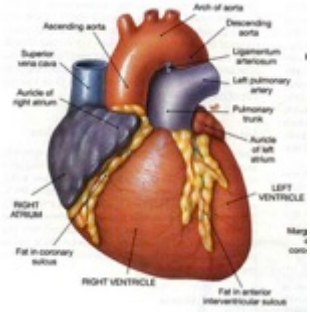
PATHOLOGY II: BLOCK 1

By: Brad Trent, Fall 2024

CARDIAC PATHOLOGY



THE HEART: A Pump

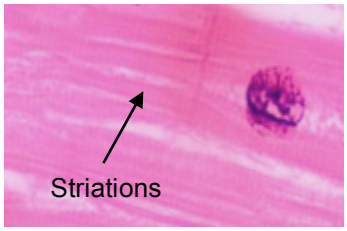
- HEART DISEASE IS THE #1 KILLER, NOT CANCER
- PUMP FAILURE: results from disorders of one or more of the 4 major constituents: *myocardium, vasculature, valves, conduction system*
    - *Throughout the lectures, you should know which diseases affect which part of the heart*

CARDIO PATHOLOGY DEFINITIONS:

- **CARDIAC HYPERTROPHY:** increase in ventricular thickness or heart weight above normal limits
- **CARDIAC DILATION**: abnormally large chamber size
- **CARDIOMEGALY**: increased weight and/or size

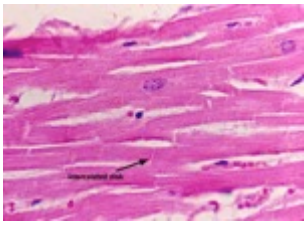
MYOCARDIUM

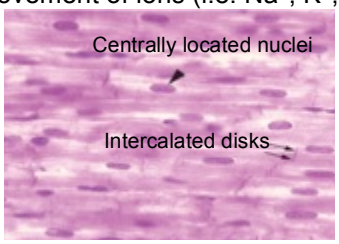
- Myocytes have 10x mitochondria of skeletal muscle cells & they contain large contractile units called sarcomeres
- **Force generated is related to degree of sarcomere contraction**
    - Moderate stretching increases distance of contraction & increases force
        - If you stretch it a little bit, it responds with an increased force!
    - Marked dilation increases distance so much there is little or no overlap of filaments with resultant marked reduction in force
- Overlapping thick & thin filaments appear as striations



MYOCYTES

- **Centrally**-located nuclei
- Intercalated discs connect cardiac myocytes
    - Facilitate cell-to-cell mechanical coupling
    - Facilitate spread of electrical impulses – contain **GAP JUNCTIONS** that enable synchronized waves of contraction by permitting rapid movement of ions (i.e. Na^+, K^+, Ca^{2+}) between cells

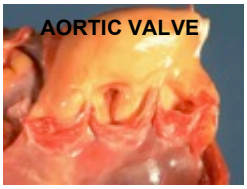




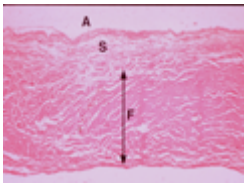
MYOFILAMENTS

- Actin (thin filament) + Myosin (thick filament, A band)
- **Troponin**, tropomyosin on thin filament
- **Nebulin**: regulates thin filament length
- **Titin**: maintains thick filament position
- **Creatine kinase:** catalyzes formation of ATP from ADP, found in the H band

VALVES

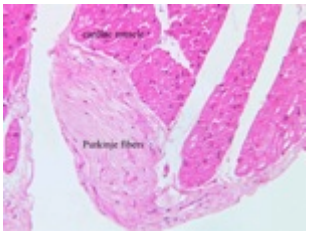


- **Atrioventricular valves + leaflets**
- **Semilunar valves + cusps**
- Valve function requires mobility, pliability, & structural integrity
- **HISTOLOGIC STRUCTURE**
  - **Atrialis:** adjacent to the atrium; elastic & collagen fibers covered with overlying endothelium
  - ★ ***SPONGIOSUM**: beneath the atrialis; core of loose connective tissue (mostly ECM)
    - **Important in Mitral Valve Prolapse**!
  - **Fibrosa**: beneath the spongiosa; major load-bearing layer; dense collagenous core of the leaflet– *functional integrity;* situated nearest to the ventricular surface of the leaflet that faces the greatest pressure during valve closure
    - **EOSINOPHILIC, THICK FIBROUS TISSUE**
  - **Ventricularis:** adjacent to the ventricle; elastic & collagen fibers covered with overlying endothelium
    - Elastin-rich layer – *functional recoil*



CONDUCTION SYSTEM

- **SA Node**: junction of RA & SVC
  - Cells in SA node spontaneously depolarize at 60-100 beats beats/minute
- **AV Node**: R atrial septum
  - Delays transmission & ensures atrial contraction precedes ventricular contractions
- **Bundle of His**: connects R atrium to ventricular spetum
- **Purkinje** network from R & L bundle branches

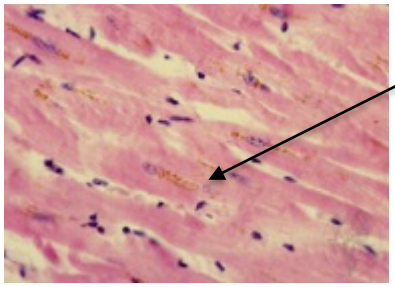


VASCULATURE

- Epicardial Coronary Arteries (**END ARTERIES** – if you block one it will block all tissue downstream!)
  - L Anterior Descending (LAD)
  - L Circumflex (LCX) – *Comes off left coronary artery*
  - R Coronary Artery (RCA)
- Blood flows to myocytes during ventricular diastole; at rest, diastole is 2/3rds of cardiac cycle
- *Need to know what arteries perfuse what area of the heart, but more on this later*

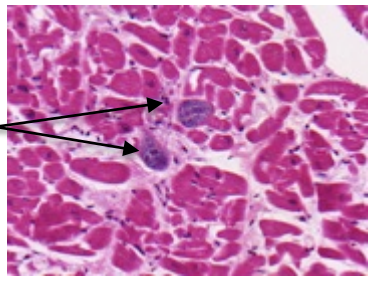
PATHOLOGY OF AGING

- *Changes in the biochemical, microscopic, gross appearance of the heart normally accumulate over a lifespan*
- **CHAMBERS:** ↑L atrial size, ↓L ventricular size, sigmoid-shaped ventricular septum
- **VALVES:** aortic valve calcific deposits, mitral valve annular calcific deposits, fibrous thickening of leaflets, buckling of mitral leaflets toward the LA, lambl excresences *(small filiform processes found on the closure lines of aortic and mitral valves; formed by the organization of microthrombi on the valve's contact margins)*
- **EPICARDIAL CORONARY ARTERIES:** tortuosity, diminished compliance, calcific deposits, atherosclerotic plaques
- **MYOCARDIUM:** ↓mass, ↑supepicardial fat, brown atrophy, **lipofuscin deposition**, **basophilic degeneration**, amyloid deposits
  - **LIPOFUSCIN:** wear & tear pigment; *what you see in an aging heart!*



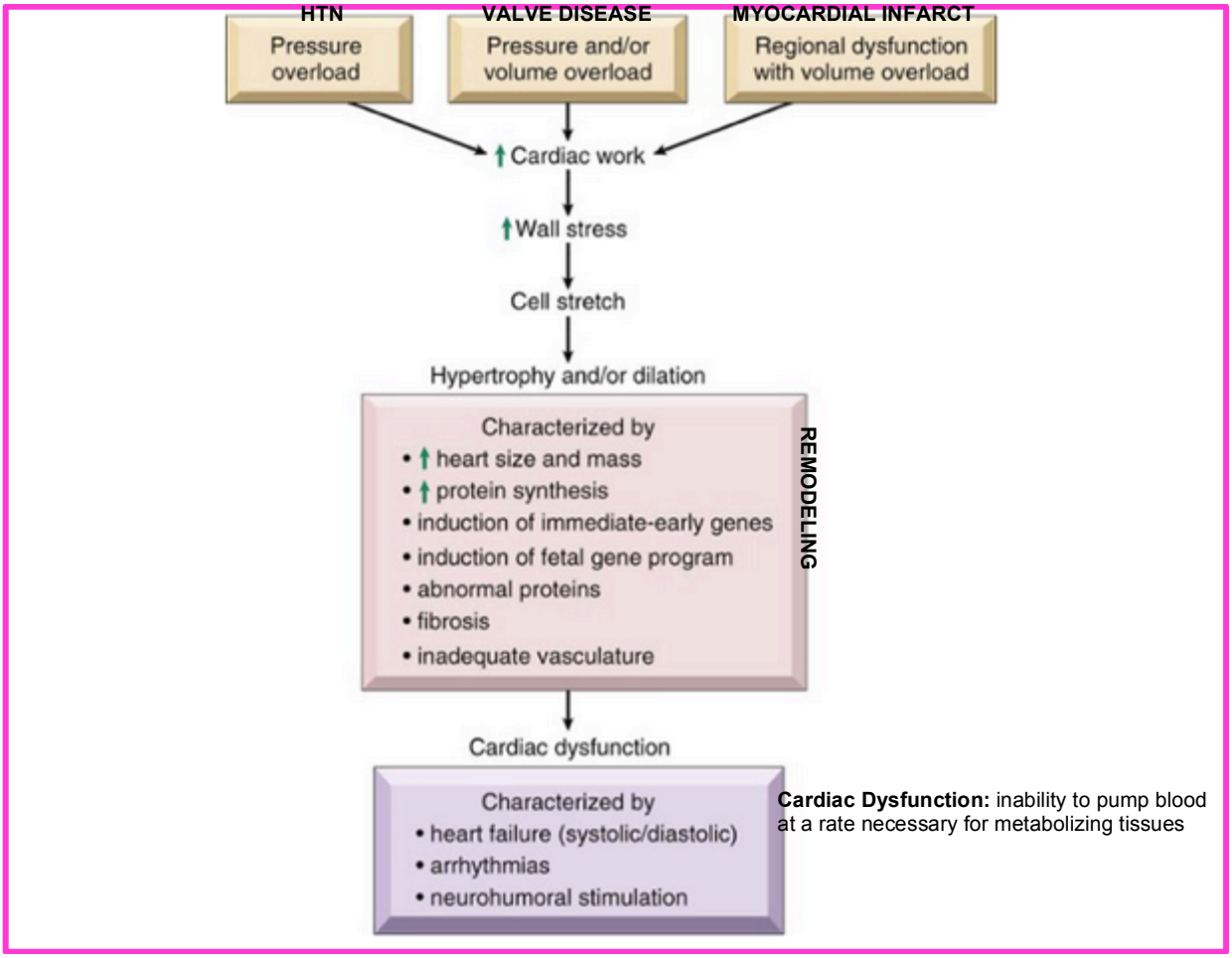
LIPOFUSCIN
"This is an important slide"

BASOPHILIC DEGENERATION



- **AORTA:** dilated ascending aorta with rightward shift, elongated (tortuous) thoracic aorta, sinutubular junction calcific deposits, elastic fragmentation & collagen accumulation, atherosclerotic plaque

HEART FAILURE



OVERVIEW OF CARDIAC PATHOPHYSIOLOGY: 6 MAJOR MECHANISMS

1. **PUMP FAILURE** (diminished myocardial contractility) – Primary Myocardiopathy, Ischemic Cardiac Disease
   - *Weak myocardial contractions (systolic) or insufficient myocardial relaxation with decreased ventricular filling (diastolic)*
2. **FLOW OBSTRUCTION** – Valvular Disease (Stenosis), Hypertensive Disease
   - *Flow obstructed in vessels (atherosclerosis) or through valves*
3. **REGURGITANT FLOW** – Valvular Disease (Insufficiency), CHD (ASD or VSD)
   - *A portion of the output from a contraction flows back through an incompentent valve*
4. **SHUNTED FLOW**
   - *Blood is abnormally channeled to a different part of the heart or vasculature*
5. **CONDUCTION DISORDERS** – Atrial Fibrillation, Sudden Death Syndromes
   - *Impaired generation or transmission of impulses with resultant non-uniform & ineffective heart contractions*
6. **RUPTURE OF HEART OR MAJOR VESSELS**
   - *Rapid exsanguination into a body cavity or externally*

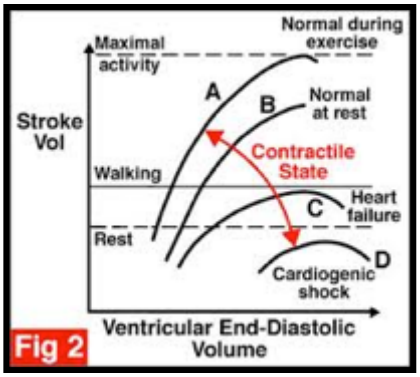
All of these mechanisms can affect the heart, but we have all of this cardiac reserve. We lose 70% of cardiac function before becoming symptomatic!

**CONGESTIVE HEART FALILURE (CHF)

- Heart is unable to pump sufficient blood to meet the metabolic needs of peripheral tissues. The inadequate cardiac output often usually associated with ***congestion of venous circulation***
  - *Congestion of venous circulation: stasis – venous flow is not flowing & pressure is building up*
- Common end-stage of chronic heart disease, but also results from acute hemodynamic dysfunction
- **PHYSIOLOGICAL ONSET OF CHF:** CHF occurs when normal cardiac adaptive mechanisms for maintaining arterial pressure are insufficient
  - **FRANK STARLING MECHANISM:** stroke volume of the heart increases in response to an increase in the volume of blood filling the heart
  - **HYPERTROPHY +/- DILATION**
  - **NEUROHUMORAL ACTIVATION:** increased autonomic nervous system activity, activation of renin-angiotensin-aldosterone system, release of atrial natriuretic peptide

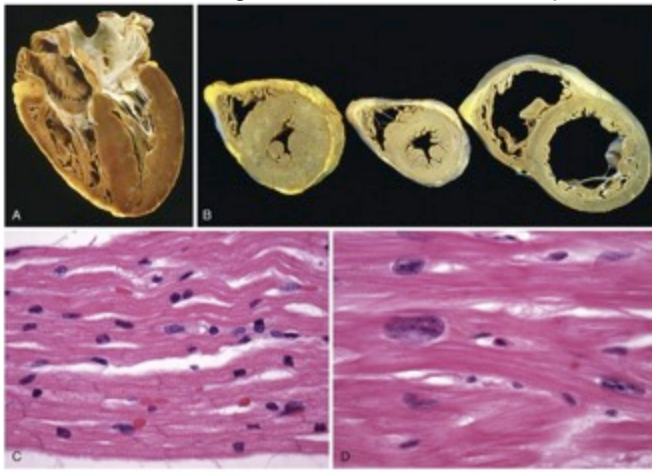
FRANK STARLING LAW OF THE HEART

- *The less the heart pumps out into systemic circulation, the greater the ESV. Blood flow continues into LV from lungs to greater EDV.*
- Greater Stretch = Greater Contraction



CHF & HYPERTROPHY

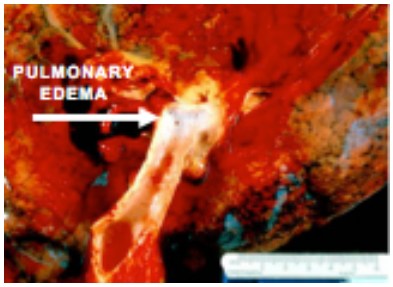
- CHF is often preceded by the initially adaptive sequence of **hypertrophy**, which at its most basic level starts with myocyte hypertrophy
- **Myocyte Hypertrophy: ↑myocyte size, both cell body & nucleus;** induced by pressure and/or volume and/or neurohumoral signals – *"This is an important slide"*
  - ↑number of sarcomeres & mitochondria
  - In PRESSURE OVERLOAD HYPERTROPHY, the new sarcomeres assemble **parallel** to cell's long axis (ventricular wall ↑ thickness)
  - In VOLUME OVERLOAD HYPERTROPHY, new sarcomeres added in **series** along long axis, leading to VENTRICULAR DILATION – *This is why the heart weight is the best measure of hypertrophy*
  - Enlarged nuclei result of DNA replication without cell division

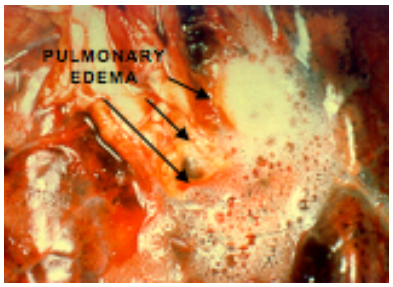


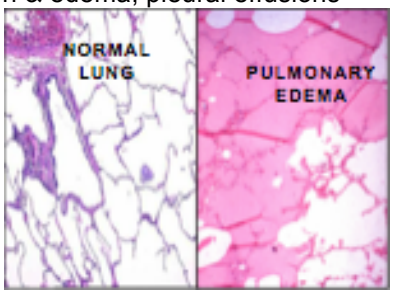
A. PRESSURE HYPERTROPHY due to LV outflow obstruction
B. LV HYPERTROPHY: (L) Concentric Hypertrophy due to pressure overload & ↑afterload, (CENTER) Normal Heart, (Right) Eccentric Hypertrophy due to volume overload & ↑preload.
C. NORMAL MYOCARIDUM
D. HYPERTROPHIED MYOCARDIUM – note the increases in both cell size & nuclear size in the hypertrophied myocytes.

**LEFT-SIDED HEART FAILURE

- "*Left-sided" refers to decompensation/failure predominantly of the left ventricle*
- *More common than R ventricular failure*
- **COMMON ETIOLOGIES:** IHD, HTN, aortic & mitral valvular disease, primary myocardial diseases
  - **SYSTOLIC DYSFUNCTION**: insufficient ejection fraction because of damaged contractile function of LV
  - **DIASTOLIC DYSFUNCTION:** inability of heart chambers to fill/relax during diastole because of abnormally still LV
    - *Flash pulmonary edema*
- **CLINICOPATHOLOGIC FINDINGS RESULT FROM:**
  - **Passive congestion of pulmonary circulation (Pulmonary Edema)**
    - *Interstitial capillaries fill with blood → focal rupture*
      - *Hemosiderin-laden macrophages (heart failure cells)*
    - *Long standing congestion leads to pulmonary interstitial fibrosis*
  - **Inadequate perfusion of downstream tissues & organs**
- **GROSS PATHOLOGY-HEART:** original disease process (i.e. MI), hypertrophic LV with varying degree of dilation
- **MICROSCOPIC PATHOLOGY-HEART:** myocyte hypertrophy, interstitial fibrosis
- **GROSS PATHOLOGY-LUNGS:** heavy & wet secondary to congestion & edema, pleural effusions

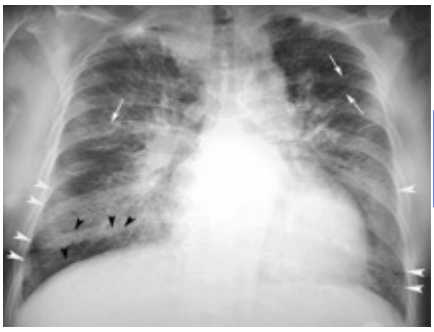




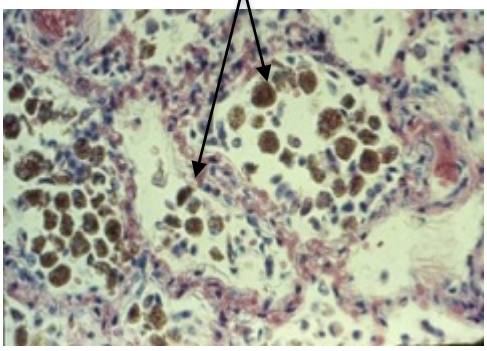


LEFT-SIDED HEART FAILURE: MICROSCOPIC SEQUENCE

1. Perivascular & interstitial edema of interlobular septa
2. Edematous widening of alveolar septa
3. Edema fluid in alveolar spaces
4. RBCs extravasation into alveolar spaces
5. Formation of hemosiderin-laden macrophages (**heart failure cells**)



KERLEY A LINES (white arrows)
KERLEY B LINES (white arrowheads)
KERLEY C LINES (black arrowheads)

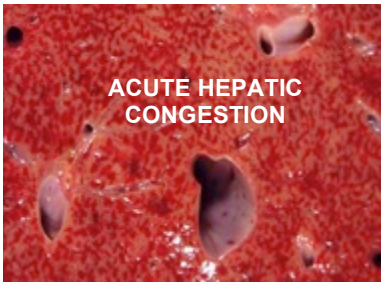


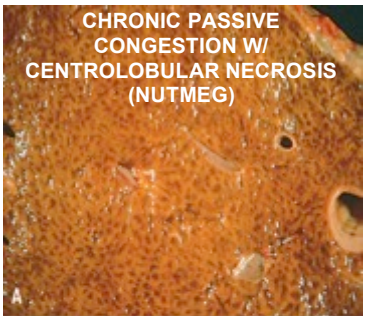
LEFT-SIDED HEART FAILURE: SIGNS & SYMPTOMS

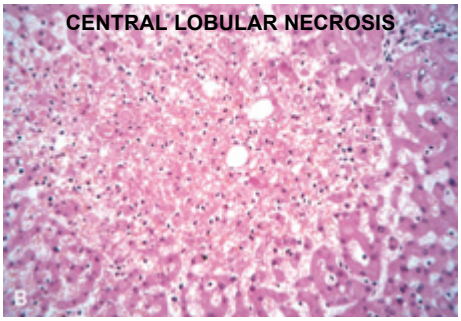
- Cough, dyspnea, orthopnea, paroxysmal nocturnal dyspnea
- Atrial fibrillation
- Pre-renal azotemia *(caused by decrease in blood flow/hypoperfusion to the kidneys, but there is no inherent kidney disease*
- Hypoxic encephalopathy

RIGHT-SIDED HEART FAILURE

- **The most common cause of R heart failure is L heart failure!**
  - L heart failure → ↑pressure in the pulmonary circulation → ↑ workload RV → R heart failure
- Less common: pulmonary HTN with pure R sided heart failure
  - Parenchymal & vascular disorders (i.e. primary pulmonary HTN)
  - ***Cor pulmonale*** = complete R heart disease secondary to lung disease
- **CLINICOPATHOLOGIC FINDINGS RESULT FROM:**
  - Marked engorgement of the systemic & portal venous system (**congestive hepatomegaly**, congestive splenomegaly)
  - Minimal pulmonary congestion → JUGULAR PULSE ELEVATION
- **GROSS PATHOLOGY-HEART:** hypertrophy & dilation of RA & RV
- **MICROSCOPIC PATHOLOGY-HEART:** myocyte hypertrophy, interstitial fibrosis
- ****LIVER PATHOLOGY!**
  - **GROSS:** congestion (**NUTMEG LIVER**); increased size & weight (hepatomegaly)
  - **MICROSCOPIC:** congested **red-brown** pericentral zones, centrilobular necrosis (if RSHF severe), cardiac cirrhosis with chronic RSHF







- **ADDITIONAL PATHOLOGIC FINDINGS:**
  - **CONGESTIVE SPLENOMEGALY:** usually mild with only doubling in size
    - **Do not give these patients platelets!**
  - Effusion in pleural, pericardial, & peritoneal spaces (ascites)
  - Edema of subcutaneous tissues ***(pitting edema)***, particularly dependent regions

RIGHT-HEART FAILURE: SIGNS & SYMPTOMS

- Peripheral edema
- Hepatic dysfunction
- Azotemia *(abnormally high levels of nitrogen-containing compounds (i.e. urea, creatinine, etc.) in the blood usually due to insufficient filtering of the blood by the kidney)*
- Encephalopathy

CONGENITAL HEART DISEASE (CHD)

- 5% incidence; 1% of newborns have significant disease diagnosed within 1st year of life
- 12 CHDs account for 75% of all cases
- MOST COMMON: VSD, ASD, PULMONARY STENOSIS, PDA, TETRALOGY OF FALLOT, COARCTATION

GENERAL PATHOGENESIS

- *Sporadic* genetic abnormalities are the major causes of CHD (most common *genetic* cause is trisomy 21)
- Genetic abnormalities lead to faulty embryogenesis during gestational weeks 3-8
- Genetic abnormalities principally affect transcription factors regulated by signal pathways (Wnt, hedgehog, VEGF, TGF-β, & notch pathways) & some signaling proteins critical for cardiac morphogenesis

SHUNTS

- Most CHDs are associated with shunts or obstructions
- **SHUNTS:** abnormal communication between cardiac chambers and/or blood vessels that follows a pressure gradient; CHD can be categorized by the type of shunt

Classification of Congenital Heart Disease
Initial Left-to-Right Shunt
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Persistent truncus arteriosus
Anomalous pulmonary venous drainage
Hypoplastic left heart syndrome
Right-to-Left Shunt
Tetralogy of Fallot
Tricuspid atresia
No Shunt
Complete transposition of the great vessels
Coarctation of the aorta
Pulmonary stenosis
Aortic stenosis
Coronary artery origin from pulmonary artery
Ebstein malformation
Complete heart block
Endocardial fibroelastosis

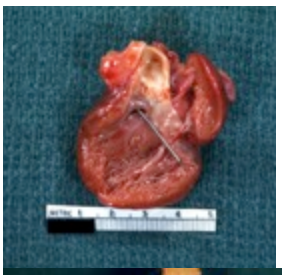
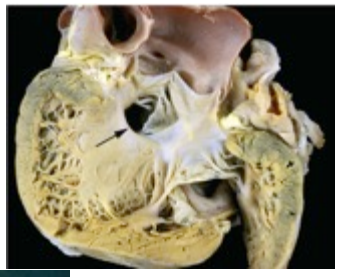
CORRECTION – This is a R to L shunt!

CHD: LEFT TO RIGHT SHUNTS

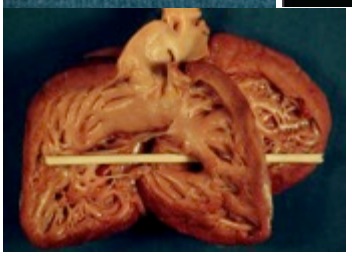
- Increased pulmonary blood flow with no initial cyanosis – *This blood is oxygenated!!*
- Secondary pathology progressively includes:
  - Medial hypertrophy & vasoconstriction of muscular pulmonary arteries (<1mm)
  - Development of obstructive arterial intimal lesions
  - Progressive RV hypertrophy
  - Severe pulmonary changes leads to conversion to a R to L shunt (**EISENMENGER SYNDROME**)
    - *Eventually the increased pulmonary blood flow will lead to pulmonary HTN. In combination with, RV hypertrophy it can cause a reversal of the shunt to R to L leading to **cyanosis***
    - Reason for early intervention in L to R shunts
- L to R shunts are the most common CHDs & include: **VSD, ASD, & PDA**

VENTRAL SPETAL DEFECT (VSD)

- **Most common form of CHD (42%!) has a LEFT TO RIGHT SHUNT**
- Only 20-30% are isolated
- **CLINICAL MANIFESTATIONS determined by size & other R-sided abnormalities**
  - 50% of small muscular VSDs close spontaneously
  - **Initially volume hypertrophy of LV & pressure hypertrophy of RV**
  - Large defects develop **irreversible pulmonary HTN** & **Eisenmenger Syndrome**
    - *Eventually the pulmonary HTN & RV hypertrophy cause a reversal of the shunt to R to L*
  - Infections are possible – **ENDOCARDITIS**
- **Membranous VSD** (90%, occur in membranous interventricular septum)
- **Infundibular VSD** (below pulmonary valve)
- **Muscular VSD** (muscular septum) – *It will close spontaneously*
- **LARGE UNCLOSED VSD CAN LEAD TO PULMONARY HTN**

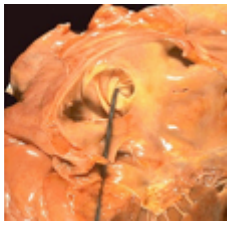
MEMBRANOUS VSD



MUSCULAR VSD

ATRIAL SEPTAL DEFECT (ASD)

- **Secundum** (most common-90%, located near center of atrial septum, involves fossa ovalis)
- **Primum** (5%, adjacent to AV valves & often associated with AB valve abnormalities or VSD)
- **Sinus Venosus** (5%, located near entrance of SVC)
- ASDs are well tolerated & may be asymptomatic... 10% will develop pulmonary HTN due to RV overload
- **Patent Foramen Ovale (PFO)** is also a form of ASD
- **CLINICAL FEATURES:**
  - Pulmonary blood flow 2-8x normal, but...
  - ASDs usually not symptomatic before age 30
  - Irreversible pulmonary HTN is **RARE**



PATENT FORAMEN OVALE

SECUNDUM ASD

PATENT DUCTUS ARTERIOSUS (PDA)

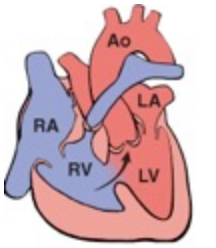
- Shunts blood from pulmonary artery to aorta in fetus to bypass lungs, but if persistent past fetal life, blood will shunt from aorta to pulmonary trunk → pulmonary HTN, cyanosis, & continuous harsh murmur
- *It normally closes by 72 hours after delivery in response to arterial oxygenations, decreased pulmonary resistance, & decreased levels of PGE2.*
- 90% of PDA cases are isolated defects
- Clinical impact based upon size & other cardiac features. Overtime, it will produce pulmonary HTN so often closed in early life.

CHD: RIGHT TO LEFT SHUNTS

- ***R to L shunts lead to hypoxemia & cyanosis (blue baby!!) because pulmonary circulation is bypassed***
- **Additional complications:**
  - **Paradoxical embolism:** an embolus originating from a venous thrombosis (often in LE or pelvis) enters the RA, & then passes through a defect in the septum between the RA & LA, entering the LA. The embolus then enters to LV & is then pumped into the aorta → brain, kidney, etc. → infarct/stroke
  - **Hypertrophic osteoarthropathy:** periosteal new formation at the end of long bones (i.e. digital **clubbing**), which can be caused by cyanotic CHD
  - **Polycythemia**
- R to L shunts include Tetralogy of Fallot & Transposition of the Great Arteries

*TETRALOGY OF FALLOT

- Most common of congenital R to L shunts
- ***FOUR FEATURES:**
  - **VSD**
  - **Subpulmonary stenosis** obstructing RV outflow tract
    - *Protects the pulmonary vasculature from pressure overload*
    - *May be accompanied by pulmonary valve stenosis or pulmonary valve atresia*
  - **Aorta overrides VSD**
  - **RV hypertrophy**

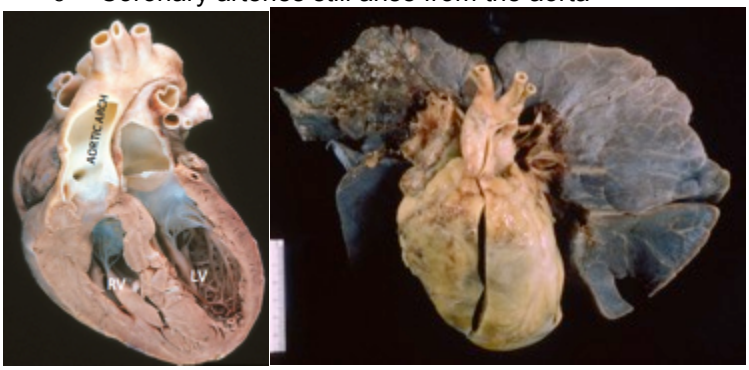


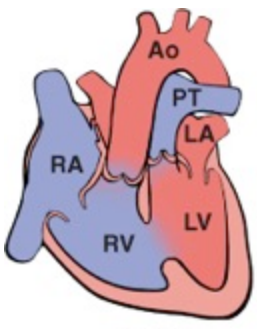
A Classic Tetralogy of Fallot

- **PATHOLOGY:**
  - **Enlarged heart with "boot shape" on CXR**
  - VSD is large & adjacent to the aortic valve
  - Pulmonary valvular stenosis or atresia may be present
    - *If atresia of the pulmonary valve occurs, a PDA is life saving & necessary for survival. This is because there will be shunting of blood from the aorta to the pulmonary arteries through the PDA – This would be the only way there would be perfusion of the lungs to oxygenate blood!*
  - Right aortic arch in 25% of cases
- **CLINICOPATHOLOGY**
  - 10% of untreated patients are alive at 20 years; 3% of untreated patients are alive at 40 years
  - Clinical course depends upon degree of subpulmonary fibrosis
    - *Will cause hypoplasia of the pulmonary artery due to lack of blood flow*
  - **Most common is severe stenosis with baby cyanotic at birth**

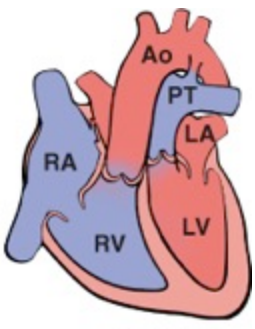
TRANSPOSITION OF THE GREAT ARTERIES

- Abnormal formation of truncal/aortopulmonary septae
- Atrial & ventricular connections are normal (concordant), but ventricular artery connects are switched (discordant)
- Incompatible with life unless there is a shunt that allows mixing of blood
  - WITH **VSD, PATENT FORAMEN OVALE (ASD), OR PDA** = COMPATIBLE WITH LIFE
    - This allows for some mixing of blood so there can be some oxygenated blood flowing to systemic circulation
- **CHARACTERISTICS**
  - RV outflow tract to aorta & LV outflow tract to pulmonary artery
    - ***RV hypertrophy** becomes prominent because RV becomes systemic ventricle & LV atrophies because of low resistance of pulmonary circulation*
  - Ventricular-arterial discordance
  - Aorta is the more anterior artery with the pulmonary artery positioned posteriorly
  - Coronary arteries still arise from the aorta





With VSD

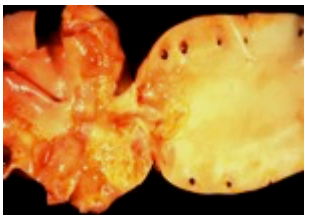


Without VSD

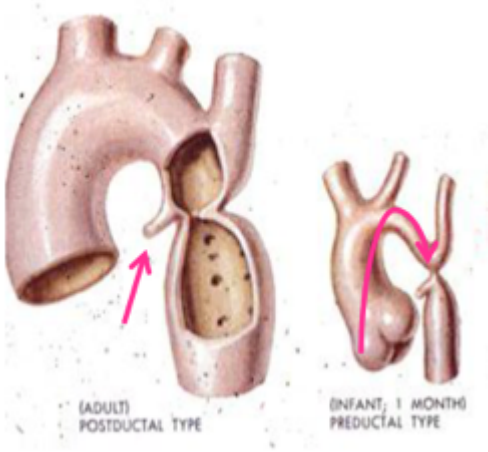
CHD: OBSTRUCTIVE CHD

- Obstructive CHD is caused by abnormal narrowing of chambers, valves, & blood vessels
- A complete obstruction is called **atresia**
- Coarctation of Aorta

COARCTATION OF AORTA



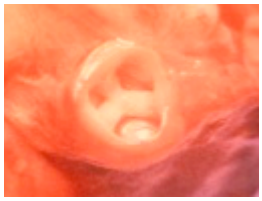
- Variable narrowing of aortic arch
- More common in MALES
- 50% of cases associated with **bicuspid aortic valve**
- Increased in **Turner's Syndrome**
- **Two Forms:**
  - **Infantile:** tubular hypoplasia of aortic arch proximal to **patent ductus arteriosus**
    - ***Always contain PDA***
    - ***Cyanosis*** *of LE & trunk due to coarctation & blood flowing from pulmonary arteries through PDA to the aorta & into systemic circulation of lower body*
    - *Regular pulses in UE & head because blood still flows through the great vessels*
  - **Adult:** ridge of enfolded tissue in aortic arch opposite closed ductus arteriosus *(ligamentum arteriosum)*
    - ***No PDA***
    - HTN of UE with weak pulses & hypotension of lower body → claudication & coldness
    - Increased collaterals through intercostal & internal mammary arteries with **"notching" of ribs**
- *O_2 is higher in vessels going to the brain & LE blood pressure will be low*
- With long term obstruction: **CONCENTRIC hypertrophy of LV** (due to pressure)



COARCTATION OF AORTA
(LEFT) ADULT: POSTDUCTAL; arrow is pointing to wear the ductus is closed (Ligamentum arteriosum)

(RIGHT) INFANTILE: PREDUCTAL;

PULMONARY STENOSIS & ATRESIA



- Mild to severe obstruction
- Often associated with TOF & TGA
- **ASSOCIATED PATHOLOGY:**
  - RV hypertrophy
  - Post-stenotic dilation of pulmonary artery
  - In atresia, hypoplastic RV with ASD & PDA

PULMONARY STENOSIS & ATRESIA

- Isolated in 80% of cases
- If severe stenosis or atresia, development of "Hypoplastic Left Heart Syndrome" associated with LV endocardial fibroelastosis & a PDA that is essential for survival
- **PATHOLOGY:**
  - 3 locations: subvalvular, valvular, & supravalvular
  - In valvular variant cusps, may be hypoplastic, dysplastic, or abnormal in number

ISCHEMIC HEART DISEASE

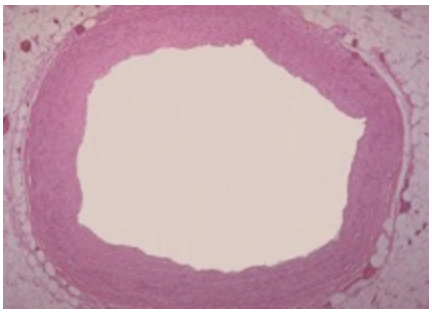
- Imbalance between heart oxygen supply & demand resulting in **myocardial ischemia**
- 90% of cases result **atherosclerotic occlusion of coronary arteries**
  - Less frequent causes include coronary emboli, myocardial vascular inflammation, & vascular spasms
- *Progressive atherosclerotic narrowing of epicardial coronary arteries with variable degrees of acute plaque change, thrombosis, & vasospasms*
- Most frequent distribution is in multiple epicardial arteries: **LAD, LCX, RCA**
  - Lesions predominate in the first several centimeters

MYOCARDIAL ISCHEMIA CONSEQUENCES

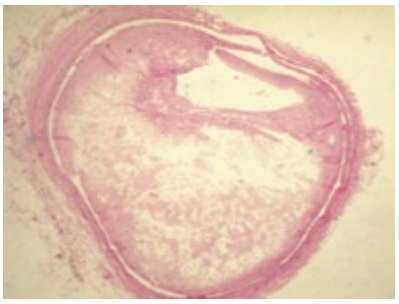
- ANGINA PECTORIS: STABLE & UNSTABLE
- MYOCARDIAL INFARCTION (MI)
- SUDDEN CARDIAC DEATH
- **CHRONIC ISCHEMIC HEART DISEASE**

ANGINA PECTORIS

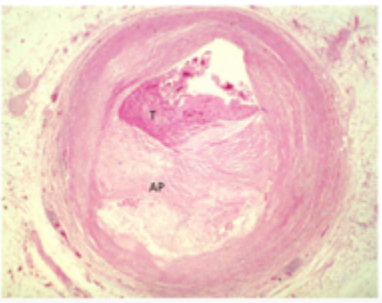
- ***Paroxysmal & recurrent attacks of substernal or precordial chest pain caused by transient ischemia that is insufficient to cause myocyte necrosis***
- ≥ 75% narrowing of epicardial artery begins to result in symptoms, initially with exertion but as % stenosis increases, symptoms begin to present at rest
- **STABLE ANGINA**: Most common
  - *Decreased perfusion secondary to fixed-narrowing of chronic stenosing coronary atherosclerosis* (**CAD**)
  - Predictable; presents with exertion – *indicates stable, flow-limiting plaque*
- **PRINZMETAL VARIANT ANGINA:** coronary artery spasm may/may not have CAD
- **UNSTABLE or crescendo ANGINA**: more intense, longer, increasing frequency
  - Unpredictable; often presents at rest – *indicates ruptured atherosclerotic plaque + superimposed clot (acute plaque change) partially obstructing the vessel lumen*
  - Signals plaque disruption
  - 50% evidence of myocyte necrosis (Prof: *"rarely have myocyte death/necrosis")*
  - *Precursor for MI*



NORMAL CORONARY ARTERY



SEVERE CORONARY ATHEROSCLEROSIS



CORONARY ATHEROSCLEROSIS WITH HEMORRHAGE
AP = Atherosclerotic Plaque
T = Thrombus

MYOCARDIAL INFARCTION

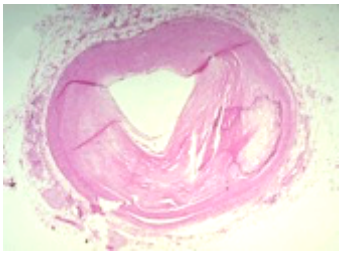
- Death of cardiac muscle secondary to *prolonged, severe ischemia*
- Incidence: 1.5 million in US/year
- Increasing frequency with age
  - 10% younger than 40 y/o
  - 45% younger than 65 y/o
- Decreased incidence in pre-menopausal women (estrogen is protective)

MI: CLINICAL FEATURES

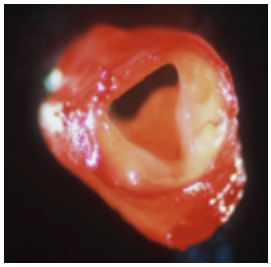
- Classic acute onset symptoms & signs:
  - **Severe substernal chest pain with radiation of pain down L arm, neck, jaw, epigastrium**
  - Weak, rapid pulse
  - Sweating profusely (diaphoretic)
  - Nausea
  - Dyspnea (difficulty breathing) secondary to pulmonary congestion & edema
- 10-15% of MI patients may be asymptomatic during the acute cardiac event
- Occurrence of the MI discovered by EKG: Q waves, ST-segment changes, T-wave inversion
  - **ELEVATED ST SEGMENT – STEMI**

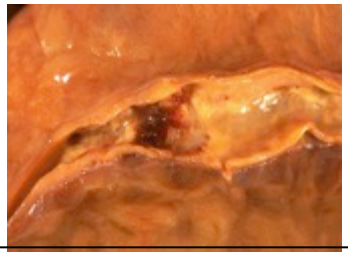
MI: PATHOGENESIS

1. **Atheromatous plaque in coronary artery** undergoes an acute change in **90% of cases**
   - *Intraplaque hemorrhage, erosion or ulceration, or rupture or fissuring*
2. Platelets adhere to exposed endothelial collagen & necrotic material
   - Platelets release granules
   - Platelets aggregate to form microthrombi
3. Vasospasm from platelet granules
4. Coagulation pathway activated by TF with subsequent expansion of thrombus to fill vessel lumen

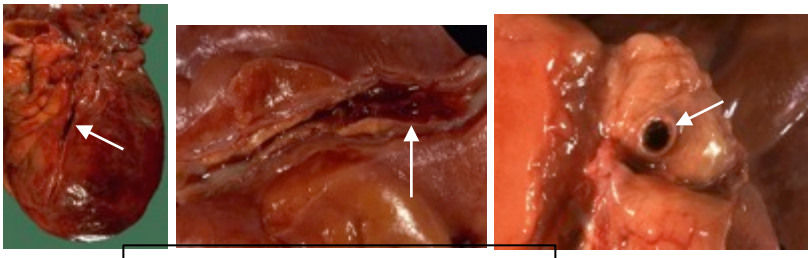


SEVERE CORONARY ATHEROSCLEROSIS



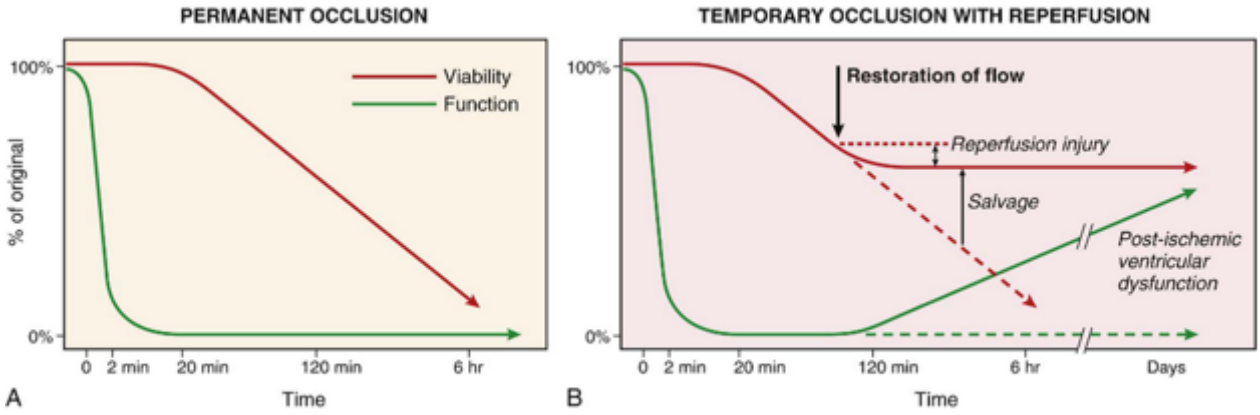


CORONARY ATHEROSCLEROTIC PLAQUE WITH HEMORRHAGE



CORONARY ARTERY THROMBUS

- In 10% of MI cases, the following mechanisms are responsible:
  - Vasospasm; platelet aggregation or drug ingestion (cocaine, ephedrine)
  - Emboli from:
    - LA with a-fib, L sided mural thrombus, vegetations of infective endocarditis, intracardiac prosthetic material, paradoxical emboli through PFO
  - Ischemia without above or CAD
    - Vasculitis of small intramural coronary arteries
    - Hematologic disorders, such as sickle cell disease
    - Amyoidosis of vessels
    - Vascular dissection
    - Severe ventricular hypertrophy
    - Shock
    - Inadquate perfusion during cardiac surgery



Following coronary occlusion, **contractile function is lost within 2 minutes** & viability begins to diminish after approximately **20 minutes**. If perfusion is not restored (A), then nearly all myocardium in the affected region will die. If flow is restored (B), then some necrosis is prevented, myocardium is salvaged, & at least some function will return. The earlier reperfusion occurs, the greater the degree of salvage. However, the process of reperfusion itself may induce some damage (*reperfusion injury)*, & return of function of salvaged myocardium may be delayed for hours to days (*post-ischemic ventricular dysfunction)*

Feature	Time
Onset of ATP depletion	Seconds
Loss of contractility	<2 min
ATP reduced	
to 50% of normal	10 min
to 10% of normal	40 min
Irreversible cell injury	20-40 min
Microvascular injury	>1 hr

ATP, Adenosine triphosphate.

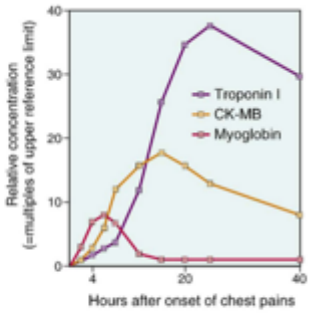
MI: LOCATION, SIZE, & MORPHOLOGIC FEATURES

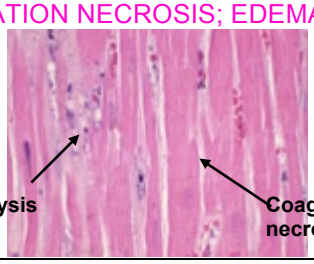
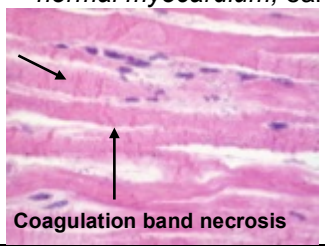
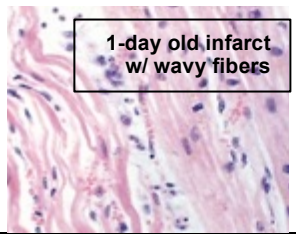
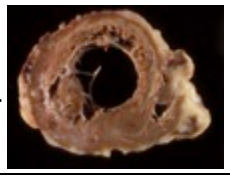
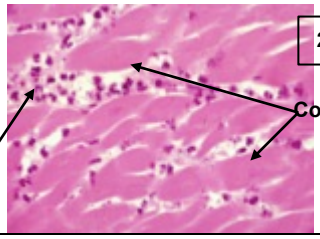
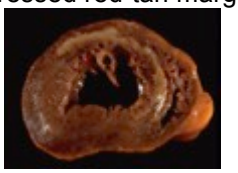
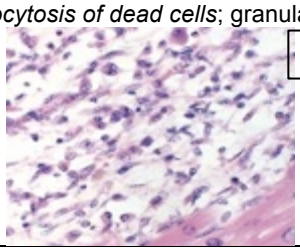
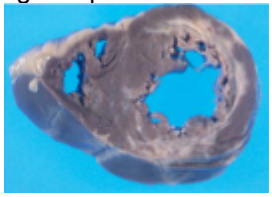
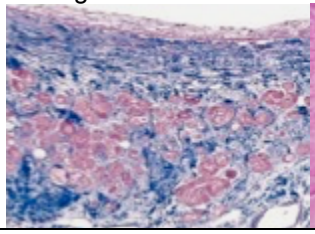
Location, size, & specific morphologic features are dependent upon the following factors:

- Location, severity, & development rate of coronary obstructions
- Size of vascular bed perfused by obstructed vessels
- Duration of occlusion
- Metabolic & oxygen needs of the myocardium at risk
- Extent of collateral blood vessels
- Presence, sit, & severity of coronary spasms
- Heart rate, cardiac rhythm, & blood oxygenation

LABORATORY EVALUATION OF MI

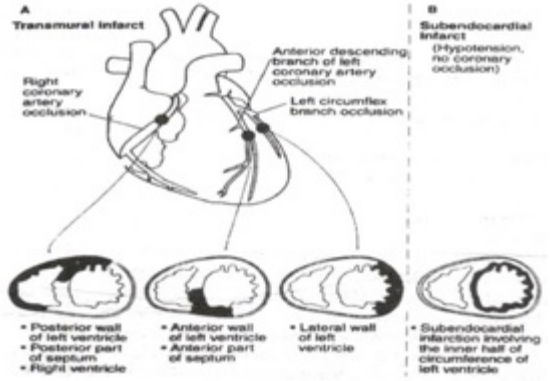
- Measurement of blood levels of proteins that have leaked from damaged/leaky myocardium into circulation
- Cardiac-specific **troponins** T & I (cTnT, cTnI)
- **Creatine kinase** MB fraction (CKMB)
- *Almost all protein levels start within 4-6 hours. TROPONIN STAYS FOR 1-2 WEEKS.*



TIME	GROSS FEATURES	LIGHT MICROSCOPE
0 - ½ hour	None	None
½ - 4 hours	None	Usually none Variable waviness of fibers at border
4 – 12 hours	DARK MOTTLING	EARLY COAGULATION NECROSIS; EDEMA; HEMORRHAGE 
12 – 24 hours	Dark mottling	Ongoing coagulation necrosis; pyknosis; myocyte hypereosinophilia; marginal contraction band necrosis; *wavy fibers due to stretching of normal myocardium;* early neutrophilic infiltrate  
1 – 3 days	Mottling with YELLOW TAN INFARCT CENTER 	Coagulation necrosis with total loss of nuclei & striations – *only outlines of cells*; brisk interstitial infiltrate of **NEUTROPHILS** 
3 – 7 days	Hyperemic border; central yellow-tan softening (*transmural*)	Beginning disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border
7 – 10 days	Maximally yellow-tan & soft, with depressed red-tan margins 	Well-developed *phagocytosis of dead cells*; granulation tissue at margins 
10 – 14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels & collagen deposits
2 – 8 weeks	Gray-white scar, progressive *from border toward core of infarct*	Increased collagen deposition with decreased cellularity 
> 2 months	Scarring complete – *Healed infarct* 	Dense collagenous scar – *Healed infarct with extensive fibrosis*  

**PATTERNS OF INFARCTION – *"This is an important slide."*

- **TRANSMURAL** (*across the wall*)
  - Full thickness of ventricular wall **in region supplied by the occluded vessel** (usually **thrombus**)
  - ***Most frequently caused by acute plaque change with associated occluding thrombus***
- **SUBENDOCARDIAL** (*just right inside of the endocardium)*
  - THIS REGION OF THE HEART IS THE MOST SUSCEPTIBLE TO DECREASED PERFUSION
  - Inner 1/3 of the ventricular wall
    - **LOCATION OF LYSED THROMBUS**: if we lyse the thrombus in time, we won't get the transmural effect... only the subendocardial region that's most sensitive to hypoxia is damaged!
      - Lyses of the thrombus must happen within < 24 hours, but ideally < 12 hours!
    - Shock/global HTN circumferential damage
- **MULTIFOCAL: Disease** of small intramural vessels (vasculitis, vascular spasms-i.e. drugs)

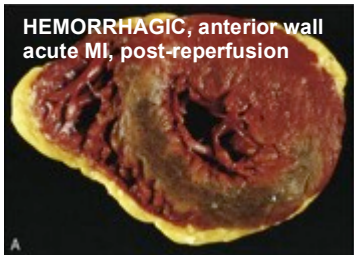


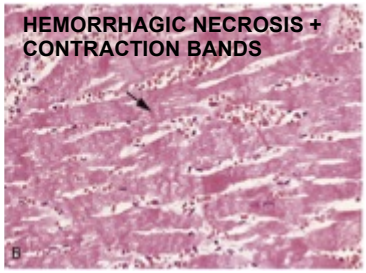
**CORONARY ARTERY OCCLUSION & ASSOCIATED MI REGION – *"This is an important slide."*

- *Each coronary artery has an area that it perfuses, if you block that artery, you block perfusion to that area*
- **LEFT ANTERIOR DESCENDING**: 40-50% OF MI
  - Anterior wall of LV near **apex** & Anterior portion of ventricular septum
  - **Apex circumferentially**
- **RIGHT CORONARY ARTERY:** 30-40%
  - Inferior/posterior wall of LV & Posterior portion of ventricular septum
  - Sometimes inferior/posterior RV free wall
  - **INFERIO-SEPTAL MYOCARDIAL INFARCT**
- **LEFT CIRCUMFLEX CORONARY ARTERY:** 15-20%
  - Lateral wall of LV, not the apex
  - *Generally the vessel that is LEAST affected!*

MYOCARDIAL INFARCT & REPERFUSION

- Reperfusion is the restoration of blood flow to ischemic myocardium with the goal of limiting infarct size
- Reperfusion methods: thrombolysis, angioplasty↓, stent placement, CABG
  - The balloon is inflated & crushes the plaque within the artery wall
  - The balloon expands again to press the stent against the inner lining of the artery
  - DES: drug-eluting-stents have a polymer coating, which slowly releases drugs to keep the artery from narrowing again, a process called restenosis
- *Reperfusion saves reversibly damaged myocytes & alters the morphology of lethally injured myocytes*
- It is associated with its own cause & effect secondary to Ca^{2+} overload, recruitment of inflammatory cells, & other mediators
- **GROSS PATHOLOGY: hemorrhagic myocardium**
- **MICROSCOPIC PATHOLOGY:**
  - **CONTRACTION BANDS IN IRREVERSIBLY** DAMAGED MYOCYTES**
    - *Eosinophilic intracellular stripes composed of densely packed sarcomeres*
    - *Hypercontraction of myocytes due to massive Ca^{2+} influx!*
  - Occlusive capillary endothelial swelling
  - RBC extravasation





**MI COMPLICATIONS – *"This is important."*

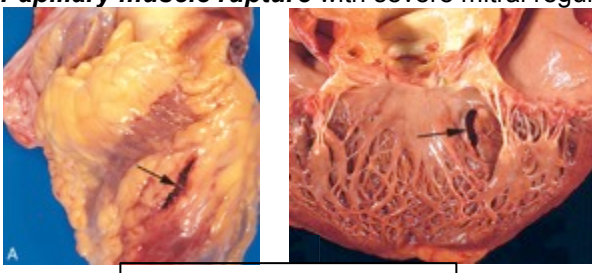
Arrhythmias, Myocardial rupture, Papillary muscle dysfunction, Mural thrombus, Contractile dysfunction, Ventricular aneurysm, Pericarditis, Infarct expansion, Progressive late heart failure

1. ARRHYTHMIAS

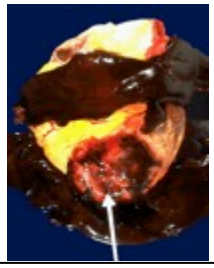
- Wide range from sinus bradycardia to ventricular fibrillation ("*quivering*")
- Infarcts of INFERIO-SEPTAL myocardium can involve bundle of His & be associated with heart block
  - R CORONARY ARTERY!

2. MYOCARDIAL RUPTURE, secondary to TRANSMURAL NECROSIS

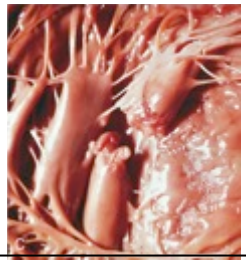
- **Most common:** rupture of ventricular free wall, 2-4 days post-MI (mushy, dead tissue), with hemopericardium & **CARDIAC TAMPONADE**
- Rupture of ventricular septum with acute VSD
- ***Papillary muscle rupture*** with severe mitral regurgitation



MYOCARDIAL RUPTURE



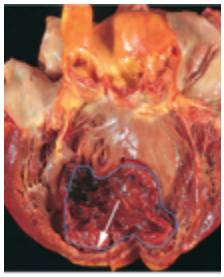
POST-MI VENTRICULAR WALL RUPTURE – CARDIAC TAMPONADE



POST-MI PAPILLARY MUSCLE RUPTURE

3. MURAL THROMBUS

- **PICTURED**: Post-MI apical ventricular wall thinning & **mural thrombus** over the region of the infarct (because the endocardium there is damaged) – *pieces can breakoff & can cause infarcts of the brain/kidney/etc.*

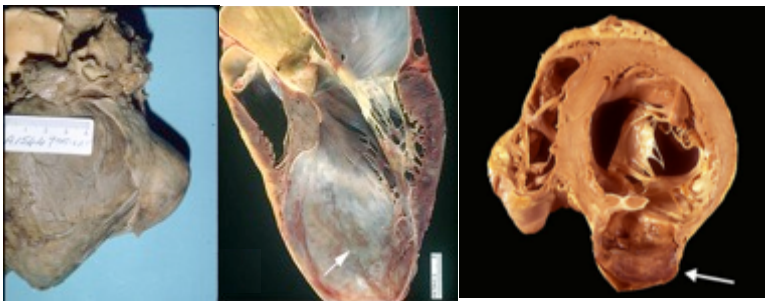


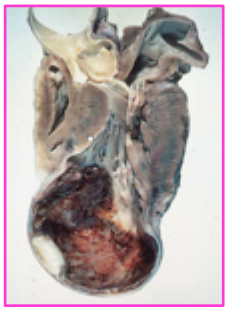
4. CONTRACTILE DYSFUNCTION

- 10-15% develop severe pump failure & cardiogenic shock (cardiogenic shock as 70% mortality rate & accounts for 2/3 of MI-associated in hospital deaths)

5. VENTRICULAR ANEURYSM

- Late complication of **transmural MI**; rare rupture of aneurysm as the wall is fibrotic
- Complications of VA include: mural thrombus, arrhythmias, & heart failure



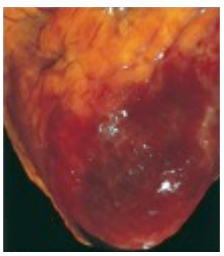


POST-MI APICAL LEFT VENTRICULAR ANEURYSM & MURAL THROMBUS
"This is an important slide."

Every time it wants to pump blood, it is having to fill up this "balloon." It will expand & contract with the heartbeat.

6. PERICARDITIS

- Fibrinous or fibrinohemorrhagic 3-4 days post-MI (**Dressler Syndrome**)
- **PICTURED**: bottom of the apex of the heart; fibrinous pericarditis with a *granular appearance*



CHRONIC ISCHEMIC HEART DISEASE: "*Ischemic Cardiomyopathy*"

- Progressive CHF resulting from accumulated ischemic myocardial damage and/or inadequate compensatory responses
- Most commonly, post-MI due to functional decompensation of hypertrophied non-infarcted myocardium
- Can also happen chronically without MI
- Leads to 50% of cardiac transplant recipients
- **HYPERTROPHY → If it continues to fail → DILATED → CHF**
- **GROSS PATHOLOGY:**
  - Cardiomegaly with LV ***hypertrophy & dilation***
  - Healed mural infarcts
  - Patchy fibrous endocardial thickening
  - Coronary artery stenosis
- **MICROSCOPIC PATHOLOGY:**
  - Myocyte hypertrophy
  - Fibrosis
  - Subendocardial myocytes vacuolization

SUDDEN CARDIAC DEATH

- Unexpected death from cardiac causes *without symptoms or within 24 hours of symptoms*
- SCD most often is the result of lethal **arrhythmia** (i.e. v-fib)
- Severe CAD, but generally not due to thrombus
- **ETIOLOGY**
  - **80-90% CAD usually with >75% stenosis (atherosclerosis)**
  - Acute plaque disruption in 10-20% of cases
  - ≥80% show **no evidence on ECG or enzymatic evidence** of myocyte damage

CAUSES OF NON-ATHEROSCLEROTIC SCD

- *Frequent in younger age groups*
- Hereditary or acquired abnormalities of the cardiac conduction system
- Congenital coronary arterial abnormalities
- MVP
- Myocarditis or sarcoidosis
- Dilated or hypertrophic cardiomyopathy
- Pulmonary HTN
- Myocardial hypertrophy
- Pericardial tamponade, PE, catecholamines, cocaine, methamphetamine
- **IN PATIENTS > 35 YEARS OLD, ATHEROSCLEROSIS/CORONARY HEART DISEASE IS THE #1 CAUSE. IN PATIENTS <35 YEARS OLD, **HYPERTROPHIC CARDIOMYOPATHY** IS THE #1 CAUSE.

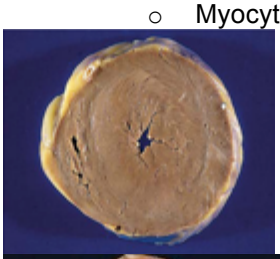
ARRHYTHMIAS

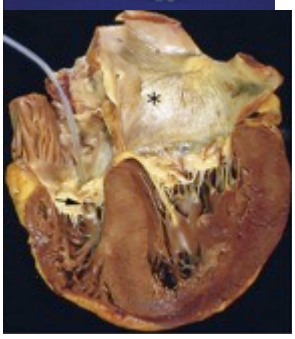
- Abnormalities in cardiac conduction that can be sustained or sporadic (paroxysmal)
- May cause SCD
- Can be initiated at any level of conduction system, down to the myocyte level
- Arrhythmias follow several general patterns: tachycardia, bradycardia, fibrillation, asystole, irregular heart beat
- **Arrhythmias are generally secondary to disruption of gap junctions**
- **CAUSATIVE DISORDERS:** IHD, dilated cardiomyopathies, myocyte hypertrophy, myocarditis
- *Some arrhythmias are primary electrical disorders with **no visible structural abnormality of heart***
  - i.e. **Heritable channelopathies** caused by mutations in genes required for normal ion channel function
  - *"This is an important thing about arrhythmias."*
- **SICK SINUS SYNDROME:** SA node damaged with AV node taking over at slower rate
- **ATRIAL FIBRILLATION:** Secondary to irritated atrial myocytes with SA node signal being variably transmitted & irregularly irregular heart beat
- **HEART BLOCK**: AV node dysfunction; First degree with prolonged PR interval to complete failure of in third degree heart block

HYPERTENSIVE HEART DISEASE (HHD)

SYSTEMIC (LEFT-SIDED) HHD

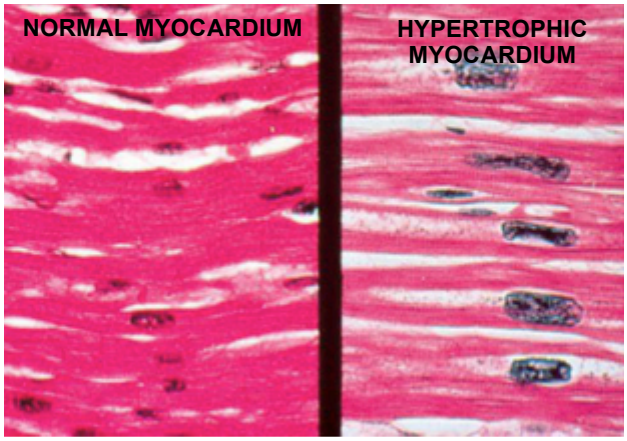
- Initially an adaptive response to the pressure overload of chronic HTN
- *Chronic HTN causes increased systemic resistance (affecting blood flow out of LV) → Pressure overload in LV w/ subsequent concentric hypertrophy → impaired diastolic filling of LV causes volume overload & dilation of LA (eccentric hypertrophy)*
- Clinical outcomes (related to severity, duration, basis of HTN, extent of Rx)
  - Normal longevity & die of other causes
  - Develop IHD
  - Develop progressive heart disease
- **PATHOLOGY: Classic**
  - Concentric LV hypertrophy (thickness 2cm, & may weigh >500g)
  - LV stiffness
  - LA dilation secondary to impaired diastolic filling of LV
  - Increased interstitial connective tissue
  - Myocyte hypertrophy & interstitial fibrosis





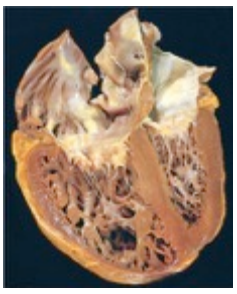
HTN-ASSOCIATED LV HYPERTROPHY

Classic HTN affects:
LV – thickened wall, *concentric hypertrophy*
LA – dilation because blood isn't pumping effectively, *eccentric hypertrophy*



PULMONARY (RIGHT-SIDED) HHD: *Cor Pulmonale*

- *Although LV failure can cause pulmonary HTN & subsequent RV overload & failure, '**Cor Pulmonale**' refers to R heart failure due to a PRIMARY **LUNG** DISEASE*
- **CAUSES:**
  - Disease of the pulmonary parenchyma
  - Diseases of the pulmonary vessels
  - Disorders affecting chest movement
  - Disorders inducing pulmonary arterial constriction
- **PATHOLOGY**
  - Marked dilation of RV (& RA) without gross hypertrophy in acute cor pulmonale
  - Chronic cor pulmonale associated with RV hypertrophy ≥ 1 cm & RA hypertrophy
- ***COR PULMONALE***
  - *Chronic severe pulmonary HTN → R heart failure due to primary lung disease*



VALVULAR HEART DISEASE

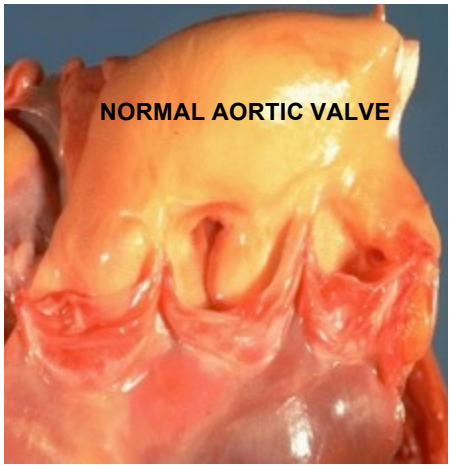
Calcific Valvular Degeneration (calcific aortic stenosis, calcific stenosis of congenitally bicuspid aortic valve, mitral annular calcification), Mitral Valve Prolapse (MVP), Rheumatic Heart Disease, Infective Endocarditis, Non-infected Vegetations

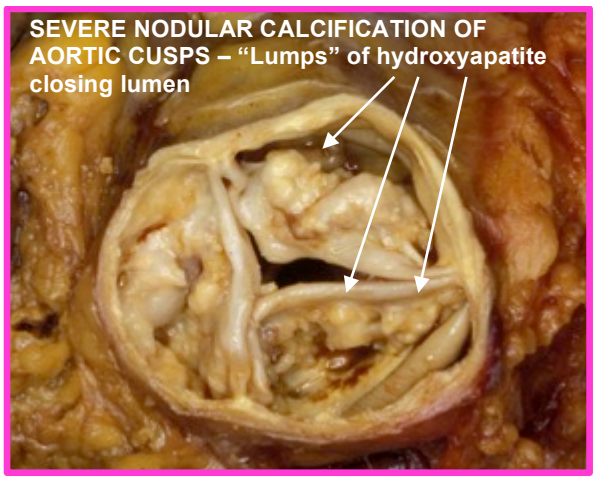
COMMON CAUSES OF FUNCTIONAL VALVULAR LESIONS → STENOSIS & REGURGITATION

- **STENOSIS:** failure of valve to open completely with reduction in forward flow of blood
  - *Will lead to pressure overload (concentric hypertrophy)*
  - AORTIC STENOSIS: calcification of anatomically normal & congenitally bicuspid aortic valves
  - MITRAL STENOSIS: rheumatic heart disease
- **REGURGITATION (incompetence, insufficiency):** failure of valve to close with subsequent back flow; *common with mitral valve*
  - *Will lead to volume overload (eccentric hypertrophy)*
  - AORTIC INSUFFICIENCY: dilation of the ascending aorta due to HTN & aging
  - MITRAL INSUFFICIENCY: myoxomatous degeneration (MVP)

CALCIFIC AORTIC STENOSIS

- ***Most common of all valvular abnormalities*** *(prevalence: 2% of total population; more in pt population)*
- Results from **age-associated "wear & tear" –** *Normal aging process*
- Clinical symptoms onset between 60-80 years of age
- Develop **LV PRESSURE-LOAD HYPERTROPHY** (*concentric hypertrophy*) with eventual *angina, CHF, & syncope*
- Untreated patients will die: within 5 years of angina onset, 3 years of developing syncope, 2 years of CHF onset
- **PATHOLOGY**
  - Mounded/nodular calcified masses ***within aortic cusps*** that ultimately extend into the Sinuses of Valsalva & prevent cuspal opening; in severe cases can reduce opening to ½-1cm^2 (*normal, 4 cm^2*)
  - Free edges of cusps are usually not involved!
  - Cusp commissure fusion not present
    - ***FYI****: A commissure is the area where two valve leaflets/cusps have abnormally come together.*
    - *(Valve commissures are NOT fused in calcific aortic stenosis; in contrast to post-rheumatic aortic stenosis where they ARE fused!)*
  - **Mitral valve rarely involved**
  - Calcific process begins in the valvular fibrosa on the outflow surface of the valve with deposition of **HYDROXYAPATITE** → Metastatic bone formation may occur
    - *This is NOT atherosclerosis. Statins do NOT stop the development. The calcific process is similarly a response to damage, BUT it is NOT atherosclerosis!!!*

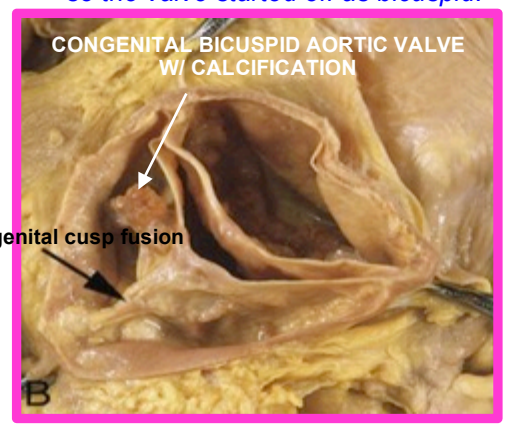


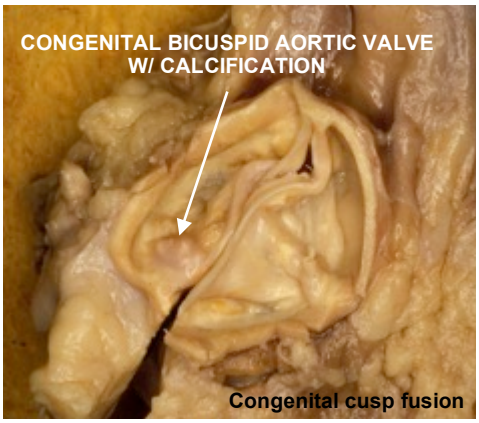


"Here's an important slide."

**CALCIFIC STENOSIS OF CONGENITALLY BICUSPID AORTIC VALVE

- **Congenital bicuspid aortic valves are very susceptible to calcific aortic stenosis**
- Prevalence: 1%; ***accounts for 50% of adult cases of Aortic Stenosis***
- Can be **heritable** with links to loci on chromosomes 18q, 5q, & 13q or acquired
  - *BAVs are most often congenital, while an acquired bicuspid valve occurs when there is fibrous fusion between the right & left cusps of a pre-existing tri-leaflet aortic valve (i.e. post-rheumatic aortic stenosis)*
- More common in **MALES** than females (3:1)
- BAV are normally functional for many years before stenosis sets in
- Clinical symptoms onset generally in **5th or 6th decade** *(earlier than the normal aging stenosis from wear & tear)*
- **BAV complications** include *aortic stenosis, aortic insufficiency* (myxomatous degeneration), *infective endocarditis, & aortic dilation or dissection*
  - *These already weak valves become incredibly dysfunctional at some point in life*
- **PATHOLOGY**
  - 2 functional cusps, unequal in size
  - Larger cusp with raphe, which is the major site of calcium or hydroxyapatite deposition
    - DON'T CONFUSE THIS WITH FUSED COMMISURES FROM POST-RHEUMATIC AORTIC STENOSIS – *Remember that in post-rheumatic aortic stenosis, the aortic valve was once "normal" with 3 leaflets, 2 of which fused together causing the valve to become "bicuspid". In the congenitally bicuspid aortic valve, it was never normal. The 2 cusps fused together congenitally, so the valve started off as bicuspid.*

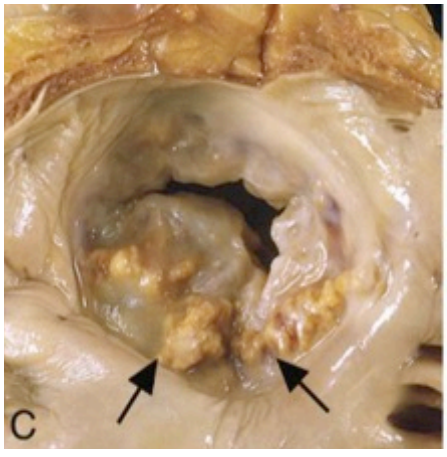




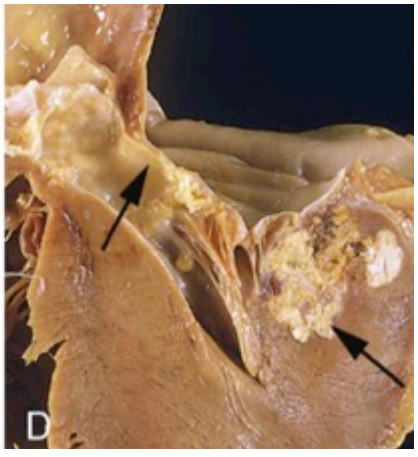
"This is important."

MITRAL ANNULAR CALCIFICATION (MAC)

- Calcific nodular deposits, 2-5mm in diameter, *in the peripheral **fibrous** ring **(annulus)**, not the cusps*
- Ca^{2+} deposits may extend *into the myocardium* & impinge on the AV conduction system *(→ arrhythmias)*
- USUALLY DOES NOT AFFECT VALVULAR FUNCTION! Rarely may lead to regurg, stenosis, & **arrhythmias**
- *"Ring-like opacities" on an XR*
- *Provide a site for thrombus formation*



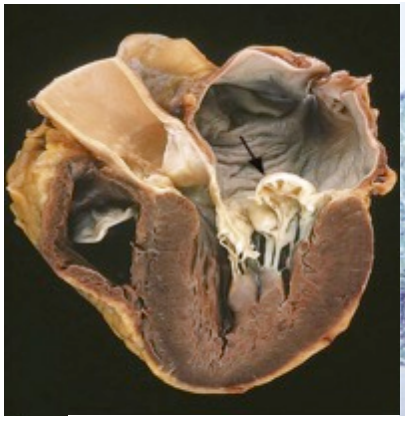
Granular, hard, tan nodules (Does not look like thrombi)

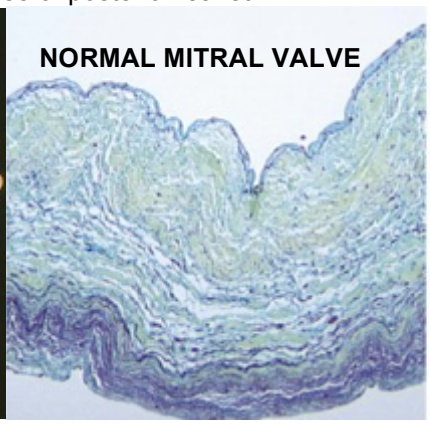


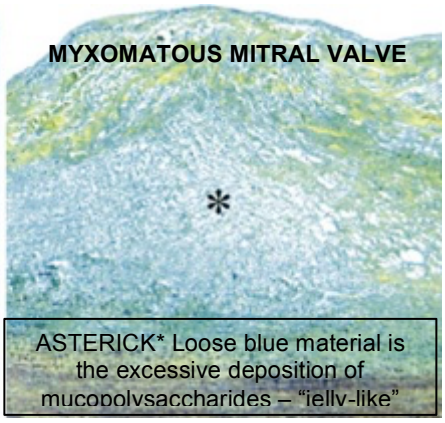
Note the calcific deposits extending into the wall of the myocardium

**MITRAL VALVE PROLAPSE (MVP)

- One or both mitral valve leaflets are floppy & prolapse/balloon back into the LA (during systole)
- 2-3% of adults in the US with a 7:1 female to male ratio
- *MOST COMMON REASON FOR MITRAL VALVE SURGERY IN THE US
- **PATHOGENESIS:**
  - Unknown in most cases
  - Can be associated with CT disorders, such as **Marfan's Syndrome**
    - *Marfan's Syndrome – fibrillin-1 mutations with secondary alteration of cell-matrix interactions*
- **CLINICAL FEATURES:**
  - Mostly asymptomatic with **mid-systolic click**
    - *Also called mitral valve "hooding"*
  - Minority: angina & dyspnea
  - 3% develop: infective endocarditis, mitral insufficiency (with chord rupture), stroke as a result of leaflet thrombi, arrhythmias, or SDC
- **GROSS PATHOLOGY:**
  - Enlarged, thickened, rubbery leaflets
  - Interchordal ballooning
  - Chords may be elongated, thin, or ruptured
- **MICROSCOPIC PATHOLOGY:**
  - **Spongiosa layer thickened by myxomatous degeneration** (*ASTERICK in image below)*
    - *FYI: Myxomatous degeneration refers to pathological weakening of connective tissues with deposition of mucoid (myxoid) material*
- **SECONDARY PATHOLOGY CONSEQUENCES:**
  - Fibrous thickening of valve leaflets
  - Linear fibrous thickenings of LV endocardium secondary to cords snapping
    - As mitral valve prolapses, cords snap against endocardium causing thickening
  - Thickening of LA & LV endocardium secondary to prolapsing valves
    - ***Slaps the LA, damages endothelium → possible thrombus formation + damaged endothelium initiates coagulation pathway***
  - Thrombi on atrial aspect of valves & LA endocardium
  - Focal calcifications at base of posterior leaflet





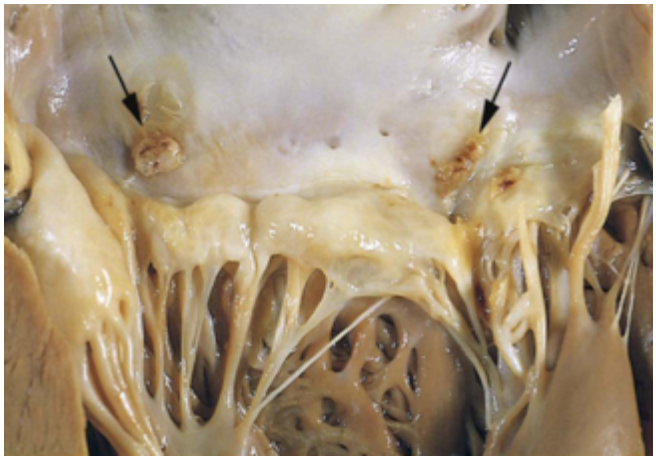


"Classic picture of MVP."

MITRAL VALVE PROLAPSE: Arrows are pointing to thrombotic plaques at sites of contact between the LA & the leaflets. *This is where they are snapping back & hitting the atrial wall.*

PROBLEM: Thrombi embolize → can cause strokes, brain infarcts, renal infarcts

Complications arise anywhere there is single arterial circulation.



RHEUMATIC FEVER & RHEUMATIC HEART DISEASE

**RHEUMATIC HEART DISEASE

- Acute, immunologically-mediated, multisystem inflammatory disease
  - *Essentially an autoimmune disease*
- Onset 10 days to 6 weeks post Group A Streptococcal pharyngitis (3% of patients, usually 5-15 years old)
- Sometimes occurs after a streptococcal skin infection
- **PATHOGENESIS**
  - Adaptive immune response (T cells, antibodies) to Group A Streptococci ***cross-reactivity*** *with cardiac self-antigens – HSR to M protein cross-reacting with glycoproteins in the mitral valve*
- **CLINICAL FEATURES – JONES CRITERIA:**
  - *Migratory polyarthritis, acute carditis, subcutaneous nodules, erythema marginatum of skin, chorea (involuntary extremity movements),* possible fever, arthralgia, elevated CRP

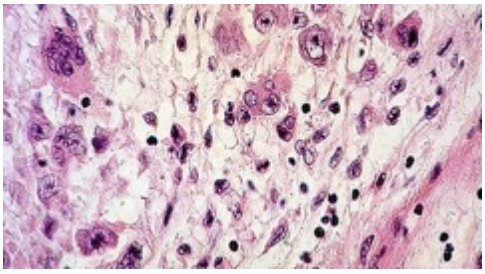
TWO MANIFESTATIONS OF RHEUMATIC HEART DISEASE:

- *Rheumatic heart disease is a deforming fibrotic valvular disease due to antibody & T cell mediated reactions leading to* ***pancarditis (inflammation of the entire heart).*** *Presence of murmurs, hypertrophy/dilation, a-fib, thrombosis, & endocarditis*
- **SUBACUTE INFLAMMATION OF MYOCARDIUM**
- **CHRONIC**, primarily involving valves (mostly **MITRAL VALVE****)
  - ***Primary etiology of mitral stenosis***

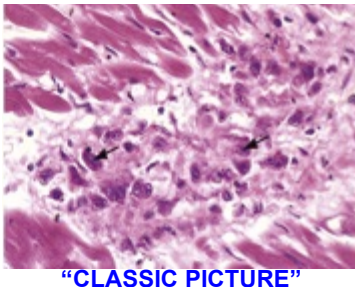
ACUTE RHEUMATIC CARDITIS**

- **PATHOLOGY:**
  - **PANCARDITIS** involving pericardium, myocardium, endocardium & valves
  - Inflammatory foci "****ASCHOFF BODIES**" – *Classic finding of acute pancarditis!*
    - **Aschoff bodies**: T cell foci with plasma cells in myocardium interstitium
    - ****ANITSCHKOW CELLS**: *giant activated macrophages with prominent nucleoli found within Aschoff bodies* that frequently have unique ***caterpillar cell*** *chromatin pattern*
  - ****FIBRINOID NECROSIS** of valves & cords with overlying vegetations *"verrucae"*
  - Fibrous pericarditis
  - **MacCallum plaques:** irregular fibrous thickening of endocardium, most frequently in left atrium
- **CLINICAL FEATURES:**
  - Pericardial **friction rubs** *(because you have pericarditis...)*
  - Tachycardia
  - Arrhythmias (**Aschoff bodies** could be interfering with the conduction system)
  - Cardiac dilation with mitral valve insufficiency or heart failure
  - 1% of those with acute carditis die
  - *If you could catch this early, what drug would you use to treat myocarditis?* ***STEROIDS***
    - *Steroids are a common treatment for immune-mediated diseases*

ASHCOFF BODIES CONTAINING ANITSCHKOW CELLS

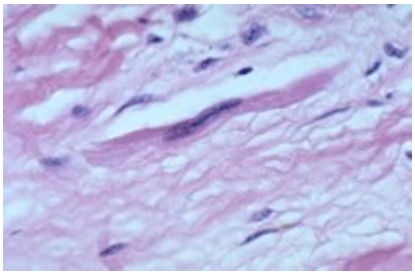


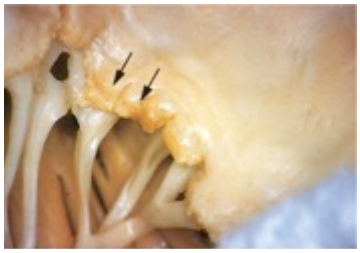
ASHCOFF BODIES CONTAINING ANITSCHKOW CELLS (arrows)



"CLASSIC PICTURE"

Anitschkow Cells – CATERPILLAR CELLS

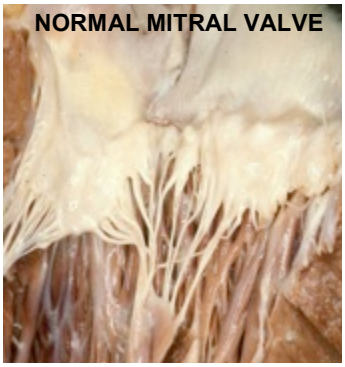


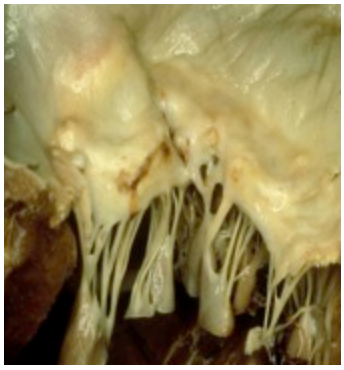


ACUTE RHEUMATIC MITRAL VAVULITIS WITH VEGETATIONS (VERRUCAE) ALONG THE LINE OF CLOSURE OF THE MITAL VALVE LEAFLET

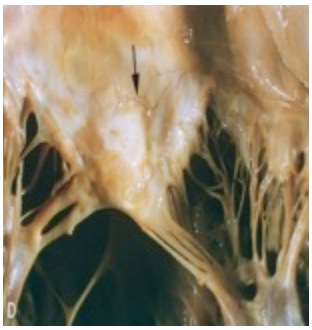
**CHRONIC RHEUMATIC HEART DISEASE

- Disease of just mitral valve in 66% of cases; additional 25% of cases with aortic valve disease
- **GROSS PATHOLOGY:**
  - Diffuse fibrosis of valve
  - Shortening & fusion of chordae tendineae
  - Calcification & fibrous bridging across commissures
    - FISH MOUTH DEFORMITY
- **MICROSCOPIC PATHOLOGY**
  - Neovascularization & transmural fibrosis
  - ***Rare*** *Ashcoff bodies*
- **PATHOLOGY OF LONG-STANDING, SEVERE MITRAL STENOSIS**
  - LA dilation
  - **LA mural thrombi**
  - Pulmonary changes with associated RV hypertrophy
- **CLINICAL FEATURES**
  - Cardiac hypertrophy & dilation, murmurs, arrhythmias (**a-fib**), thromboembolic disease, infective endocarditis
  - *You should be noticing that a PATTERN IS DEVELOPING – With an abnormal valve, any number of things can happen. But at some point → hypertrophy/dilation, murmur, arrhythmia!*

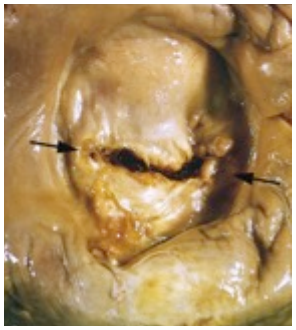




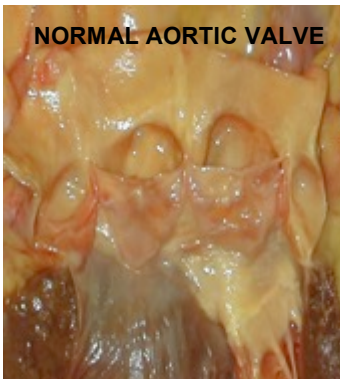
CHRONIC RHEUMATIC MITRAL VALVE DISEASE
Leaflets are thickened & fibrotic with commissural fusion (between arrows)

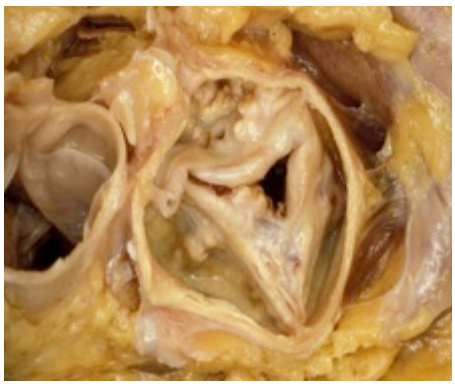


CHRONIC RHEUMATIC MITRAL VALVE DISEASE
Neovascularization of mitral valve leaflet & thickening of the chordae tendineae



CHRONIC RHEUMATIC MITRAL VALVE DISEASE
MITRAL STENOSIS with diffuse fibrous thickening & commissural fusion (arrows) – *FISH MOUTH DEFORMITY*





CHRONIC RHEUMATIC AORTIC VALVE DISEASE
Leaflets are thick & fibrotic with areas of calcification.

All 3 commissures are fused – This does not happen with calcific aortic stenosis!!!

**INFECTIVE ENDOCARDITIS (IE)

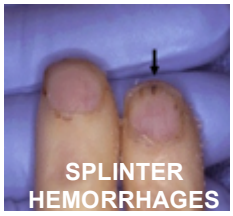
- Microbial infection of heart valves and/or mural endocardium
- Destruction of heart valves or mural endocardium, usually due to bacteria
- Formation of vegetations composed of fibrin, platelet clots, & organisms
    - *Acutely disruptive of the valve*
    - *It can embolize (emboli from infective mass → infarct + infection = ABSCESS)*

TWO VARIATIONS OF INFECTIVE ENDOCARDITIES

- **ACUTE INFECTIVE ENDOCARDITIS**: Infection of previously **NORMAL valve** by highly virulent organism (i.e. *Staph aureus*) that causes marked tissue necrosis (20-30% of cases)
- **SUBACUTE INFECTIVE ENDOCARDITIS**: Infection of **DEFORMED/DISEASED/ABNORMAL valves** by lower virulence organisms (i.e. *Strep viridans*) associated with less acute destruction (50-60% of cases)

IE: CLINICAL HISTORY

- Fever, chills, weakness
- Murmurs in 90% with LEFT sided IE
- DIAGNOSIS: DUKE CRITERIA
- **Splinter hemorrhages = "CLASSIC"**



GROSS PATHOLOGY

- Vegetations on heart valves, most commonly aortic & mitral.
- Usually involves the LEFT valves, except for in IV drug abusers → RIGHT HEART INFECTIVE ENDOCARDITIS
    - *Introducing infection to the venous system, going directly to the R heart*
- Friable
- Infrequent valve ring abscess formation
    - *Systemic microemboli with disseminated bacteria leading to vascular infarcts & microabscesses*
- Embolization with septic infarcts

MICROSCOPIC PATHOLOGY

- Fibrin, acute inflammatory cells, & bacteria (composition of vegetations)
- **Granulation tissue** at base of vegetations in those with subacute IE

COMPLICATIONS: *"Important to know about, but not important enough to have right at the frontal lobe."*

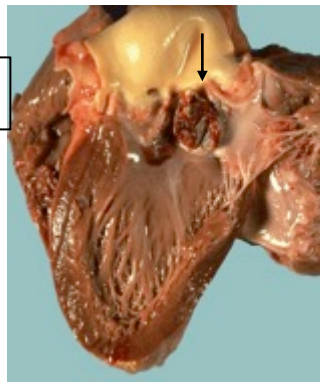
- Glomerulonephritis, microthromboemboli (splinter hemorrhages), hemorrhagic erythematous lesions on palms & soles (Janeway lesions), subcutaneous nodules on palms & soles (Osler nodes), retinal hemorrhages, Roth spots

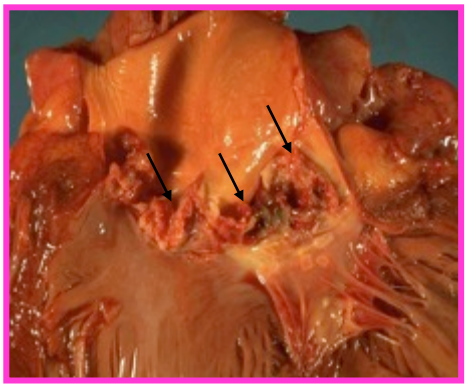
*IMPORTANT INFECTIOUS ENDOCARDITIS COMPLICATIONS TO KNOW!

- ***Rupture of chordae tendineae** [Note: rupture of *papillary muscles* in MI]
- Contiguous spread of infection
- Thromboembolism
- Septic embolic with abscesses
- Valvular regurgitation (often result from rupture of chordae tendineae)

IMAGES FOR INFECTIVE ENDOCARDITIS

VEGETATIONS OF INFECTIVE ENDOCARDITIS

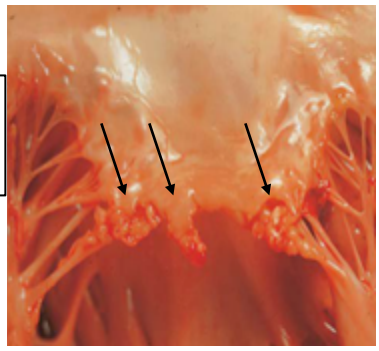


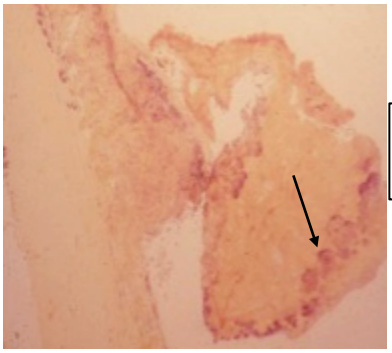


VEGETATIONS OF INFECTIVE ENDOCARDITIS
Destroying aortic valve cusps (arrows) – abnormal function of valve + complications (i.e. regurg), murmur because abnormal blood flow, & pieces of vegetations can break off leading to infarct + abscesses

"This is an important slide."

VEGETATIONS OF INFECTIVE ENDOCARDITIS DESTROYING VALVE LEAFLETS (arrows)

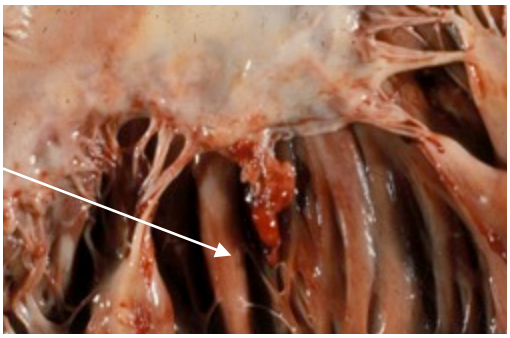


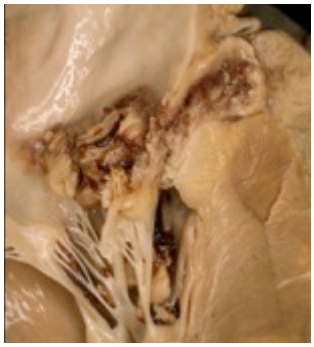


GRAM STAIN SHOWING BACTERIAL COLONIES (arrow) IN A VEGETATION

BACTERIAL ENDOCARDITIS IN A MITRAL VALVE WITH RUPTURED CHORDAE TENDINEAE

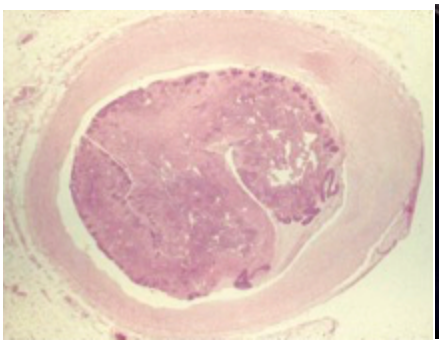
***Note**: rupture of papillary muscles in MI; rupture of chordae tendineae seen in IE*

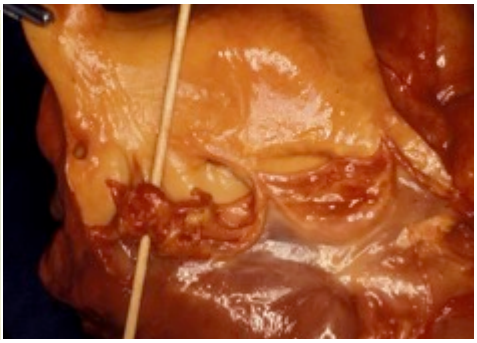




BACTERIAL ENDOCARDITIS IN A MITRAL VALVE WITH PERIVALVULAR ABSCESS (*rare complication*)

SEPTIC EMBOLUS
In a coronary artery from bacterial endocarditis

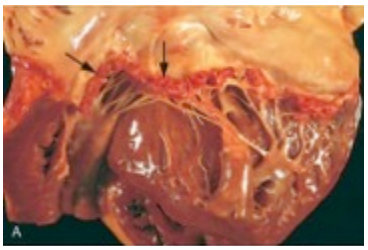




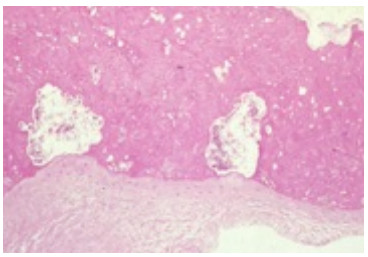
BACTERIAL ENDOCARDITIS IN AORTIC VALVE WITH SECONDARY PERFORATION

**NON-BACTERIAL THROMBOTIC ENDOCARDITIS

- Deposition of small, 1-5mm **STERILE**, non-invasive thrombi on lines of closure of valve leaflets
- **NO INFLAMMATION**
- Thrombus histology
- **ETIOLOGY:**
  - **HYPERCOAGULABLE STATES**
    - Associated with DVT, PE, mucinous adencardinomas
  - ENDOCARDIAL TRAMA from catheters
- **COMPLICATION:**
  - Source of systemic thrombi with infarcts in brain, heart, etc.



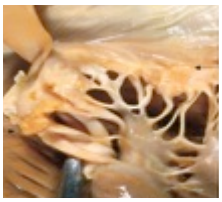
NON-BACTERIAL THROMBOTIC ENDOCARDITIS
With thrombotic vegetations along the line of closure of mitral valve leaflets (arrows)



Histology of VEGETATION from NON-BACTERIAL THROMBOTIC ENDOCARDITIS
Shows fibrin, *few if any inflammatory cells, no bacterial colonies, etc. – NOT GOING TO GET A TREMENDOUS DESTRUCTION OF THE VALVES!*

**ENDOCARDITIS OF SYSTEMIC LUPUS ERYTHEMATOSUS: LIBMAN-SACKS DISEASE

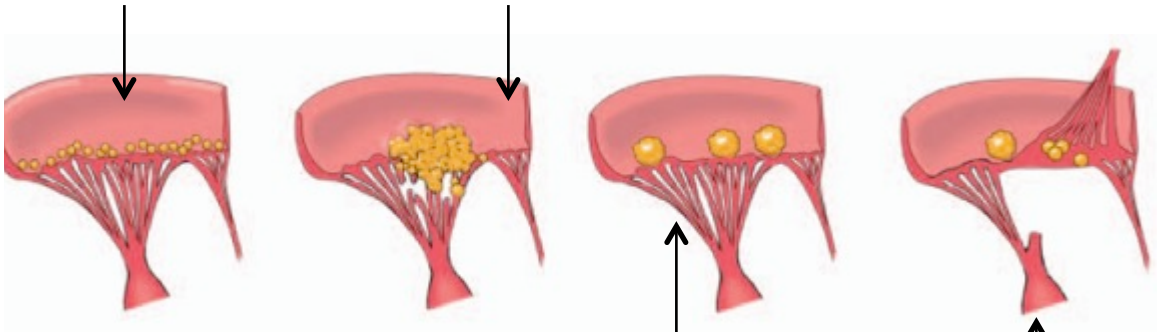
- **GROSS PATHOLOGY**
  - Mitral & tricuspid valvulitis with SMALL (1-4mm) STERILE (*non-infectious*), single or multiple VEGETATIONS with a verrucous appearance
  - Undersurface of AV valves, on chordae tendineae, on atrial or ventricular mural endocardium
    - *Occur on both sides of the valve leaflets*
  - Fibrinoid necrosis of valves
- **MICROSCOPIC PATHOLOGY**
  - Vegetations are finely granular, fibrinous eosinophilic material with nuclear debris



"People will lupus can get an endocarditis/non-infective vegetations that are very small"

ACUTE RHEUMATIC HEART DISEASE (RHD) marked by small, watery verrucae along the lines of closure.

INFECTIVE ENDOCARDITIS (IE) typically shows large, irregular masses on the valve cusps that can extend onto the chordae.



NON-BACTERIAL THROMBOTIC ENDOCARDITIS (NBTE) marked by small, bland vegetations, usually attached at the line of closure. One or many.

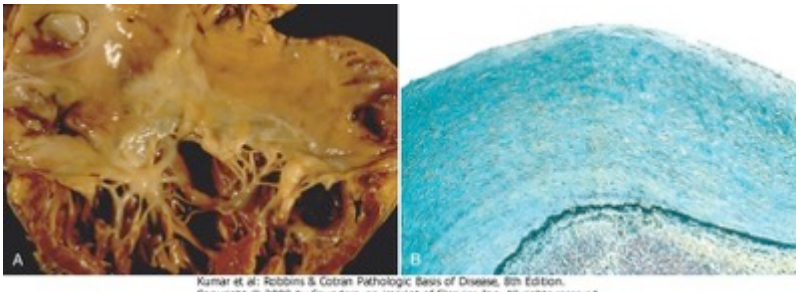
LIBMAN-SACKS ENDOCARDITIS (LSE) has small-medium vegetations on either or both sides of the valve leaflets, or elsewhere on the endocardial surface.

CARCINOID HEART DISEASE

- *Systemic disorder caused by compounds released by carcinoid tumors that result in flushing, diarrhea, dermatitis, & bronchoconstriction*
- Cardiac manifestations caused by **systemic bioactive compounds** in carcinoid syndrome
  - Due to metastatic carcinoid tumor-producing **serotonin** & its urinary metabolite, 5-hydroxytryptamine, correlated best with cardiac lesion severity
- Occurs in 50% of patients with carcinoid tumor
- Carcinoid Heart Disease is most common after **massive liver metastatic burden** associated with high levels of mediators not metabolized by liver & directly released in post-hepatic venous return to heart.

Carcinoid Heart Disease: CARDIAC PATHOLOGY

- **GROSS PATHOLOGY**
  - White, intimal plaque-like thickenings of the endocardium surfaces of the heart chambers & valves
  - **Right chambers & valves** most commonly affected
- **MICROSCOPIC PATHOLOGY**
  - Smooth muscle cells & sparse collagen fibers in an acidic mucopolysacchiarde-rich matrix
- **COMPLICATIONS**
  - Tricuspid insufficiency & pulmonary stenosis



CARCINOID HEART DISEASE – Fibrous thickenings of the R heart endocardium (RV, tricuspid & pulmonary valves). Smooth muscle proliferation & increased mucopolysaccharide matrix.

TYPES OF PROSTHETIC VALVES

- *He won't ask anything about the designs or anything, but he **will ask about differences in pathology that relate to MECHANICAL VALVES & BIOPROTHESIS***

BILEAFLET MECHANICAL VALVE (ST. JUDE)

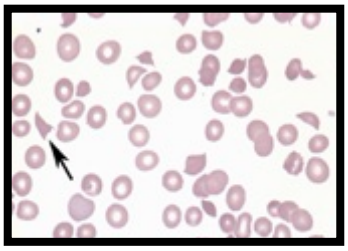
MONOLEAFLET MECHANICAL VALVE (MEDTRONIC HALL)

CAGED BALL VALVE (STARR-EDWARDS)

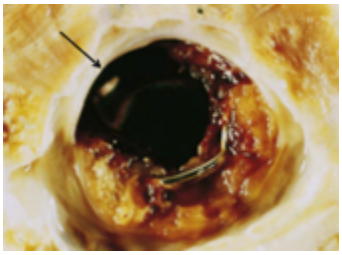
STENT PORCINE BIOPROTHESIS (MEDTRONIC MOSAIC)

COMPLICATIONS OF PROSTHETIC VALVES

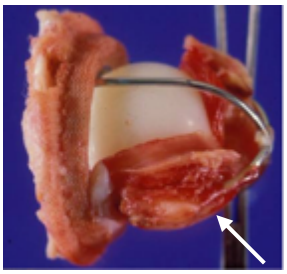
- 60% of prosthetic valve recipients develop serious complication within 10 years of surgery
- ***Complications related to valve type: mechanical valves, bioprosthetic valves***
- **THROMBOEMBOLISM**: most common of MECHANICAL valves
  - ****Can also get hemolysis due to artificial structure of valves → RBCs are chewed up by them***
  - **SCHISTOCYTES due to HEMOLYTIC PHENOMENON**
- **STRUCTURAL DETERIORATION**: occurs in most BIOPROSTHETIC valves over time, which become incompetent secondary to calcification & tearing
- **Infective endocarditis**
  - Increased risk as compared to native valves
  - Involves valve-tissue interface with ring abscess formation
  - Staphylococcal skin contaminants
- Paravalvular leak secondary to poor healing
- Healing overgrowth
- Intravascular hemolysis



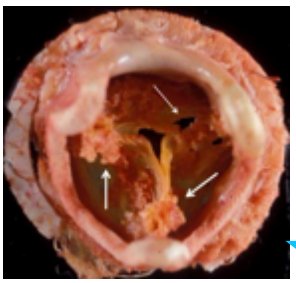
SCHISTOCYTES due to HEMOLYTIC PHENOMENON caused by **MECHANICAL VALVE**



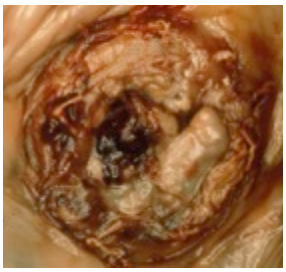
THROMBUS OF A MECHANICAL VALVE
"Would never show something like this"



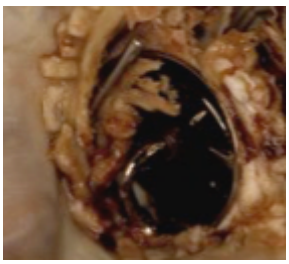
THROMBUS ON VALVE STRUTS (arrow)



PORCINE BIOSYNTHETIC VALVE W/ CALCIFICATION (thick arrows) **& PERFORATIONS** (thin arrows)
"This is an important slide."



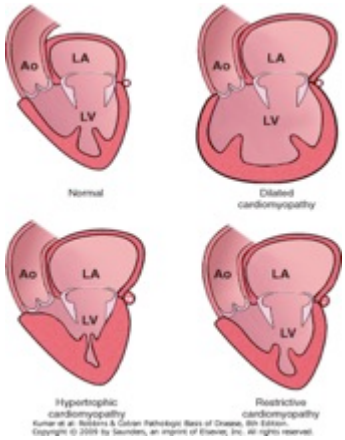
TILTING DISC-TYPE VALVE W/ INFECTIVE VEGETATIONS COVERING THE SURFACE



TILTING DISC-TYPE VALVE W/ INFECTIVE VEGETATIONS & METAL PROBE THROUGH A FISTULA TRACT

CARDIOMYOPATHIES

- ***Cardiomyopathy**: heart disease resulting from a primary abnormality in the myocardium (includes inflammatory & immunologic disorders, muscular dystrophies, & genetic disorders of myocardium)*

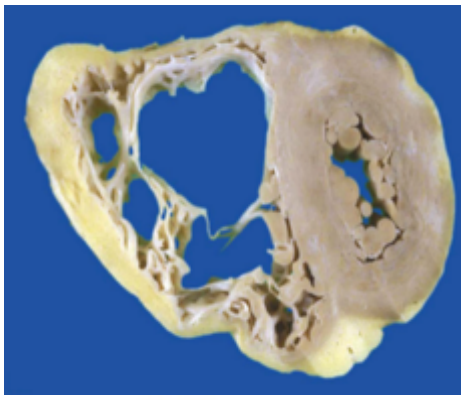


CLASSIFICATION: CARDIOMYOPATHIES WITH ANATOMIC ABNORMALITIES

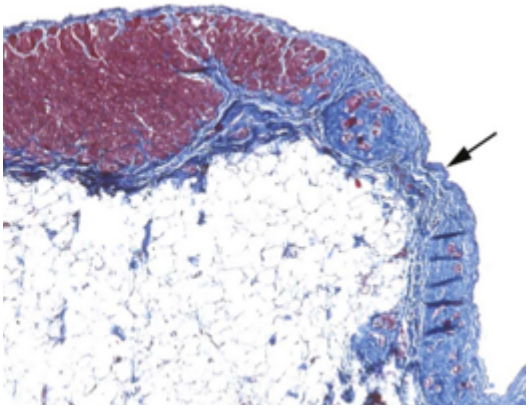
- **CARDIOMYOPATHIES ARE NOT CAUSED BY ATHEROSCLEROSIS!/CORONARY HEART DISEASE
- **DILATED CARDIOMYOPATHY**: Large flabby heart; all chambers are dilated
  - Includes Arrhythmogenic Right Ventricular Cardiomyopathy
- **HYPERTROPHIC CARDIOMYOPATHY**: markedly thickened LV
- **RESTRICTIVE CARDIOMYOPATHY**: mild increase in cardiac mass without increase in volume of LV

**ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

- A FORM OF **DILATED CARDIOMYOPATHY**
- ***INHERITED DISEASE** of myocardium: **RV FAILURE & ARRHYTHMIA***, particularly RV tachy & fibrillation
- **PATHOGENESIS**
  - **AUTOSOMAL DOMINANT inheritance** with variable penetrance
  - **DEFECTIVE** cell adhesion proteins in **DESMOSOMES** between myocytes
  - Naxos Syndrome: ARVC with plantar & palmar hyperkeratosis
- **PATHOLOGY**
  - Marked thinning of RV wall secondary to loss of myocytes
  - Fatty infiltration of RV wall with fibrosis
- **CLINICAL**
  - *RHF with V-tach & V-fib*



ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY: Dilation of the RV. Near-transmural replacement of the RV free-wall by fat & fibrosis.

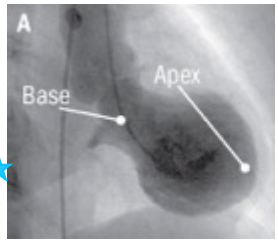


ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY: Histologic section of the RV free wall demonstrating replacement of myocardium (red) by fibrosis (blue, arrow) & fat.

**DILATED CARDIOMYOPATHY (DCM)

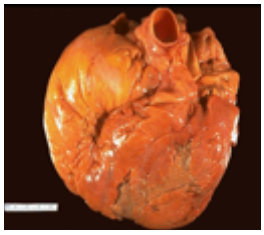
- **Most common cardiomyopathy: 90% of cases**
- Progressive cardiac dilation & **contractile (SYSTOLIC) dysfunction** – *lowest ejection fraction*
  - Few cases associated with congenital abnormalities in conduction
- ECCENTRIC hypertrophy from volume overload
- **CLINICAL FEATURES**
  - Most common between ages 20-50
  - High mortality rate
  - Significant symptomatic CHF & pulmonary involvement
  - **Slowly progressive CHF**: ejection fraction < 25%
  - **Arrhythmias common** & may be fatal (atrial & ventricular)
  - Secondary mitral **regurgitation**
  - Thromboembolic disease
  - *Most common indication for cardiac transplantation*
- **PATHOGENESIS**
  - GENETIC INFLUENCES
    - **Familial** in 50% or less of cases (AD is predominant pattern)
    - **20% of cases secondary to mutation in TTN, which encodes TITIN *(myocyte cytoskeleton)***
    - Abnormality in over 20 genes *(He didn't go over this information)*
      - Mt defects in pediatric population
      - Mutation may be in membrane-associated dystrophin gene in a subset of X-linked cases, present in early adulthoods
  - MYOCARDITIS: With or without viral infection (coxsackie B)
  - ***ALCOHOL**: Highly associated with DCM – *"This is huge..... I STUDIED THIS***"*
    - May be secondary to direct toxicity of alcohol or acetylaldehyde
    - OTHER TOXINS: chemotherapy agents (doxorubicin/Adriamycin), heavy metals (Cobalt)
  - **CHILDBIRTH-ASSOCIATED DCM** – *"These are important concepts of pathogenesis"*
    - Late **PREGNANCY*** & post-partum *(not alcohol-associated)*
    - **Multifactoral etiology:**
      - Pregnancy-associated HTN, volume overload, nutritional deficiencies, etc.
      - May be secondary to microvascular angiogenic imbalance with 2nd MI
        - VEGF inhibitors (sFLT1) & Prolactin anti-angiogenic cleavage products
  - IRON OVERLOAD: *Most common serious sequelae of iron excess (**Hemochromatosis**)*
    - Secondary to hereditary hemochromastosis or multiple transfusions
  - **SUPRAPHYSIOLOGIC STRESS** – *"..something I find interesting"*
    - Etiology includes persistent tachy, hyperthyroidism, congenital lesion in fetus of IDDM mothers, & EXCESS CATECHOLAMINES (also seen with **cocaine** & sometimes dopamine)
    - Excess catecholamines: pheochromocytoma, intense autonomic stimulation
      - Catecholamine effect: multifocal myocardial contraction band necrosis leading to DCM, as a result of direct toxicity or focal vasoconstriction of macro & microcirculation
    - **TAKOTSUBO CARDIOMYOPATHY (BROKEN HEART SYNDROME)**
      - *"There's one I find specifically interesting..."*
      - LV contractile dysfunction with apical ballooning *(image to right)*

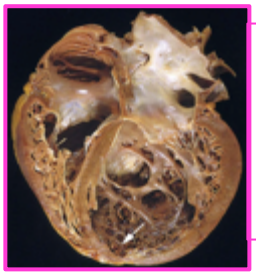
*This is in contrast to **Hypertrophic Cardiomyopathy** where almost all cases have genetic basis.*



PATHOLOGY OF DCM

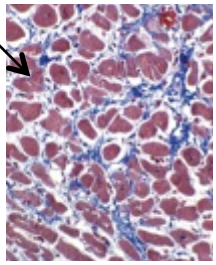
- **MASSIVE/ENLARGED, HEAVY, floppy heart w/ dilation of all chambers & THIN WALLS**
- **Mural thrombi** – *high association due to stasis of LV*
- No primary valve alterations
  - Functional tricuspid & mitral regurgitation from ventricular dilation
- No CAD, or insufficient CAD for cardiac dysfunction
- **MICROSCOPIC PATHOLOGY**
  - Myocyte **hypertrophy** with scattered attenuated, stretched, & irregular myocytes
  - Interstitial & endocardial **fibrosis** *(myocyte hypertrophy associated with fibrosis)*, variable

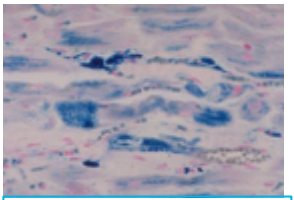




DCM with 4 chamber dilation, hypertrophy, & mural thrombus (arrow) at the apex of LV

"They're not going to get CHF & pulmonary edema, they're going to get nutmeg liver."

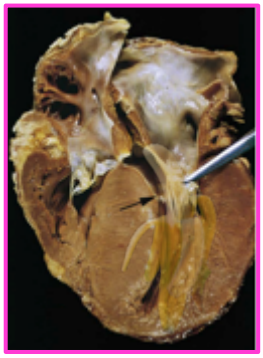




HEMOCHROMATOSIS

**HYPERTROPHIC CARDIOMYOPATHY (HCM)

- Common (1/500) genetic disorder; usually AD pattern of inheritance
- Leading cause of LV hypertrophy in those cases without another cause (i.e. HTN)
- **SUDDEN CARDIAC DEATH IN YOUNG ATHLETES** (most commonly in basketball & football)
- CONCENTRIC hypertrophy from pressure overload
- **CLINICAL FEATURES** – *"There's really nothing they don't get"*
  - Exertional dyspnea in patients with secondary increases in pulmonary venous pressure
  - A-fib
  - Mural thrombus formation with embolization
  - Cardiac failure
  - Ventricular arrhythmias
  - Sudden cardiac death
- **PATHOBIOLOGY**
  - MYOCARDIAL HYPERTROPHY: poorly compliant LV with abnormal **DIASTOLIC** filling & reduced SV
  - INTERMITTENT LV OUTFLOW OBSTRUCTION (25% of cases) → *systolic ejection murmur*
  - *Markedly thickened LV & hypercontractility*
- **PATHOGENESIS –ALL ARE GENETIC IN ORIGIN!!!*****
  - Mutation in genes encoding sarcomeric proteins
  - 400 different mutations associate with 9 genes
  - 70-80% of all cases secondary to: mutation in gene encoding β-**myosin heavy chain** (majority) OR mutation in genes encoding cardiac TnT, α-tropomyosin, & myosin-binding protein C
- **PATHOLOGY**
  - Massive myocardial hypertrophy without ventricular dilation
  - Asymmetric **SEPTAL** hypertrophy (3x the LV wall thickness) in 90% of cases
    - Prominent in **subaortic** region
    - *Septal hypertrophy → obstruction of LV outflow tract → harsh systolic ejection murmur & possible sudden death*
  - Fibrous endocardial plaque in LV outflow track with thickening of anterior mitral valve leaflet (secondary to both surfaces abnormally in contact during systole)
- **HISTOPATHOLOGY**
  - Massive myocyte hypertrophy, often 2-2.5X normal diameter (**THICK WALLS**)
  - Haphazard disarray of bundles of myocytes, individual myocytes, & contractile elements in sarcomeres (AKA lack of organization of myofibers)
  - Interstitial & replacement fibrosis

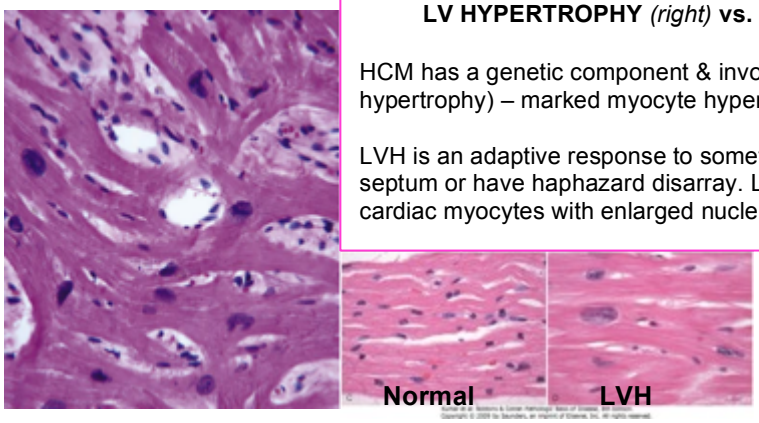


HYPERTROPHIC CARDIOMYOPATHY WITH ASYMMETRIC SEPTAL HYPERTROPHY (arrow) – *Septum is almost so large that it's oval & could occlude subaortic region causing aortic stenosis*
**Note the banana shape to the LV
"This is so classic, I'm showing you a picture of it"

***KNOW THE DIFFERENCE BETWEEN THE IMAGES:**
LV HYPERTROPHY *(right)* **vs. HYPERTROPHIC CARDIOMYOPATHY** *(left)*

HCM has a genetic component & involves the SEPTUM (asymmetrical *septal* hypertrophy) – marked myocyte hypertrophy & haphazard disarray of myocyte bundles.

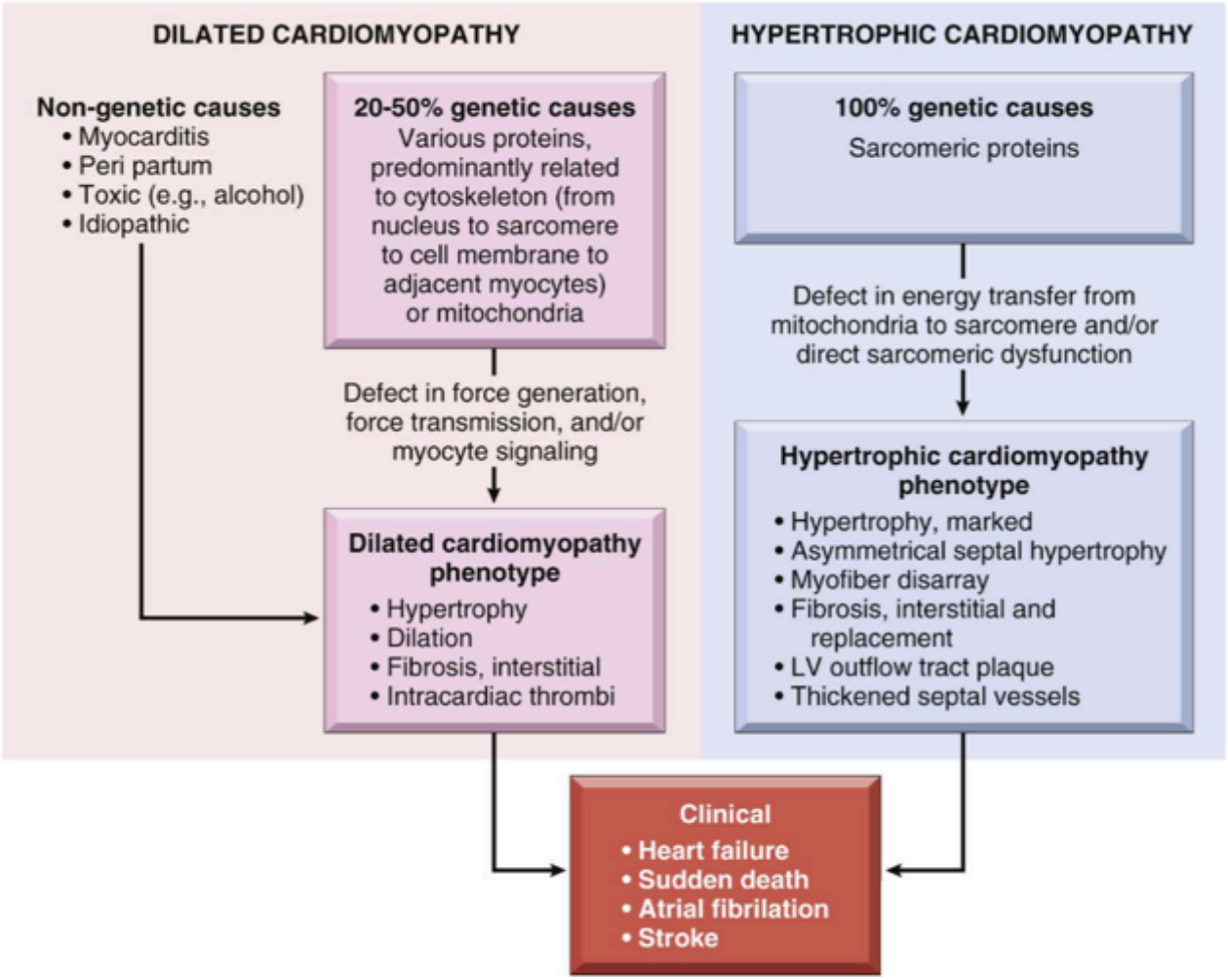
LVH is an adaptive response to something like systemic HTN & does NOT involve the septum or have haphazard disarray. LVH is just your standard hypertrophy with enlarged cardiac myocytes with enlarged nuclei.



**DILATED CARDIOMYOPATHY vs. HYPERTROPHIC CARDIOMYOPATHY

- Some DCMs & virtually all hypertrophic cardiomyopathies are genetic in origin
- In contrast, the mutated genes that cause **HCM** encode proteins of the **sarcomere**.
- Although these 2 forms of cardiomyopathy differ greatly in subcellular basis & morphologic phenotypes, they are a common set of clinical complications → *heart failure, sudden death, a-fib, stroke*

DILATED CARDIOMYOPATHY	**HYPERTROPHIC CARDIOMYOPATHY**
Heart is flabby, dilated, & hypocontracting	Heart is thick-walled & hypercontracting
Systolic dysfunction	Diastolic dysfunction
Long history of progressive CHF	Exertional dyspnea, but no CHF
Mutations involve abnormalities of the cytoskeleton	Mutations involve proteins of the sarcomere



RESTRICTIVE CARDIOMYOPATHY (RCM)

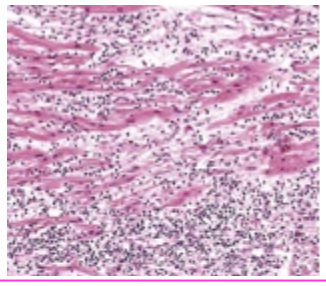
- *Rare disease of the myocardium & is the least common of the 3 clinically-recognized/described cardiomyopathies*
- Primary decrease in ventricular compliance with **impaired ventricular filling** (diastolic dysfunction)
- **ETIOLOGY**
  - **Idiopathic**
  - Secondary to radiation fibrosis, **amyloidosis**, sarcoidosis, metastatic tumors, inborn errors of metabolism
- **GROSS PATHOLOGY**
  - Normal or slightly enlarged ventricles
    - *Mild increase in cardiac mass without increase in volume of the LV*
  - Biatrial dilation, no ventricular dilation
  - Firm & non-compliant myocardium
- **HISTOPATHOLOGY**
  - Interstitial fibrosis, patchy or diffuse
- The importance of an accurate diagnosis of RCM is to distinguish this condition from constrictive pericarditis, a clinically & hemodynamically similar entitiy that also presents with restrictive physiology but is frequently curable by surgical intervention

RESTRICTIVE HEART DISEASE (NON-CARDIOMYOPATHY)

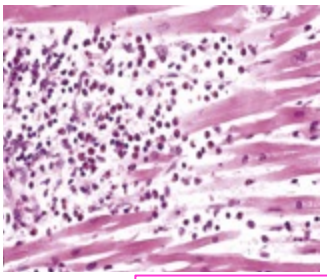
- ENDOCARDIAL FIBROSIS – *These are rare; skipped slide*
  - Disease of children & young adults in **Africa**
  - Unknown etiology
  - Fibrosis of ventricular endocardium & subendocardium that extends from apex to mitral & tricuspid valves
  - Restrictive functional defect
  - Mural thrombi
- LOEFFLER ENDOMYOCARDITIS – *Skipped slide*
  - Often rapidly fatal
  - **PATHOLOGY**
    - Eosinophilic endomyocarditis *(damage is due to eosinophil Major Basic Protein)*
    - Endomyocardial fibrosis similar to EF
    - Mural thrombi
  - **PATHOGENESIS**
    - Myeloproliferation disorder
    - Abnormality of platelet-derived growth factor receptors (PDGFR) & subsequent constitutively active PDGFR tyrosine kinase
- ENDOCARDIAL FIBROELASTOSIS – *Skipped slide*
  - **CLINICAL FEATURES**
    - Most common in the first 2 years of life
    - Diffuse involvement associated with rapid cardiac decompensation & death
  - **PATHOGENESIS**
    - Common morphologic endpoint of different insults (i.e. intrauterine mumps, mutation of tafazzin gene – mitochondrial integrity)
  - **PATHOLOGY**
    - Fibroelastic thickening primarily involving the LV endocardium

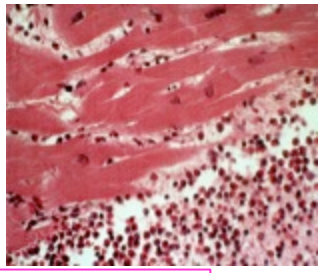
MYOCARDITIS

- Inflammation of the heart secondary to infection or a primary inflammatory process
  - *Inflammation that is not secondary to ischemic events or cardiac rejection of transplantation – AKA not a response to myocardial injury*
- Spectrum of mild to severe disease
  - Fatigue, dyspnea, fever, chest pain
  - Sudden onset of heart failure, arrhythmias, or sudden cardiac death
- **PATHOGENESIS**
  - VIRAL INFECTIONS are most common cause
    - COXSACKIE A & B*
    - Cytomegalovirus, HIV, influenza
  - IMMUNE-MEDIATED RESPONSE associated cytokines can produce myocardial dysfunction out of proportion to myocyte damage
  - NON-VIRAL INFECTIONS
    - Protozoan infection – Trypanosoma cruzi (**Chagas Disease**)
      - 10% mortality in acute myocarditis
    - Helminthic infection – Trichinella spiralis
    - Bacterial infection – Corynebacterium diptheriae (toxin-induced myocarditis)
- **GROSS PATHOLOGY**
  - Normal or dilated (hypertrophy, if chronic)
  - Heart is flabby in severe disease
  - In severe disease, pale & hemorrhagic foci
  - Mural thrombi may be present
- **HISTOPATHOLOGY**
  - **CLASSIC MYOCARDITIS**
    - Mononuclear cell infiltrate, principally lymphocytic, diffuse or patchy
    - Myocyte necrosis
  - **HYPERSENSITIVITY MYOCARDITIS**
    - Interstitial eosinophils with lymphocytes & macrophages
  - **GIANT CELL MYOCARDITIS**
    - Diffuse inflammatory infiltrate with giant cells, lymphocytes, plasma cells, eosinophils, & macrophages
    - Extensive myocyte necrosis
  - **CHAGAS DISEASE – Trypanosoma cruzi**
    - Parasites within myocytes transported by insect vector, **triatomine insect** *("kissing bug")*
    - Mixed acute + chronic inflammatory infiltrate
    - **BRAZIL –** *regions of South America*

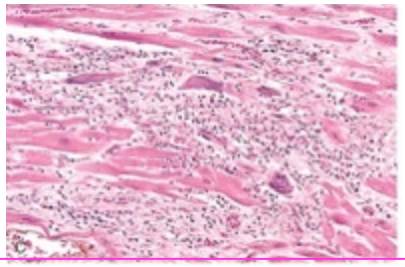


LYMPHOCYTIC MYOCARDITIS
Round, blue cells = inflammatory cells

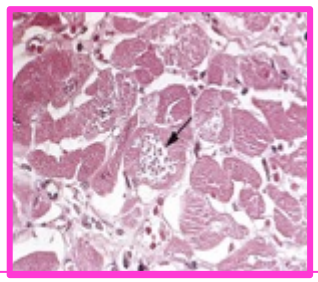




HYPERSENSITIVITY MYOCARDITIS
Containing numerous eosinophils



GIANT CELL MYOCARDITIS
With mononuclear inflammatory infiltrate containing lymphocytes & macrophages, extensive loss of muscle, & multinucleated giant cells.



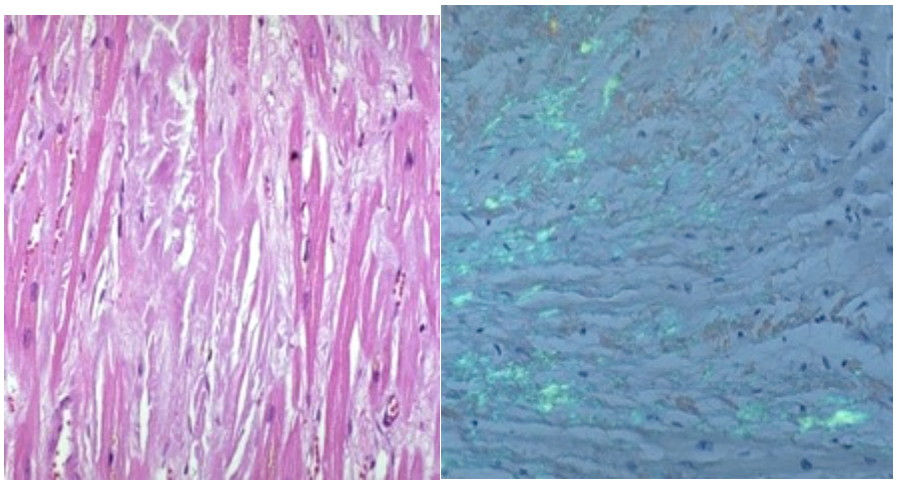
CHAGAS DISEASE (MYOCARDITIS)
Myofiber distended with trypanosomes (arrow).

CARDIAC AMYLOIDOSIS

- Results from Primary "Senile Cardiac Amyloidosis" or secondary/systemic amyloidosis
  - *Primary systemic amyloidosis involves most visceral organs & almost always there is deposition of amyloid in myocardial interstitium leading to **Restrictive Cardiomyopathy** with arrhythmias*
- Restrictive cardiomyopathy most frequent
- Clinical presentation secondary to principal site of deposition: interstitium, conducting system, vasculature, valves
- **GROSS PATHOLOGY:**
  - Consistency: normal to firm & rubbery
  - Chambers usually of normal size
  - Atrial (L>R) endocardial nodules: small, semitranslucent
- **HISTOPATHOLOGY**
  - Hyaline eosinophilic deposits in all cardiac tissues
    - *Homogenous pink amorphous material in myocyte interstitium*
  - Congo red positive (apple-green birefringence)
  - Deposits in small vessel walls may occlude lumen

SENILE CARDIAC AMYLOIDOSIS

- Most common >70 years old
- Better prognosis than systemic disease
- **PATHOGENESIS**
  - Deposits principally contain **transthyretin**
    - **Mutant transthyretin** accelerates disease
      - Isoleucine substituted for valine resulting in amyloidogenic protein (highly susceptible to β-pleated sheet folding)
    - Mutation present in 4% of African-Americans



CARDIAC AMYLOIDOSIS
Left, H&E stain of cardiac amyloidosis.
Right, showing apple-green birefringence with Congo Red stain.

PERICARDIAL DISEASE

- Pericardium normally contains <50mL of thin, staw-colored fluid
- **PERICARDIAL EFFUSION:** pericardial space distended by serous fluid
- **HEMOCARDIUM:** pericardial space extended by blood
- **PURULENT PERICARDITIS:** pericardial space extended by pus
- *Slow accumulation:* no cardiac dysfunction until VERY large (>500mL)
- *Rapid accumulation:* compression of venae cavae & atriums and/or cardiac tamponade (200-300mL)

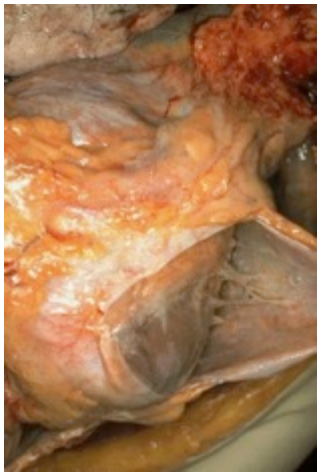
ACUTE SEROUS PERICARDITIS

- Caused by non-infectious inflammatory disorders
- **PATHOLOGY**
  - Pericardial space distended by serous fluid
  - Mild mononuclear cell infiltrate in epicardial fat
  - If tumor associated, neoplastic cells may float within the fluid

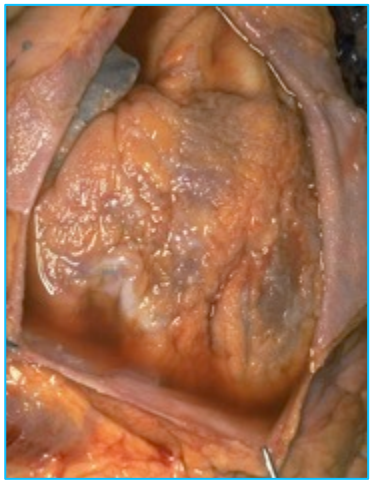
ACUTE FIBRINOUS & SEROFIBRINOUS PERICARDITIS

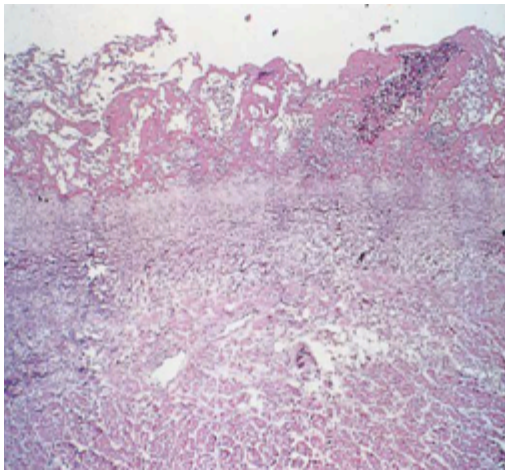
- *"If there's one type of pericarditis that you should remember, it's this one. That's not saying I'm going to test on this one, but I'm saying this is important because this is the one people classically go about."*
- Serous fluid containing fibrin
- **Most frequent form of pericarditis**
- **PATHOGENESIS**
  - Acute MI
  - Post-infarction Syndrome (Dressler Syndrome – autoimmune response)
  - Uremia
  - Chest radiation
  - Rheumatic Fever
  - SLE
  - Trauma
- **PATHOLOGY**
  - FIBRINOUS PERICARDITIS – finely granular dry surface
  - SEROFIBRINOUS PERICARDITIS – granular wet roughening of pericardial surfaces with accumulation of yellow to brown fluid (contains WBCs, RBCs, & fibrin)
  - *"Robbins divides these too precisely. So in your mind, let's just put these two together."*
- **CLINICAL FEATURES**
  - PAIN: sharp, position dependent, pleuritic
  - Fever
  - CHF may be present
  - Loud pericardial friction rub

"It's an absolutely classic picture of serofibrinous pericarditis"



FIBRINOUS PERICARDITIS



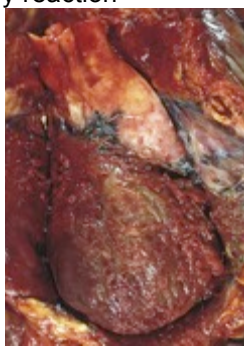


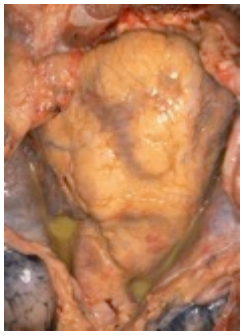
SEROFIBRINOUS PERICARDITIS
Left, gross image.
Right, histology of serofibrinous pericarditis showing extensive fibrin & admixed inflammatory cells.

ACUTE PERICARDITIS – PURULENT/SUPPURATIVE PERICARDITIS

- Active infection of pericardial space – *Will likely be caused by bacterial organism*
- **CLINICAL**
  - Spiking fevers
  - Symptoms of pericarditis
  - Congestive failure possible
  - Development over time of constrictive pericarditis
- **PATHOGENESIS**
  - Direct extension from empyema *(pus in pleural cavity)*, lobar pneumonia, mediastinitis, extension of ring abscess *(abscess around the valve)*
  - Seeding from the blood
  - Lymphatic extension
  - Direct introduction during a surgical procedure (i.e. cardiotomy)
- **GROSS PATHOLOGY**
  - ACUTE: red, granular, coated with exudate
  - CHRONIC: scarring
- **HISTOPATHOLOGY**
  - Acute inflammatory reaction

ACUTE SUPPURATIVE PERICARDITIS

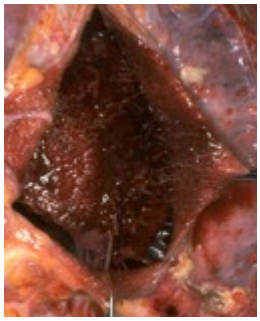




ACUTE SUPPURATIVE PERICARDITIS W/ PUS

HEMORRHAGIC PERICARDITIS

- Blood admixture with fibrinous or suppurative effusion
- **PATHOGENESIS**
  - Metastatic **tumor** to pericardium most common
  - Bacterial infections in patients with coagulopathy
  - Tuberculosis
  - Cardiac surgery

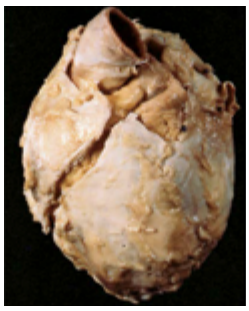


CASEOUS PERICARDITIS

- Caused by tuberculosis
  - Infrequently by fungal organisms
- Direct spread from tracheobronchial nodes
- Frequently leads to fibrocalcific constrictive pericarditis

CHRONIC/HEALED PERICARDITIS – CONSTRICTIVE PERICARDITIS

- Heart encased in dense fibrous or fibrocalcific scar
  - May be up to 1 cm in thickness
  - Rare extreme calcification *"concretio cordis"*
- **CLINICAL MANIFESTATIONS**
  - Severe constrictive pericarditis
  - Muffled heart sounds, elevated jugular pressure, peripheral edema
  - Reduced response to increased systemic demands on heart



HEART DISEASE ASSOCIATED WITH RHEUMATOLOGIC DISORDERS

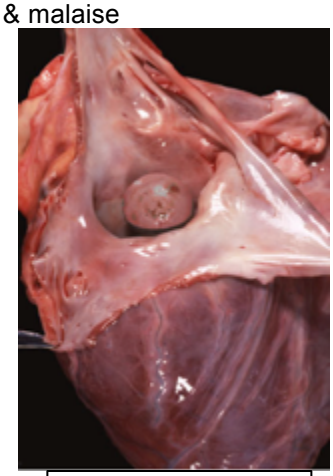
- Heart involvement in several chronic rheumatologic disorders
  - RA, SLE, systemic sclerosis, ankylosing spondylitis, psoriatic arthritis
- Findings in Rheumatic Arthritis
  - Cardiac involvement in 20-40% of cases
  - Fibrinous pericarditis most common
  - Granulomatous rheumatic nodules in myocardium, endocardium, valves, & aortic root
  - Rheumatic valvulitis: fibrous thickening & secondary calcification

PRIMARY CARDIAC TUMORS

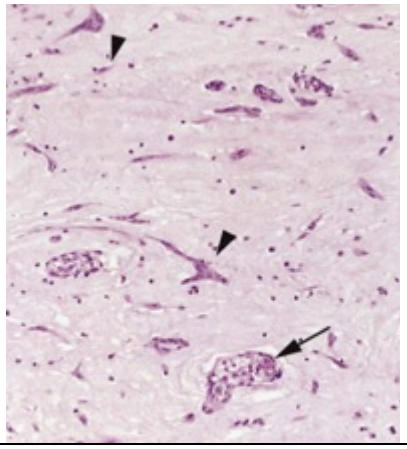
- PRIMARY cardiac tumors occur less frequently than METASTATIC tumors to the heart
  - **Myxomas (most common tumor arising in the heart)**
  - Lipomas – benign tumors of fat
  - Papillary fibroelastomas – *"Not going to talk about that."*
  - **Rhabdomyoma**
  - Sarcomas – *"Will not talk about this. These are tumors of CT, muscle, fat."*

MYXOMAS

- **Most common primary heart tumor!**
- Benign neoplasms arising from primitive multipotent mesenchymal cells
- **PATHOGENESIS**
  - Sporadic & familial
    - Familial associated with mutations in GNAS1 gene (G protein) or in PRKAR1A, encoding a protein kinase
- **PATHOLOGY**
  - 90% in atria, with L:R ratio of 4:1 – *AKA Most are in **L ATRIUM***
  - Sessile or pedunculated (TOOTSIE POP shape)
  - <1 cm to > 10cm
  - Globular, hard, & hemorrhagic OR soft, translucent, papillary, & gelatinous
- **HISTOPATHOLOGY –** *"Very classic histology."*
  - **Stellate** or globular myxoma cells
  - Acid **mucopolysaccharide-rich matrix**
  - **Vessel-like/gland-like structures**
  - Hemorrhage
  - Mononuclear cell infiltrations
- **CLINICAL FEATURES**
  - "Ball-valve" obstruction of mitral or tricuspid valve by pedunculated tumor
  - Embolization
  - Fever & malaise



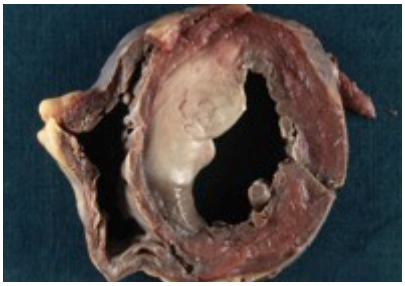
ATRIAL MYXOMA

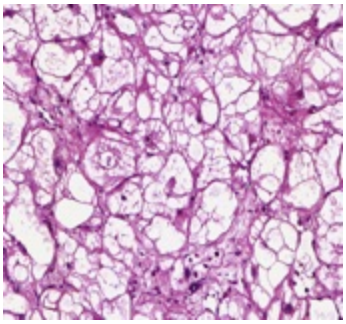


MYXOMA – Stellate & multinucleate myxoma cells (arrow heads), acid mucopolysaccharide-rich matrix, vessel-like/gland-like structures (arrows)

**RHABDOMYOMA

- **MEDSCAPE:** *Cardiac rhabdomyoma is the most common primary pediatric tumor of the heart and is considered to be a hamartoma of developing cardiac myocytes. This tumor may demonstrate mild atypical histologic features, but it lacks the capacity for metastasis or invasion. Although the behavior of a cardiac rhabdomyoma is benign, the positioning within critical areas in the heart can lead to lethal arrhythmias and chamber obstruction. The natural history of cardiac rhabdomyomas is one of spontaneous regression.*
- **CLINICAL**
  - **MOST FREQUENT PRIMARY TUMOR OF THE PEDIATRIC HEART!**
  - May cause obstruction of valvular orifice or cardiac chamber
  - Often regress spontaneously suggesting they are hamartomas
- **PATHOGENESIS**
  - 50% spontaneous; 50% associated with tuberous sclerosis
    - Mutation in TSC1 or TSC2 tumor suppressor gene with subsequent myocyte overgrowth
- **GROSS PATHOLOGY**
  - Gray-white myocardial masses
  - Multiple
  - Most are in the **VENTRICLES** – can protrude the lumen
- **HISTOPATHOLOGY**
  - Large myocytes cytoplasmic threads to cell membrane: **"SPIDER CELLS"**

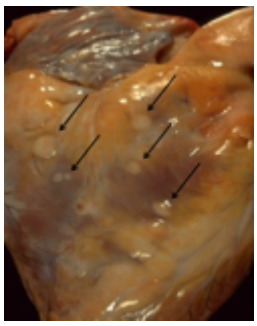




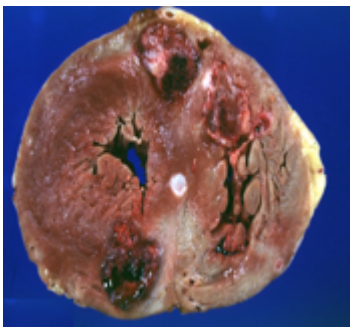
RHABDOMYOMA
Spider cells of rhabdomyoma

METASTATIC TUMORS

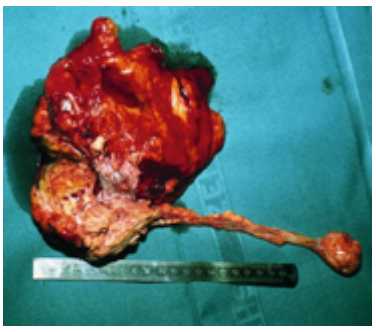
- Tumor Types
  - *"Most common tumors metastasizing to the heart originate from lung or breast; but if a patient has melanoma, the heart is one of the most likely sites it will metastasize to."*
  - **Carcinomas of lung, breast**
  - Lymphomas & leukemias
- Mechanisms of spread to the heart:
  - Lymphatic extension, hematogenous seeding, contiguous extension (lung, breast, esophagus), **venous extension (kidney)**



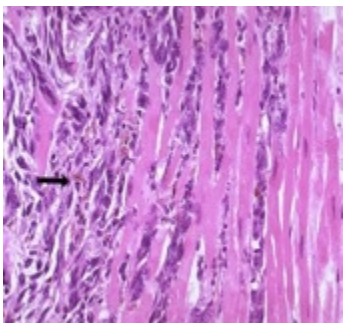
METASTATIC CANCER (arrows)



METASTATIC CARCINOMA W/ EXTENSIVE TUMOR NECROSIS



RENAL ADENOCARCINOMA EXTENDING INTO R ATRIUM
(Tumor was removed from RA)



MELANOMA METASTATIC TO HEART – Arrow points to melanin-rich tumor cell with dark brown granules

"This is a classic tumor they talk about when they talk about a venous extension of a tumor – "What tumor extends through the venous circulation & goes into the heart? RENAL ADENOCARCINOMA!"

CARDIOVASCULAR EFFECTS OF NON-CARDIAC NEOPLASMS

Direct Consequences of Tumor
Pericardial and myocardial metastases
Large vessel obstruction
Pulmonary tumor emboli
Indirect Consequences of Tumor (Complications of Circulating Mediators)
Nonbacterial thrombotic endocarditis
Myeloma-associated amyloidosis
Effects of Tumor Therapy
Chemotherapy
Radiation therapy

CARDIAC TRANSPLANATION

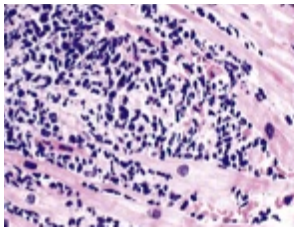
- 1st human to human transplant
- 1 year survival 90%; 5 year >60%
- Treatment for intractable heart failure
  - MOST COMMONLY RESULTING FROM **DILATED CARDIOMYOPATHY** & IHD

CLINICAL COMPLICATIONS

- INITIAL POST-OP PERIOD:
  - Surgical complications
  - Primary graft failure
- EARLY POST-OP PERIOD:
  - Infections (i.e. cytomegalovirus)
- WEEKS TO YEARS POST-OP:
  - Acute & chronic rejection
  - Cancer (skin cancer, EBV-associated lymphoma)

ACUTE REJECTION

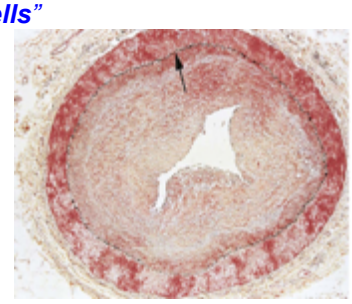
- **Cell-mediated rejection**: mononuclear infiltrate with myocyte damage or necrosis
  - Treat by increasing the amount of immunosuppressant
- **Antibody-mediated rejection**



ACUTE REJECTION of cardiac allograft

CHRONIC REJECTION

- Allograft arteriopathy/vasculopathy
  - Single largest impediment to long term graft survival
  - Develops in 50% of patients with 5 years
  - Can result in CHF or ***sudden cardiac death***
  - Fibro-intimal hyperplasia containing smooth muscle cells – *"Fancy way of saying the area between the endothelium & internal elastic lamina is markedly **expanded by fibroblasts**, fibrous matrix, & there are **lots of new muscle cells**"*



CHRONIC VASCULAR REJECTION
Arrow points to internal elastic lamina