

→ Warthin Finkeldy Cell  
 ↓  
 Seen in measles

**Anaplasia: Lack of Differentiation**

↳ **Hallmark of malignancy**

↓  
**Morphologic changes:** • Pleomorphism (Shape & Size)

• Abnormal Nuclear changes

N:c ratio → (1:1) ↓

(1:4 Normal)

- Atypical mitosis
- Loss of polarity of the cell → disorganized cells
- Central Necrosis

Difference Between

## Anaplasia & Neoplasia

### Anaplasia

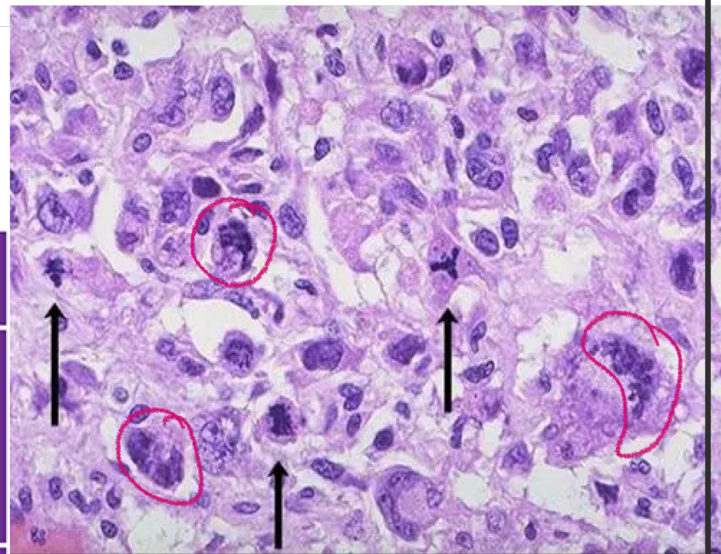
Cells loss of ability to be specialized in nature and function as a specialized tissue, leading to unpredictability.

- Brain
- Brain lining
- Thyroid
- Blood and skin

### Neoplasia

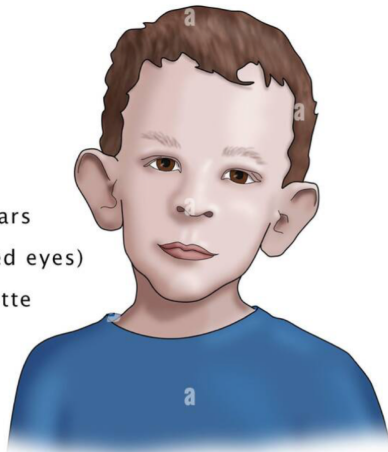
New cell growth coupled with mutations that result in cells growing continuously and/or cells not dying when they usually would

- Breast
- Lymph nodes
- Skin



# FRAGILE X SYNDROME

- Broad forehead
- Elongated face
- Large prominent ears
- Strabismus (crossed eyes)
- Highly arched palette



- Hyperextensible Joints
- Hand calluses
- Pectus Excavatum (indentation of chest)
- Mitral valve prolapse
- Hypotonia (low muscle tone)
- Soft, fleshy skin
- Enlarged testicles
- Flat feet
- Seizures in 10%

- C/f: • Mental Retardation  
(2nd m/c/c of Mental Retardation)  
(m/c → Down's Syndrome)
- Long faces, Large ears, Large Mandible
  - Macro-orchidism (large testes) (most characteristic feature)

Δsis: • Southern Blotting  
• PCR [IOC]

Mnemonic:

↓  
South - Dosa  
North - Roti  
West - Pizza

Southern → DNA Blotting

Northern → RNA Blotting

Western → Protein Blotting

[CGG] repeat — Normal < 55

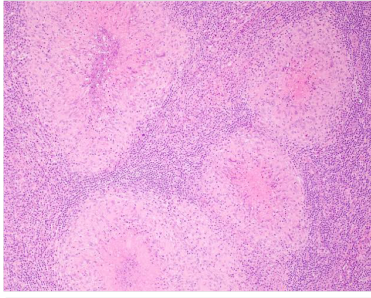
— Fragile X-Tremor/Ataxia: 55-200 pre mutation

— Fragile X syndrome: 200-4000 Full mutation

Sherman's Paradox / Anticipation

- Repeat will increase with each passing generation.
- Disease will " " " " " "
- Severity ↑↑

## Stellate Granuloma: Cat scratch Disease



↓  
Self Limited Lymphadenitis caused by *Bartonella Henselae*  
↓  
Transmitted by Cats

Opsonisation: Adding opsonin to bacteria (Makes WBC to eat Bacteria quickly)

↓  
[Not a mandatory Step]

↓  
an antibody or other substance which binds to foreign micro-organisms or cells making them more susceptible to phagocytosis.

Molecules of opsonin: IgG → M/I opsonin

- C3b, C4b, C5b
  - Plasma protein - Fibrinogen, Fibronectin.
- M/I complement opsonin

## Hemochromatosis: Iron overload

↓  
• Defect in HFE gene on chr 6

C/F: infertility  
Liver cirrhosis (CM/C)  
Diabetes (↓ insulin)  
Bronze pigmentation of skin

Δsis: Liver Biopsy: Prussian blue / Perl's stain

TOC - Phlebotomy

DOC - Iron chelator e.g. Desferrioxamine

### Triad of hemochromatosis

Micronodular cirrhosis (most common)



Diabetes mellitus



Bronzing of skin

Triad of hemochromatosis

**Apoptosis** is a programmed cell death.

- Not after inflammation
- Active process: ATP used
- Caspase dependent programmed cell death.
- Can be physiological as well as pathological

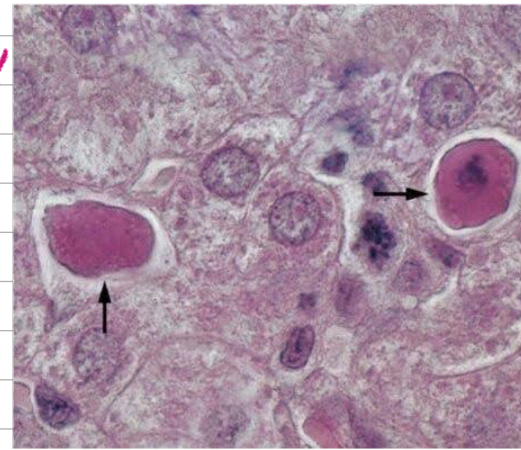
Neurons don't have Caspases

- e.g.
- Embryogenesis
  - Organogenesis

• Viral Hepatitis → Councilman Bodies

• chemotherapy induced cancer cell death

(apoptosis >> Necrosis)



**Caspases**

Initiators

Executors

8, 9, 10

3, 6, 7

Not involved in Human Apoptosis

Most important

**Extrinsic pathway**

**Intrinsic pathway**

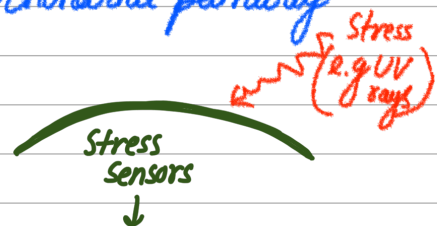
- The Death Receptor pathway
- activates 8, 10

mitochondrial pathway

• Trimerisation occurs here.

Brings FADD with them  
↳ Fas associated Death Domain.

Procaspase 8, 10  
↳ Caspase 8, 10



BIM, NOXA, BID, PUMA, BAD } gets activated

↑ Proapoptotic factors

↓ anti-apoptotic factors

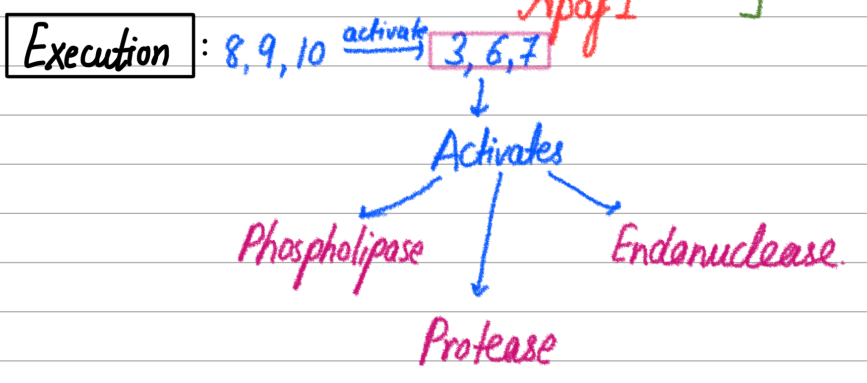
- P53
- Bax
- Bax
- Bcl X5

- BCL2
- Mcl1
- BCL XL

• Glucocorticoids are proapoptotic

• Sex steroids are anti-apoptotic

Mitochondria  $\xrightarrow{\text{releases}}$  Cytochrome C + Apaf1  $\rightarrow$  Apoptosome (Wheel-like hexamer)



Apoptotic Bodies: Cell membrane bound organelles with nucleus or without nucleus

• Phosphatidylserine movement from inside to out

↓

Eat me signal to macrophage

Note: Endonuclease cut at 180-200 base pairs (or break)

↓

Internucleosomal cleavage

↓

Stepladder pattern

Detection of Apoptosis:

- Marker  $\rightarrow$  Annexin V
  - Molecular Marker  $\rightarrow$  CD95 / FAS
  - M/E  $\rightarrow$  Nuclear chromatin condensation
- ↓
- Hallmark of Apoptosis

Anexin A1  $\rightarrow$  Hairy cell Leukemia

• TUNEL stain: +ve Positive - Apoptosis  
-ve Negative - Necrosis

• Gel electrophoresis  $\rightarrow$  we see Stepladder pattern  $\leftarrow$  Apoptosis  
Smearing pattern  $\leftarrow$  Necrosis

## Kawasaki disease

- Medium vessel vasculitis.
- m/c vasculitis of childhood in india.
- Age group : < 5 years
- Etiology : Idiopathic / unknown.

## Signs & Symptoms of Kawasaki Disease



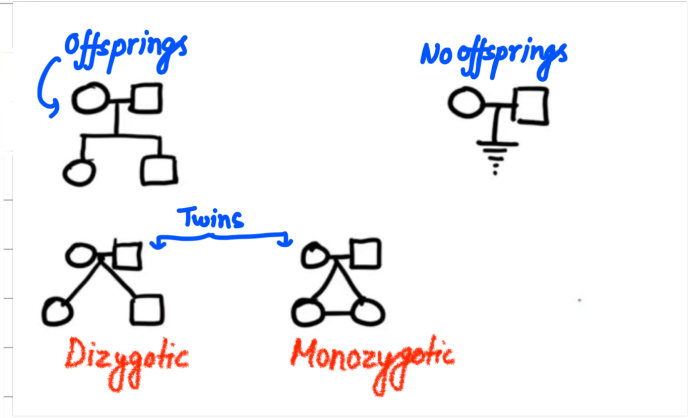
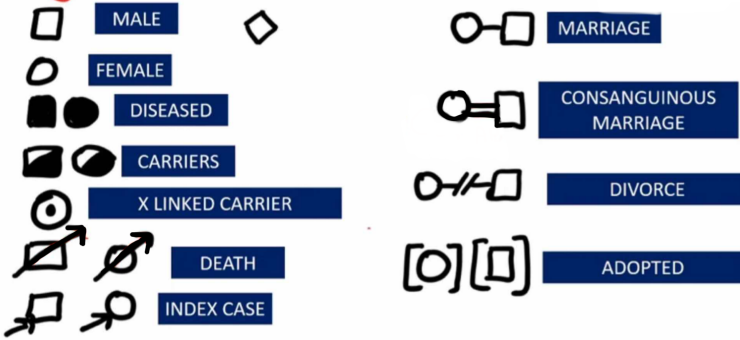
Images courtesy of the Kawasaki Foundation

### Three phases :

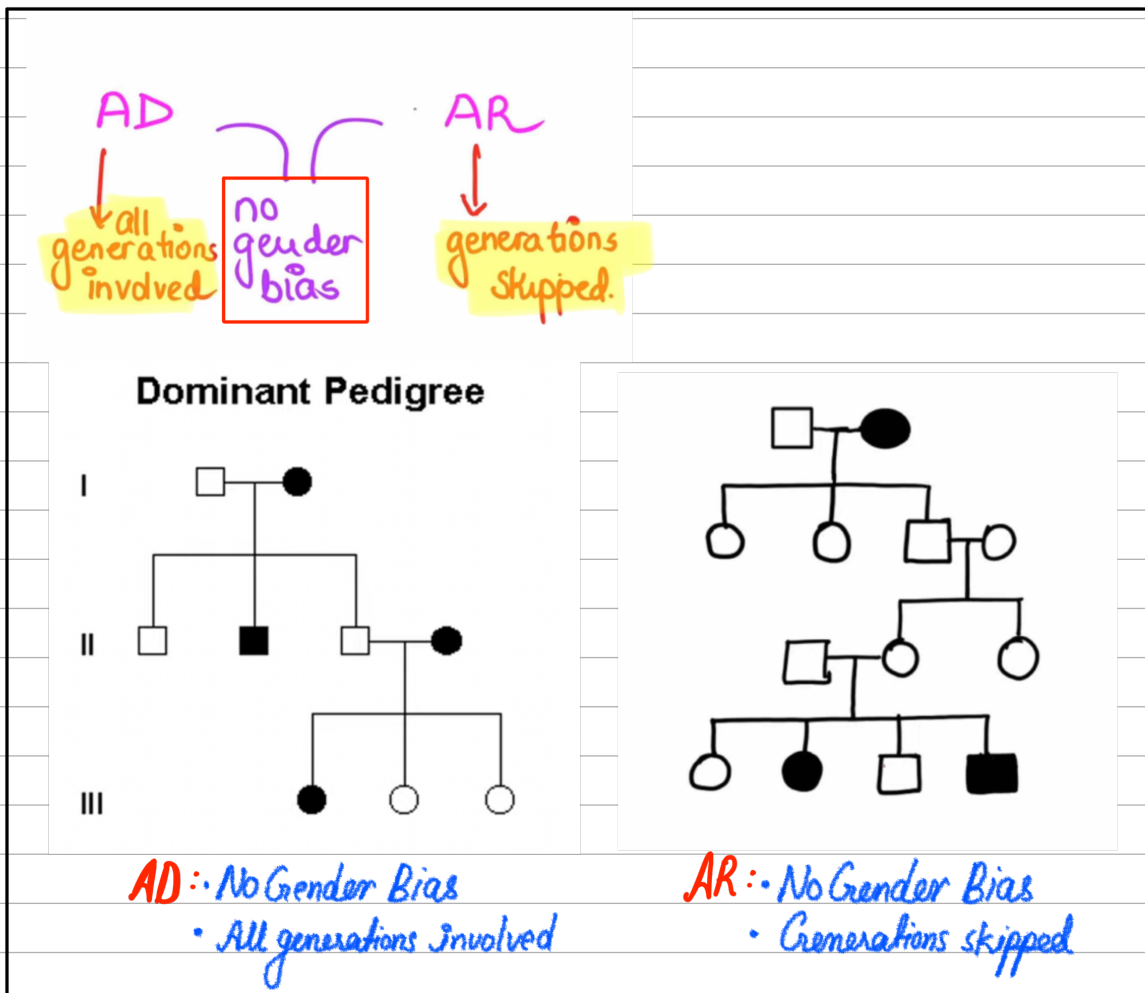
	Acute phase	Subacute phase	Convalescent / Recovery Phase
Duration	1-2 weeks	3-4 week	6-8 wks
Feature	Prolonged fever > 5 days <u>Other manifestation</u> ↓ Conjunctivitis - B/L, non purulent Rash - Non-specific, maculopapular rash Extremities - Erythema of edema, Periungual desquamation Adenopathy - Lymphadenopathy usually single, cervical Mucosal - involvement: Cheilitis/glossitis (strawberry tongue)	• Periungual desquamation (peeling of the nails) • Thrombocytosis	Recovery from illness.
Complications:	Acute: Myocarditis (50-70%)	Subacute: Coronary Aneurysm (20-30%)	Risk of mortality due to thrombosis & rupture.
Rx:	DOC: IVIG: 2g/kg infusion	• High dose aspirin (80-100 mg/kg)	• Anti-inflammatory • Low Dose Aspirine (3-5mg/kg/day) continued till 6-8 wks

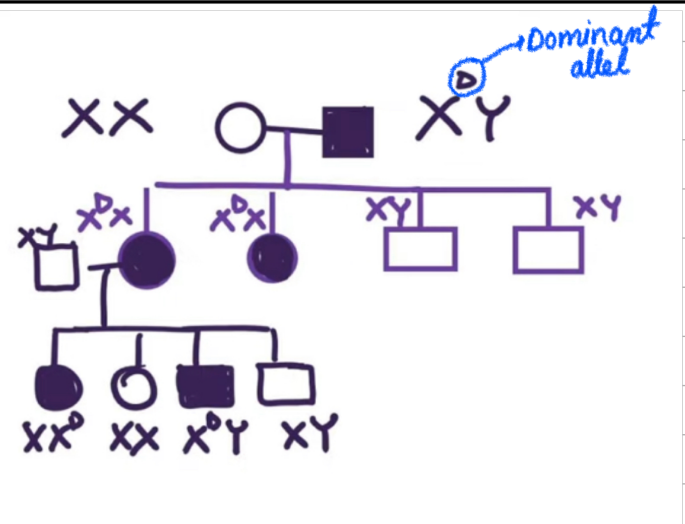
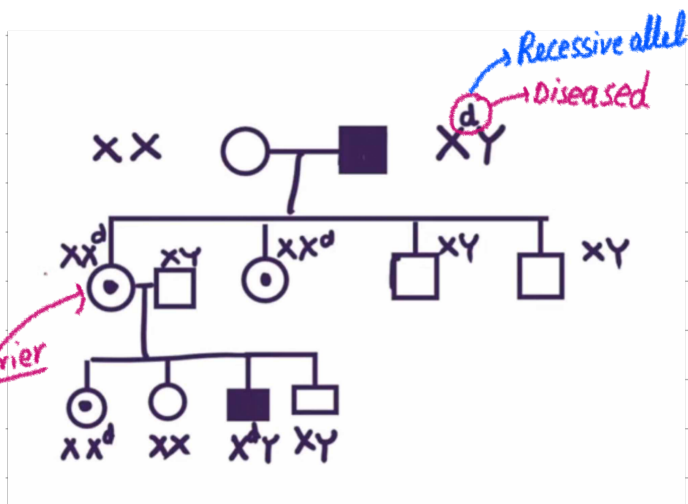
# Pedigree chart Analysis

## Symbols



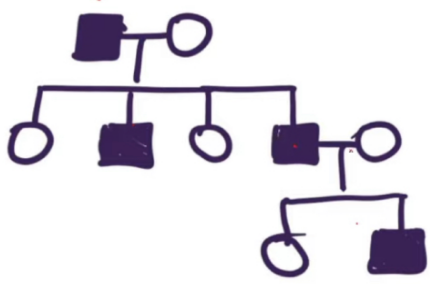
Mendelian disorders : AD  
 AR  
 XLR  
 XLD  
 Y-linked/Holandric disorders





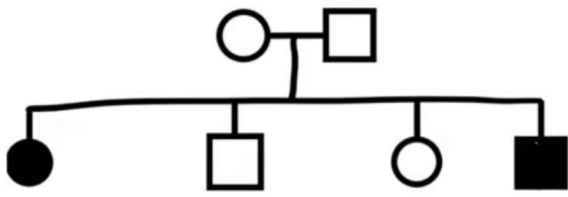
**X-LR** :: Females are carriers  
 • Usually males are diseased

**XLD** :: No Gender Bias  
 • Father gives disease to all the daughters



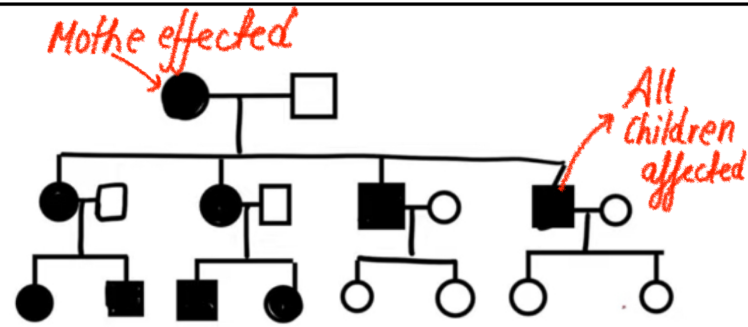
**Y Linked / Holandric inheritance**  
 • Father to son  
 • All males affected

**Non-Mendelian Disorders** :: Gonadal Mosaicism  
 ↳ aka Germline Mosaicism.  
 • Mitochondrial inheritance



### Gonadal Mosaicism: aka Germline Mosaicism

- Both parents are normal
- Variable Numbers of kids affected
- No Gender Bias
- Post Zygotic Mutation.
- Seen in:
  - Osteogenesis imperfecta
  - Tuberous Sclerosis.



### Mitochondrial inheritance:

- Mother affected
- All children affected.
- Female offspring transmits the disease further
- Male offspring Do not transmit the disease further

Sickle cell anemia → AR, point mutation → Missense mutation

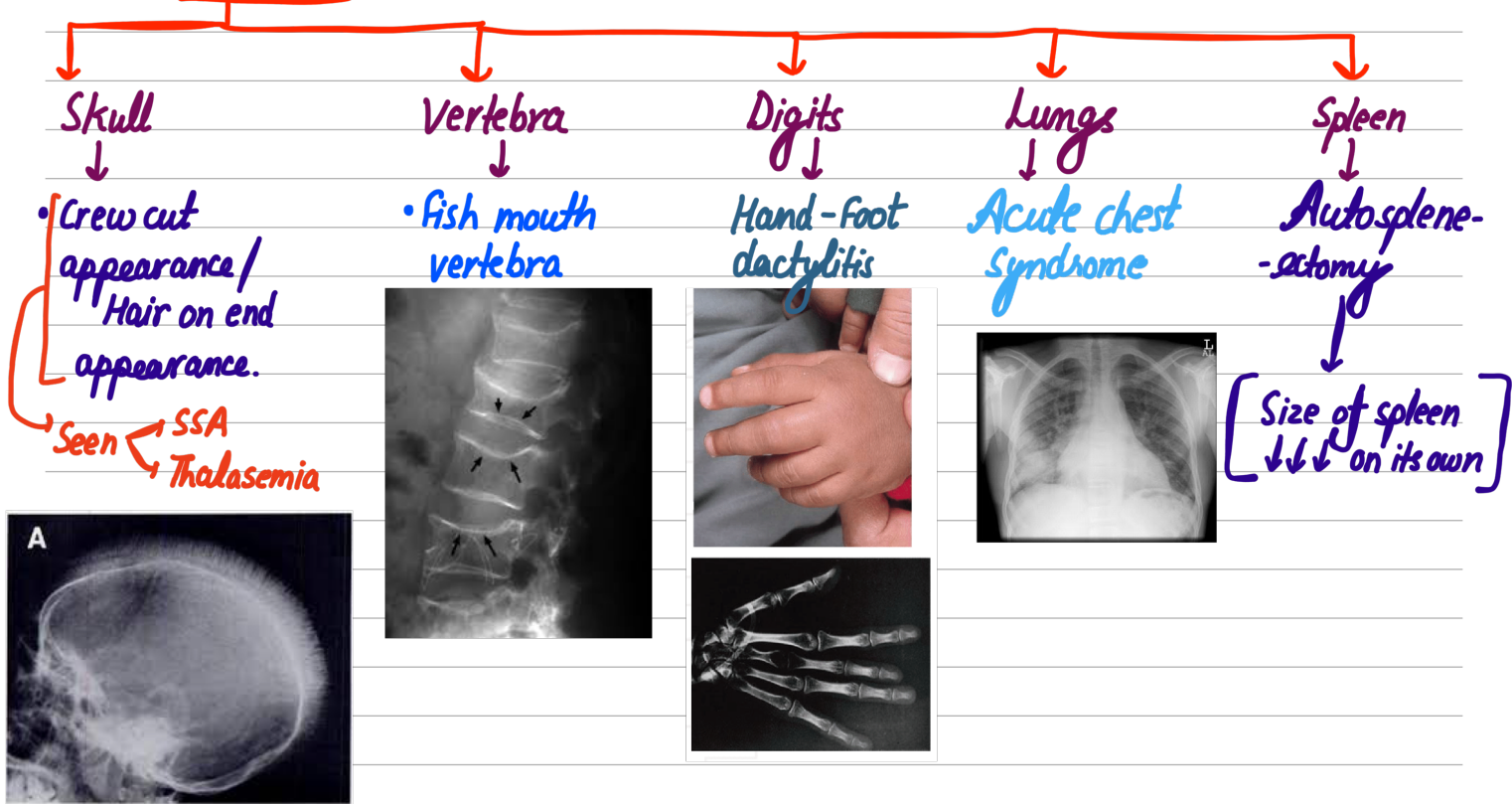
B<sub>6</sub> → Glutamic acid → (Glutamate G<sup>-</sup>O)  
 ↓ Replaced by  
 Valine → (Valine Welcome)

Hb A ⇌ Hb S  
 Sickly Sticky → all cells starts sticking to each other  
 Solubility ↓  
 ↓  
 Occlude Blood vessels

HbAA - Adult Hb
HbAS - Sickle cell carrier
HbSS - Sickle cell anemia

Features:

1. Vaso-occlusive crisis:



2. Sequestration crisis → all sickle cells sequestered in spleen.

3. Aplastic crisis → d/t parvovirus B19 (BM suppression)

RBC  
 WBC  
 Platelets } → ↓↓

Δsis →

1. P/S: sickled RBC
2. Sickling test → uses 2% Na<sup>+</sup> Meta-Bisulphite
3. ESR ↓
4. Hb electrophoresis
5. HPLC - High Performance Liquid chromatography. (Gold standard)

Rx: ↑O<sub>2</sub> → give drug i.e. Hydroxy-urea (↑↑ HbF)

# Cardiomyopathy

## Dilated Cardiomyopathy

- All 4 chambers are dilated
- Cause - idiopathic - Alcoholism - a/w Titin protein Defect

Largest protein in our body ~ 3000 AA

## Takotsubo Cardiomyopathy

- Broken Heart Syndrome
- Stress → ↑ Catecholamines
- Left ventricular enlargement

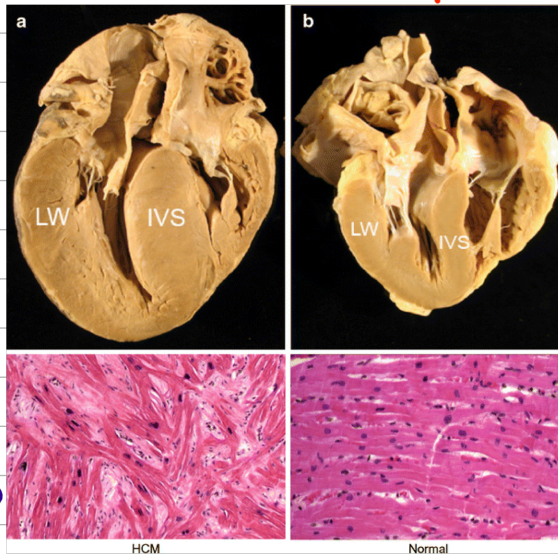
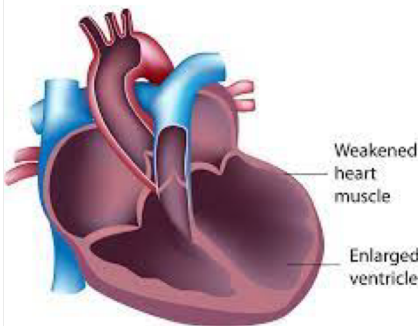
m/c/c of sudden death in young athletes → Hypertrophic myopathy

- Hypertrophy of Intra-ventricular Septum
- Left vent. Narrow
- Banana shaped Heart
- Mutation:  $\beta$ -myosin heavy chain (β-MHC)

## Restrictive myopathy

- Seen in dia-stole
- Diastolic function is affected
- M/C/C of Restri. Myopa-thy → Amyloid

Dilated cardiomyopathy



M/E → Helter skelter arrangement of muscle fibers.

Restrictive Cardiomyopathy

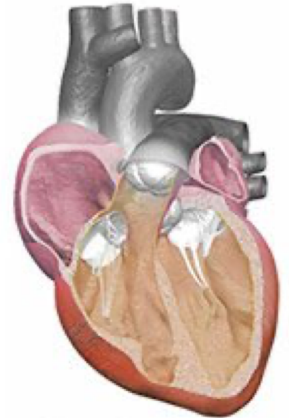


image courtesy of Medtronic

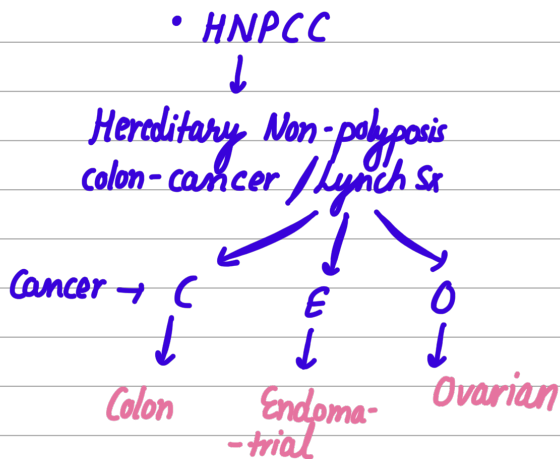
# DNA Repair defect



## NER Defect:

- Xeroderma Pigmentosa

## MMR Defect:



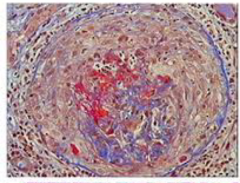
## HR defect:

- Fanconi Anemia
- Blood Sr
- Ataxia Telangiectasia

a/w chr11q 22

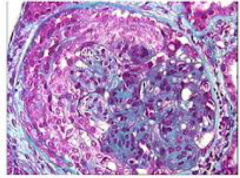
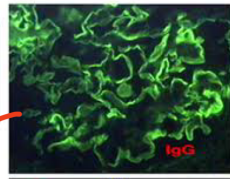
# RPGN / Crescentic GN :

Rapidly progressive glomerulonephritis



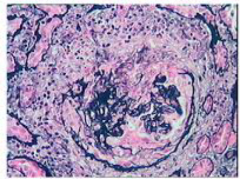
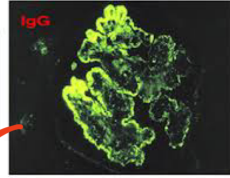
**TYPE 1**  
Anti-GBM (linear IF)  
- with alveolar haemorrhage (Goodpasture)  
- without alveolar haemorrhage (anti-GBM GN)

Linear



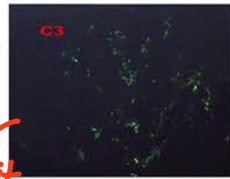
**TYPE 2**  
Immune-complexes (granular IF)  
- post-infective (post-streptococcal)  
- secondary to SLE, HSP, Cryo  
- complicating primary GN  
- Idiopathic

Granular



**TYPE 3**  
ANCA (pauci-immune)  
- Wegener's granulomatosis  
- microscopic polyangiitis  
- renal limited vasculitis  
- Churg-Strauss syndrome

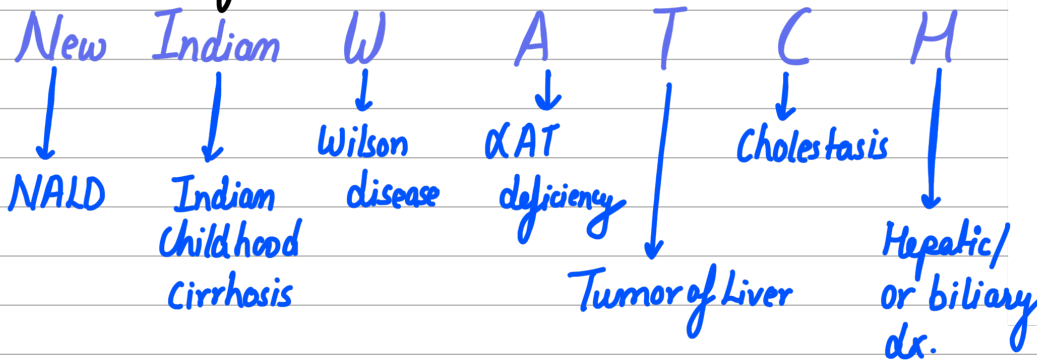
No deposit



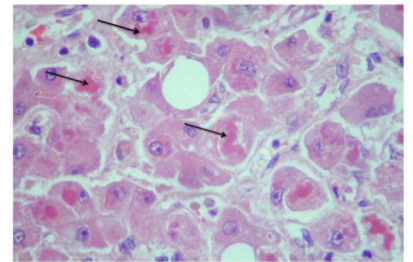
**CRESCENT** - F = FIBRIN  
L = Leukocytes  
P = Parietal epi cell >>> visceral epi cell

↑ No. of crescent worse prog.

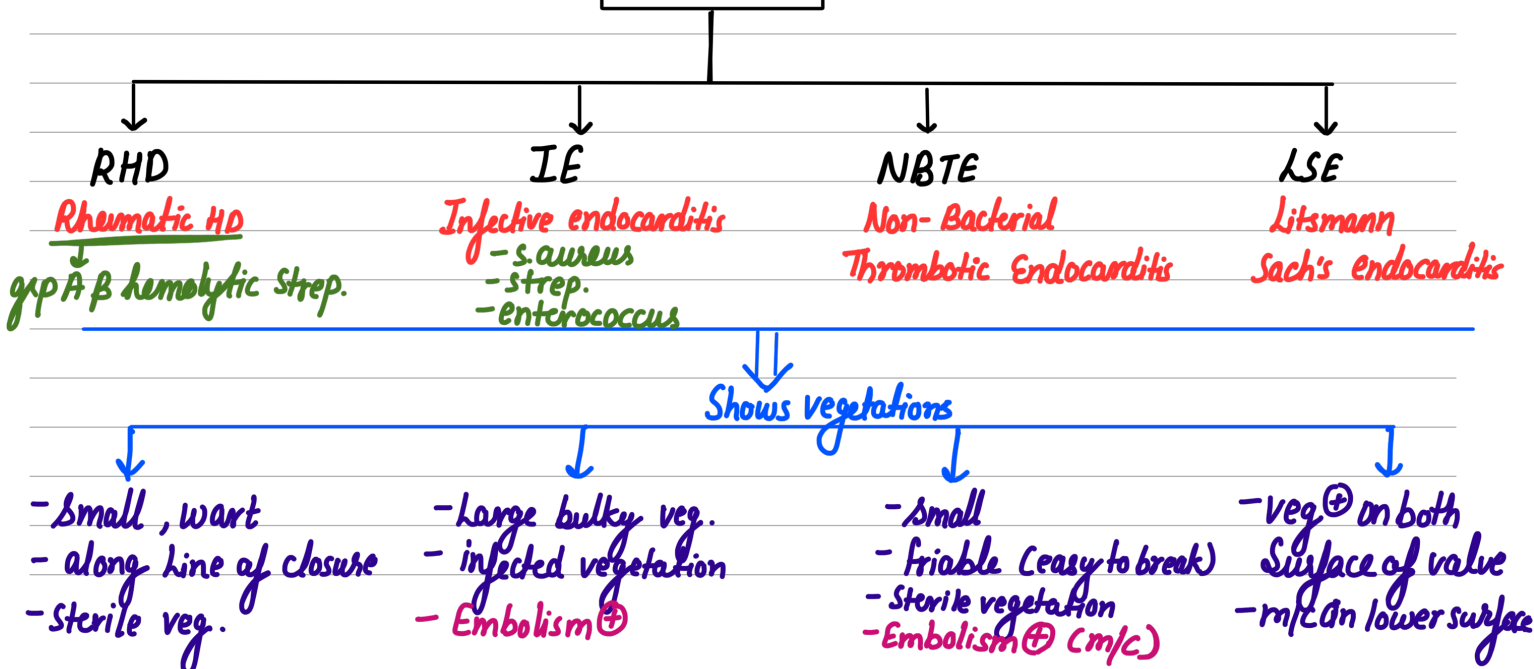
## Mallory Heyaline / Denk Bodies



Mallory-Denk bodies



## Endocarditis

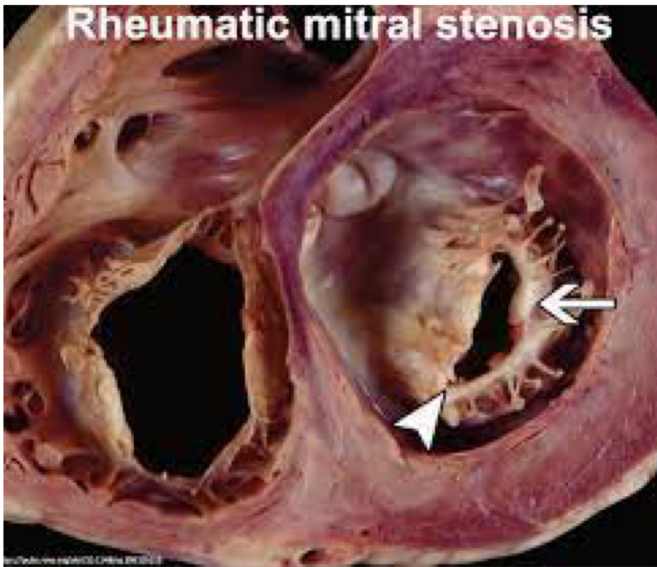


# Jones Criteria for Rheumatic Fever

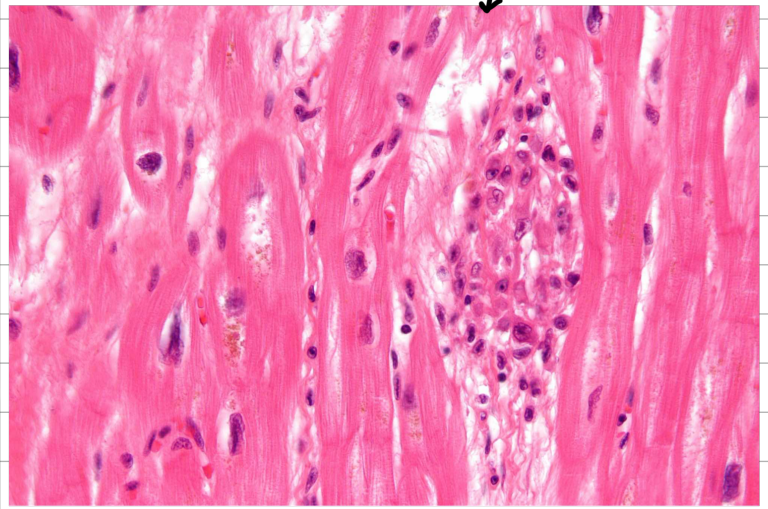
Major Criteria	Minor Criteria
Pancarditis (pericarditis, endocarditis, myocarditis)	Fever
Polyarthritits	Arthralgia
Sydenham Chorea	Prolonged PR interval
Subcutaneous Nodules	Increased ESR or CRP*
Erythema marginatum	Leukocytosis

\*Erythrocyte sedimentation rate or c-reactive protein

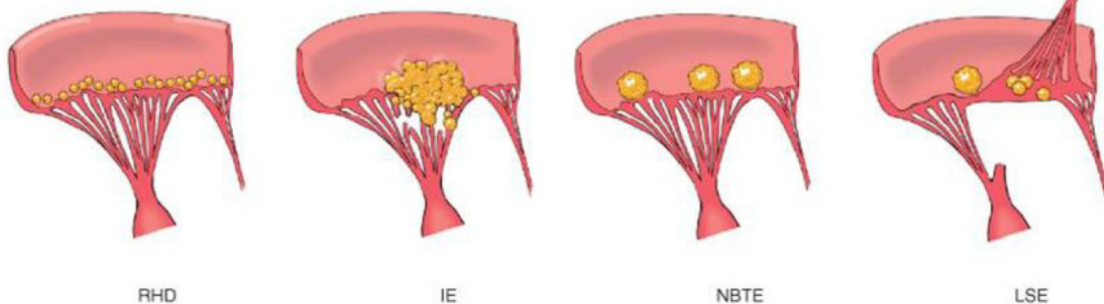
\*\*Two major or 1 major and 2 minor must be present to diagnose rheumatic fever



*Aschoff Nodules*



## Types of vegetations



RHD	IE	NBTE	LSE
Small, Firm, Friable	Large, bluky, irregular	Small friable	Medium sized flat verrucous
Along the lines of closure	Valve cusps and mural endocardium	Along the lines of closure	Both surface of valves involved

**TRALI**: Transfusion Related Acute Lung injury

- Development of fever, dyspnea, respiratory symptoms within 6 hours of Blood Transfusion.
- m/c/c of death due to blood transfusions.
- Usually occurs due to antibodies against HLA 2 or anti neutrophilic antibodies.
- m/c with plasma products like FFP.

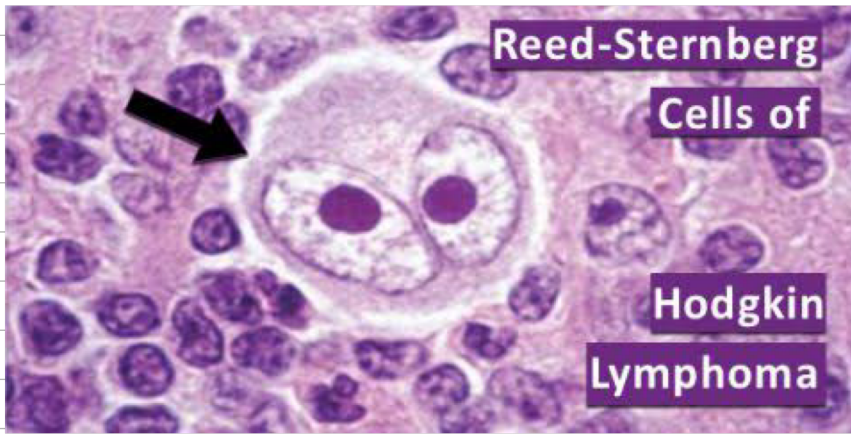
## HODGKIN'S DISEASE

- Hodgkin's disease (HD) primarily arises **within the lymph nodes and involves the extranodal sites secondarily.**
- The term "Hodgkin lymphoma" encompasses a group of lymphoid neoplasm that is characterized by the presence of distinctive neoplastic giant cells called **Reed-Sternberg cells**
- This group comprises about 8% of all cases of lymphoid neoplasms.

• HD is a group of lymphoid neoplasms arising in a single node and spreads from the nodes to Spleen, then liver and finally bone marrow.

LN → Spleen → Liver → BM

- **Bimodal peaks** —one in young adults between the age of 15 and 35 years and the other peak after 5th decade of life.
- The HD is more in **adult males** than females.
- The classical diagnostic feature is the presence of **Reed-Sternberg (RS) cell (or Dorothy-Reed- Sternberg cell)**
- RS cells are derived from **B-cells of germinal center**



The classification is based on : *Immunophenotyping of RC cells.*

1. **Classical HD** → All subtypes into this group have Reed-sternberg cells with same immunotype ie. **positive for CD 15 and CD 30**
2. **Non-classical /Nodular lymphocytic predominance type** → This subtype is histogenically distinct from other (classical) subtypes in that the Reed-sternberg cells are **positive for CD 20 and BCL-6** but are **negative for CD 15 and CD 30**.

Classic subtypes	CD 15+	CD 30+	Non classical	CD 15 <sup>⊖</sup> / CD 20+	CD 30 <sup>⊖</sup> / BCL-6+
• Nodular sclerosis			• Lymphocyte predominant		
• Mixed cellularity					
• Lymphocyte-rich					
• Lymphocyte depletion					

**Aplastic Anemia** : It is Pancytopenia - All Blood cells are ↓sed.

\* Anemia + Leukocytopenia + Thrombocytopenia.

• Autoimmune destruction of Hematopoietic stem cells

↳ Due to alteration immunological appearance of hematopoietic stem cells because of

- genetic disorders
- Environmental agents - radiation, toxins.

Complications →

↓ RBS → Tissue cannot oxygenates  
↳ Heart pumps hard - chest pain, SOB

↓ Platelets → ↑ Risk of bleeding

↓ WBC → inability to fight off infections.  
↳ Sepsis.

Causes: • Idiopathic

• Radiation and toxins

• Drugs - Chemotherapy agents, anti seizure.

• infections - EBV, HIV

• Fanconi's Anemia - m/c inherited cause

↳ Pancytopenia

↳ Physical abnormalities.

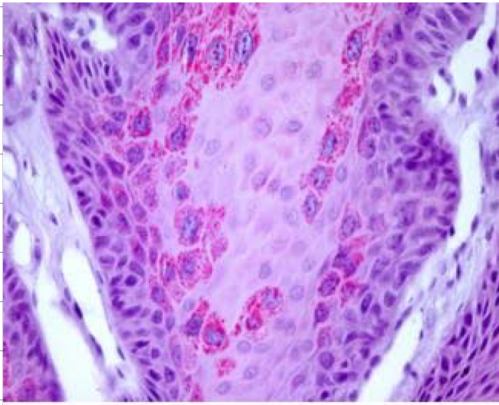
Diagnosis: • ↓ RBC, Leukocytopenia, Thrombocytopenia

• ↑ Erythropoietin, ↓ Reticulocyte.

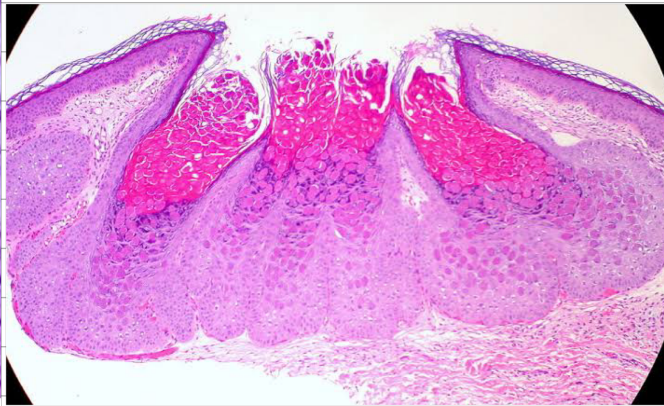
• BM Biopsy - Empty marrow and dry tap

# Viral inclusion bodies

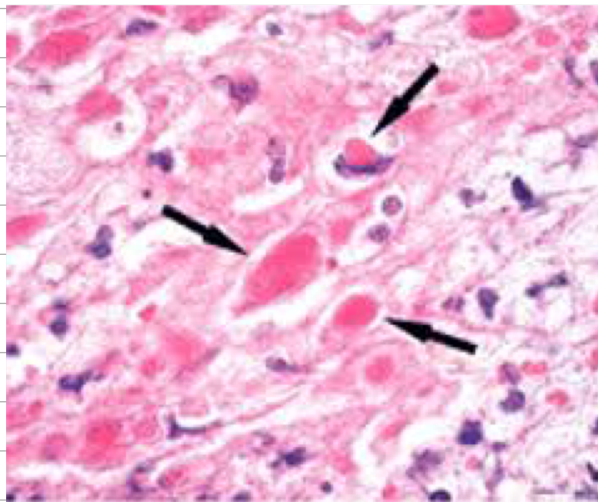
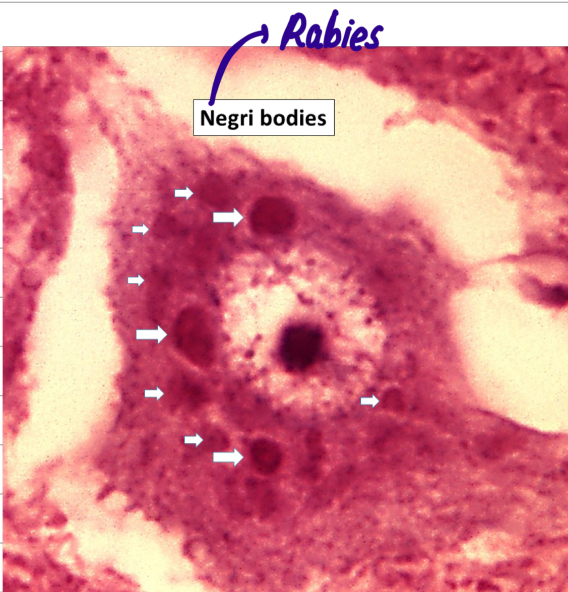
Intracytoplasmic	Henderson-Peterson bodies (Molluscum Contagiosum)		
	Negri bodies (Rabies)		
	Guarnieri bodies (Small pox)		
	Paschen bodies (Small pox)		
	Bollinger bodies (Fowl pox)		
	Borrel bodies (Fowl pox)		
Intranuclear	Acidophilic	Cowdry type A	Varicella zoster virus
			Herpes simplex virus
		Yellow fever virus	
	Basophilic	Cowdry type B	Polio virus
		Cowdry type B	Adeno virus
			Cytomegalo virus



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*Henderson - Patterson bodies : Molluscum Contagiosum*

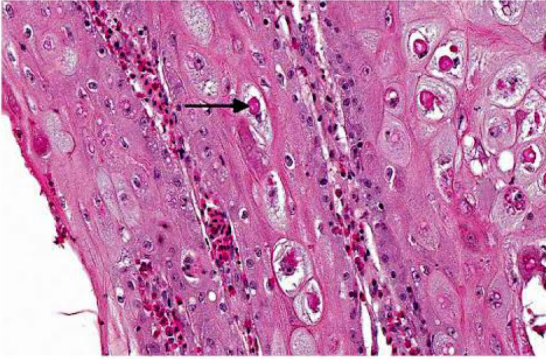


*Guarnieri Bodies : Small pox.*

## Bollinger bodies in Avipox

Oral cavity Hematoxylin and Eosin | 260x

Epithelial cells within the hyperplastic mucosa often undergo ballooning degeneration and contain a 15-30 um, eosinophilic, intracytoplasmic inclusion/Bollinger body (arrow)



## COWDRY TYPE A



Hepatocyte with a large intranuclear inclusion body. Surrounded by a clear halo

→ Cowdry Type A : Varicella Zoster Virus  
 HSV  
 Yellow fever virus

## COWDRY TYPE B

### COWDRY TYPE B



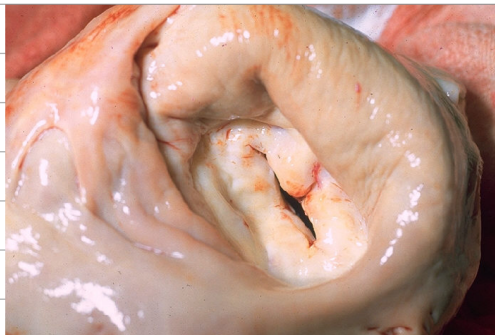
→ Cowdry type B : Polio virus  
 • Adeno virus  
 • CMV

## Mitral stenosis :



### major causes :

- Rheumatoid fever
- Congenital (Parachute valve, cor triatriatum)
- Severe mitral annular calcification with leaflet involvement.
- SLE, RA
- Myxoma
- IE & large vegetations.



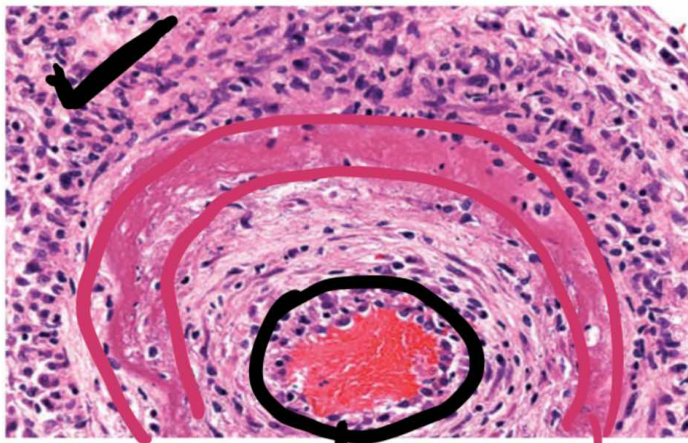
Q. Normal valve surface area :  $4-6\text{ cm}^2$

Q. m/c site for thromboembolism is  $\rightarrow$  **left atrial appendage.**

Q. Largest valve in the body  $\rightarrow$  **Tricuspid valve.**

	Mild	Moderate	Severe
Valve area ( $\text{cm}^2$ )	$>1.5$	1–1.5	$<1$
Mean gradient (mmHg)	$<5$	5–10	$>10$
Pulmonary artery pressure (mmHg)	$<20$	30–50	$>50$

Adapted from Vahanian<sup>9</sup>



**PAN** (Poly Arteritis Nodosa)

Q1) VIRAL MARKER = **HBs Ag**

Q2) NECROSIS

**FIBRINOID**  
**NECROSIS**

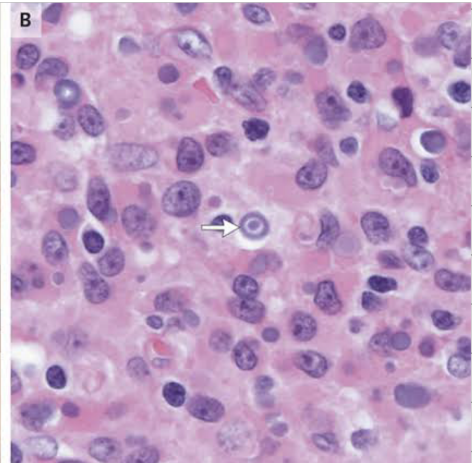
PAN

BV

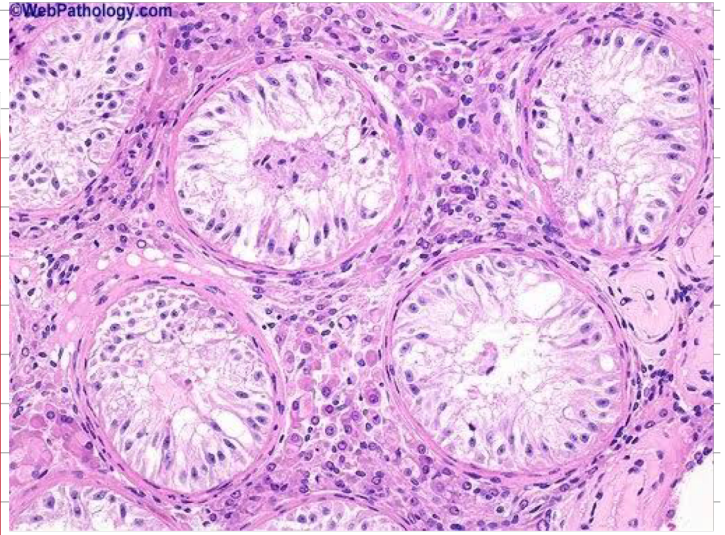
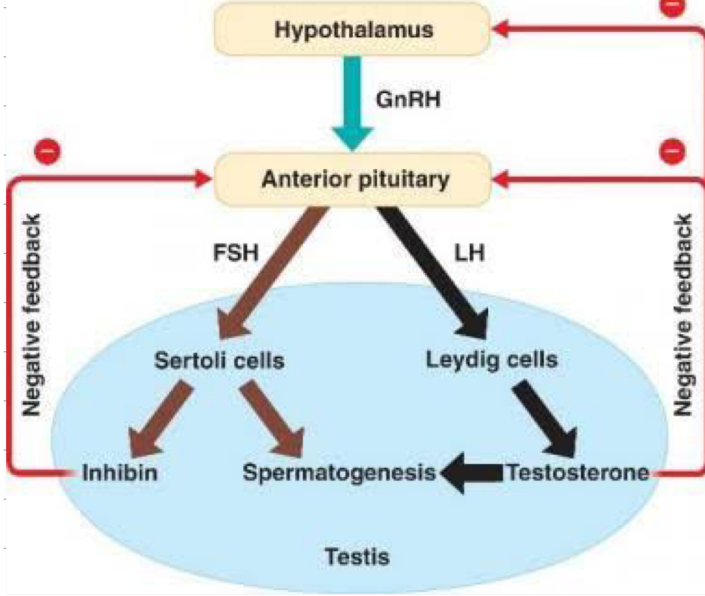
**P<sub>α</sub>P** Pulmonary **NOT** affected

**Michaelis Gutmann Body**

Seen in **Malakoplakia**



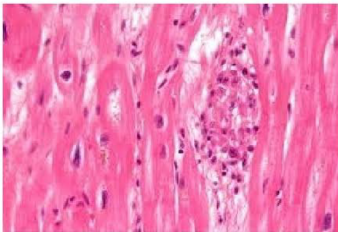
## Sertoli Cell only Syndrome



Sertoli cell-only syndrome, also known as del Castillo syndrome or germ cell aplasia, is **one of the most common causes of azoospermia in infertile men**. In this syndrome, only Sertoli cells line the seminiferous tubules of the testes, and the patients have very low or absent spermatogenesis.

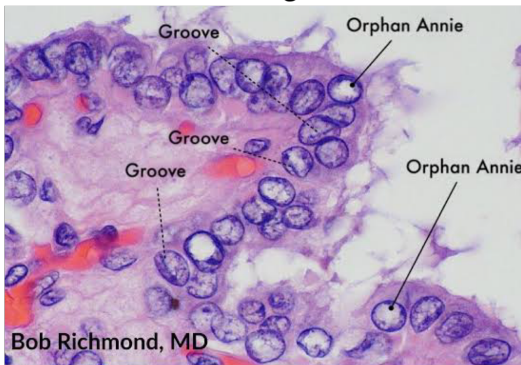
**RHD**: Rheumatic Heart Disease → group A  $\beta$  Hemolytic strep.

**ASCHOFF GRANULOMA (ASCHOFF BODY)**



- Small, wart
- along line of closure
- Sterile veg.

## Orphan Annie eye nuclei



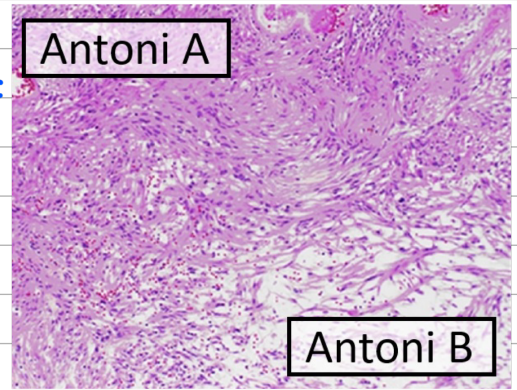
**Orphan Annie-eye nuclei are characteristically seen in**

- Papillary thyroid carcinoma.
- Polymorphous low-grade adenocarcinoma.
- Cribriform adenocarcinoma of the tongue.
- Hashimoto's disease.
- Grave's disease.
- Nodular goiter.



## Schwannoma

- Arises from Schwann cells. Aka bilateral acoustic neuroma.
- Associated with NF-2 gene mutation on Chr 22.
- Arises from inferior vestibulocochlear nerve.
- Well circumscribed and well encapsulated tumor.
- HPE:
  - Hypercellular area: Antoni A pattern
  - Hypocellular area: Antoni B pattern
  - Verocay bodies

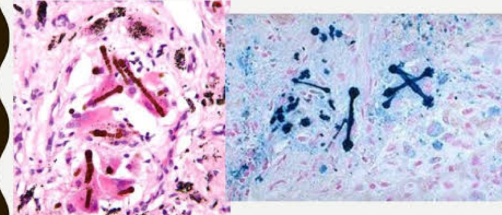


## Asbestosis

- Exposure: >10 years
- Pleural (firstly), Parenchymal involvement seen.
- Associated w/ only parenchymal involvement and Malignancy.
- Smoking is not associated.
- Serpentine / chrysotile (curly strands) is seen in 90% and is less toxic.
- Amphibole are brittle long straight rod like structures (dangerous types)
- most dangerous: Amosite.



Asbestosis- Ferruginous body

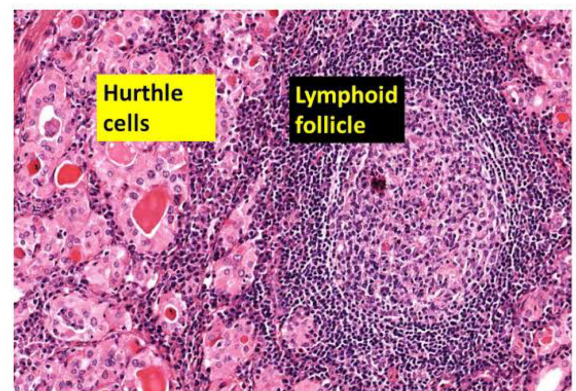


As Iron containing-  
Perls/Prussian blue positive

Golden brown, fusiform or beaded rods with a translucent center that consists of asbestos fibers coated with an iron-containing proteinaceous material

## Hashimoto Thyroiditis

- Female > Males
- most common cause in iodine sufficient area of the world.
- Autoimmune destruction of the thyroid gland.
- Anti-bodies responsible:
  - Anti-TSH receptor antibody
  - Anti-Thyroglobulin antibody
  - Anti-mitosomal antibody



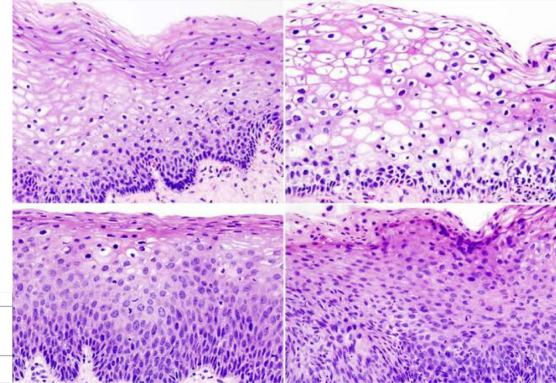
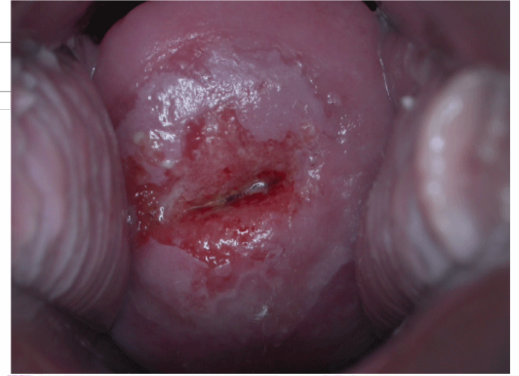
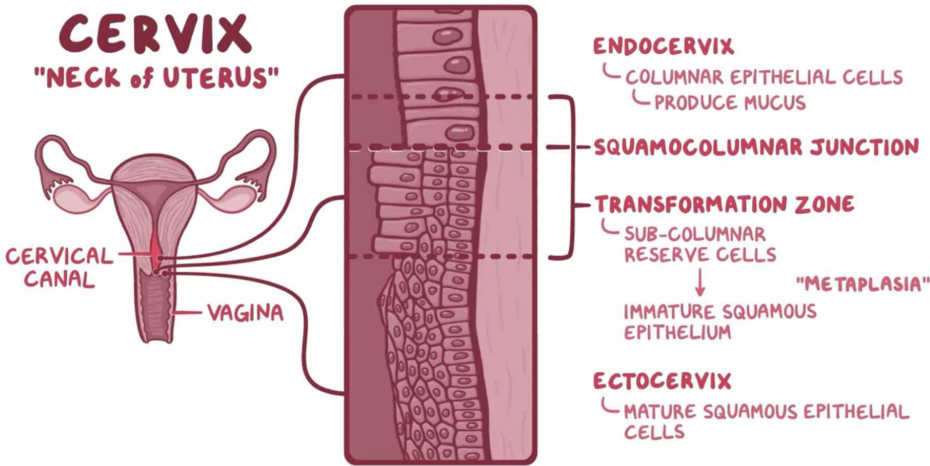
Associated genes :: CTLA4

• PTPN22

• HLAB8

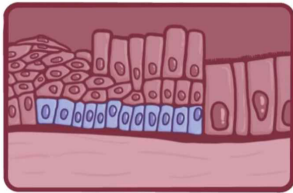
Initially patient presents with Hashitoxicosis, followed by Hypothyroidism.

## Cervical intraepithelial Neoplasia

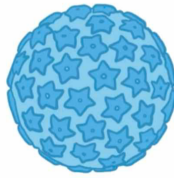


### CERVICAL INTRAEPITHELIAL NEOPLASIA/ SQUAMOUS EPITHELIAL LESION

↳ MOSTLY CAUSED BY HPV INFECTION



BASAL LAYER of TRANSFORMATION ZONE  
(IMMATURE SQUAMOUS EPITHELIUM)



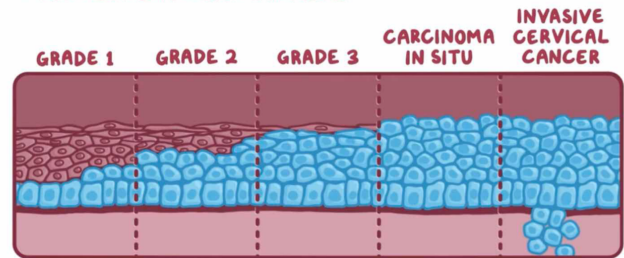
HPV-16

\* > HALF of ALL CERVICAL CANCERS

~ 15 TYPES LINKED w/  
> 100 CERVICAL CANCER

### STAGES

\* HOW MUCH EPITHELIUM is INVOLVED



↳ MORE LIKELY DYSPLASIA → CANCER

### SYMPTOMS

\* FIRST:

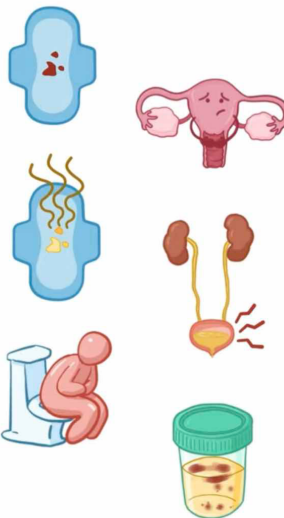
- ↳ ABNORMAL VAGINAL BLEEDING
- ↳ ESP. AFTER SEXUAL INTERCOURSE

\* OTHER:

- ↳ VAGINAL DISCOMFORT
- ↳ VAGINAL DISCHARGE with UNPLEASANT SMELL
- ↳ PAIN when URINATING

\* IF CANCER HAS SPREAD BEYOND PELVIC WALL:

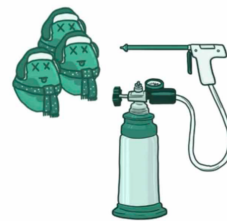
- ↳ CONSTIPATION
- ↳ BLOODY URINE



### TREATMENT

#### CERVICAL INTRAEPITHELIAL NEOPLASIA

\* CRYOSURGERY



\* CONIZATION



COLD-KNIFE CONIZATION



LASER



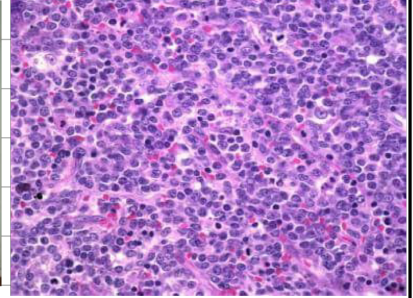
LEEP or LLETZ



## Myeloid Sarcoma

aka :- Chloroma

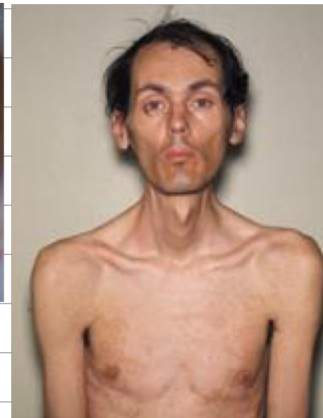
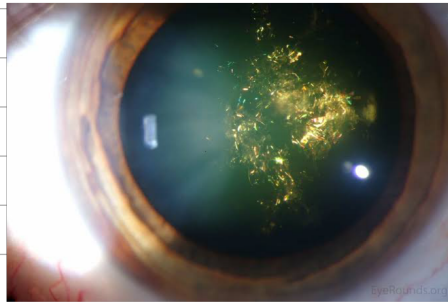
- granulocytic Sarcoma
- myeloblastoma.



- Soft tissue involvement of AML
- It is MPO positive, has greenish colour.
- Most common site is Orbit.
- Patient presents with Proptosis
- Arbuskel cell : monocytes which are present in a chloroma.

## Myotonic Dystrophy

- Autosomal Dominant
- Trinucleotide Repeat : CTG
- DMPK1 gene on Chromosome 19q, 13.3

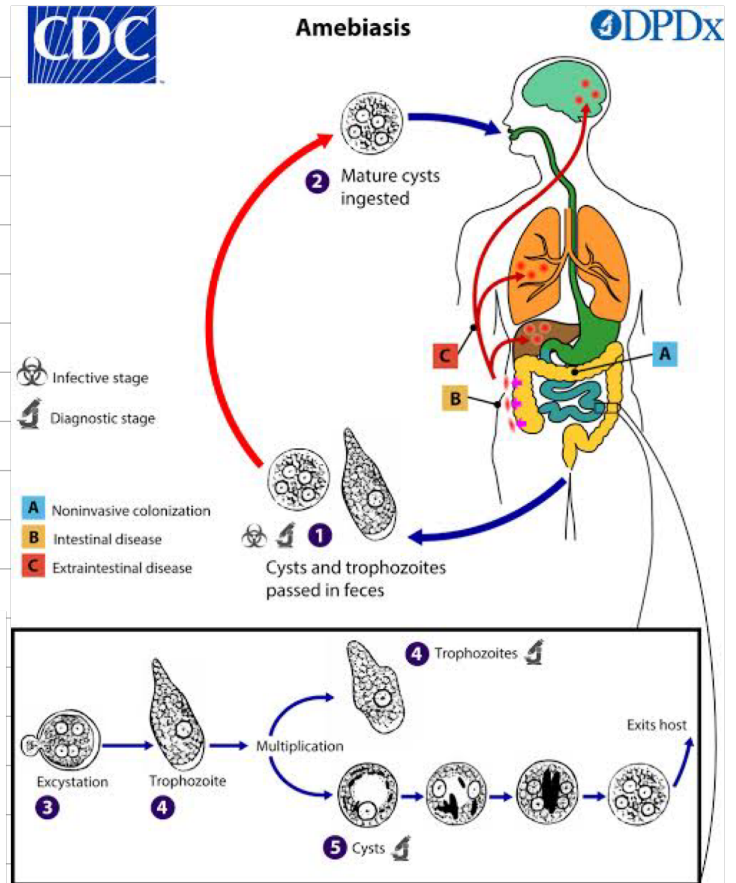


C → Christmas tree cataract  
T → Testicular atrophy  
G → Hypogammaglobulinemia

## Flasked shaped Ulcer

- Undermined / water bottle Ulcers
- Entamoeba Histolytica binds to the host cells by Gal/Gal NAC Lectin at Caecum and colon.
- Phagocytic ingestion of the host cells by small bites, known as Trophocytosis.





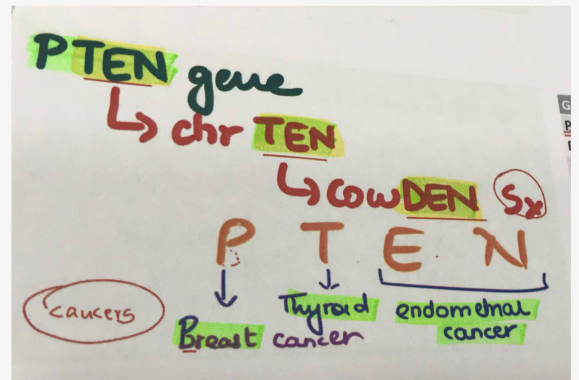
## Cowden Disease

Autosomal dominant

Mutation of **PTEN** gene on chromosome **10q23.3**

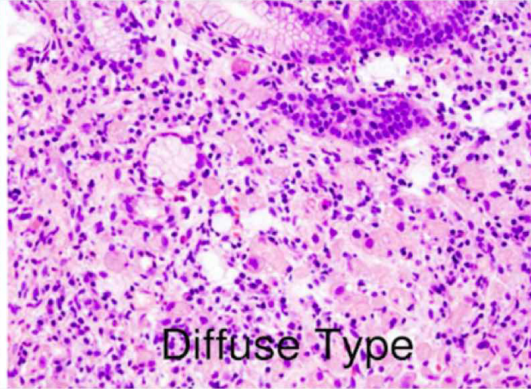
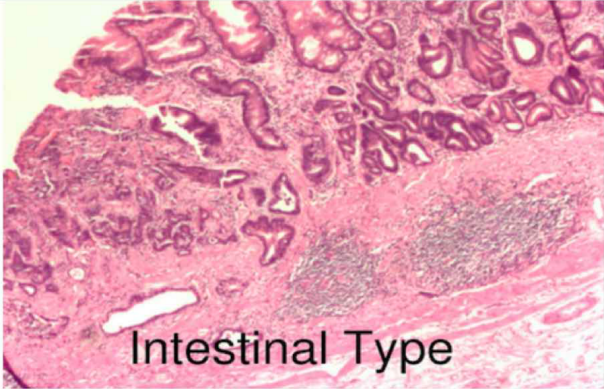
Components:

- Hamartomas of all three embryonal cell layers
  - Intestinal hamartomatous polyp – usually **ectodermal**, most common in **colon**
- **Facial trichilemmomas – most common feature.**
- Cancer of the
  - Breast (30–50%)
  - Thyroid (10% - **Mainly FTC**, rarely PTC and Hurthle cell tumors)
  - Endometrium
- CNS – 2<sup>nd</sup> most commonly involved system
  - Megalencephaly, ataxia, epilepsy, dysplastic gangliocytoma of cerebellum – **Lhermitte Duclos syndrome.**
- **Developmental anomalies – high arched palate**, adenoid facies, prominent forehead, Hypoplastic mandible.
- **Skin disease – acral keratosis.**



## Types of Gastric Adenocarcinoma

Intestinal type	Diffuse type
Male-to-female ratio, 2:1	Equal frequency in males and females
Bulky masses	Diffusely infiltrative growth
Glandular structures	Signet-ring cells
Increased signaling via WNT pathway	Loss of E-cadherin
Precursor lesions are flat dysplasia and adenomas.	No identified precursor lesions



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