Arteriosclerosis

- Simply means hardening (sclerosis) of arteries
- May affect small arteries/arterioles (arteriolosclerosis)
- A rare type is fibromuscular dysplasia
- The big one is atherosclerosis

Clinical Consequences of Arteriosclerosis

- Ischemia of distal organs/tissues:
  - Myocardial infarct
  - Brain infarct (stroke)
  - Small bowel and kidney infarcts
  - Gangrene of lower extremities
- Abdominal aortic aneurysm

Note: Ischemia in general is worse than hypoxia. With ischemia, tissues are hypoxic and cellular waste products are not removed. Some degree of adjustment to pure hypoxia is possible, e.g. accommodation to high altitude.

Fibromuscular Dysplasia

- The Wall Street Journal says many medical schools do not address this!
- Refers to focal/segmental thickening of the walls of medium to large muscular arteries (usually medial, arteries may have a “string of beads” appearance)
- Can affect renal, splanchnic, carotid, vertebral arteries
- F > M, typical age 20 to 50 years
- Can be asymptomatic or cause hypertension, headaches, dizziness, tinnitus (depending on the artery involved), even with aneurysm formation or rupture or stroke if severe
- Condition is developmental and familial in some cases
- Treatment may be antihypertensive and antithrombotic meds or angioplasty if necessary

Notes: The Wall Street Journal, June 27 & 28, 2009, ran a front page story about missed diagnoses of this disorder. Missed diagnoses of rare (or fairly rare) diseases make for great lay press stories (eg. celiac disease). FMD may present with bizarre clinical manifestations depending on what organ/tissue is ischemic, leading to incorrect or non-diagnoses. Robbins, 9th ed. has a paragraph on FMD in the blood vessel chapter and another in the kidney chapter, the latter organ being the one most commonly affected by FMD. Diagnosis is by thinking of it and obtaining imaging studies. A bruit over a large artery in the neck or abdomen may occur (although atherosclerosis is a more common cause of this).

Atherosclerosis

- This is the most significant type of arteriosclerosis, and is responsible for approximately half of deaths in the Western world
- It primarily affects the aorta and the larger elastic and muscular arteries (the arteries that have names that you know)

Involved Arteries in Atherosclerosis
- Aorta, abdominal > thoracic; worse around major ostia
- Popliteals, internal carotids, Circle of Willis
- Coronaries
- Usually spared are the upper extremity arteries, mesenteric & renals except at ostia
- Pulmonary arteries not involved except with severe pulmonary hypertension; veins not involved

Note: If the ascending thoracic aorta is severely involved, the causes include diabetes mellitus, hyperlipidemia type II, and syphilis.

**Basic Lesion: The Atherosclerotic Plaque**

- Start out as small intimal plaques \(\rightarrow\) get larger \(\rightarrow\) more numerous \(\rightarrow\) coalesce
- Plaques are typically patchy and eccentric
- Plaques secondarily compress and thin the media
- Plaques consist of varying amounts of lipid and fibrous tissue
- Some compensatory dilatation of the vessel may occur (up to a point)

Notes:
The three principle components of the plaque are:
- Cells: Modified smooth muscle cells, macrophages recruited from blood, monocytes, and T lymphocytes
- Lipid: Intracellular and extracellular. Mostly cholesterol and cholesterol esters
- Other extracellular stuff: Collagen and elastin, proteoglycans, calcium

Proportions vary in different plaques. Plaques may be mainly fibrous without much central lipid.

**Complicated Atherosclerotic Plaques**

- Calcification – may be extensive
- Focal rupture or ulceration – may be accompanied by:
  - Hemorrhage into plaque
  - Thrombus formation on plaque
  - Escape of lipid from plaque \(\rightarrow\) cholesterol emboli (atheroemboli)
- Weakening of media \(\rightarrow\) aneurysm formation

Note:
Thrombus may occlude the lumen \(\rightarrow\) infarct, or may cause thromboemboli. Hemorrhage into a plaque may also cause occlusion of lumen & hematoma formation in vessel wall.

**The Fatty Streak**

- Yellow, minimally raised intimal lesions seen in children & young adults
- Microscopically see lipid-laden macrophages in the intima – streaks go away as AS takes over
- Location of streaks is similar (not identical) to later AS plaques
- Relationship to later AS is complex and unclear

Note:
Both fatty streaks and atherosclerotic plaques are related to increased blood lipids and smoking. Fatty streaks may be seen in populations where atherosclerosis is not prevalent.

**Epidemiology of Atherosclerosis**

- Ubiquitous in N. America, Europe, Australia, New Zealand, Russia, other developed nations
- Much less prevalent in Central & S. America, Africa, Asia

Notes:
Age: Starts in childhood & progresses over decades. Early AS is a common autopsy finding in teens & 20s, but not clinically significant until middle age or later when AS causes symptoms/organ injury.
Sex: M>F, Uncommon in women of child bearing age (unless other strong risk factors are present). The difference equals out by about age 60 – 70. Estrogen replacement may offer some protection if initiated in younger postmenopausal women, but in some studies postmenopausal estrogen replacement actually increased cardiovascular risk.
Genetics: There is a well-established genetic predisposition to atherosclerosis, probably polygenic & related to the genetics of the other risk factors; i.e. diabetes, hyperlipidemia, hypertension. Parents with no significant atherosclerotic disease well into old age may be your best protection.

The Big Risk Factors

- Hyperlipemia (increased LDL and decreased HDL cholesterol)
- Hypertension (blood pressure >130/80 mm Hg or on antihypertensive medication)
- Cigarette smoking
- Family history of premature AS (coronary heart disease in 1st degree male relative <55 years old or 1st degree female relative <65 years old)
- Diabetes mellitus

Hyperlipidemia

- Mostly means hypercholesterolemia – triglycerides are less significant
- Major ↑ risk due to LDL cholesterol
- Inverse relationship to HDL cholesterol
- Exercise and moderate EtOH → ↑HDL
- Obesity and smoking → ↓HDL
- Treatable by diet and pharmacologic means

Notes:
The significant hyperlipidemia subtypes for increased AS risk are types IIa, IIb, and III . HDL is believed to mobilize cholesterol from AS plaques and return it to the liver for excretion in the bile. See text for further evidence implicating hyperlipidemia.
Pearl: Cholesterol lowering can actually cause AS plaques to regress to some extent.

Hypertension

- Risk factor at all ages, but stronger risk factor if past age 45 (even if on antihypertensive meds!)
- Both systolic and diastolic are important
- Antihypertensive therapy reduces the incidence of atherosclerosis related events, especially stroke and ischemic heart disease
- Some evidence now that even “high-normal” BP increases risk (systolic 130 to 139, diastolic 85 to 89) – see NEJM 345:1291-1339, 2001

Cigarette Smoking

- A pack per day for several years doubles the risk of death from ischemic heart disease
- Cessation cuts in half

Diabetes Mellitus

- Induces hypercholesterolemia and markedly increases predisposition to atherosclerosis
- 100X increased risk of gangrene of lower extremities (rare in non-diabetics)
• Complex mechanisms

**Emerging Risk Factors**

• Obesity
• Physical inactivity
• Atherogenic diet
• Homocysteine
• Prothrombotic and proinflammatory factors
• Impaired fasting glucose

Note: Atherosclerosis may occur in the absence of any risk factors (i.e. half of heart attacks occur in persons with normal cholesterol), or some persons with risk factors may not have significant disease. Conclusions:

1. We don’t know everything about the disease.
2. Genetics is important!

**The Metabolic Syndrome**

- Abdominal obesity (waist > 40 inches for men, > 35 inches for women)
- Atherogenic dyslipidemia (↑ LDL & triglyceride, small LDL particles, ↓ HDL
- ↑ blood pressure, > 130/85 mm Hg
- Insulin resistance, fasting glucose >110 mg/dl
- Prothrombotic & proinflammatory states
- Treatment involves “therapeutic lifestyle changes” – diet, weight reduction, increased physical activity (see ATP III study in JAMA 285:2485-97, 2001)

Note: This is not the only online medical app. There are now about 40,000 smartphone/tablet medical apps covering everything from everything from hypertension to depression, and these are largely as yet unregulated (Indpls. Star, 6/24/2012).

**Homocysteine**

- Homocysteine is known to be toxic to endothelium
- Children with homocystinuria may develop first MI by age 20 years
- Homocysteine may be mildly elevated in adult patients without the classic childhood disorder – correlates with increased risk of symptomatic AS
- Treatment with folate, B6 or B12 may lower homocysteine, but it is controversial whether this lessens mortality from heart attack/stroke per recent large studies

Note: Homocysteine and may interfere with antithrombotic and vasodilator functions (decreases availability of nitric oxide) and increases collagen production.

**Inflammation/C-Reactive Protein**

- CRP is an acute phase reactant from the liver – a nonspecific indicator of systemic inflammation
- CRP levels have a strong value for predicting cardiovascular events independent of serum cholesterol
- Suggests that inflammation plays a major role in the pathogenesis of AS
- Diet, weight loss, cessation of smoking all lead to ↓ CRP
- Statins, other cholesterol lowering drugs, and ASA all ↓ CRP
- There is some evidence that the strength of CRP as an independent risk factor may have been overestimated; increased WBC may also serve as a marker for systemic inflammation and is a lot cheaper
Notes:
Dr. Paul Ridker at Harvard Medical School has received much attention in the lay press as well as academia in the last few years for his publications relating C-reactive protein to cardiovascular risk. See Ridker, et al., NEJM 347:1557, 2002, for an “original” paper, and Ridker, Circulation 107:363, 2003 for a brief review of the CRP topic. In an article in Fortune magazine in October 27, 2003, Ridker’s and others discuss ideas about “anti-aging” for the layman. A recent NEJM article on the “Jupiter” study provides evidence that a statin drug (Crestor) reduces the rate of cardiovascular problems in persons with ↑ CRP even if they have normal cholesterol (see The Wall Street Journal, November 10, 2008, for the business-oriented summary).

There are numerous other markers for AS risk. One recent one is cystatin (google it). This is a marker for renal function (somewhat like creatinine). It is known that patients with renal insufficiency are at higher risk for cardiovascular events. Even low birth weight as been associated with increased risk of AS in later life!

Pathogenesis of Atherosclerosis

- Postulate: Atherosclerosis is an inflammatory disease, and advanced lesions in the arteries are similar to end-stage inflammatory changes in other tissues (e.g. cirrhosis in liver, glomerulosclerosis in kidney)

Notes:
Chlamydia pneumoniae has been demonstrated in plaques. Antibiotics against *C. pneumoniae* have reduced recurrent events in patients with ischemic heart disease.

Certain viruses cause atherosclerotic plaques in chickens.

Some areas of endothelium may generate more superoxide dismutase, accounting in part for the nonrandom localization of atherosclerosis.

Medial smooth muscle may have a heterogeneous embryologic origin & may respond differently, accounting in part for the nonrandom localization of atherosclerosis.

“Inflammatory lesion” is an oversimplification. AS is perhaps better described as an ongoing process of injury and imperfect repair.

Could plaques be benign neoplasia or caused by an oncogenic virus? Unlikely – some plaques probably are monoclonal, but probably just arise from pre-existing developmental clones.
There is evidence that the fine particulate matter (soot) in diesel exhaust may act synergistically with cholesterol to activate genes that cause inflammation of blood vessels (Genome Biology 2007, 8:R149).

**Aneurysm**

- Def: An abnormal dilatation or outpouching of a blood vessel, usually the aorta (or even the heart!)
- True: Has all layers of vessel wall (c.f. true diverticulum in bowel)
- False: Not all layers (pseudoaneurysm – c.f. false diverticulum in bowel)
- Most common causes: Atherosclerosis and cystic medial degeneration

Notes:
An extravascular hematoma or dissection of blood into the media of a vessel are examples of false aneurysms.

**Other Causes of Aneurysms**

- Syphilis (typical in thoracic aorta/arch)
- Infections (“mycotic”)
- Congenital defects
- Trauma
- Vasculitis (Kawasaki disease, polyarteritis nodosa)

Notes:
“Mycotic” refers to any infection, bacterial or fungal. Can be true of false.
See Appendix II for Kawasaki pearls.

**Abdominal Aortic Aneurysms**

- Occur most commonly from below the renal arteries to the bifurcation, & may extend into the iliacs
- Are “true”
- Are due to weakening and thinning of the media by atherosclerosis
- Occurs >50 yo, M>F
- There is a genetic predisposition, possibly related to a weaker media
- Can be saccular, fusiform, cylindroid, serpiginous
- Can contain abundant mural thrombus
- Can obstruct ostia of renals, SMA, IMA, vertebrals
- Variants are inflammatory and mycotic

Notes:
AAA’s are usually not initiated by a primary abnormality of the media (although a weaker media may predispose). The media is secondarily weakened by severe atherosclerotic involvement of the intima.
Inflammatory AAA’s feature dense periaortic fibrosis and lymphoplasmacytic inflammation. The cause may be a recently recognized entity, “immunoglobulin G4 (IgG4)-related disease.” This fibrosing, autoimmune disorder can also affect the pancreas, salivary glands and biliary system. It responds to steroid therapy.
A typical AAA can become secondarily infected (mycotic) esp. from Salmonella gastroenteritis – this may lead to rapid dilatation and rupture.

**AAA Rupture**

- The dreaded complication
- 4 cm is the “cutoff” for risk of surgery less than risk of rupture (varies a little among institutions)
- Newer stent devices now available – can be placed via intravascular route

Note:
At 4 cm, about 5 – 10% per year rupture.

**Other AAA Complications**
- Occlusion of a branch
- Embolization of thrombus or atheromatous material
- Compression of a ureter
- Compression/erosion of a vertebral body causing back pain

**Syphilitic (Luetic) Aneurysms**

- A complication of tertiary syphilis – not common now
- Is due to obliterative endarteritis which weakens the media
- Is more typical in the thoracic aorta (not abdominal)
- May cause very irregular intimal scarring (tree barking)
- Accelerates atherosclerosis of root and arch

Note:
Syphilitic thoracic aortic aneurysms may cause dramatic dilation of the aorta with protrusion of the aneurysm through the thoracic inlet into the neck!

**Complications of Syphilitic (Luetic) Aneurysms**

- May extend to the aortic valve ring and cause dilatation and valvular insufficiency, leading to volume overload hypertrophy of heart, sometimes massive – *cor bovinum*
- Most pts with syphilitic AA die of heart failure secondary to AV incompetence

**Aortic Dissection**

- AKA dissecting hematoma
- Old term “dissecting aortic aneurysm”
- Occurs in two clinical settings:
  - Middle aged men with hypertension
  - Connective tissue disorders like Marfan’s (usually younger)
- Usually not seen with severe atherosclerosis (the extensive scarring of AS may be protective)
- May occur rarely in pregnancy, or even without an obvious cause
- Starts as an intimal tear in the ascending aorta, then blood dissects along the media
- May extend proximal and distal to the intimal tear
- Common cause of death: rupture into a serous cavity

Notes:
The entity is not strictly an aneurysm since there is no dilatation.
In Marfan’s, the dissection typically occurs between the middle and outer 1/3 of the media.
Look at but do not memorize the DeBakey types pictured in Robbins. The dissection may extend into the great head/upper extremity arteries. The dissection may also disrupt the aortic valve apparatus.

**Aortic Dissection in Marfan’s Syndrome**

- Marfan’s syndrome is among the best known genetic causes of aortic dissection. The cardiac manifestations include:
  - Cystic medial degeneration and aortic dissection
  - Dilatation of the aortic root
  - Mitral valve prolapse (floppy mitral valve)
  - Microscopic of aorta wall shows fragmentation of elastic fibers and cleft-like spaces known as cystic medial degeneration

Notes:
The changes are referred to as “cystic medial degeneration” rather than the old term “cystic medial necrosis.” The changes are not specific for Marfan’s and are also seen as an ageing change. The cleft-like spaces contain amorphous extracellular material and are not true, epithelial lined cysts.

**Aortic Dissection Clinical Course**

- Typically presents with excruciating pain which progresses downward
- Used to have a high mortality, but now most are salvaged with aggressive control of hypertension and surgical plication of aorta
- May result in a "double barreled" aorta if the dissection ruptures back into the lumen of the aorta

**Ischemic Heart Disease**

- Nearly synonymous with atherosclerotic cardiovascular disease (90%)
- Divisible into 4 clinical syndromes:
  - Myocardial infarct
  - Angina pectoris (3 types)
  - Chronic ischemic heart disease with heart failure
  - Sudden death

**Notes:**
These four groups are heterogeneous and overlapping.
Angina may be stable (the usual type), unstable (dangerous – preinfarction angina), or Prinzmetal angina (atypical – occurs at rest – due to cor. artery vasoconstriction).

**Pathogenesis of Atherosclerotic Cardiovascular Disease**

- Pathogenesis involves the interplay of 4 factors:
- Fixed narrowing of coronary arteries – takes 75% to be hemodynamically significant
- Acute plaque change
- Thrombosis
- Vasoconstriction

**Acute Plaque Change**

- Thought to trigger sudden cardiac events (and maybe unstable angina)
- May be due to:
  - Rupture or fissuring of a plaque
  - Erosion/ulceration of a plaque
- May be followed by thrombus formation on the plaque surface, which may:
  - Totally occlude the lumen ➔ MI
  - Partially occlude the lumen ➔ ? unstable angina, subendocardial infarct, sudden death
  - Embolize ➔ microinfarcts
  - Organize ➔ contribute to growth of plaque

**Notes:**
The most dangerous plaques are moderately stenotic (50 – 75%) with a relatively large, soft lipid core and a thin cap. More stenotic lesions may actually be more stable. More stenotic lesions may actually protect the myocardium against MI by preconditioning (mechanism unknown).
For a good review of vulnerable plaque change, see Circulation 108:1664, 2003

**What causes acute plaque change?**

- Mechanisms are uncertain; may include:
• Adrenergic stimulation – accounts for more MI’s in AM or when stressed (increased MI’s after earthquakes, 9/11 attacks)
• Vasoconstriction may contribute to plaque fracture
• Inflammation may play a role in destabilizing the plaque

Myocardial Infarct

• Cause:
  o ~90% due to disrupted plaque ➔ platelet adhesion ➔ occlusive thrombus
  o Other 10%, who knows?
    ▪ Prolonged, severe vasospasm
    ▪ Emboli from left atrium or paradoxical emboli through patent foramen ovale
    ▪ Abnormalities of intramural coronary arteries, vasculitis, hemoglobinopathies
    ▪ Unexplained

Risk Factors for MI – Same as for Atherosclerosis

• Older age
• Hypertension
• Smoking
• Diabetes mellitus
• Hypercholesterolemia
• Male > female (declines progressively with age past reproductive years)

Notes:
Review the coronary artery anatomy:
LAD – supplies the apex, anterior LV wall, and anterior 2/3 of the ventricular septum.
RCA – Posterior LV and posterior 1/3 of septum in the right dominant heart, whole RV
LCx – lateral LV
The left and right coronary artery systems each supply about 50% of the left ventricle in the right dominant heart.

Morphology of an MI

• Location depends on coronary artery affected (may be fooled by well-developed collateral flow)
• The subendocardial zone is the "end" of the blood flow
• Subendocardial MI = inner 1/3 to ½, may be circumferential in the distribution of all 3 cor. arts.
• Transmural MI = more than half of ventricle wall thickness, usually in the distribution of one cor. art.
• The necrosis is coagulative (apoptosis may play a role)

Notes:
In MI, occlusions almost always involve one of the 3 named coronary arteries or a secondary branch (diagonal branch of LAD, marginal branch of LCx).
A pure right ventricular MI is rare, but the RV may be involved by extension from LV.
Myocyte cell death occurs first in the subendocardial zone and the advances outward as a wave with an “at risk” zone at the leading edge.
The extent of the MI depends on several factors including:
  Duration of occlusion
  Metabolic/O2 needs of myocardium
  Hypotension, arrhythmias, spasm

What happens to a cardiac myocyte when blood is cut off?

• It resorts to anaerobic glycolysis within seconds
• It stops contracting within about a minute (can ➔ acute heart failure)
• Myocyte death occurs in 20 to 40 minutes
• >1 hour, vascular injury occurs

Gross Changes in MI

<table>
<thead>
<tr>
<th>Time (0 to 24 hours)</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 12 hours</td>
<td>Nothing (triphenyltetrazolium chloride stain can show in 2 – 3 hours)</td>
</tr>
<tr>
<td>24 hours</td>
<td>Dark mottling (trapped blood)</td>
</tr>
<tr>
<td>3 to 7 days</td>
<td>Yellow-tan center, hyperemic margin</td>
</tr>
<tr>
<td>7 to 10 days</td>
<td>Max. necrosis of yellow-tan center</td>
</tr>
<tr>
<td>2 months</td>
<td>Mature scar</td>
</tr>
</tbody>
</table>

Light Microscopic Changes in MI

<table>
<thead>
<tr>
<th>Time (0 to 24 hours)</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 hours</td>
<td>Not much – wavy fibers at edge</td>
</tr>
<tr>
<td>4 to 24 hours</td>
<td>Beginning coagulation necrosis, nuclear pyknosis, early neutrophilic infiltrate</td>
</tr>
<tr>
<td>1 to 3 days</td>
<td>Well developed coagulative necrosis with loss of nuclei and cross striations, lots of neutrophils</td>
</tr>
<tr>
<td>Up to 10 days</td>
<td>Progressive dissolution of myocytes &amp; ingrowth of granulation tissue</td>
</tr>
<tr>
<td>2 months</td>
<td>Dense collagenous scar</td>
</tr>
</tbody>
</table>

Reperfusion After Acute MI

• By thrombolytic therapy (TPA, streptokinase) or mechanical (angioplasty)
• May limit infarct size and improve function & survival
• Must be done within 3 – 4 hours of onset of Sx (if done in first 20 min, may prevent all necrosis)
• Causes its own type of injury (reperfusion injury)
  o Hemorrhage due to damaged, leaky blood vessels
  o More rapid disintegration of critically damaged myocytes – get “contraction band necrosis” in irreversibly injured myocytes
  o Some new cellular injury may occur due to O2 free radicals
  o Arrhythmia
  o Increased apoptosis of myocytes
  o May cause swelling of endothelial cells ➔ occlusion ➔ stops reperfusion ("no-reflow")

Note: "Stunned" myocardium refers to reversible myocyte dysfunction after an ischemic event. The myocardium may take several days to recover.

Complications of MI

• Nearly ⅓ have one or more:
• LV contractile dysfunction with heart failure, hypotension, shock if >40% of LV is lost
• Arrhythmias – may cause sudden death
• Pericarditis
• Myocardial rupture (Most frequently 2 – 4 days post MI)
  o Through septum to RV
  o Through free wall ➔ tamponade
  o Partial rupture through free wall ➔ pseudoaneurysm filled with thrombus
  o Papillary muscle rupture ➔ acute mitral insufficiency
• Infarct extension
• Mural thrombus may ➔ thromboembolus
• LV aneurysm – late complication
• Papillary muscle dysfunction
• Progressive heart failure (“ischemic heart disease”)

Notes:
In 10 – 15% of pts, usually with >40% LV infarct, there is 70% mortality.
Pericarditis after an MI is typically fibrinous or fibrinohemorrhagic. Typical onset 2 – 3 days after acute MI, then resolves.
Large anterior transmural MI’s have a higher risk of rupture, expansion, aneurysm, thrombi & in general have a worse prognosis than posterior MI's.
Large posterior transmural MI’s have a higher risk of heart blocks, RV infarct (or both).
Compensatory remodeling occurs with healing of MI with compensatory hypertrophy and areas of thinning, scarring and dilatation. May get late decompensation of the myocardium.
The conventional wisdom has been that cardiac myocytes cannot regenerate and are replaced by scar tissue when they die. There is some evidence to the contrary, but myocyte regeneration, if it occurs, does not play much of a role in the healing of an MI.

**Chronic Ischemic Heart Disease**

- Results in progressive failure due to ischemic myocardial damage
- Usually in pts with prior MI, but may see with severe obstructive coronary artery disease without MI
- Hearts are typically large and heavy due to areas of compensatory hypertrophy & areas of dilatation & fibrosis
- “Ischemic cardiomyopathy” is used for this, but it is not strictly a "primary" abnormality of the myocardium

**Sudden Cardiac Death**

- Def: Rapid (<1 hr) unexpected death due to cardiac causes
- IHD the most common cause in older persons (acute plaque change → thrombus → arrhythmia)
- In younger persons, non-atherosclerotic causes are more common

**Non-atherosclerotic Causes of Cardiac Sudden Death**

- Hypertrophic cardiomyopathy/isolated hypertrophy of unknown cause
- Congenital heart disease, including coronary artery anomalies
- Aortic stenosis (congenital or acquired)
- Myocarditis
- Pulmonary hypertension
- Conduction system or ion channel abnormalities (prolonged QT interval)
- Mitral valve prolapse (floppy mitral valve)
- SCAD (sudden coronary artery dissection)

Note:
SCAD is a rare condition that is morphologically similar to what happens in aortic dissection; i.e. blood dissects into the wall of the artery through an intimal tear. It affects the coronary arteries, typically in younger women, often in association with pregnancy or the postpartum state. It has a high mortality, since it may result in sudden coronary artery blockage. See the Wall Street Journal, August 30, 2011 (I couldn’t find it in Robbins).

**Valvular and Endocardial Heart Disease**

**Valvular Disorders Cause:**

- Stenosis
- Regurgitation (aka insufficiency)
- Both
- Murmurs
- Dysfunction ranging from trivial to rapidly fatal depending on how bad the defect is and how rapidly it developed
May cause secondary changes in heart and blood vessels

Notes:
The valve leaflets are simple, mostly avascular laminated structures. The strength of the leaflet comes from the middle layer, the lamina fibrosa. A lamina spongiosa is a cushioning layer on the inflow surface. Elastic fibers are also present. The outer surfaces are covered with endothelium. Valvular interstitial cells within the leaflets maintain the matrix. The chordae tendineae are also avascular and blend with the lamina fibrosa.
The arterial valves work passively. The mitral and tricuspid valves require a functioning tensor apparatus (papillary muscles and chordae tendineae) to prevent gross incompetence. The most important secondary changes from valve damage include myocardial hypertrophy, atrial dilatation and hypertensive changes in pulmonary vasculature.

Causes of Valvular Lesions

- May be congenital or acquired, and acquired lesions may be acute or chronic
- Most lesions are acquired, chronic and affect the left-sided valves

Notes:
Congenital causes include malformed (dysplastic) valves, which are stenotic, regurgitant, or both. Congenital valvular lesions are relatively rare. Bicuspid aortic valve is one of the most common congenital valvular abnormalities affecting 1 – 2% of the population.
Acquired causes include degenerative diseases, infection, autoimmune disorders, and papillary muscle dysfunction (e.g. as a complication of MI). Inheritable connective tissue disorders are technically congenital, but the manifestations are “acquired” later in life (e.g. Marfan’s, floppy mitral valve). It is now recognized that adult survivors of childhood cancers who have received high dose irradiation to the chest may develop secondary abnormalities of cardiac valves or coronary arteries starting in early middle age.
See Table 12-7, p. 561, Robbins 8th Ed. for a listing of the major causes of acquired valvular heart disease.

Most Frequent Chronic Valve Lesions of Major Functional Significance:

- Mitral stenosis secondary to rheumatic heart disease
- Mitral insufficiency secondary to myxomatous degeneration (floppy mitral valve)
- Aortic stenosis secondary to calcification
- Aortic insufficiency due to dilatation of the aortic ring secondary to hypertension or aging

Calcific Aortic Stenosis

- Not exactly the same as atherosclerosis, but chronic injury due to hypertension and hyperlipidemia play a role
- Typically presents in 70s & 80s (50s & 60s if bicuspid aortic valve)
- Hallmark is heaped up masses of calcium on the downstream side of the leaflets preventing opening of valve

Notes:
Calcification begins in the fibrosa layer at the attachment of the leaflet, which is the point of maximum flexion – usually does not involve free edges. The early lesion is “aortic valve sclerosis.” Rather than accumulating smooth muscle cells, the abnormal valves contain cells resembling osteoblasts. The commissures are not fused (at least early on) as in rheumatic. Also the mitral valve is not involved (although calcium may extend through aortic annulus to involve anterior leaflet of the mitral valve).

Calcific Aortic Stenosis Clinical Features

- Progresses at a variable (slow) rate and causes an increasing pressure gradient, 75 – 100 mm Hg → LV hypertrophy
• Angina or syncope may ensue
• Ca++ may rarely extend into septum & cause AV conduction block (not mentioned in Robbins but true)
• Eventually get cardiac decompensation & CHF → end stage with 50% mortality in three years

Bicuspid Aortic Valve

• 1 – 2% of population
• The larger cusp usually has a raphe (pronounced RAY-fee)
• Valves work OK, but are predisposed to early Ca++ with raphe as the main site
• Bicuspid aortic valves also predisposed to infectious endocarditis
• Bicuspid valves associated with coarctation, aneurysm, dissection

Note: A bicuspid valve may be associated with structural abnormalities in the aortic wall. Trivia: The raphe is most commonly between what would have been the left and right cusps (80%).

Mitral Annular Calcification

• Refers to degenerative calcification of the mitral annulus (ring)
• Most common in >60 yo women, associated with floppy MV and ↑ LV pressure
• Usually is innocuous, but can cause regurgitation by impairing ring contraction during systole
• Ca++ can extend into septum & cause AV block & even sudden death due to arrhythmia
• Can provide a nidus for infective endocarditis or thrombi → stroke

Myxomatous Degeneration of the Mitral Valve

• AKA Floppy Mitral Valve, Mitral Valve Prolapse
• The most common valvular disease in the industrialized world, affects ~ 3% of adults, mostly young women
• Characterized by redundant, myxoid mitral valve leaflet tissue that protrudes into left atrium on systole
• May see with Marfan’s, but cause usually unknown – probably a disorder of connective tissue
• PE: May show a mid or late systolic “click” due to snapping of the chordae or scallop ± late systolic or holosystolic regurg. murmur
• Echocardiogram → diagnostic
• Clinical: Usually asymptomatic, but may have dyspnea, fatigue, chest pain, or even psychiatric symptoms

Note: The leaflets balloon into the LA with “interchordal hooding.” The chordae are frequently elongated and thinned and occasionally rupture. The TV is also affected in 20 – 40% & sometimes even the AV and PV. Can see “friction lesions” where leaflets strike the LA walls or rub against each other. Can get thrombi on these surfaces.

Microscopic: Attenuation of the fibrosa layer with increased myxoid tissue. Ditto in chordae. Valves may show secondary fibrous thickening, especially in friction areas. Psychiatric symptoms include depression, anxiety, and personality disorders.

Strictly speaking, if MV prolapse is due to a connective tissue disorder, it might be reasonable to classify it as a congenital valvar disorder.

Complications of Floppy MV (3%)

• Infective endocarditis
• Mitral insufficiency – slow onset or sudden with chordal rupture
• Stroke (thrombi on atrial side)
• Arrhythmia or sudden death
• Higher risk for complications in men, older persons, and in patients who already have an arrhythmia, LV enlargement, or MV regurgitation
Rheumatic Heart Disease

- Rheumatic fever is an immune mediated attack on the heart after a bout of pharyngitis due to group A (beta hemolytic) streptococcus
- The acute phase of RF causes a pancarditis with:
  - Serofibrinous (“bread and butter”) pericarditis
  - Myocarditis
  - Valvulitis, mainly of left-sided valves

Notes:
Rheumatic disease is an immune mediated inflammatory disease that occurs about 3 weeks (range 1 to 5 weeks) after a bout of acute pharyngitis due to group A (beta hemolytic) streptococcus (not after infections of skin or other sites; not after infections with other strep.) usually in children 5 – 15 years.
Occurs in only about 3% of pts with group A strep pharyngitis & has been declining over 30 years (? Better treatment, ? decreased virulence of bug).
Diagnosed clinically by the Jones criteria – need 2 major or 1 major + 2 minor along with evidence of a preceding group A strep infection:
Major criteria:
- Migratory polyarthritis in large joints
- Carditis
- Subcutaneous nodules
- Erythema marginatum of skin
- Sydenham chorea
Minor criteria: Fever, arthralgias, increased serum acute phase reactants

After an initial attack of rheumatic fever, the pt is more vulnerable to a future attack & carditis is likely to worsen with each subsequent attack. Valve damage is cumulative.
Histologically, granuloma-like lesions called Aschoff bodies characterize the acute phase. Aschoff bodies contain plump macrophages called Anitschkow cells, T-lymphocytes, ± a few plasma cells, and fibrinoid material. Aschoff bodies may be found in any layer of the heart (recall from C603 Lab).
The acute valvulitis is characterized by inflammation & fibrinoid necrosis along the lines of closure, especially on the left-sided valves, with small (1 – 2 mm) verrucous vegetations along the lines of closure. Mitral valve regurgitation may cause plaques in the LA (jet lesion) called MacCallum plaques.

Chronic Rheumatic Disease

- Involves the valves – not the pericardium or myocardium
- Is due to post-inflammatory thickening and deformation of the leaflets
- Involves:
  - Mitral valve virtually always (65 – 70% alone)
  - MV + AV if two valves
  - MV + AV + TV if three valves
- Four valve involvement rare

Basic Features of Chronic Rheumatic Heart Disease

- Fibrous thickening of the valve leaflets with fusion of the commissures → “button hole” or “fish mouth” appearance
- Thickening, shortening and fusion of the chordae tendineae
- LA may dilate & harbor thrombus
- LV is “protected” – if MV only
- May eventually get RV hypertrophy

Note:
Microscopic of valves in chronic heart disease shows fibrosis with vascularization and loss of the normal lamination. Rarely, Aschoff bodies may be seen.

**Rheumatic Heart Disease – Pearls**

- The severity of joint involvement is inversely proportional to heart involvement
- In acute RF, heart involvement is typically not symptomatic unless there is heart failure or pericarditis
- The long term prognosis is highly variable – prosthetic MV replacement may be required
- Mitral regurgitation may develop quickly (due to restricted mobility of leaflets or ventricular dilatation), but stenosis takes years
- Chorea is a late manifestation of RF, male > female
  - May last from a week to >2 years!
  - Chorea is never seen with arthritis, but may coexist with carditis
  - Hypotonia and emotional disturbances are typical
- Subcutaneous nodules – attached to tendon sheaths – extensor surfaces & over bony prominences of upper & lower extremities & mastoid. Histologically → Aschoff bodies
- Erythema marginatum – red margins progress as center clears – see on trunk and proximal limbs
- Death in acute RF is rare, and is usually due to myocardial involvement (heart failure)
- RF and post-streptococcal glomerulonephritis rarely coexist
- See Appendix I for more

**Infective Endocarditis**

- Infection of the heart valves or other endocardial surfaces by a wide variety of bacterial and fungal organisms
- Can be divided by clinical and pathologic features into acute and subacute types

**Acute Endocarditis**

- Rapidly destroys heart valves & has a high mortality ∼ 50%
- Virulent organisms; example *Staph. aureus*
- Rapid development of chills, fever
- May rapidly destroy valve → insufficiency
- May → ring abscess → perforation of heart
- Large vegetations common, may embolize
- May cause acute glomerulonephritis due to Ag-Ab complexes deposited in glomeruli

Note:
Embolic complications: If right-sided, may embolize to lungs & cause abscesses. If left-sided, may embolize to brain, kidneys or other sites & cause abscesses, or may embolize to coronary arteries & cause MI.

**Subacute Endocarditis**

- May have a long course – weeks to months
- Lower virulence organisms; example *Strep. viridans*
- Smaller vegetations, less destructive than acute
- Is on the differential diagnosis of “fever of unknown origin”
- Clinical features range from flu-like symptoms, fever, wt loss, murmur especially if left-sided
- Most can be successfully treated with antibiotics

Note:
Subungual hemorrhages, petechiae and Roth spots in the eyes may be seen with subacute bacterial endocarditis secondary to embolized bits of vegetations.
Bugs That Cause Infectious Endocarditis

- *Staph. aureus* – 10 to 20% of cases, can attack normal or abnormal valves, highly virulent
- *Strep. viridans* (alpha hemolytic strep.) can attack damaged native valves
- Other bugs include *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella & Kingella* (HACEK group)
- Many others can cause, including GNRs and fungi
- About 10% of cases are blood culture negative

Infectious Endocarditis – Predisposing Lesions

- Any anatomic cardiovascular lesion predisposes to IE. Examples:
  - Bicuspid aortic valve
  - Any type of congenital heart disease
  - Calcific aortic stenosis; calcified mitral annulus
  - Rheumatic valve disease
  - Prosthetic valves
  - Previously damaged native valves
  - Floppy mitral valve

Note:
Dentists and cardiologists have long known of the need for prophylactic antibiotics with any dental or surgical procedure that may cause bacteremia in patients with predisposing anatomic lesions.

Two Types of Non-infectious Valvular Vegetations

- Non-bacterial thrombotic endocarditis (marantic endocarditis) – occurs in extremely debilitated patients (cancer, sepsis)
- Endocarditis of systemic lupus erythematosus (Libman-Sacks endocarditis)

Note:
Marantic endocarditis probably results from a hypercoagulable state such as disseminated intravascular coagulation (DIC) or some forms of cancer (can be part of Trousseau syndrome). The vegetations are sterile, small and do not damage valves, but can embolize. The vegetations form on normal valves. Microscopically there is no inflammation. SLE vegetations are small and sterile, and frequently form on the undersides of AV valves. They may be seen on the endocardium and chordae too. Microscopically there may be intense inflammation and fibrinoid necrosis involving the leaflet. Scarring of the valves can occur.

Diseases of the Myocardium

General categories:

- Myocarditis (including transplant rejection)
- Cardiomyopathy (noninflammatory myocardial dysfunction of unknown [now sometimes known] cause)
- Other (cardiac tumors, metabolic and storage diseases, toxic injury)

Note:
There is some overlap. Old, burned out viral myocarditis may become dilated cardiomyopathy. A metabolic disease of the myocardium may also, in a sense be considered a cardiomyopathy.

Myocarditis

- Refers to inflammation of the heart which injures cardiac myocytes
- May be infectious or noninfectious:
  - Viruses, Chlamydia, Rickettsiae, bacteria, fungi, protozoa, helminths
  - Diphtheritic – due to a toxin released by the bug – not direct infection of the heart
Rheumatic fever, postviral, lupus, drug hypersensitivity, other autoimmune
Heart transplant rejection
Unknown cause (sarcoidosis, giant cell myocarditis)

Note:
See Table 12-13, p. 571, Robbins 9th Ed. for major causes of myocarditis.

**Viral Myocarditis**
- The most common cause of myocarditis in the US is viral, usually due to coxsackieviruses A and B and other enteroviruses (less commonly CMV, HIV, influenza)
- These are very difficult to isolate by viral culture of a myocardial biopsy; PCR may help
- The inflammatory injury in viral myocarditis may be secondary to an immune cross reaction with myocytes and not by direct viral cytopathic injury

**Viral Myocarditis Clinical**
- May be asymptomatic or minimally symptomatic
- May rapidly develop heart failure, arrhythmias, or may cause sudden death
- There may be a murmur due to cardiac dilatation causing mitral regurgitation
- May heal completely, or may progress to dilated cardiomyopathy years later

Notes:
Grossly, hearts with active myocarditis are described as soft and flabby. The myocardium may be mottled and the heart may be dilated. Microscopically, viral myocarditis is characterized by a (nonspecific) lymphocytic infiltrate with myocyte necrosis.

**Chagasic Myocarditis**
- Chagas disease – the protozoan bug is Trypanosoma cruzi
- Important in South America – 80% with heart involvement – may be lethal or may go into chronic phase
- Transmitted by insects such as reduvid bug
- Microscopically see parasites within myocytes and mixed inflammation

Note:
T. Cruzi may also cause destruction of the myenteric plexus of the esophagus, duodenum, colon and ureter with subsequent dilatation of these viscera (megacolon).

**Giant Cell Myocarditis**
- Has a rapid onset with a poor prognosis
- Microscopically see myocardial necrosis with lymphocytes, plasma cells, eosinophils and giant cells
- Has some overlap with sarcoidosis, but sarcoidosis has a more insidious onset
- Some patients may recover completely or with some myocardial fibrosis
- Etiology is unknown

**Hypersensitivity Myocarditis**
- Due to hypersensitivity reaction to drugs such as methyldopa, sulfonamides
- Microscopically see interstitial inflammatory infiltrates, mainly perivascular, with lymphocytes, macrophages, and lots of eosinophils
Some Causes of Metabolic Myocardial Injury

- Iron overload (hemochromatosis)
- Hyperthyroidism → tachycardia, palpitations, cardiomegaly, sometimes arrhythmias
- Hypothyroidism → ↓ stroke volume & rate, sluggish flow, may get myxedema of heart
- Disorders of energy use (carnitine def, FOX disorders, mitochondrial disorders)

Note:
Iron accumulates in cardiac myocytes and interferes with metal dependent enzyme systems. Hypothyroidism may cause myxedema of the heart with myofiber swelling, basophilic change, loss of cross striations, and increased mucopolysaccharide content of the interstitium. Some disorders of energy metabolism can cause death in infancy and be confused with SIDS (example LCHAD deficiency).

Cardiomyopathy

- Originally defined as a “primary” abnormality of the myocardium, i.e. cause unknown (not always true now)
- Excludes so-called “ischemic” CM
- CM may be divided into three classic clinical/functional/pathologic patterns:
  - Dilated CM – most common ~ 90%
  - Hypertrophic CM
  - Restrictive – rarest

Dilated Cardiomyopathy

- Features a rounded, dilated heart (esp LV) which also usually is hypertrophied
- The heart is hypocontractile → CHF
- Poor prognosis, 50% mortality in 2 years
- May affect any age
- May be treated by cardiac transplant
- A variant is arrhythmogenic right ventricular dysplasia (cardiomyopathy) – a heritable defect that causes heart failure and may cause sudden death in young persons (see Robbins text)

Note:
Dilated CM is also known as congestive cardiomyopathy. Dilated CM may cause death either by heart failure or arrhythmia.

Causes of Dilated CM

- Burned out myocarditis
- EtOH or other toxicity
- Peripartum CM occurs late in pregnancy or several weeks to months postpartum – poorly understood – possibly related to circulating anti-angiogenic factors
- Genetic – 30% to 50% of cases, variable inheritance, mostly autosomal dominant, & variable defects - one is abnormal cytoskeletal protein like Duchenne & Becker muscular dystrophy
- Mostly the cause is unknown

Notes:
The progression from viral myocarditis to dilated cardiomyopathy has been demonstrated by serial myocardial biopsies. However, in most cases of DCM, the heart shows little or no residual inflammation. Toxic causes of DCM are hard to prove – no good way to tell apart from other DCM. The etiology of peripartum CM may be multifactorial, including factors such as hypertension, volume overload, poor nutrition, possible metabolic abnormalities or autoimmune phenomena; recent evidence suggests that it may be related to circulating anti-angiogenic factors (see Robbins text).
Morphology of Dilated CM

- Rounded, dilated heart, 2–3x expected weight
- LV wall may be thinner due to dilatation
- May see endocardial fibrosis, may see mural thrombus in chambers
- Coronary arteries OK
- Valves OK, but possible regurg of AV valves due to annulus dilatation
- Histology not too exciting – myocyte hypertrophy, some interstitial fibrosis, rarely some residual myocarditis

Hypertrophic Cardiomyopathy

- Has many names:
  - Idiopathic hypertrophic subaortic stenosis
  - Hypertrophic obstructive cardiomyopathy
  - Asymmetric septal hypertrophy
- Features a heart that is normal in shape, but with marked wall thickening due to hypertrophy (esp LV) often with asymmetric thickening of the septum and narrowing of the LV cavity
- The heart is hypercontractile without LV cavity dilatation
- The problem is diastolic filling and LVOT obstruction
- Has a better prognosis than DCM, but may cause angina, CHF, A-fib, mural thrombus, infective endocarditis of MV
- Can affect children or adults
- HCM is one of the most common causes of sudden death in young athletes

Notes:
The septum may bulge into the left ventricular outflow tract. This acts in concert with the adjacent anterior leaflet of the mitral valve to produce left ventricular outflow tract obstruction. A harsh systolic ejection murmur may be present.
Late cardiac dilatation in the course of HCM may actually relieve the LVOT obstruction.
To diagnose HCM, it is necessary to rule out other causes of myocardial hypertrophy such as hypertension and aortic stenosis.
Sudden death may be due to blockage of the left ventricular outflow by the anterior leaflet of the mitral valve. The leaflet may be sucked into the LVOT by “venturi” action of the blood flowing through the narrowed passage.
HCM can be managed medically better than DCM.

Causes of Hypertrophic CM

- Has a genetic basis in all cases. Most are familial and typically autosomal dominant with variable expression; the rest are sporadic
- Often genetic errors are in coding for contractile proteins; >100 mutations known
- Newer evidence suggests that HCM may arise from a defect in energy transfer from mitochondria to sarcomeres
- Investigation of family members of patients with HCM is indicated.

Morphology of Hypertrophic CM

- Thickened LV wall at the expense of the cavity, often with asymmetric septal thickening and bulge of septum into LVOT
- Heart may be normal in shape (may look normal on a routine chest X-ray), but 2-3x expected weight
- Anterior leaflet of MV is thickened, and there may be a “friction lesion” on the LVOT
- Histology shows myocyte hypertrophy, some interstitial fibrosis, and sometimes myofiber disarray, especially in septum
Restrictive Cardiomyopathy

- This is a disorder of ventricular compliance – The heart is normal in shape but stiff
- Constrictive pericarditis is clinically similar – heart is mechanically prevented from contracting well

Causes of Restrictive CM

- Things that infiltrate and stiffen the myocardium:
  - Amyloidosis
  - Sarcoidosis
  - Metastatic tumor
  - Some storage diseases
  - Endomyocardial fibrosis (a tropical disease of unknown cause)

- Things that thicken and stiffen the myocardium and endocardium:
  - Endocardial fibroelastosis (in children - occurs with some types of congenital heart disease and rarely occurs alone)
  - Loeffler endomyocarditis (assoc. with eosinophilia or eosinophilic leukemia)
  - Endomyocardial fibrosis (a tropical disease of unknown cause)
- Idiopathic restrictive CM – myocardium shows patchy or diffuse fibrosis

Note:
In RCM the heart is about normal size and the myocardium is firm (“waxy” in amyloidosis).

Cardiac Transplantation

- ~2500/year worldwide; ~7 in 2013 at Riley
- Acute cellular rejection is a form of lymphocytic myocarditis – controllable with drugs
- Transplant arteriopathy is a long term complication (aka graft vascular disease, graft arteriosclerosis) – years to a decade or more – may cause sudden death

Note:
Acute cellular rejection is cell mediated and is controllable by drugs such as cyclosporine. Transplant vasculopathy on the other hand, may be mediated more by humoral means, and as yet is not controllable by drugs.

Congenital Heart Disease (CHD)

- Def: Abnormality of heart or great vessels present at birth (although may be discovered as an adult)
- Usually refers to structural abnormalities such as abnormal chamber and vessel relationships, abnormal connections (holes), obstructions, absence or maldevelopment of structures, and other anatomic abnormalities
- By convention, usually does not include congenital tumors, infections, cardiomyopathies
- Ranges from trivial (bicuspid aortic valve) to lethal (absent left ventricle)
- If severe, causes delayed development, failure to thrive, increased susceptibility to infectious diseases in childhood, cardiac failure, and rarely sudden cardiac death
- Increased risk for endocarditis (generally true for any structural abnormality, congenital or acquired; i.e. prosthetic valve)
- Increased risk during pregnancy for women with CHD
- Hyperviscosity due to polycythemia
Nearly twice as many children die from CHD in the U.S. as from all forms of childhood cancer combined (Am. Heart Association, 2005)

Causes of CHD

- Usually unknown - probably multifactorial (may see discordance of CHD in identical twins!)
- Around 5% chromosomal (Trisomies, Turner’s)
- A major known cause is sporadic genetic abnormalities such as single gene mutations or small chromosomal losses (examples include Noonans, DiGeorge, numerous others)
- May be seen in many malformation associations (VATER, polysplenia)
- Rare infectious cause (rubella)

Note: Robbins 9th edition has a good overview on gene defects that cause congenital heart defects (p. 532)

Major CHD Defects Can Be Lumped into 3 Categories

- Cyanotic - when blood from the right side of the heart (deoxygenated blood) enters the left side without going through the lungs (right to left shunt)
- Noncyanotic - when blood from the left side of the heart enters the right side (left to right shunt)
- “Other” (i.e. no shunts, example - obstructions)

Right to Left Shunts

- Cause cyanosis from early infancy (blue baby)
- May be complicated by paradoxical emboli

Left to Right Shunts

- No (initial) cyanosis (pink baby)
- Causes pressure (or volume) overload of the pulmonary circulation
- Eventually can reverse shunt direction and become cyanotic (see below)

Eisenmenger’s Syndrome

- Is a switch from noncyanotic to cyanotic CHD due to reversal of shunt flow
- Due to right ventricular hypertrophy and pulmonary vascular changes after prolonged pulmonary HTN
- Too late to surgically repair since pulmonary vascular changes become irreversible
- Not the same as Eisenmenger’s complex

CHD with Right to Left Shunt (Cyanotic)

- Tricuspid Atresia
- TAPVR (TAPVC)
- TOGV
- Truncus Arteriosus
- Tetralogy of Fallot (if sufficient pulmonary outflow restriction)
- Hypoplastic left heart syndrome probably should be considered as cyanotic

Note: All the cyanotic types start with a T except the last one.

CHD with Left to Right Shunt (Noncyanotic)

- ASD (increased pulmonary blood volume more than pressure)
- VSD
• AV septal defect (AV canal)
• PDA

Note: All the noncyanotic types have a D.

Atrial Septal Defect (ASD)

• 90% are “secundum” (at foramen ovale) - the rest are rare
• Not the same as patent FO (present in up to 1/3 of normals)
• Shunts left to right (noncyanotic)
• May be asymptomatic for a long time (30 yo) or a life time
• Increased lung volume of flow more than pressure
• May eventually get volume hypertrophy of right ventricle, <10% develop irreversible pulmonary HTN

Ventricular Septal Defect (VSD)

• Most common cardiac anomaly
• Frequently associated with other cardiac defects - about 30% isolated
• Shunts left to right (noncyanotic) initially
• About 90% involve membranous septum, others in muscular septum or below pulmonic valve
• Small defects - well tolerated, may close spontaneously
• Large defects - usually don’t close, and over time Eisenmenger’s
• Large defects - may have pulmonary hypertension and right ventricular hypertrophy even at birth
• Large subaortic defects – may cause prolapse and insufficiency of aortic valve

Tetralogy of Fallot (TOF) Four Cardinal Features

1. RVOT obstruction (subpulmonic or valvular)
2. VSD
3. Overriding Aorta
4. RV Hypertrophy - boot shaped heart
   • Most common cyanotic CHD
   • Sometimes ASD too (pentalogy)
   • Basic lesion is anterosuperior displacement of infundibular septum
   • May shunt either way depending on RVOT obstruction, but most are cyanotic from birth or soon after

   • Treated initially by systemic-to-pulmonic surgical shunt (Blalock -Taussig) to direct more blood to lungs
   • Even untreated, may survive to adulthood (if PS not too bad)
   • May have paroxysmal hypoxemic spells (“tet” spells)

Hypoplastic Left Heart Syndrome (HLHS)

• Term for lesions that cause under-development (hypoplasia) of the left ventricle and ascending aorta
• Significant aortic valvular stenosis or atresia are the usual causes (but not known what causes valve stenoses)
• HLHS is surgically treatable by the Norwood procedure, but HLHS is a common indication for cardiac transplants in infants
• The heart grossly appears to be “all right ventricle” with the left ventricle very small, sometimes slit-like or undetectable
• The left ventricle may show thick endocardial fibroelastosis (EFE) due to high intraventricular pressure
• Infants are dependent on the ductus after birth, and also need an “ASD” to shunt left atrial blood to the right

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Appendix I – Rheumatic Fever Pearls

- The interval between group A strep pharyngitis and RF = 1 to 5 weeks – average is about 3 weeks

- Acute RF and poststreptococcal glomerulonephritis usually do not coexist

- Severity of joint involvement is inversely proportional to heart involvement

- In acute RF, heart involvement is typically not symptomatic unless there is heart failure or pericarditis

- Mitral regurgitation may develop quickly (due to restricted mobility of leaflets or ventricular dilatation), but stenosis takes years

- Sydenham’s chorea – a late manifestation of RF, female > male
  - May last for a week to >2 years!
  - Chorea is never seen with arthritis, but may coexist with carditis
  - Hypotonia and emotional disturbances are typical

- PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus) (see Wall Street Journal, December 13, 2011)
  - Includes obsessive compulsive disorder, tics, anxiety, irritability, hyperactivity, anorexia and urinary problems
  - May resolve with antibiotics, but may return & worsen if exposed to strep again
  - May be a version of Sydenham’s

- Subcutaneous nodules – attached to tendon sheaths – extensor surfaces & over bony prominences of upper & lower extremities & mastoid. Histologically → Aschoff bodies

- Erythema marginatum – red margin progresses as center clears, see on trunk and proximal limbs

- RF complications may include pleural pain, pneumonia, abdominal pain, and appendicitis secondary to vasculitis
Appendix II – Kawasaki Syndrome (Mucocutaneous Lymph Node Syndrome)

- Kawasaki syndrome is rare, but it is the leading cause of acquired heart disease in children in the United States (great exam question?).
- Kawasaki syndrome is an arteritis involving medium and small arteries, often unfortunately the coronary arteries.
- The mucocutaneous lymph node syndrome in children is manifested by fever, conjunctival and oral erythema and erosion, erythema of the palms and soles, a skin rash often with desquamation, and enlargement of the cervical lymph nodes. It is usually self-limited.
- Approximately 20% develop cardiovascular sequelae ranging from coronary artery ectasia to aneurysm formation to giant (>7 to 8 mm) aneurysm formation.
- Death may occur in the acute phase of the disease or shortly thereafter due to coronary artery rupture or thrombosis, or aneurysms may persist after resolution of the acute disease and cause death years later.
- The cause of Kawasaki’s is unknown, but it is probably a form of autoimmunity triggered by a variety of infections, most likely viral, in genetically susceptible individuals.