anemia; regular blood transfusions required
β-Thalassemia intermedia	Variable (β^0/β^+, β^+/β^+, β^0/β, β^+/β)	Moderately severe anemia; regular blood transfusions not required
β-Thalassemia minor	Heterozygous β-thalassemia (β^0/β, β^+/β)	Asymptomatic with mild or absent anemia; red cell abnormalities seen
α-Thalassemias		
Silent carrier	$-/\alpha$, α/α	Asymptomatic; no red cell abnormality
α-Thalassemia trait	$-/-$, α/α (Asian) $-/\alpha$, $-/\alpha$ (black African, Asian)	Asymptomatic, resembles β-thalassemia minor
HbH disease	$-/-$, $-/\alpha$	Moderately severe; resembles β-thalassemia intermedia
Hydrops fetalis	$-/-$, $-/-$	Lethal in utero without transfusions

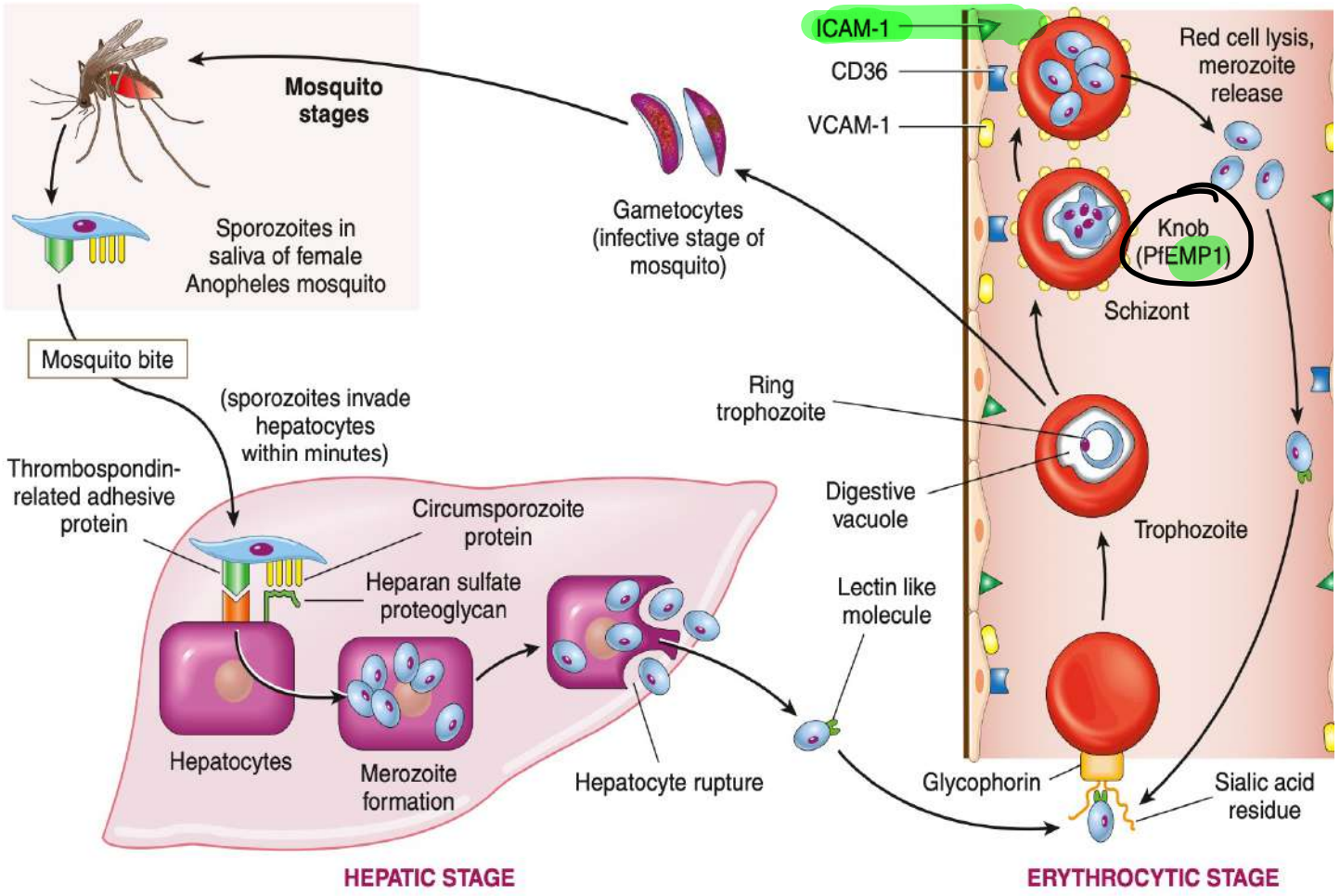
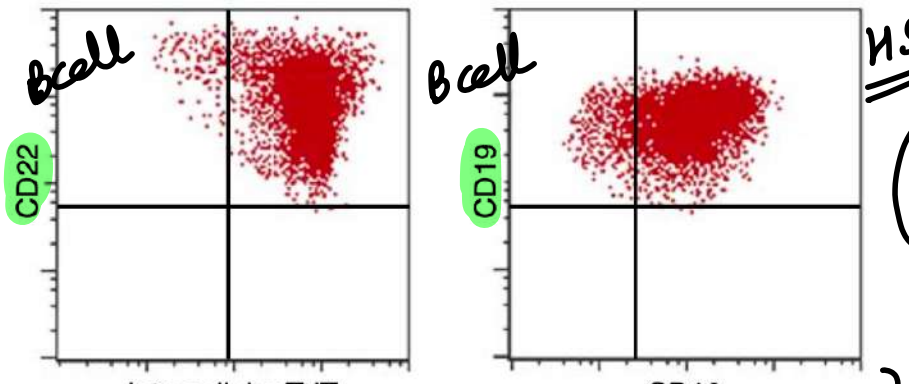


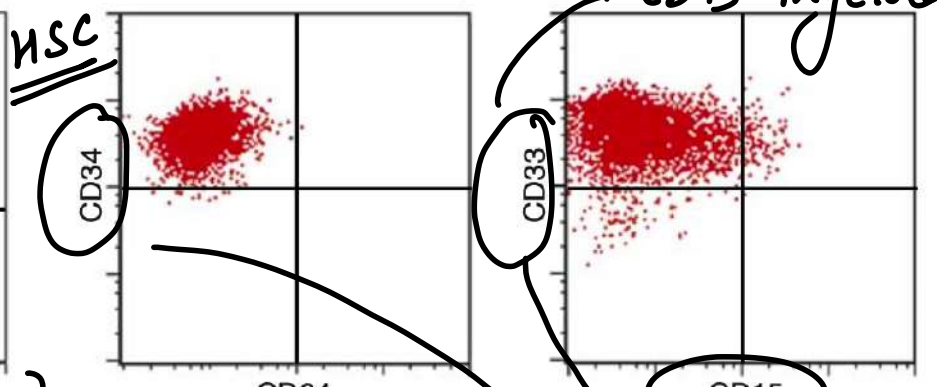
Table 10.5 Pathophysiologic Classification of Polycythemia

Relative
Reduced plasma volume (hemoconcentration)
Absolute
Primary — EPO ↓
Abnormal proliferation of myeloid stem cells, normal or low erythropoietin levels (polycythemia vera)
Inherited activating mutations in the erythropoietin receptor (rare)
Secondary EPO ↑
Increased erythropoietin levels
Adaptive: Lung disease, high-altitude living, cyanotic heart disease
Paraneoplastic: Erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma)
"Blood doping": Endurance athletes

Gaisbock → obese
Sx → Hemoconcent
→ Hyln

Cap sequestration → P. falciparum





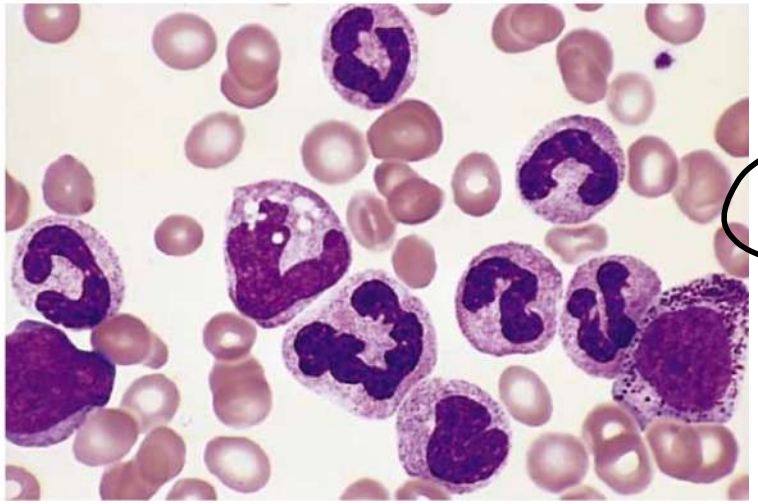
BLAST

Lymphocyte

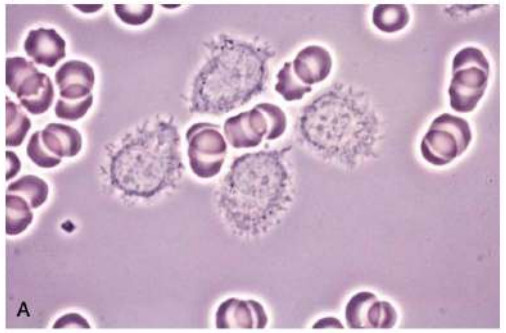
B-cell ALL

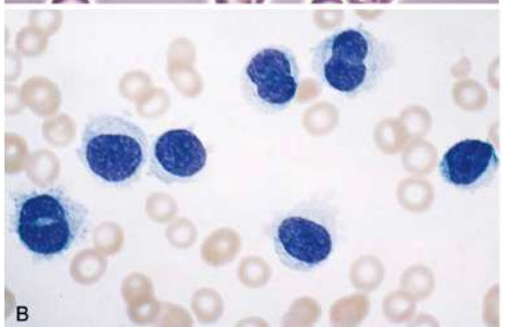
Monocyte

AML

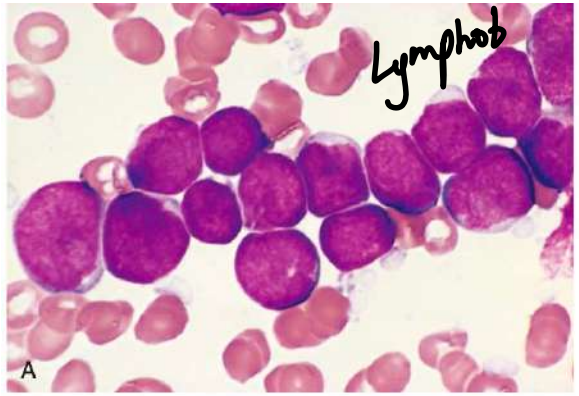


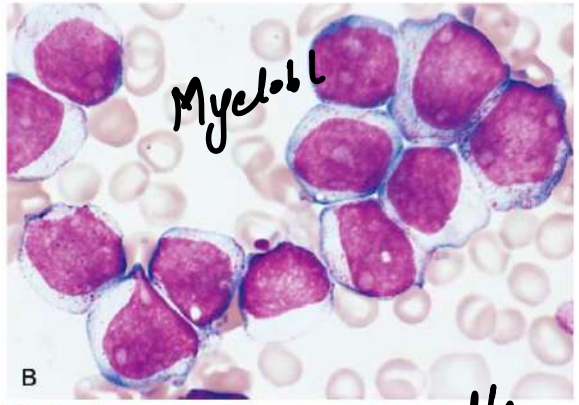
CML

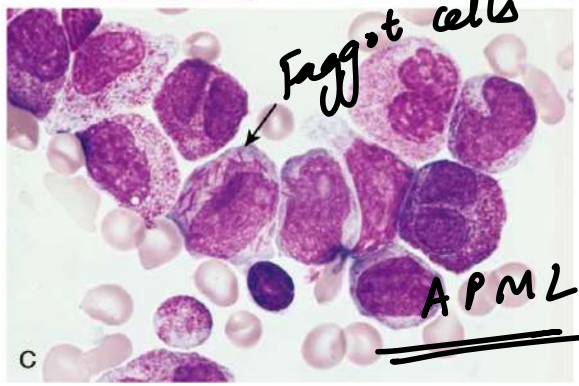




HCL







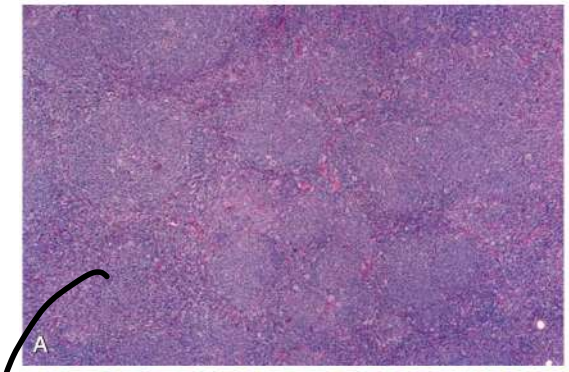
CD 3 – T cell

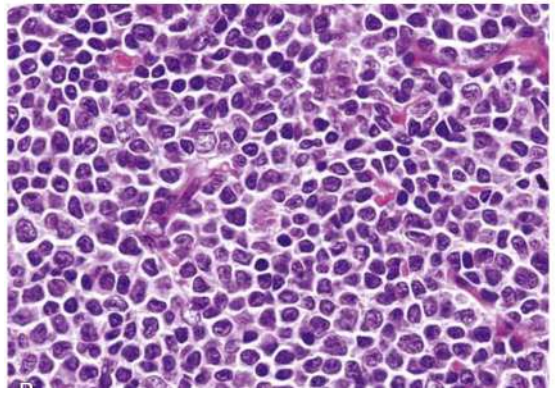
CD 19/20 – B cell

TdT – Lymphoblast

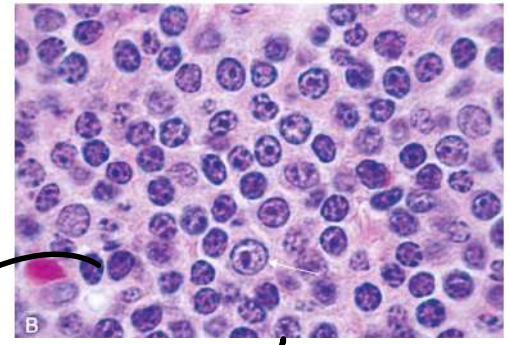
CD 13/33 – Myeloblast

Clinical Entity	Frequency	Salient Morphology	Cell of Origin	Comments
Small lymphocytic lymphoma/chronic lymphocytic leukemia	3%–4% of adult lymphomas; 30% of all leukemias	Small resting lymphocytes mixed with loose clusters of large activated cells; lymph nodes diffusely effaced	CD5+ B cell	Occurs in older adults; usually involves nodes, marrow, spleen; and peripheral blood; indolent
Follicular lymphoma	40% of adult lymphomas	Frequent small "cleaved" cells mixed with large cells; nodular (follicular) growth pattern	Germinal center B cell	Associated with t(14;18); indolent
Mantle cell lymphoma	6% of adult lymphomas	Small to intermediate-sized irregular lymphocytes; diffuse or vaguely nodular pattern	CD5+ B cell overexpressing cyclin D1	Associated with t(11;14); moderately aggressive
Diffuse large B-cell lymphoma	40%–50% of adult lymphomas	Variable; most resemble large germinal center B cells; diffuse growth pattern	Germinal center or postgerminal center B cell	Heterogeneous, may arise at extranodal sites; aggressive
Burkitt lymphoma	<1% of lymphomas in the United States; endemic in Africa	Intermediate-sized cells with several nucleoli; diffuse growth pattern; frequent apoptotic cells ("starry sky" appearance)	Germinal center B cell	Associated with t(8;14) and EBV (subset); highly aggressive
Plasmacytoma/multiple myeloma	Most common lymphoid neoplasm in older adults	Plasma cells in sheets, sometimes with prominent nucleoli or inclusions containing immunoglobulin	Postgerminal center B cell	CRAB (hypercalcemia, renal failure, anemia, bone fractures)



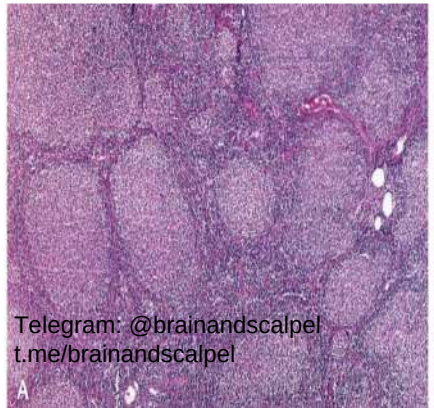


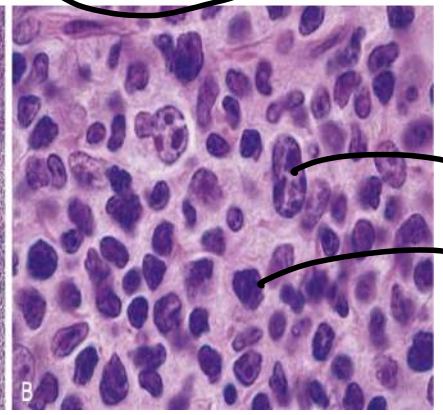
Mantle



SLL / CLL

Small = centrocytes

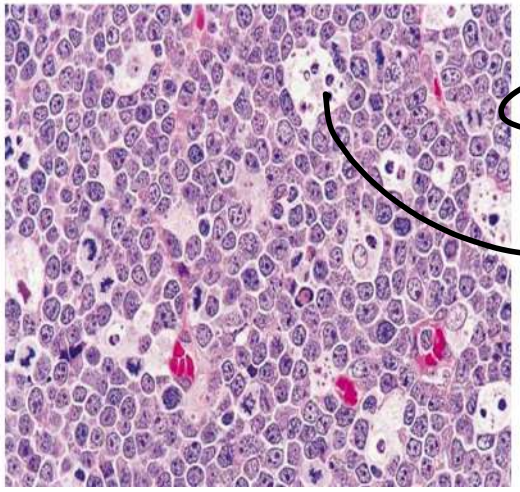




Follicular L

centroblast +

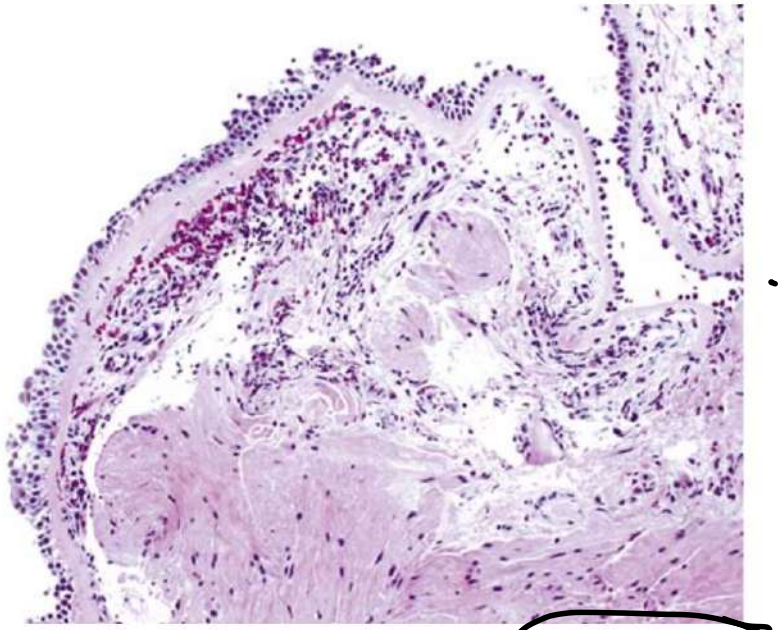
centrocytes



BURKITT

macrophage

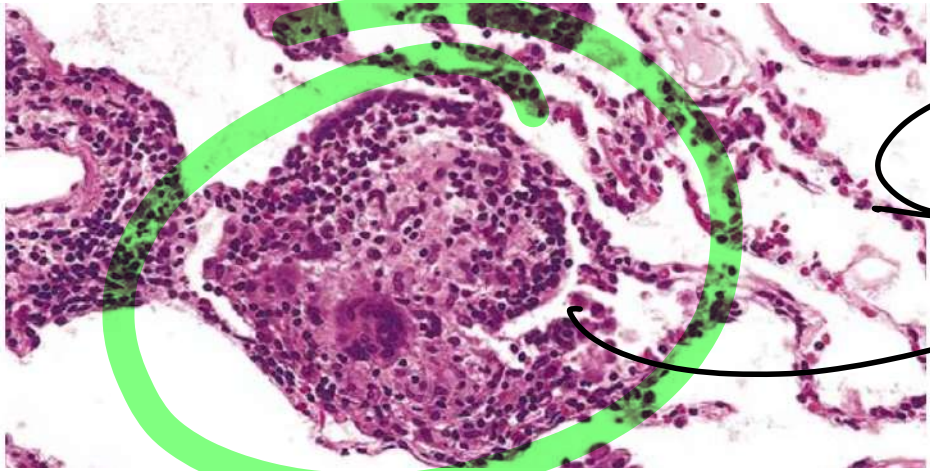
Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, paraaortic)	More frequent involvement of multiple lymph node groups
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring commonly involved
Extranodal involvement uncommon	Extranodal involvement common



. CL crystals

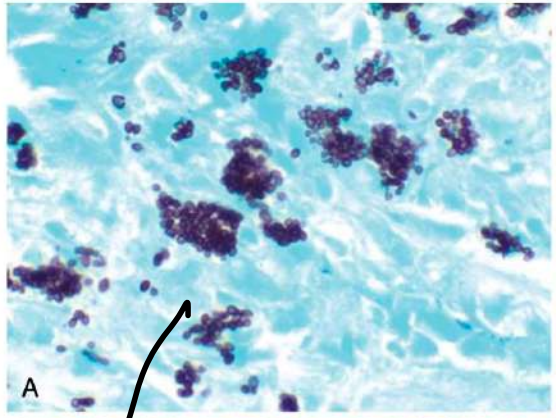
FIG. 11.11 Bronchial biopsy specimen from an asthmatic patient showing subbasement membrane fibrosis, eosinophilic inflammation, and smooth muscle hyperplasia.

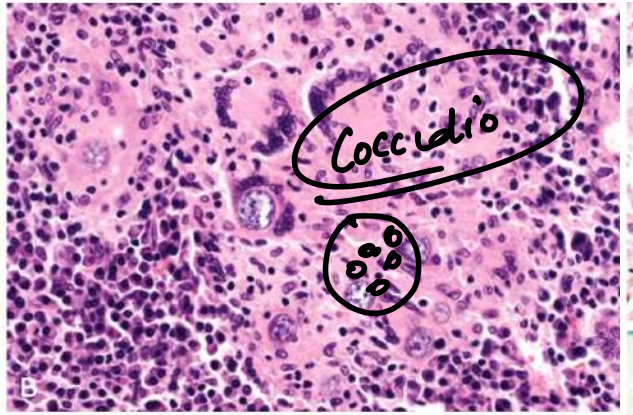
Source of Antigen	Types of Exposures
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria (Thermophilic actinomycetes)	Dairy barns (farmer's lung) mc
M. avium complex (MAC)	Metalworking fluids, sauna, hot tub
Birds	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

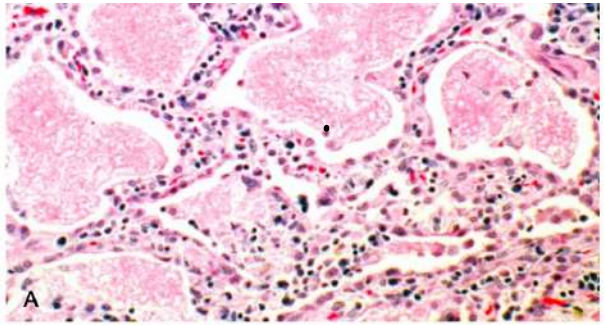


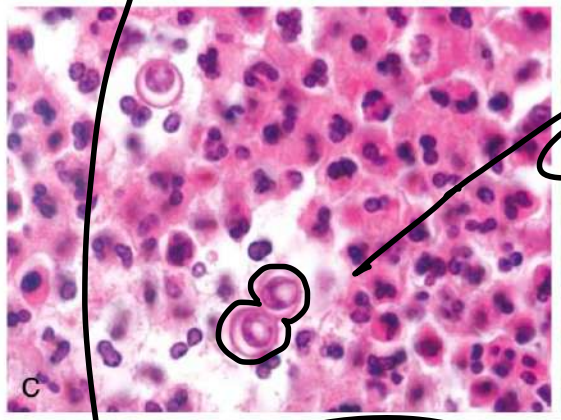
HSP

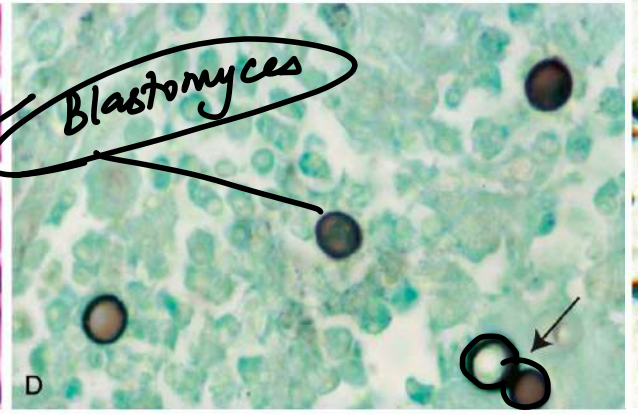
type IV + type III

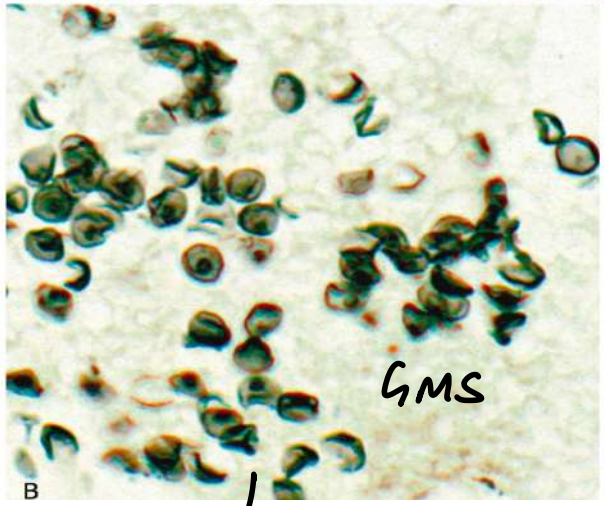












Lobar

Congestn → Red

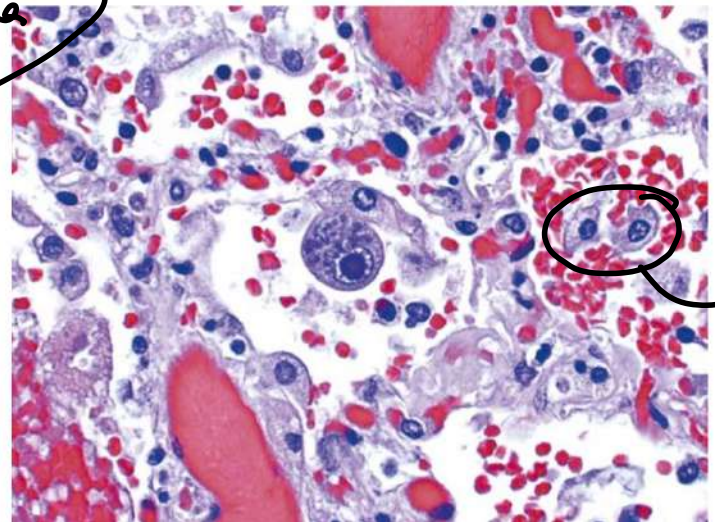
Hepatisn

Gray

Resolution

Histoplasma

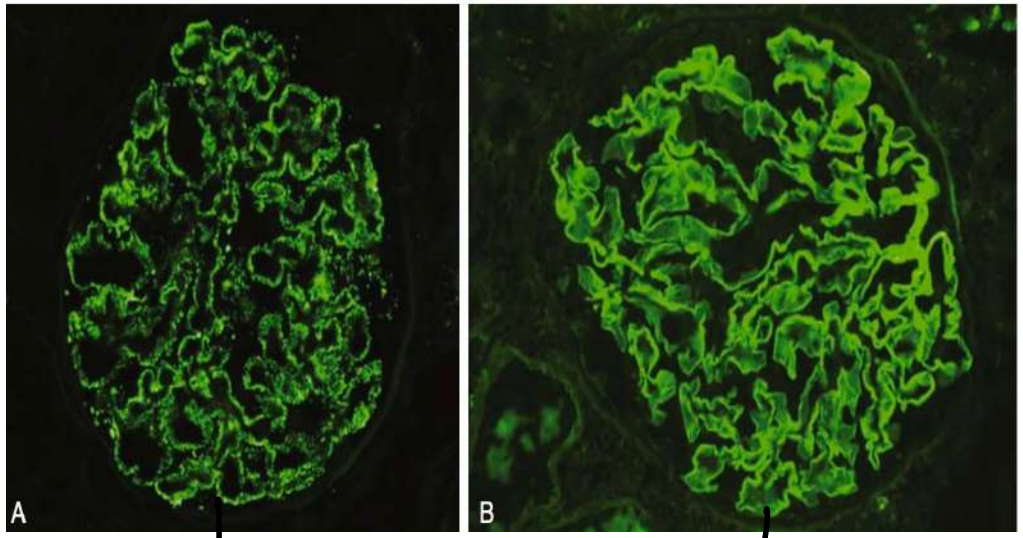
PCP



CMV

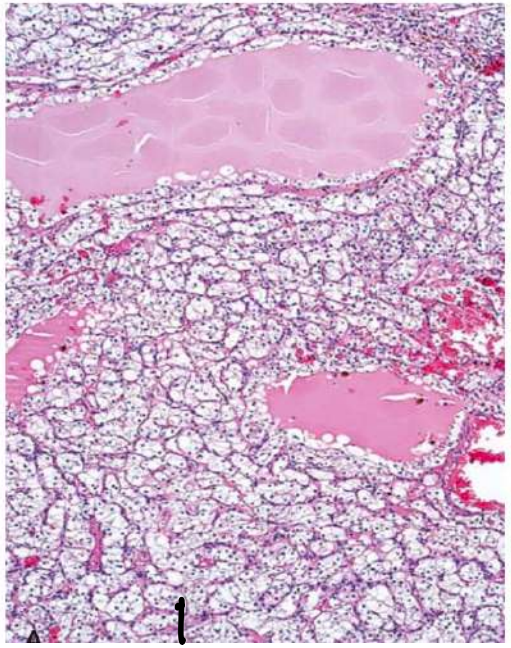
Feature	Small Cell Lung Carcinoma	Nonsmall Cell Lung Carcinoma
Morphology		
Microscopic appearance	Scant cytoplasm; small, hyperchromatic nuclei with fine chromatin pattern; indistinct nucleoli; diffuse sheets of cells	Abundant cytoplasm; pleomorphic nuclei with coarse chromatin pattern; prominent nucleoli; glandular or squamous architecture
Neuroendocrine Markers		
Dense core granules on electron microscopy; expression of chromogranin, synaptophysin, and CD56	Present	Absent
Epithelial Markers		
Epithelial membrane antigen, carcinoembryonic antigen, and cytokeratin intermediate filaments	Present	Present
Mucin	Absent	Present in adenocarcinomas
Peptide hormone production	Adrenocorticotropic hormone, antidiuretic hormone, gastrin-releasing peptide, calcitonin	Parathyroid hormone–related peptide (PTH-rp) in squamous cell carcinoma
Tumor Suppressor Gene Abnormalities		
3p deletions	>90%	>80%
RB mutations	~90%	~20%
p16/CDKN2A mutations	~10%	>50%
TP53 mutations	>90%	>50%
Dominant Oncogene Abnormalities		
KRAS mutations	Rare	~30% (adenocarcinomas)
EGFR mutations	Absent	~20% (adenocarcinomas, nonsmokers, women)
ALK rearrangements	Absent	4%–6% adenocarcinomas, nonsmokers, often have signet ring morphology
Response to Therapy		
Response to chemotherapy and radiotherapy	Often complete response but invariably recur	Incomplete
Response to checkpoint inhibitor therapy	Unresponsive	Responsive

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Minimal change disease	Nephrotic syndrome	Unknown; podocyte injury	Normal	Negative	Effacement of foot processes; no deposits
Focal segmental glomerulosclerosis	Nephrotic syndrome; nonnephrotic range proteinuria	Unknown; reaction to loss of renal mass; plasma factor?	Focal and segmental sclerosis and hyalinosis	Usually negative; IgM and C3 may be present in areas of scarring	Effacement of foot processes; epithelial denudation
Membranous nephropathy	Nephrotic syndrome	In situ immune complex formation; PLA2R antigen in most cases of primary disease	Diffuse capillary wall thickening and subepithelial "spike" formation	Granular IgG and C3 along GBM	Subepithelial deposits
Membranoproliferative glomerulonephritis (MPGN) type I	Nephrotic/nephritic syndrome	Immune complex	Membranoproliferative pattern; GBM splitting	Granular IgG, C3, C1q, and C4 along GBM and mesangium	Subendothelial deposits
C3 glomerulopathy (dense deposit disease and C3 glomerulonephritis)	Nephrotic/nephritic syndrome; nonnephrotic proteinuria	Activation of alternative complement pathway; antibody-mediated or hereditary defect in regulation	Mesangial proliferative or membranoproliferative patterns	C3	Mesangial, intramembranous and subendothelial electron-dense or "waxy" deposits
Acute postinfectious glomerulonephritis	Nephritic syndrome	Immune complex mediated; circulating or planted antigen	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG and C3 along GBM and mesangium	Primarily subepithelial humps
IgA nephropathy	Recurrent hematuria or proteinuria	Immune complexes containing IgA	Mesangial or focal endocapillary proliferative glomerulonephritis	IgA ± IgG, IgM, and C3 in mesangium	Mesangial and paramesangial dense deposits
Rapidly progressive glomerulonephritis	Rapid onset of nephritic syndrome, usually with proteinuria; progression to renal failure	Varies: autoantibodies against collagen type IV α3 chain (anti-GBM antibodies); immune complexes; no immune deposits	Extracapillary proliferation with crescents; necrosis	Linear or granular IgG and C3; fibrin in crescents	Immune complexes or no deposits; GBM disruptions; fibrin

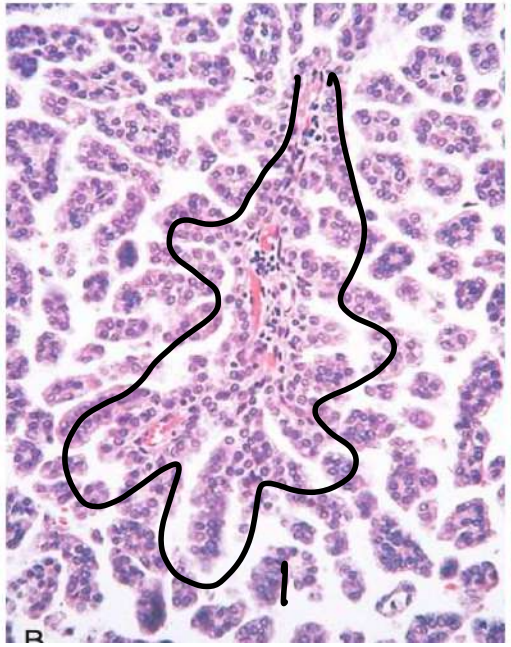


Granular

LINEAR
anti-GBM

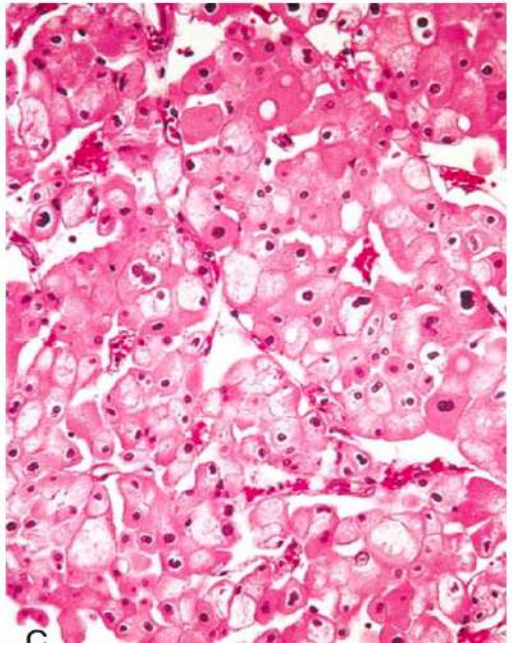


clear cell

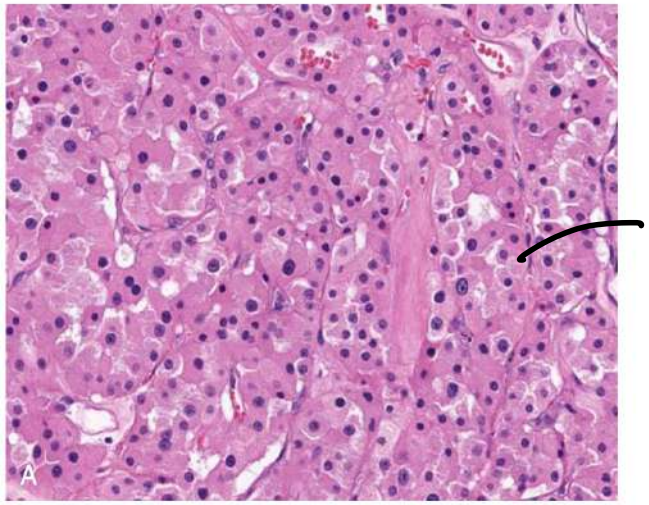


Papillary RCC

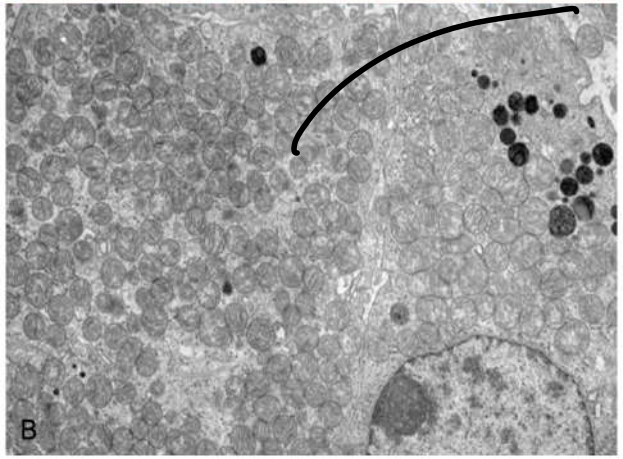
h/o dialysis



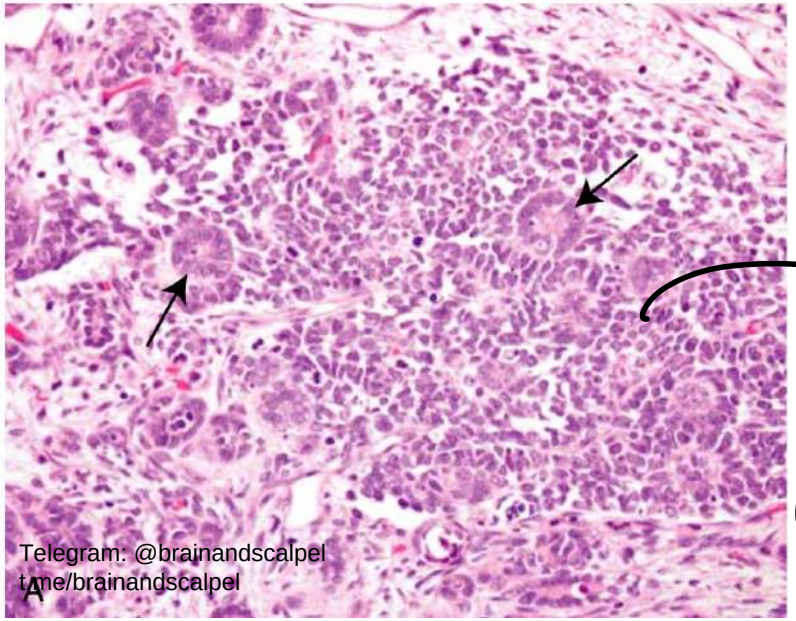
Chromophobe



oncocytoma



dense bodies EM



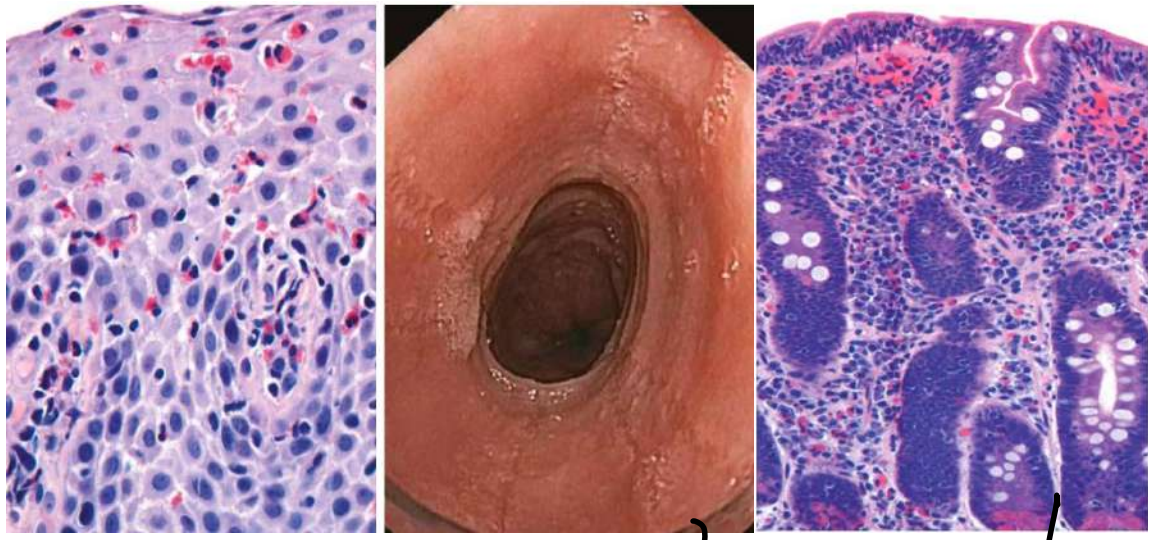
WT

"triphasic"

stromal

blastemal

tubules (epithelium)



eosinophilic Esoph = FELINE

celiac D

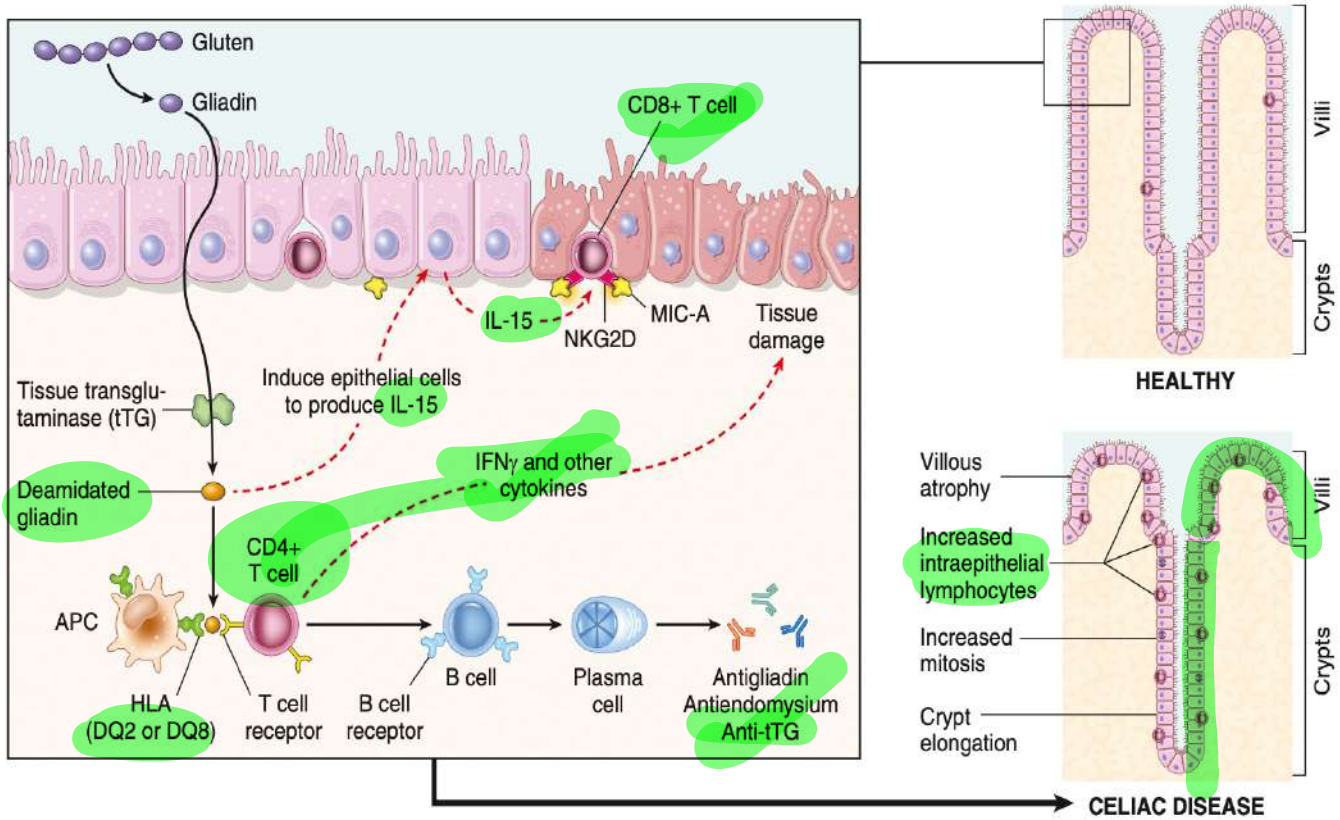


Table 13.2 Characteristics of *Helicobacter pylori*–Associated and Autoimmune Gastritis

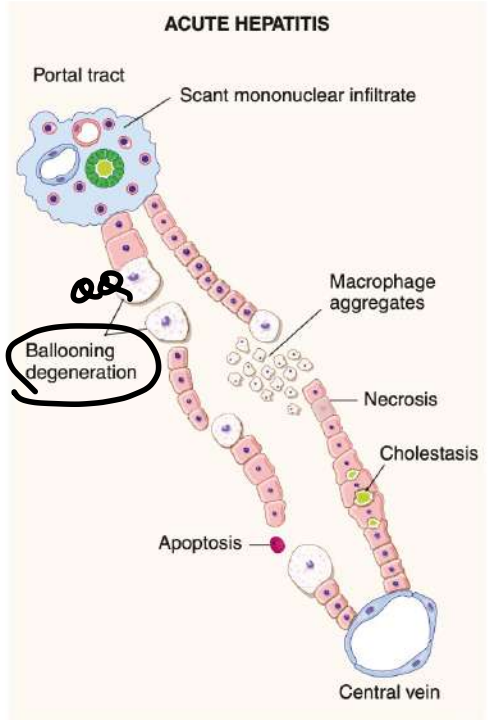
Feature	*H. pylori*–Associated	Autoimmune
Location	Antrum	Body (parietal)
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells, germinal centers	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to markedly increased	Markedly increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, lymphoma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Lower economic status, residence in rural areas	Autoimmune disease; thyroiditis, diabetes, Graves disease

Table 13.7 Common Patterns of Sporadic and Familial Colorectal Neoplasia

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

Table 13.6 Gastrointestinal (GI) Polyposis Syndromes

Syndrome	Mean Age at Presentation (Years)	Mutated Gene(s)	GI Lesions	Selected Extragastrointestinal Manifestations
Peutz-Jeghers syndrome	10–15	*LKB1/STK11*	Arborizing polyps—small intestine > colon > stomach; colonic adenocarcinoma	Mucocutaneous pigmentation; increased risk for thyroid, breast, lung, pancreas, gonadal, and bladder cancers
Juvenile polyposis	<5	*SMAD4, BMPR1A*	Juvenile polyps; increased risk for gastric, small-intestinal, colonic, and pancreatic adenocarcinoma	Pulmonary arteriovenous malformations, digital clubbing
Cowden syndrome	<15	*PTEN*	Hamartomatous polyps, lipomas, ganglioneuromas, inflammatory polyps; increased risk for colon cancer	Benign skin tumors, benign and malignant thyroid and breast lesions
Tuberous sclerosis	Infancy to adulthood	*TSC1, TSC2*	Hamartomatous polyps (rectal)	Facial angiofibroma, cortical tubers, renal angiomyolipoma
Familial adenomatous polyposis (FAP)				
Classic FAP	10–15	*APC*	Multiple adenomas	Congenital RPE hypertrophy
Attenuated FAP	40–50	*APC*	Multiple adenomas	
Gardner syndrome	10–15	*APC*	Multiple adenomas	Osteomas, desmoids, skin cysts
Turcot syndrome	10–15	*APC*	Multiple adenomas	CNS tumors, medulloblastoma



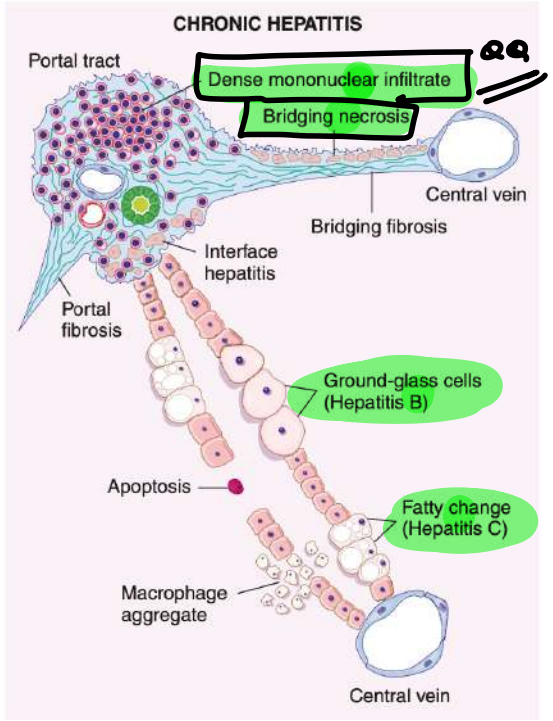
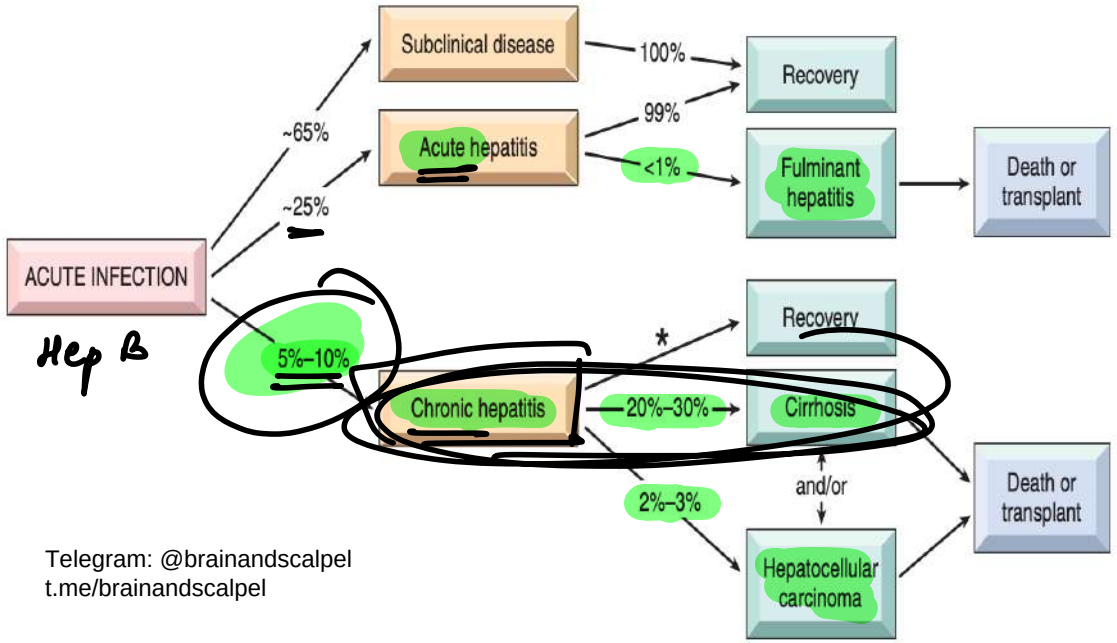


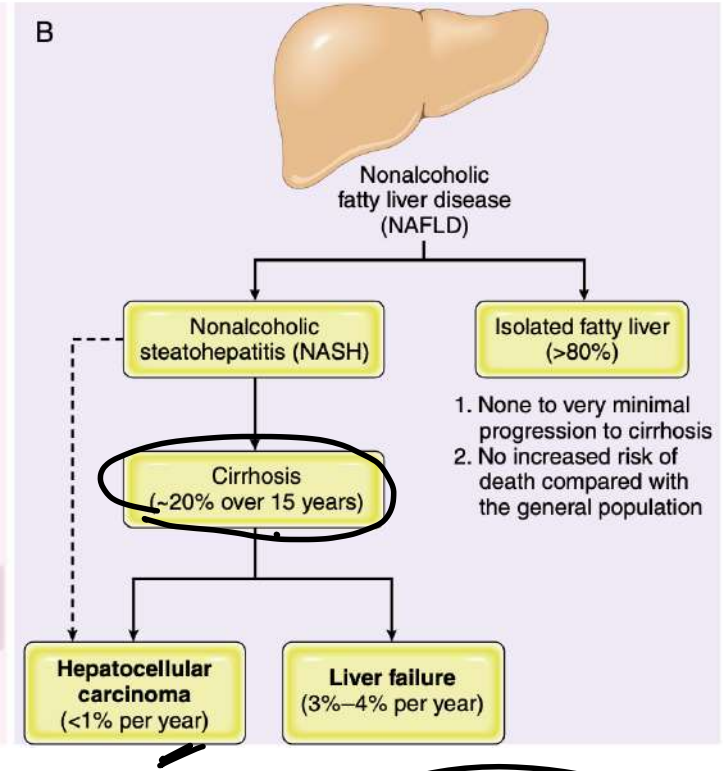
Table 14.2 The Hepatitis Viruses

Virus	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
Viral genome	ssRNA	Partially dsDNA	ssRNA	Circular defective ssRNA	ssRNA
Viral family	Hepatovirus; related to picornavirus	Hepadnavirus	Flaviviridae	Subviral particle in Deltaviridae family	Hepeviridae family, *Hepevirus* genus
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contact, perinatal	Parenteral; intranasal cocaine use is a risk factor	Parenteral	Fecal-oral
Incubation period	2–6 weeks	2–26 weeks (mean 8 weeks)	4–26 weeks (mean 9 weeks)	Same as HBV	4–5 weeks
Frequency of chronic liver disease	Never	5%–10%	>80%	10% (coinfection); 90%–100% for superinfection	In immunocompromised hosts only
Diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg; PCR for HBV DNA	ELISA for antibody detection; PCR for HCV RNA	Detection of IgM and IgG antibodies, HDV RNA in serum, or HDAg in liver biopsy	Detection of serum IgM and IgG antibodies; PCR for HEV RNA



In contrast to HBV, chronic disease occurs in the majority of individuals infected with HCV (80%-90%), and cirrhosis eventually occurs in approximately 20% over a period of 20 to 30 years.

80-90%
mcc of Liver Transplant

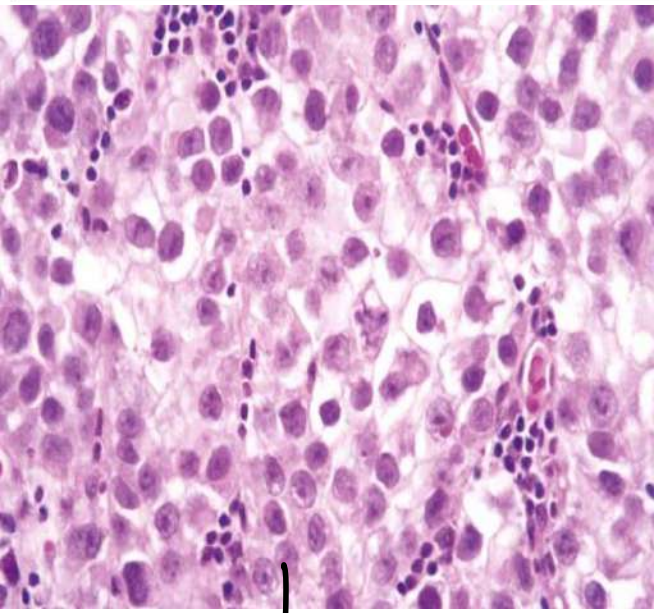


Parameter	Primary Biliary Cholangitis	Primary Sclerosing Cholangitis
Age	Median age 50 years	Median age 30 years
Sex	90% female	70% male
Clinical course	Progressive	Unpredictable, but progressive—may progress to cholangiocarcinoma
Associated conditions	Sjögren syndrome (70%)	Inflammatory bowel disease (70%)
	Scleroderma (5%)	Autoimmune pancreatitis
	Thyroid disease (20%)	IgG4 related fibrosing diseases
Serology	95% AMA-positive	0%–5% AMA-positive (low titer)
	20% ANA-positive	6% ANA-positive
	40% ANCA-positive	65% ANCA-positive
Radiology	Normal	Strictures and beading of large bile ducts; pruning of smaller ducts
Duct lesion	Florid duct lesions and loss of small ducts only	Inflammatory destruction of extrahepatic and large intrahepatic ducts; fibrotic obliteration of medium and small intrahepatic ducts

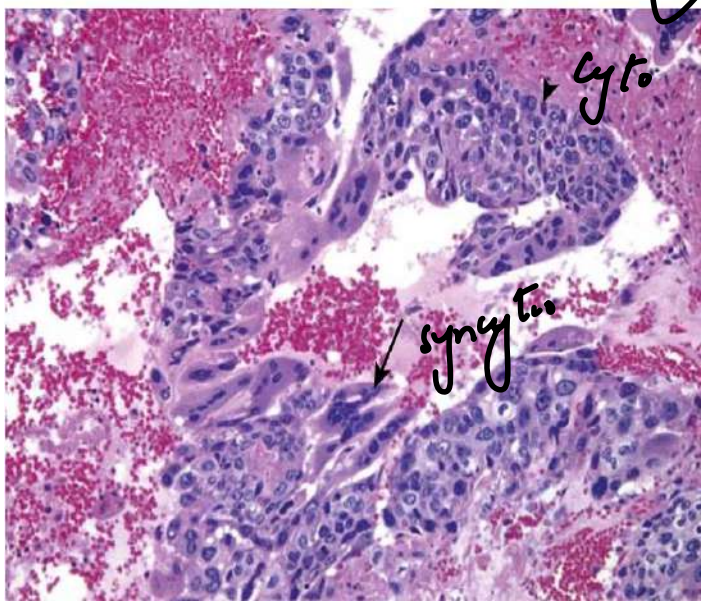
Rezdiffra

Resmetirom

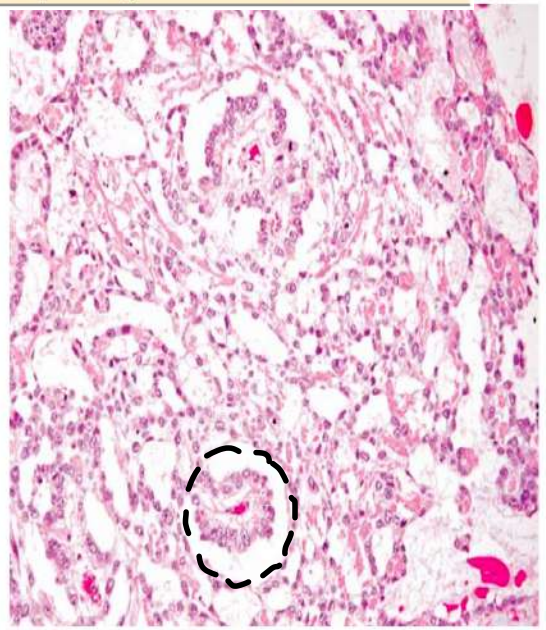
Tumor	Peak Patient Age (years)	Morphology	Tumor Marker(s)
Seminoma	40–50	Sheets of uniform polygonal cells with clear cytoplasm; lymphocytes in the stroma	10% of patients have elevated hCG
Embryonal carcinoma	20–30	Poorly differentiated, pleomorphic cells in cords, sheets, or papillary formation; most contain some yolk sac and choriocarcinoma cells	AFP may be elevated
Spermatocytic tumor	50–60	Small, medium, and large polygonal cells; no inflammatory infiltrate	Negative
Yolk sac tumor	3	Poorly differentiated flattened, cuboidal, or columnar cells	90% of patients have elevated AFP
Choriocarcinoma	20–30	Cytotrophoblast and syncytiotrophoblast without villus formation	100% of patients have elevated hCG
Teratoma	All ages	Tissues from all three germ cell layers with varying degrees of differentiation	20%–25% have elevated AFP
Mixed tumor	15–30	Variable, depending on mixture; commonly teratoma and embryonal carcinoma	AFP and hCG are variably elevated, depending on mixture



Seminoma

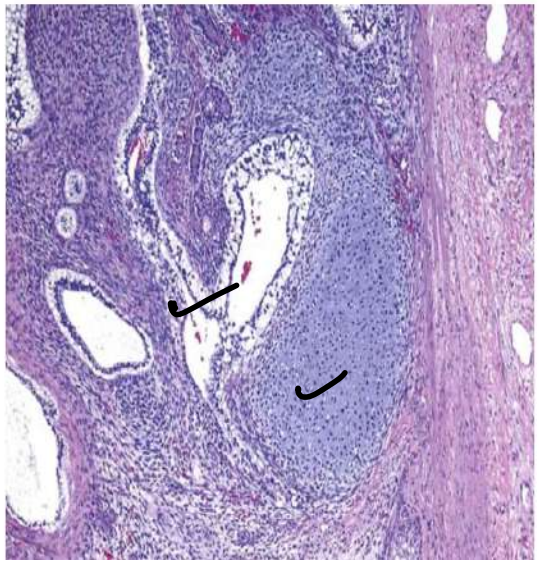


CCA

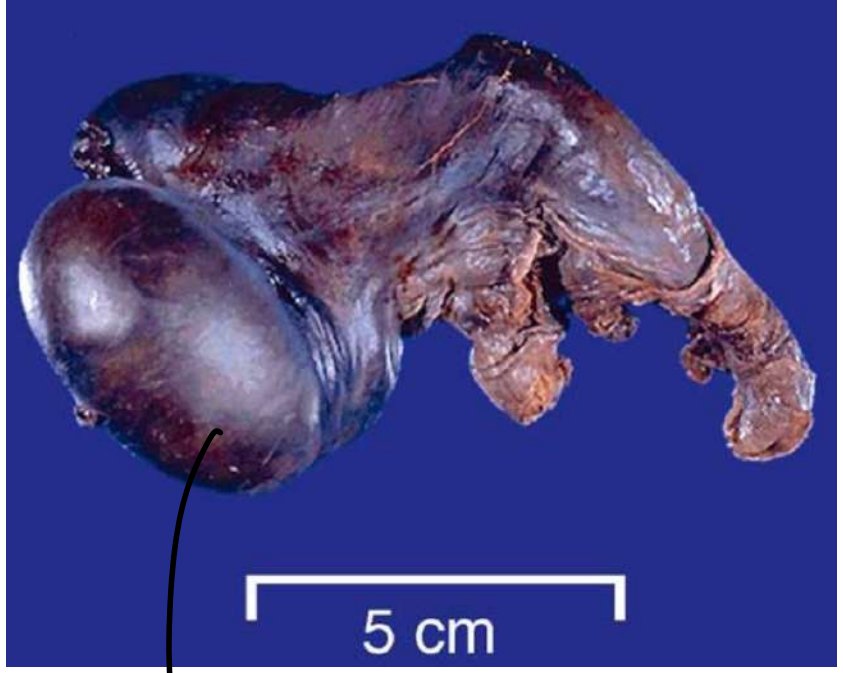


Schiller–Duval

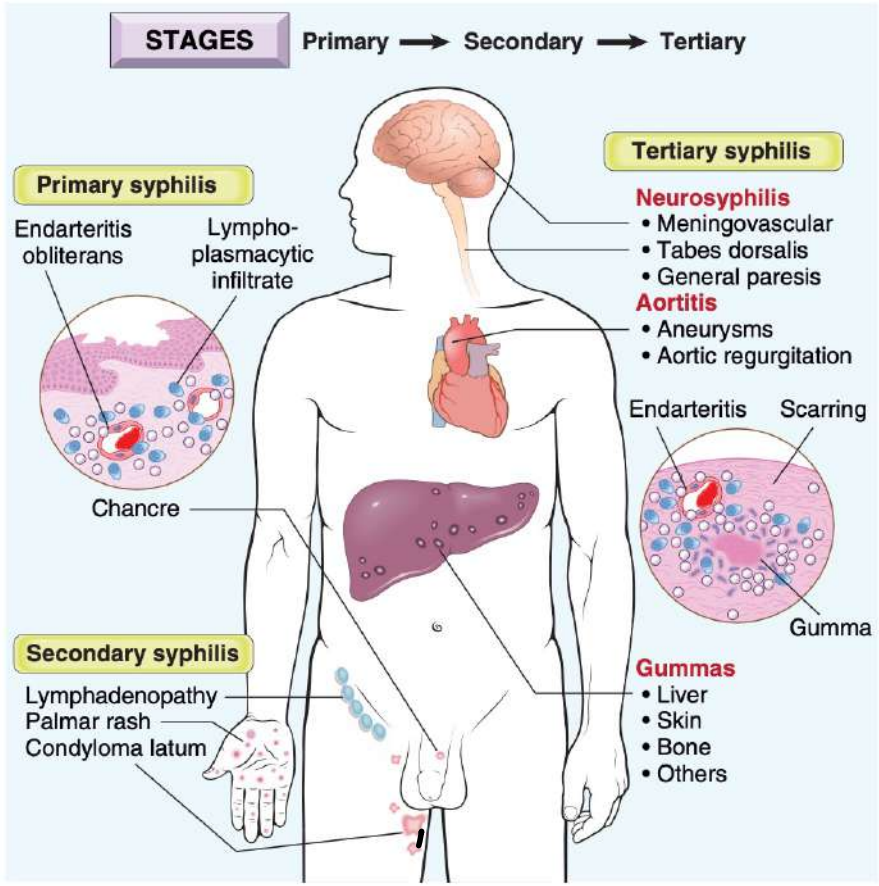
YST

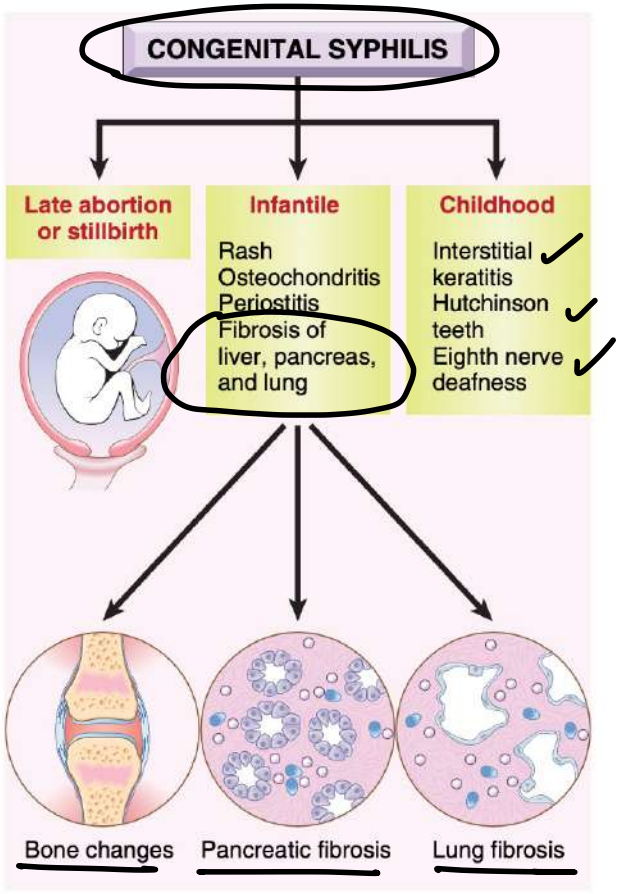


teratoma mature



test torsin





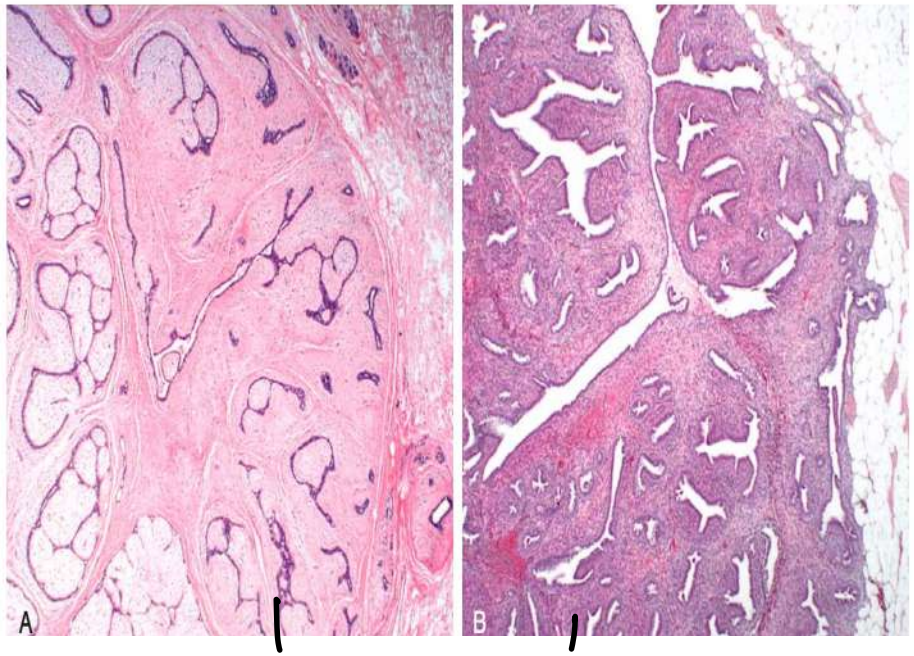
Neoplasm	Peak Incidence	Usual Location	Morphologic Features	Behavior
Germ Cell Origin				
Dysgerminoma	Second to third decade of life; associated with gonadal dysgenesis	Unilateral in 80%–90%	Counterpart of testicular seminoma; sheets or cords of large cells with clear cytoplasm; stroma may contain lymphocytes and granulomas	Malignant but only one-third metastasize; radiosensitive; 80% cure rate
Choriocarcinoma	First 3 decades of life	Unilateral	Identical to placental tumor; two types of cells: cytotrophoblast and syncytiotrophoblast	Metastasizes early and widely; elaborate hCG; resistant to chemotherapy
Sex Cord Tumors				
Granulosa cell tumor	Most postmenopausal, but may occur at any age	Unilateral	Composed of mixture of cuboidal granulosa cells and spindled or plump lipid-laden theca cells Granulosa elements may recapitulate ovarian follicles	May elaborate large amounts of estrogen; may be malignant (5%–25%)
Thecoma-fibroma	Any age	Unilateral	Plump yellow (lipid-laden) thecal cells admixed with fibroblasts	Most hormonally inactive; about 40% produce ascites and hydrothorax (Meigs syndrome); rarely malignant
Sertoli-Leydig cell tumor	All ages; peak 2nd to 3rd decades	Unilateral	Recapitulates development of testis with tubules or cords and plump pink Sertoli cells	Many masculinizing or defeminizing; rarely malignant
Metastases to Ovary				
	Older ages	Mostly bilateral	Anaplastic tumor cells, cords, glands, dispersed through fibrous background; mucin-secreting cells may be "signet ring	Primaries are gastrointestinal tract (Krukenberg tumors), breast, and lung; associated with pseudomyxoma peritonei

Table 17.1 Natural History of Squamous Intraepithelial Lesions (SILs)

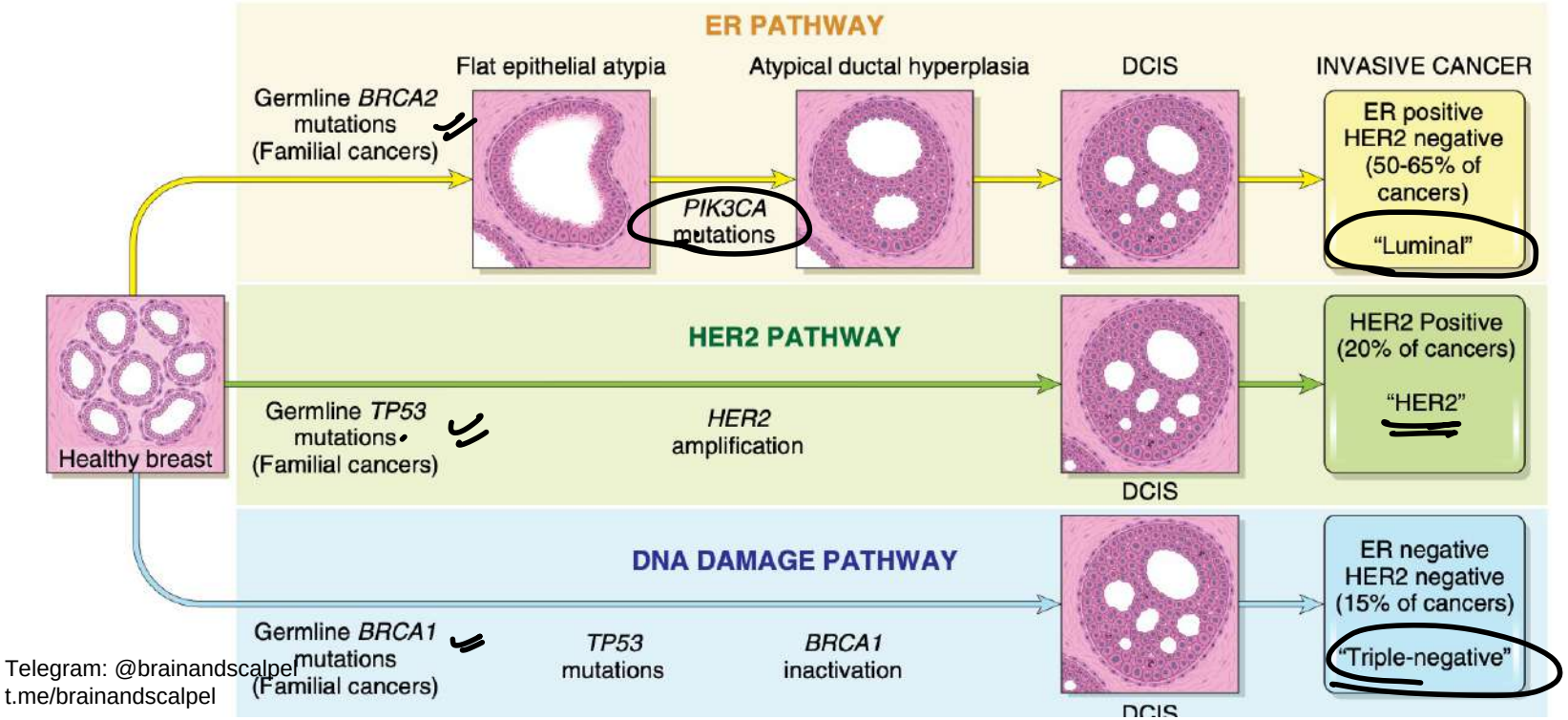
Lesion	Regress	Persist	Progress
LSIL (CIN I)	60%	30%	10% (to HSIL)
HSIL (CIN II, III)	30%	60%	10% (to carcinoma)[a]

Table 17.9 Most Common Single Gene Mutations Associated With Hereditary Susceptibility to Breast Cancer

Gene (Syndrome)	% of Single Gene Cancers[a]	Risk of Breast Cancer to Age 70[b]	Other Cancers	Comments
High Penetrance Germline Mutations				
BRCA1 (familial breast and ovarian cancer)	~55%	~40%–90%, females; 1%, males	Ovarian (~20%–40%), fallopian tube, pancreas, prostate, others	Majority of cancers are TNBC
BRCA2 (familial breast and ovarian cancer)	~35%	~30%–60%, females; 6%, males	Ovarian (~10%–20%), pancreas, prostate, others	Majority of cancers are ER positive. Biallelic mutations cause a form of Fanconi anemia.
TP53 (Li-Fraumeni)	<1%	~50%–60%, females; <1%, males	Sarcoma, leukemia, brain tumors, others	Majority of cancers are ER and HER2 positive
PTEN (Cowden)	<1%	~20%–80%, females; <1%, males	Thyroid, endometrium, others	Also associated with benign tumors
STK11 (Peutz-Jeghers)	<1%	~40%–60%, females	Ovarian, colon, pancreas, others	Also associated with benign colon polyps
CDH1 (hereditary diffuse gastric cancer)	<1%	~50%, females	Gastric signet ring cell carcinoma, colon	Majority of cancers are lobular in type
PALPB2 (hereditary breast cancer)	<1%	~30%–60%, females; <1%, males	Pancreas, prostate	Biallelic mutations cause a form of Fanconi anemia
Moderate Penetrance Germline Mutations				
ATM (ataxia-telangiectasia)	~5%	~15%–30%, females		Biallelic mutations cause ataxia-telangiectasia
CHEK2 (hereditary breast cancer)	~5%	~10%–30%, females	Prostate, thyroid, colon, kidney	Majority of cancers are ER positive



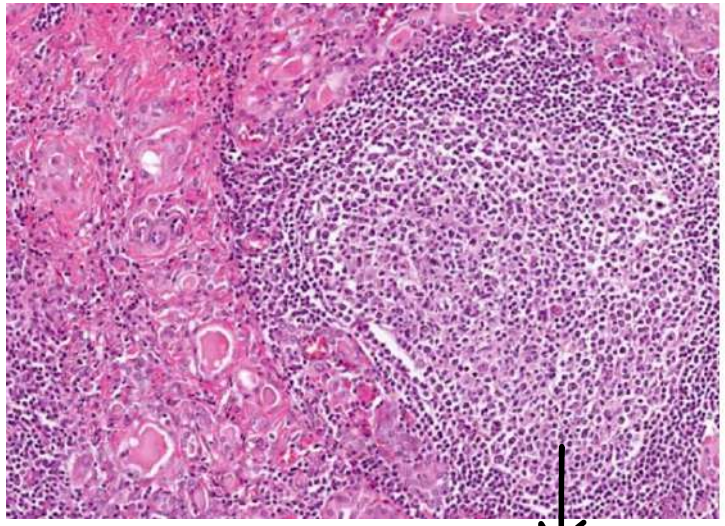
Feature	ER Positive/HER2 Negative: "Luminal"	HER2 Positive (ER Positive or Negative): "HER2"	Triple Negative (ER, PR, and HER2 Negative): "TNBC"
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline *BRCA2* mutation	Younger women; germline *TP53* mutation	Young women; germline *BRCA1* mutation carriers; African American women
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	~10%	ER positive (15%), ER negative (~30%–60%)	~30%
Timing of relapse	Low rate over many years; late recurrence possible (>10 years after diagnosis); long survival possible with bone metastases	Bimodal with early and late (10 years) peaks	Early peak at <8 years, late recurrence rare, survival with metastases rare
Metastatic sites	Bone (70%–80%), viscera (25%–30%), brain (~10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Common somatic mutations	*PIK3CA* (29%–45%), *TP53* (12%–29%)	*TP53* (70%–80%), *PIK3CA* (~40%)	*TP53* (70%–80%), *PIK3CA* (9%)



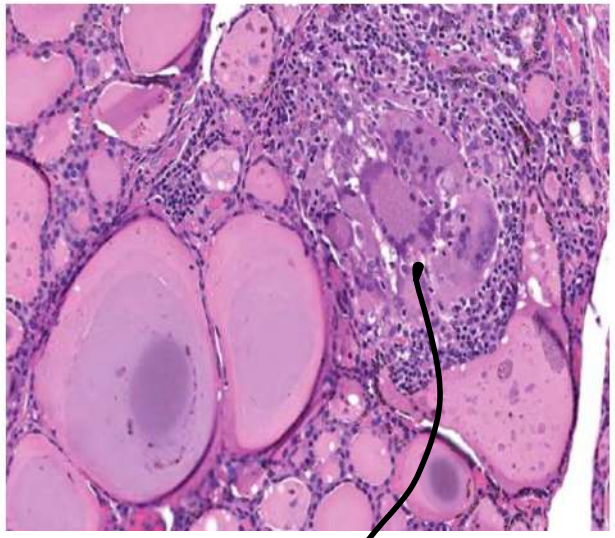
TNBC → BRCA 1
BRCA 2
Luminal → PIK3CA
her 2 + → p53

Table 18.3 Thyroiditis

	Hashimoto (Chronic Lymphocytic) Thyroiditis	Subacute Granulomatous (de Quervain) Thyroiditis	Painless Thyroiditis	Reidel Thyroiditis
Pathogenesis	Autoimmune response against thyroid antigens; destruction of the gland by CTLs and cytokine-mediated inflammation	Postulated to be viral infection or host response to a virus	Presumed autoimmune	IgG4-related disease
Histologic features	Prominent mononuclear inflammation, often with germinal centers; atrophic thyroid epithelium	Disrupted follicles; inflammation	Lymphocytic inflammation, sometimes with germinal centers	Extensive fibrosis with scattered lymphoplasmacytic infiltrate with IgG4-positive B cells
Clinical features	Painless diffuse enlargement of the thyroid; progressive hypothyroidism	Acute onset of neck pain, fever, variable thyroid enlargement, transient hypothyroidism	Painless neck mass, features of transient hyperthyroidism	Hard, fixed thyroid mass, usually euthyroid



germinal follicle



giant cells

GU tumors

Two other recently described MEN syndromes are MEN-4 and MEN-5. MEN-4 is characterized by inactivating germline mutations in the *CDKN1B* gene. Phenotypically, it mimics MEN-1. Germline mutation in the *MAX* tumor suppressor gene causes the MEN-5 syndrome. Patients with MEN-5 often develop bilateral pheochromocytomas and other tumors. Unlike MEN-2, medullary thyroid carcinomas and C-cell hyperplasia are not seen in MEN-5.

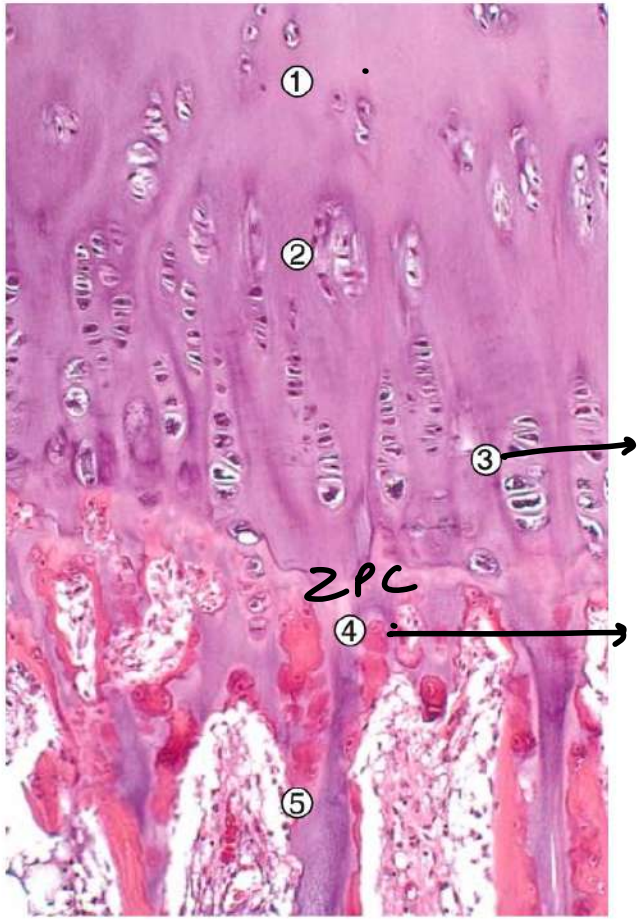


FIG. 19.3 Active growth plate with ongoing endochondral ossification. *1,* Reserve zone. *2,* Zone of proliferation. *3,* Zone of hypertrophy. *4,* Zone of apoptosis and mineralization. *5,* Primary spongiosa.

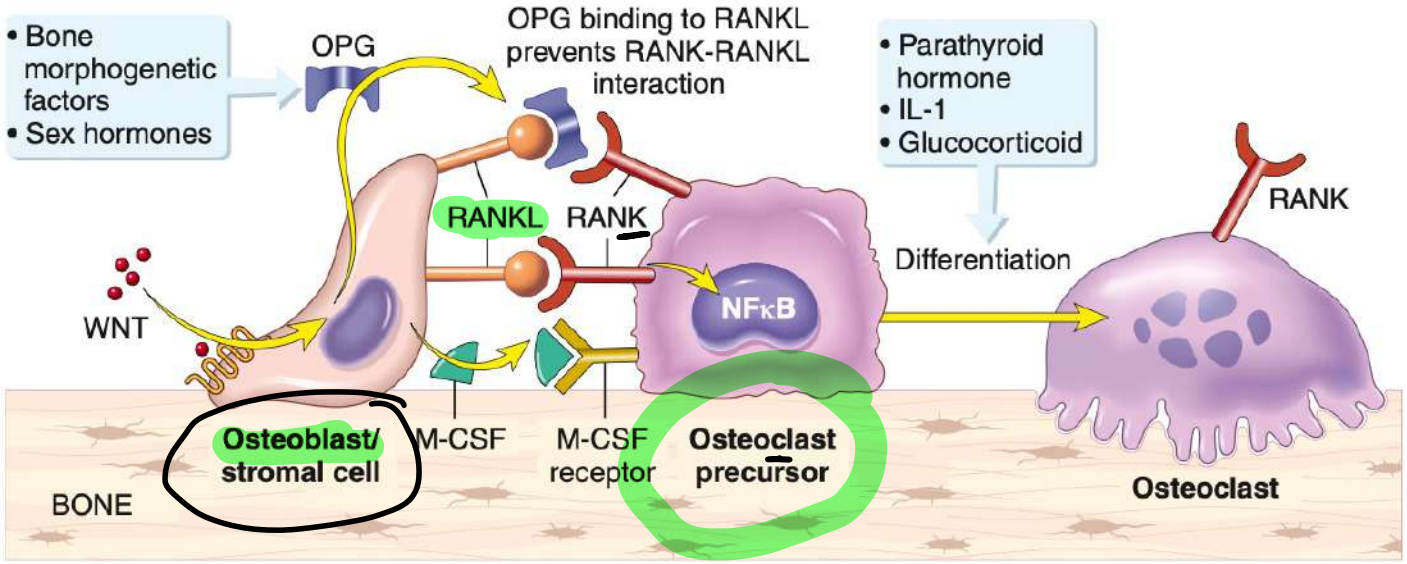


FIG. 19.4 Paracrine mechanisms that regulate osteoclast formation and function. Osteoclasts are derived from monocytes, the same cells that differentiate into macrophages. Osteoblast/stromal cell membrane-associated RANKL binds to its receptor RANK located on the cell surface of osteoclast precursors. Signals transduced by RANK and macrophage colony-stimulating factor (M-CSF) receptor cause the precursor cells to differentiate into functional osteoclasts. By contrast, WNT protein binding triggers stromal cells/osteoblasts to secrete osteoprotegerin (OPG), a "decoy" receptor that prevents RANKL from binding the RANK receptor. Consequently, OPG prevents bone resorption by inhibiting osteoclast differentiation. *IL-1,* Interleukin-1; *NFκB,* nuclear factor kappa-B; *RANK,* receptor activator of nuclear factor kappa-B; *RANKL,* receptor activator of nuclear factor kappa-B ligand.

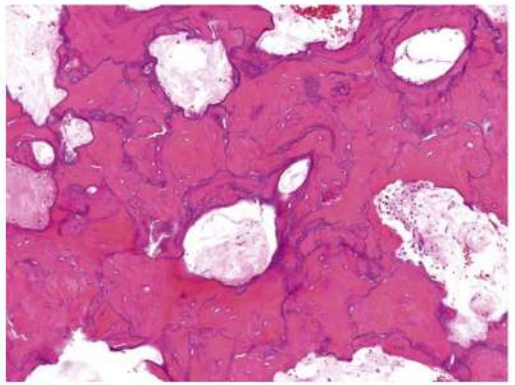
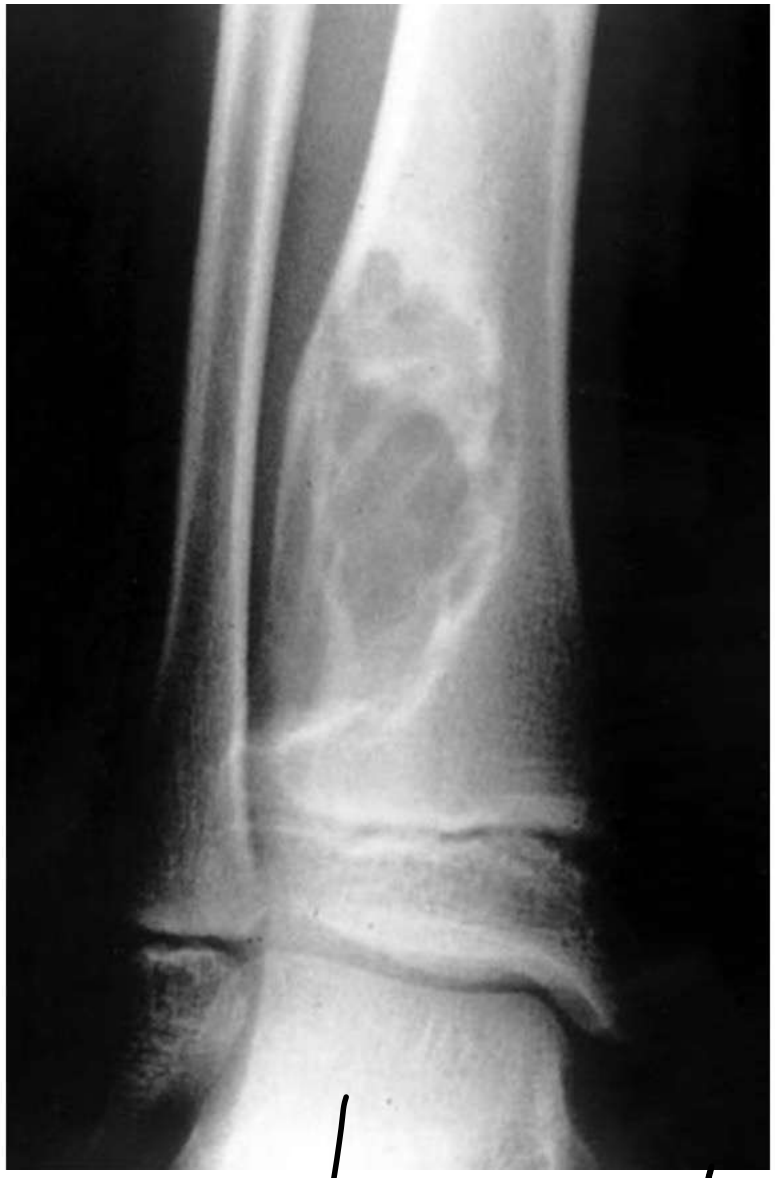
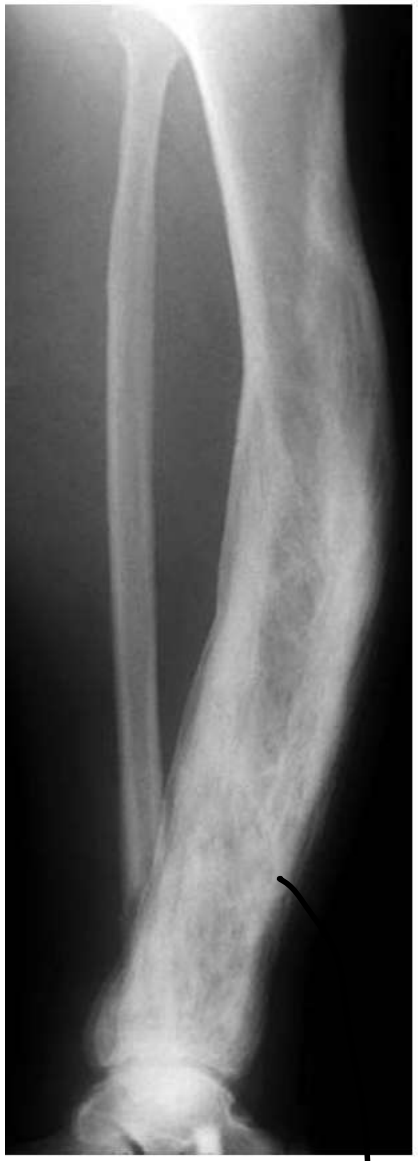


FIG. 19.10 Mosaic pattern of lamellar bone pathognomonic of Paget disease.

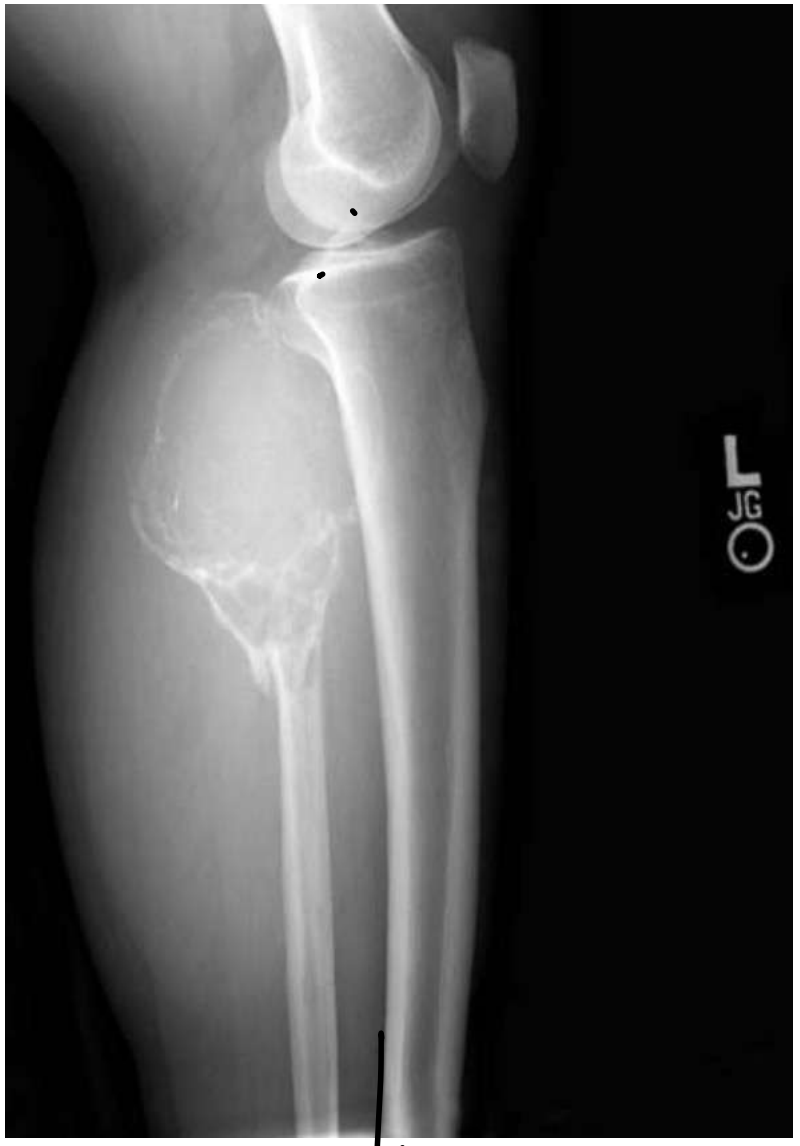


NOF
NF 1

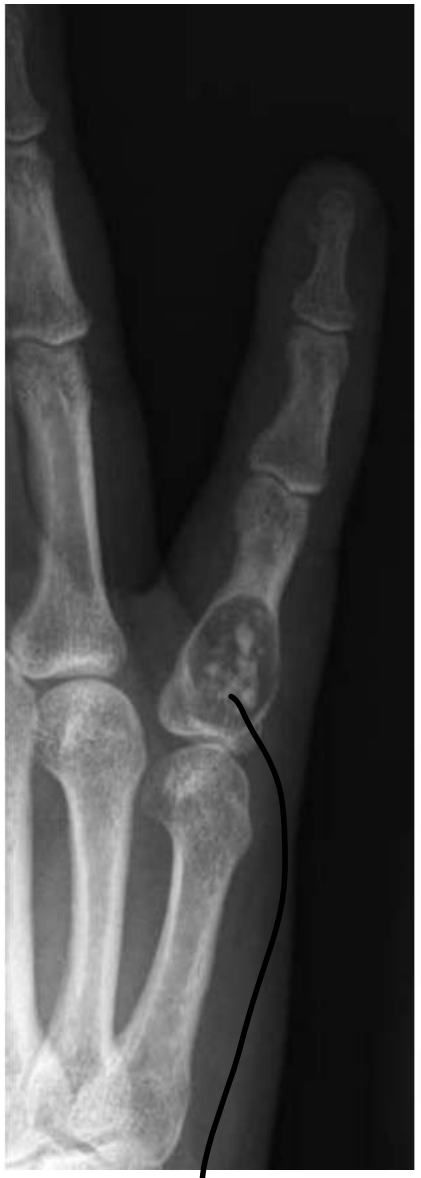


Non-ossifying fibroma

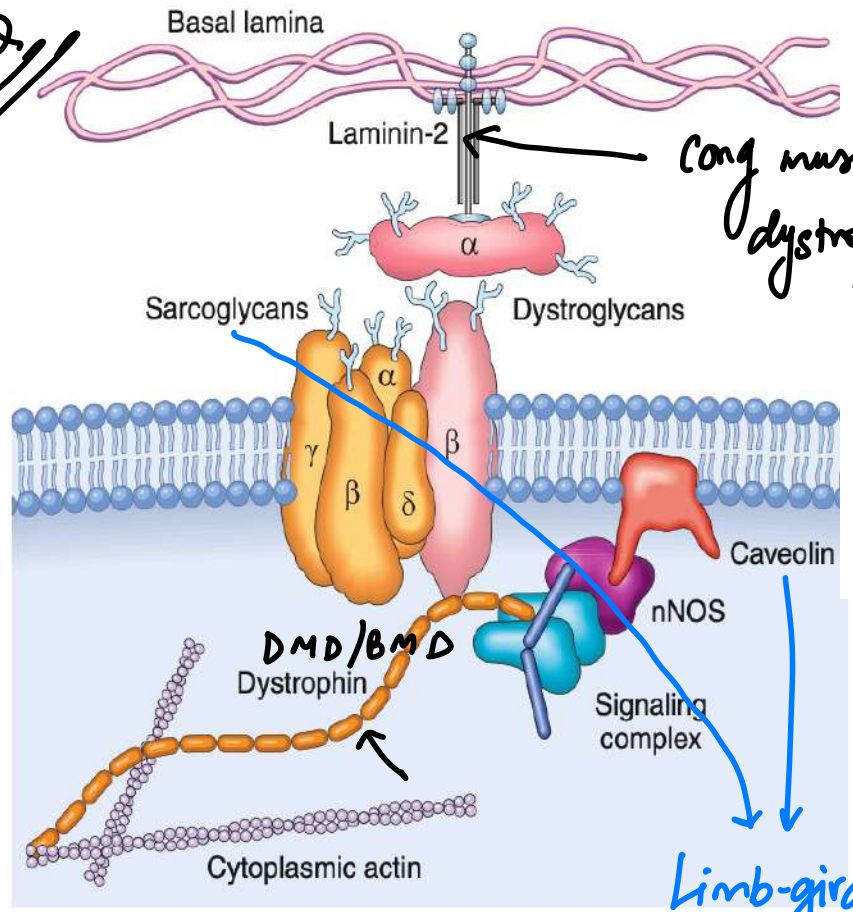
Paget's D

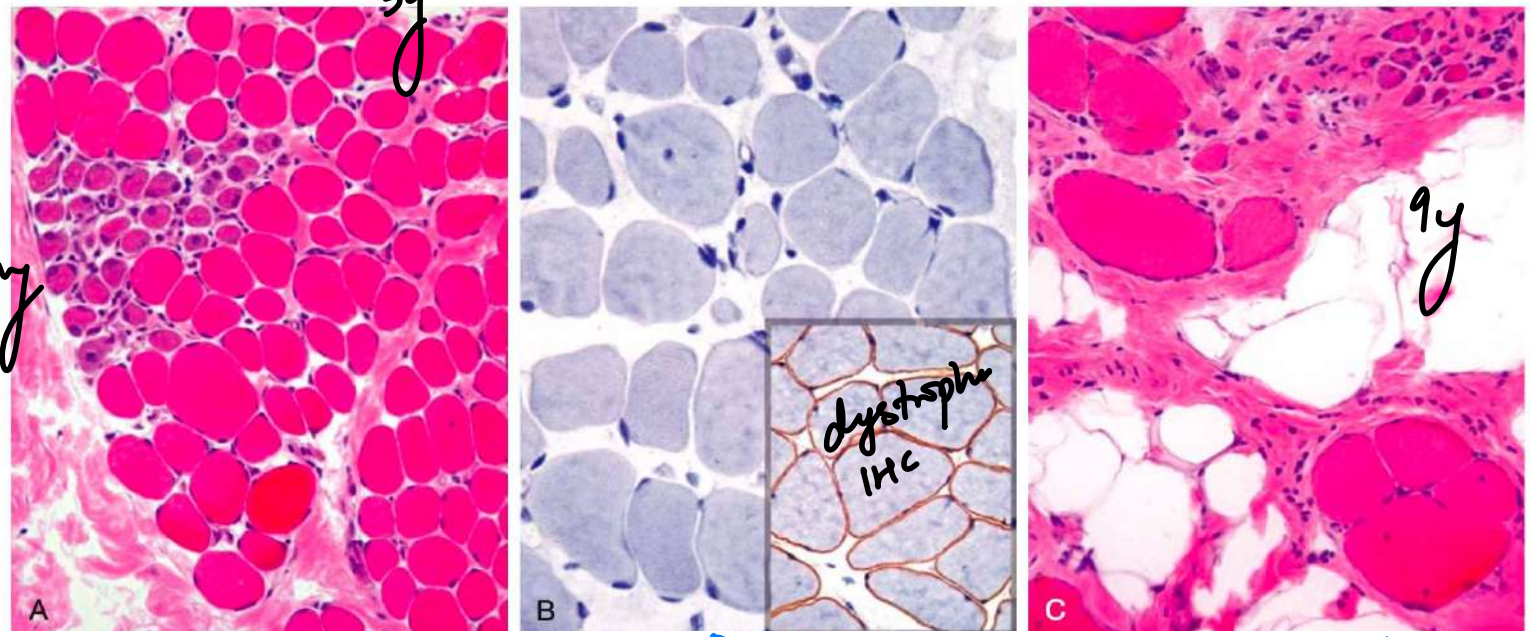


Epi - GCT



Enchander





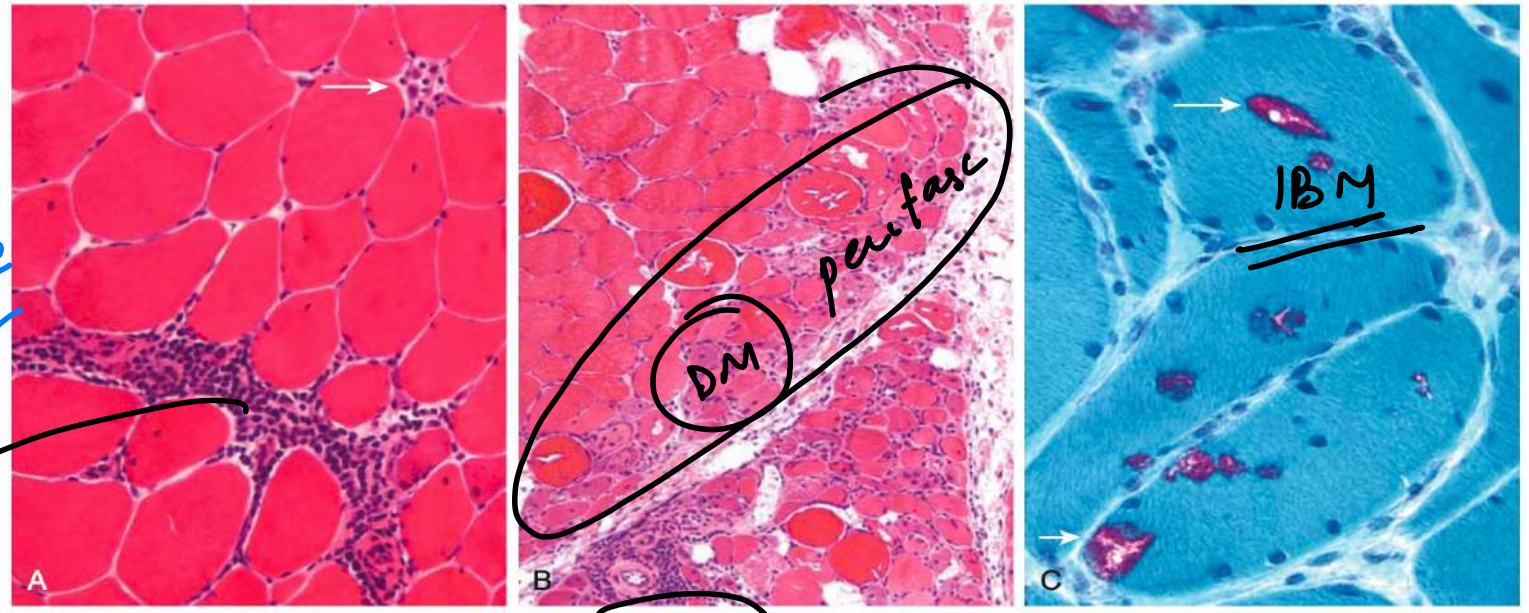
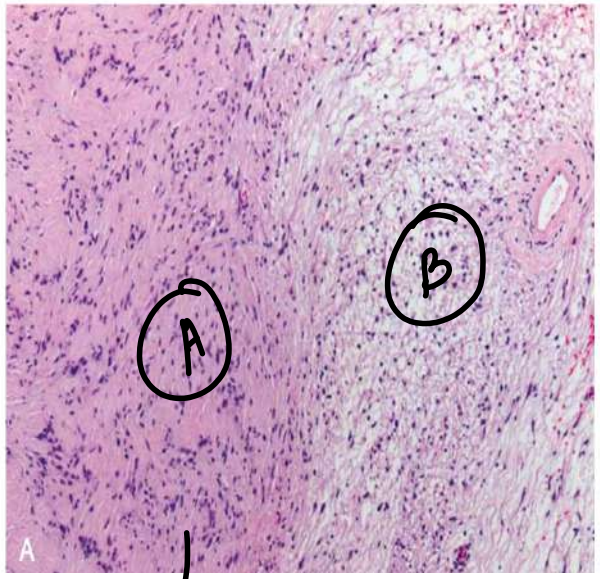
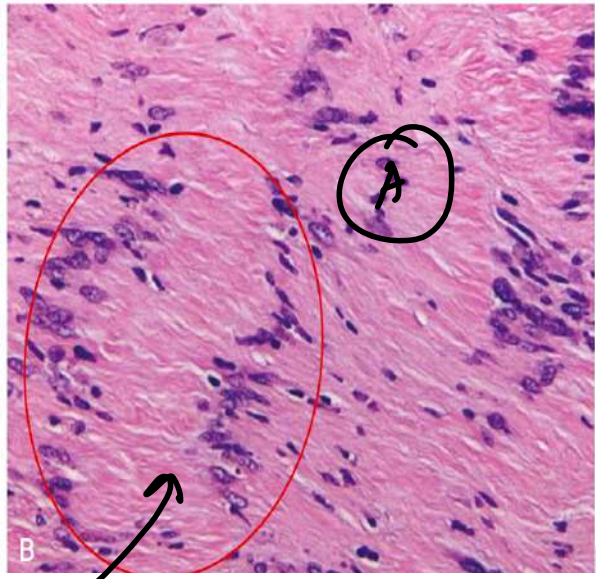
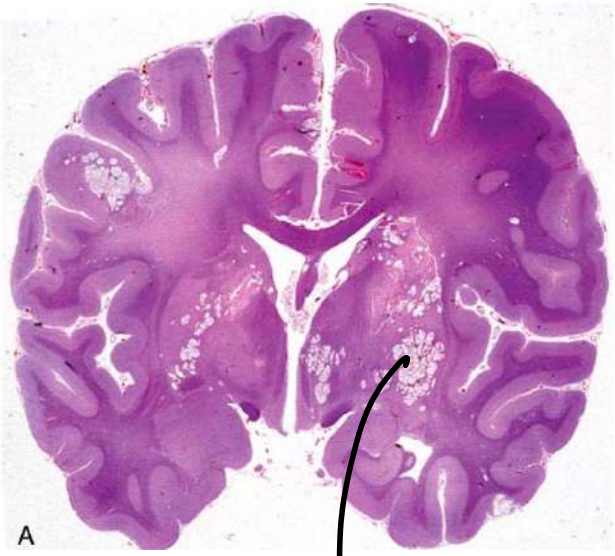
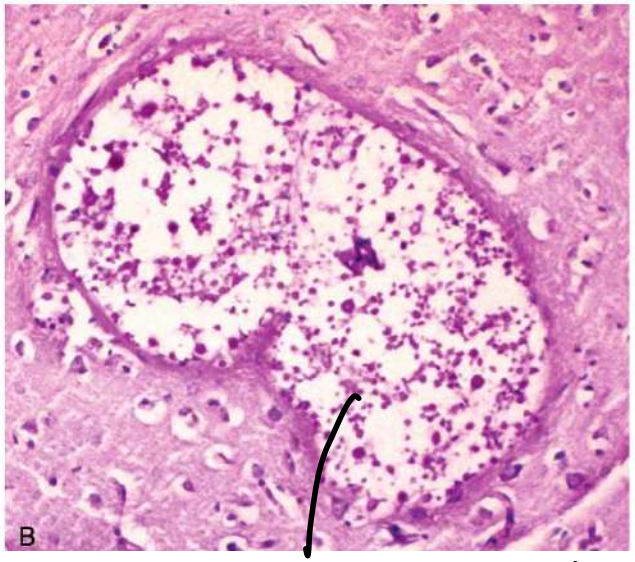


FIG. 20.5 Inflammatory myopathies. (A) Polymyositis is characterized by endomysial inflammatory infiltrates and myofiber necrosis *(arrow)*. (B) Dermatomyositis often shows prominent perifascicular and paraseptal atrophy. (C) Inclusion body myositis, showing myofibers containing rimmed vacuoles *(arrows)*. Modified Gomori trichrome stain.









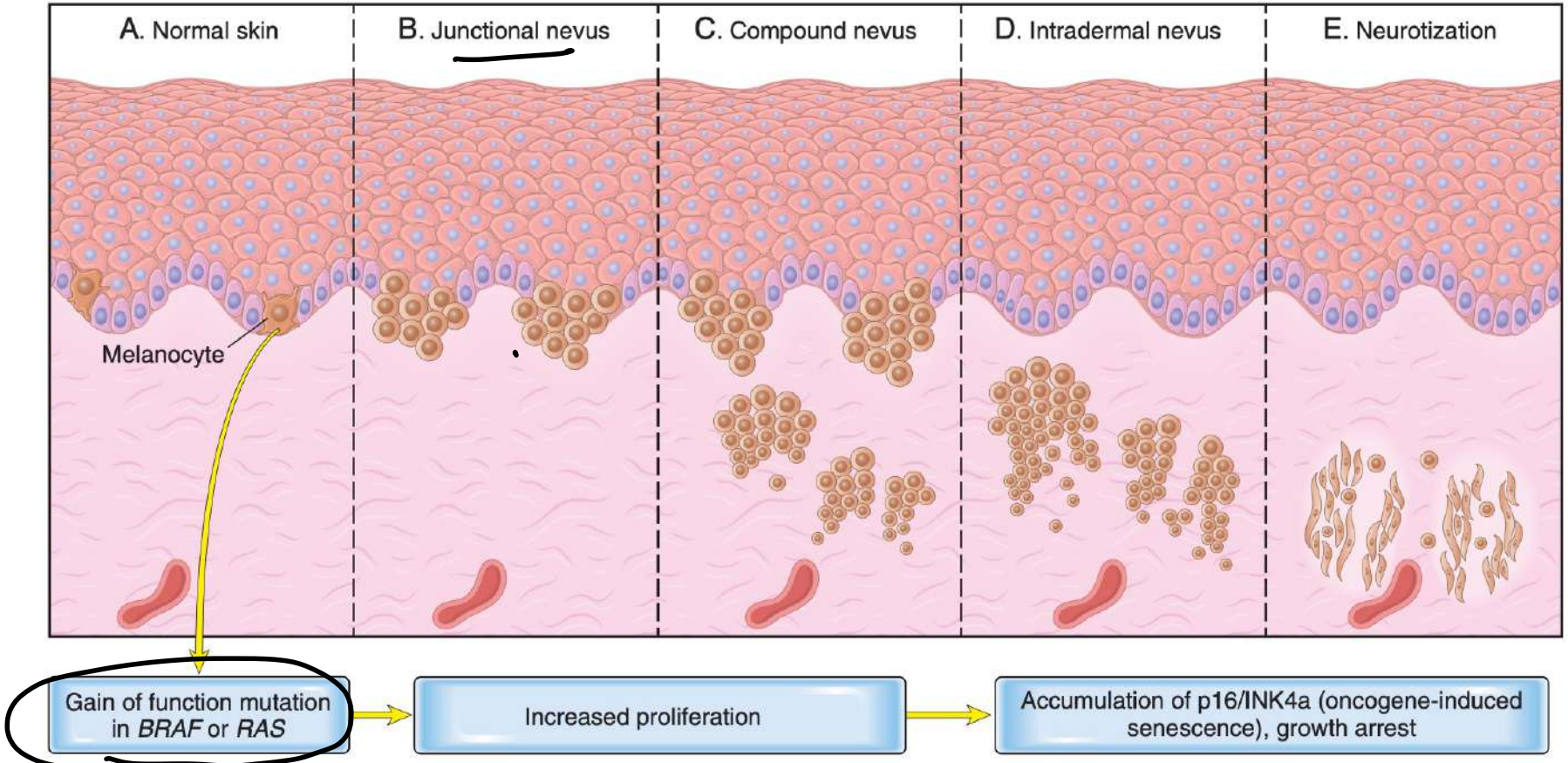


FIG. 22.18 Morphologic and molecular steps in the development of melanocytic nevi. (A) Normal skin uninvolved by nevi shows only scattered melanocytes. (B) An activating mutation in *BRAF* or *RAS* drives proliferation of junctional melanocytes, leading to the formation of a nevus. (C) Over time, nests of melanocytes may penetrate into the dermis, producing a compound nevus. (D, E). Subsequent accumulation of the tumor suppressor molecule p16 (also known as INK4a) appears to induce senescence, leading to permanent growth arrest and "maturation" of intradermal nevoid cells, a process referred to as "neurotization."