Blood Cells

Sideroblastic Anemia

Mechanism
- In each instance there is an interference with hemoglobin’s ability to use iron therefore like IDA
  - Idiopathic
  - Hereditary: protoporphyrin deficiency
  - Acquired/Reversible: ethanol (most common), lead toxicity, pyridoxine deficiency, drugs (chloramphenicol, cyclosporine, isoniazid, pyrazinamide)

Unique S/S
- HSM

Diagnosis
- PBS: microcytic, iron studies similar AOCD, Basophilic Stippling, Pappenheimer Bodies

Treatment
- Pyridoxine Replacement
- Stop Offending Drug

IDA (refer)

Electrophoresis Order

αβ = Hb-A1 (normal)
αγ = Hb-F (fetal, NB γ changes to β after ~20wks of life)
αβS = Hb-S (SCD) αβD = Hb-D (mild β dysfxn seen in Middle East)
αβA2 = Hb-A2 (seen in hemoglobinopathies) αβC/E = Hb-C/E (mild β dysfxn seen in Mediterranean-Africa/Asia)

Thalassemia

Mechanism
- Alpha Globulin Gene Mutation (Asia/Africa) NB two genes
  1 Mutated Gene: Trait
    - Hgb Nl, MCV Nl w/ asymptomatic
  2 Mutated Genes: Minor
    - Hgb 7-10, MCV 70-80 w/ mild anemia
  3 Mutated Genes: HgbH
    - Hgb <7, MCV <70 w/ moderate anemia and need for transfusions during adulthood
    - FTT / Growth Retardation
    - NO compensatory increased production of other types of Hb
    - therefore disease is less severe w/ no hemolysis
    - Extramedullary Hematopoiesis w/ HSM and Marrow Expansion and subsequent Skull Deformities (long face, high cheek, pointing/bossing of forehead, overbite) "Thalassemia Head" or "Chipmunk Face"
  4 Mutated Genes: Major/Hgb-Barts
    - Severe anemia and need for transfusions during childhood if they survive
    - Intrauterine Fetal Death

Beta Globulin Gene Mutation (Mediterranean/Middle Eastern) NB one gene, NB can be B+ with some β production or B0 with NO β production

1 Mutated Gene: Minor B+/B
- Hgb NL, MCV Nl w/ mild anemia

1-2 Mutated Genes: Intermediate B+/β or B0/β
- Hgb <7, MCV <70 w/ severe anemia and need for transfusions during childhood
- FTT / Growth Retardation
- compensatory increased production of fetal Hb-F (see on electrophoresis)
- increased alpha unit production which in turn precipitates forming insoluble tetramers that damage membrane resulting in death in BM or if they survive then removal by spleen
- Extramedullary Hematopoiesis w/ HSM and Marrow Expansion and subsequent Skull Deformities, HSM, etc

Diagnosis
- Microcytic, hypochromic, target cells, basophilic stippling
- Hgb Electrophoresis for beta vs Gene Analysis for alpha as electrophoresis is not helpful b/c all types of Hb are decreased (b/c all require alpha unit) whereas in beta there is a compensatory increase in Hb-A2 while there is a decrease in Hb-A1

Treatment
- Qmo PRBC w/ iron chelator (deferoxamine) to prevent hemosiderosis
- Folate
- Splenectomy (removes the primary site of extravascular hemolysis and should be considered if transfusion requirements increase)
<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sickle Cell Anemia</strong></td>
</tr>
<tr>
<td><strong>AR Mutation resulting in a Single AA Substitution (Glutamic Acid → Valine) on the Beta Chain of Hb Converting Hb-A to Hb-S (African American)</strong></td>
</tr>
<tr>
<td>- Heterozygous aka Hb-SA (trait) which is asymptomatic except during severe hypoxemic stress where they will get painless hematuria and pyelonephritis in pregnancy, no Tx necessary just avoid pneumonia, unpressured flying, exercise at high altitudes, general anesthesia, 8% of AA</td>
</tr>
<tr>
<td>- Homozygous aka Hb-SS (disease) which is symptomatic at around 5mo (once Hgb-F disappears) usually presenting w/ hand-foot syndrome</td>
</tr>
<tr>
<td><strong>Hb-SC (rare mutant that has lesser tendency to aggregate w/ Hgb-S therefore better)</strong></td>
</tr>
<tr>
<td><strong>Hb-SF (fetal allele that has much lesser tendency to aggregate w/ Hgb-S therefore a lot better)</strong></td>
</tr>
<tr>
<td><strong>Hb-SbetaThalassemia (milder disease)</strong></td>
</tr>
<tr>
<td><strong>Extravascular Hemolytic Anemia Crisis</strong></td>
</tr>
<tr>
<td>- Hb-S Polymerizes into Crystals when Deoxygenated which Causes the RBC to Sickle (this is reversed during oxygenation) which causes microvascular obstruction</td>
</tr>
<tr>
<td>- First Few Cycles are Reversible but after Many Cycles Membrane Damage Occurs</td>
</tr>
<tr>
<td>- Dysfunctional RBC are Recognized and Removed by MPS such that RBC Lifespan 120 → 20 days</td>
</tr>
<tr>
<td>- 2/2 infection or drugs resulting in increased retic count, unconjugated bili, jaundice etc</td>
</tr>
<tr>
<td><strong>Vaso-Occlusive Pain Crisis (#1 cause of morbidity!!!)</strong></td>
</tr>
<tr>
<td>- Sickled RBC Occlude Vessels in Various Tissue leading to Infarction</td>
</tr>
<tr>
<td>- Severe Bone Pain, Limping, etc (most common symptom)</td>
</tr>
<tr>
<td>- Hand-Foot Syndrome aka Dactylitis (sudden painful swelling of dorsal surfaces 2/2 avascular necrosis of metacarpal/tarsal bones, usually the first symptom, presenting ~6-12mo old)</td>
</tr>
<tr>
<td>- Acute Chest Syndrome (pneumonia leads to VQ mismatch and thus low O2 and thus sickling and thus infarction presenting similar to a pneumonia w/ F, rales, pleuritis, infiltrates) 20% of deaths</td>
</tr>
<tr>
<td>- Priapism</td>
</tr>
<tr>
<td>- Avascular Necrosis of Joints esp humeral/femoral heads (have high suspicion)</td>
</tr>
<tr>
<td>- Renal Papillary Necrosis resulting in hyposthenuria (inability to concentrate urine w/ nocturia and enuresis) and painless hematuria</td>
</tr>
<tr>
<td>- Eye Problems</td>
</tr>
<tr>
<td>- Hepatopathy</td>
</tr>
<tr>
<td>- Chronic Leg Ulcers</td>
</tr>
<tr>
<td>- CNS Stroke</td>
</tr>
<tr>
<td>- Gallstones</td>
</tr>
<tr>
<td>- Autosplenectomy</td>
</tr>
<tr>
<td><strong>Aplastic Crisis</strong></td>
</tr>
<tr>
<td>- Parvovirus B19 URTI → Transient BM Failure to Produce RBC for 1-2m</td>
</tr>
<tr>
<td>- Decreased RBC Compensatory Production</td>
</tr>
<tr>
<td>- Reticulocytopenia and Worsening Anemia</td>
</tr>
<tr>
<td><strong>Infection (#1 cause of mortality!!!)</strong></td>
</tr>
<tr>
<td>- Sickle RBCs Occlude Splenic Vessels</td>
</tr>
<tr>
<td>- Splenic Sequestration Crisis (spleen becomes engorged w/ blood resulting in shock)</td>
</tr>
<tr>
<td>- Splenic Dysfunction (for some reason it just doesn’t fxn well)</td>
</tr>
<tr>
<td>- Splenic Infarction and Fibrosis by 5yo</td>
</tr>
<tr>
<td>- Encapsulated Bacterial Infections PNA, Pyelo, etc and Salmonella Osteomyelitis</td>
</tr>
<tr>
<td><strong>Megaloblastic Crisis 2/2 folate deficiency esp during late pregnancy</strong></td>
</tr>
<tr>
<td>- Sequestration Crisis 2/2 pooling of RBCs in spleen, seen in young children</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microcytic</strong></td>
</tr>
<tr>
<td><strong>Sickle/Target Cells</strong></td>
</tr>
<tr>
<td><strong>Hemoglobin C Crystals if SC Dz</strong></td>
</tr>
<tr>
<td><strong>Hgb electrophoresis</strong></td>
</tr>
<tr>
<td><strong>On newborn screen</strong></td>
</tr>
</tbody>
</table>
**Treatment**

**Acute Treatment**
- If fever then check Cx and start abx
- Hydrate aggressively w/ 250cc/hr
- Keep Warm
- Morphine (talk to pharmacist/palliative care to determine protocol used at last admission or for other pts) dilaudid 2-4mg IV Q2hrs prn
- O2
- Folic acid
- Follow retic count (chronic SS pts have a retic of 10% while acute pain crisis have a retic in the 20s, therefore if in crisis and low then check for BM infection like Parvo B19)
- Assess precipitating cause
- EXCHANGE TRANSFUSION if pt is having end-organ damage esp Acute Chest Syndrome & Priapism otherwise just give normal transfusions

**Chronic Treatment**
- Hydroxyurea
  - increases Hgb-F
  - anti-inflammatory
  - add if recurrent pain crisis b/c it decreases pain crisis by 50%
  - must follow CBC b/c myelosuppressive and crisis rate b/c even if there is an increase in Hb-F if there is no clinical improvement then you need to stop b/c of the toxicity
- Prophylactic Antibiotics
  - Penicillin [125mg PO BID up until 3yo then 250mg PO BID up until 5y then stop]
- Vaccinations
  - Hib
  - Pneumococcal
  - MGPV
- Transfusions to keep Hgb-S at <30%
  - Hemosiderosis is also a problem as for Thalassemias
  - Two Types of Chelators:
    - Deferoxamine (Desferal) SC continuous 12hr infusion, wear a device on your belt, renally excreted causing orange urine
    - Deferasirox (Exjade) PO Qd, hepatobiliary excretion, expensive
- Regular ophtho exams b/c of high incidence of proliferative retinopathy which can be Tx w/ laser photocoagulation
- BM Transplantation
- Gene Therapy
- Folate 1mg PO Qd (high dose so that DNA synthesis is not impaired)
- Plavix

---

**Anemia of Chronic Disease (AOCD)**

**Mechanism**
- Chronic Infection (TB, Lung Abscesses), Cancer, Inflammation (RA, SLE, IBD), Trauma
- Inflammatory cytokines esp IL-6 via hepcidin have an evolutionary role designed to (1) decrease iron absorption (hence low iron) and keep iron stored in reticuloendothelial cells as ferritin (hence high ferritin) so that any "bad microbes" in the body can't use this essential element for growth and (2) decrease epo responsiveness

**Diagnosis**
- PBS: micro/normocytic, euchromic, anisocytosis
- Labs: ↓Fe, ↑Ferritin, ↓TIBC, ↓%Sat, normal Soluble Transferrin Receptor Assay

**Treatment**
- Treat Underlying Cause
- If epo <200 mU/mL then you can start epo to stimulate more RBC production

---

**Megoblastic Anemias (Folate and VitB12 Deficiencies)**
Mechanism

Mech: w/in cells VitB12 is dissociated and converted into is active forms methyl-cobalamin and adenosyl-cobalamin which act as coenzymes for methionine synthase and methylmalonyl coenzyme mutase which are enzymes involved in methylation of homocysteine to methionine and the conversion of methylmalonyl-CoA to Succinyl-CoA respectively

- (1) reduction in tetrahydrofolic acid (THF) 2/2 impaired demethylation results in impaired pyrimidine synthesis (specifically conversion of uridine to thymidine) → normal RNA but decreased DNA synthesis → ineffective erythropoiesis w/ intramedullary hemolysis as cells die in BM (anemia) and potentially other lineages if severe (pancytopenia)
- (2) Decreased Methionine/Succinyl-CoA and Increased Homocysteine/Methylmalonate → ? (likely responsible for extra-hematologic effects of vitb12 deficiency)
<table>
<thead>
<tr>
<th>Folate Deficiency</th>
<th>VItB12 (Cobalamin) Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td><strong>Mechanism of Absorption</strong></td>
</tr>
</tbody>
</table>
| • Decreased Intake (eg. alcoholism b/c impairs absorption along w/ decreased intake, developing countries, green leafy vegetables, liver, peanuts, beans AND produced by gut bacteria) | • Mouth: salivary gland produces Haptocorrin aka R-factor  
  o Decreased Intake of Meat and Fish (strict vegetarians, moderate vegetarians who require increased amounts as during pregnancy, malnutrition), 50% found in liver and stored hence it takes 2-5 years for deficiency to develop  
  • Stomach: parietal cell produces Intrinsic Factor aka S-binder, similar stimulants and inhibitors to gastric acid secretion but in general the secretion of IF is not coupled to acid secretion in that PPIs have no effect on IF secretion, *VitB12 released from protein by acid, haptocorrin/R-factor binds free VitB12 in acidic environment*  
    + low gastric acid impairs release of VitB12 from protein  
    + Parietal Cell Loss (pernicious anemia, gastrectomy, atrophic gastritis)  
      • Pernicious Anemia (PA)  
        • Epidemiology: ~60yo, F>M, no ethnic predilection (a large population based study in the UK revealed a prevalence of ~2% in >65yo)  
        • Other: Type II PolyGlandular Autoimmune (PGA) Syndrome aka Schmidt’s/Carpenter Syndrome (Grave’s/Hashimoto’s, Adrenal Insufficiency, T1DM, Vitiligo), HCV Tx w/ IFN!!!  
          • Mechanism: Anti-IF Ab (~45% sensitivity and ~95% spec) and Anti-Parietal Cell Ab (~80% sensitive and ~90% specific) → Atrophic gastritis of oxyntic mucosa → parietal cell hypoplasia → a/hypochlorhydria and decreased IF  
            o Anti-IF: ab prevents attachment of vitB12 to IF OR vitB12-IF to cubulin  
            o Anti-PC: ab against H/K ATPase of parietal cell  
            o demonstrated a link b/t HP infection and VitB12 deficiency and suggested that chronic HP may result in the breakdown of tolerance for self-Ags in genetically susceptible individuals or that antibodies are acquired due to molecular mimicry b/t HP Lewis Blood Group Ag X/Y and H/K ATPase  
            o eradication of HP lead to normalization of VitB12 levels  
            o dx of HP is difficult to make as HP may disappear w/ serology being the only marker  
        • Complications: higher r/o gastric adenocarcinoma b/c of metaplasia and carcinoid b/c of hypergastrinemia (surveillance is not established)  
          • Duodenum: alkaline environment and pancreatic trypsin separates VitB12 and R-factor and allows IF to bind VitB12  
            o Pancreatic Exocrine Insufficiency (decreased bicarb/trypsin output)  
            o Consumption (from bacteria, *Diphyllobothrium latum* aka fish tapeworm)  
          • Terminal ileum: *VitB12-IF complex travels to TI and binds apical CUBN/AMN/RAP/LRP-2 Receptor which activates energy dependent endocytosis, v/w in the enterocyte the IF is degraded by lysosomal enzymes and VitB12 binds to transcobalamin, the VitB12 transcobalamin complex is released into circulation thru the basolateral ATPBC Transporter and from there enters cells by similar receptor mediated endocytosis, NB 5% of free cobalamin is absorbed w/o IF  
            o Ileal Disease (eg. Crohn’s, Sprues, Resection, et al)  
            o Metformin (inhibits binding of complex to apical receptor preventing endocytosis, can be reversed w/ calcium supplementation)  
            o Imerslund-Grasbeck’s Syndrome (cubulin gene mutation, also low VitBD and proteinuria as cubulin is also expressed in the renal PCT and is responsible for the reabsorption of filtered VitD and protein)  
        • Risk Factors:  
          o Adult: GI disease, chronic alcoholism, severe malnutrition, *Helicobacter Pylori* infection, atrophic gastritis, autoimmune gastritis (type A and B), *Dipylidium caninum* infection  
          o Pediatric: celiac disease, ataxia-telangiectasia, *Grasbeck’s Syndrome*  
\| \|
<table>
<thead>
<tr>
<th><strong>Unique S/S</strong></th>
<th><strong>Neural Tube Defects in Fetuses of Deficient Mothers</strong></th>
</tr>
</thead>
</table>
| Neural Tube     | Heme: PBS: reticulocytopenia w/ macroovalocytes w/ MCV >100fL and occasional megaloblasts w/ Howell-Jolly Bodies and Cabot Rings, hypersegmented (≥5 lobes) in >5% of PMNs  
  o Why? impaired DNA synthesis w/ normal RNA synthesis → “cytonuclear” dissociation → impaired cell maturation  
| Defects in      | • Neuro: Spinal Cord (subacute combined degeneration → symmetric caudal demyelination of dorsal sensory columns and lateral motor columns → impaired lower extremity Tactile/Vibration/Baroception/Proprioception sensation and weakness → ataxia, spasticity, paresis, urinary/fecal incontinence) and Brain (dementia w/ personality changes and memory loss)  
| Fetuses of      | • Derm: Hunter’s Atrophic Glossitis and Vaginal Atrophy (b/c rapidly growing mucosal cells need VitB12 more than any other cell type)  
| Deficient       | • MS: Osteoporosis (mechanism unknown)  
| Mothers         | \|
**NB** nitrous oxide (NO₂) (used in anesthesia or abused as a drug) inactivates VitB₁₂ and may precipitate neuropsychiatric deterioration in deficient pts

**Schilling Test** (obsolete, rarely done anymore as HC/MMA is more sensitive and it is more cost effective to give oral or parental B₁₂ therapy and forego a work-up, has more historical importance, onerous test requiring creation and storage of radiolabeled reagents)

- **Phase I:** Load pt w/ IM non-radiolabeled VitB₁₂ so as to saturate tissue stores then administer Oral Radiolabeled VitB₁₂
  - NI 24-Hour Urine: dietary deficiency
  - Abl: move to phase II
- **Phase II:** Administer Oral Radiolabeled VitB₁₂ + IF
  - NI 24-Hour Urine: IF deficiency
  - Abnl: consider other causes and Tx accordingly w/ repeat testing

**Labs:**

- **↓ Folate** (nl 2.7-17ng/mL) / VitB₁₂ (nl 300-1200pg/mL, serum levels represent 0.1% of total body content) but if nl but suspicion is high then check below b/c more sensitive
  - **↑ Homocysteine** (nl 5-14μmol/L) (both)
    - both B₁₂ and folate are cofactors in the conversion of homocysteine to methionine
    - thus if either is low then homocysteine is high
    - not specific to B₁₂ many disease can cause high homocysteine
    - more sensitive than vitB₁₂/folate
    - NB hyperhomocysteinemia has been implicated as a RF for development of atherosclerosis and DVT (controversial)
  - **↑ Methylmalonic Acid** (nl 0.4μmol/L) (VitB₁₂ only)
    - important to measure to differentiate B₁₂ from folate def
    - If VitB₁₂ deficiency then check IF Antibody & Parietal Cell Antibody if antibodies are negative then pursue other causes
    - **Typical order of VitB₁₂ deficiency events:** elevated HC/MMA → low VitB₁₂ → hypersegmentation → macrocytosis → anemia → neuro Sx
      - ~25% of do not follow this order of events and develops Sx before abnormal labs or have normal hematologic indices w/ neurologic Sx

### Treatment

- **Folic Acid** 5mg PO Qd x1wk then 1mg PO QD until normal Hct and Folate then 0.4mg PO Qd (which is RDA, 0.6mg for pregnant women)
- **Normal RDA:** 2.6mcg/d
- **Deficiency:** 1000mcg Qd IM x1wk → 1000mcg Qwk IM x1mo → 1000mcg Qmo IM forever as long as the underlying disorder exists (eg. PA)
  - PO = IM
  - a second lower efficiency transport system that does not require IF or a functioning TI exists
  - very large doses (2000mcg at the same frequency) are needed, nevertheless most give parenteral route until at least neuro Sx resolve
  - Route
    - No IV b/c rapid renal elimination and reported anaphylaxis
    - SL/IN routes exist but poorly studied and expensive
    - If PO then separate from meals
      - Neuro sx begin to resolve at 1wk w/ complete resolution at 3mo (start Tx early as permanent neurologic Sx can occur)
      - Always follow pts clinically and with labs
      - hematologic abnormalities can be reversed in VitB₁₂ deficiency when inappropriately Tx w/ folic acid (neuro Sx will not improve)

---

**Hemolytic Anemias**
**Intravascular/Extrinsic/Acquired**
- Normal RBCs are being destroyed while in circulation
- Pathology does not alter the shape of RBCs rather they change shape when they are being destroyed
- Symptoms: Jaundiced and Dark Urine
- Labs: TLDH, indirect Hyperbilirubinemia, Hemosiderinuria, Haptoglobin (once haptoglobin has been consumed by hemoglobin then you have hemoglobinemia/hemoglobinuria)
- Complications: cholelithiasis

**Extravascular/Intrinsic/Genetic**
- Abnormal RBCs are taken out by Reticuloendothelial System
- Pathology does alter the shape of RBCs (spherocytes, et al) hence that is why they are being taken out by RE System
- Symptoms: Splenomegaly
- Labs: iron overload labs
- Hemolysis
- Microangiopathy resulting in Schistocytes (HUS/TTP, DIC, Prosthetic Valves, severe HTN, vasculitis)
- COLD Ab IHA
- Toxins: Chemical, Venom, Heat
- Drugs: ?
- Infection: Clostridium, Malaria, Babesiosis
- Hypophosphatemia
- PNH
- Wilson’s
- Other: Liver Dz, Renal Dz, Erythroblastosis Fetalis

## Hemolytic Disease of the Newborn Anemia “Erythroblastosis Fetalis”

### Mechanism

1. Mom gets pregnant w/ a Rh+ fetus
2. Maternal Blood has B-Cells against Rh (but cells cannot cross placenta)
3. During delivery maternal blood comes in contact with Fetal Blood that has Rh-Ags
4. Mom begins to make Rh-Abs after birth
5. Maternal Blood has Abs against Rh (unlike B-cells Abs can cross placenta)
6. 25% die in utero 25% die at birth 50% live

Hemolysis
Hyperbilirubinemia (clinically manifesting after delivery when placenta is lost b/c placenta can metabolize bili)
Extramedullar Hematopoiesis resulting in loss of liver parenchyma (HSM, ab distension 2/2 ascites)
Hydrops Fetalis (S/Sx of anemia, ascites, pleural effusions, peripheral edema, HSM)

### Other Causes:
1. Other Chronic Anemias
2. Cardiac Disease (structural defects, in utero closure of foramen ovale, paroxysmal AT)
3. Hypoproteinemia
4. Intravenous Infections
5. Chromosomal Abnormalities

## Auto-Immune Hemolytic Anemia (AIHA)

### Mechanism

- Cold Agglutinin Disease (IgM) 25%
  - Outside of body
  - complete Ig that agglutinate and then completely trigger complement activation such that they lyse intravascularly
  - Ag: I/i
    - Primary/Autoimmune
    - Secondary
      - collagen vascular disease (esp Raynauds)
      - lymphomas
      - viral viruses (esp Mycoplasma and ...

- Warm Antibody Disease (IgG) “GW” 75%
  - in body
  - partial Ig that do not agglutinate but trigger complement activation but only partially such that they don’t lyse intravascularly but extravascularly as they are trapped and destroyed by reticuloendothelial system therefore splenomegaly
  - Ag: Rh
    - Primary/Autoimmune
    - Secondary
      - collagen vascular diseases (esp SLE)
      - leukemias (esp CLL)
### Mechanism
- **Membrane Defect Anemias**
  - AD mutation in membrane proteins (ankyrin, spectrin, et al) that afford shape, strength, and stability → membrane become unstable → loss of membrane but not contents → spherocyte shape w/ hyperchromia → less deformable and more permeable to Na putting metabolic strain on cell b/c of the increased ATP required to maintain gradients → extravascular hemolysis in spleen b/c has smallest vessels in body and lowest glucose/oxygen content b/c of sluggish blood flow resulting in even less ATP, usually a chronic mild anemia that is dx in adulthood
  - Dx: Osmotic Fragility Test
  - Tx: Splenectomy after Syo

- **Enzyme Defect Anemias**
  - 1° G6PD Deficiency (X-linked)
    - Episodic w/ the following precipitating oxidizing agents: Fava beans, infection (most common), drugs (sulfas, cipro, anti-malarials, probenecid, methylene blue, aspirin et al), naphthalene (moth balls)
    - Mechanism: iron of Hgb oxidizes from Fe2+ to Fe3+ (met hemoglobin) and precipitates forming Heinz Bodies → Heinz bodies bind to membrane reducing flexibility → RBCs slow down in reticuloendothelial system allowing for macrophages to feel for Heinz bodies below RBC surface and take “bites” out of them → when there is increased oxidative stress (precipitants above) more Heinz bodies are produced → more deformity → more destruction
    - A-Variant (AA, Middle Eastern) mild b/c partial absence of enzyme such that only old RBCs are affected, usually precipitated by drugs
    - B-Variant (Mediterranean, Middle Eastern) severe b/c complete absence of enzyme, usually precipitated by Fava beans
    - VERY common like millions of people in the world
    - Dx: check G6PD levels when pt is not experiencing a hemolytic episode b/c the cells that have lowest levels of G6PD have lysed while those that have higher levels are still circulating resulting in a false negative
    - G6PD: bite RBC with Heinz Bodies
    - Tx: remove oxidant stressor, oxygen, transfusions

- **Hereditary Spherocytosis**
  - AD mutation in membrane proteins (ankyrin, spectrin, et al) that afford shape, strength, and stability → membrane become unstable → loss of membrane but not contents → spherocyte shape w/ hyperchromia → less deformable and more permeable to Na putting metabolic strain on cell b/c of the increased ATP required to maintain gradients → extravascular hemolysis in spleen b/c has smallest vessels in body and lowest glucose/oxygen content b/c of sluggish blood flow resulting in even less ATP, usually a chronic mild anemia that is dx in adulthood
  - Dx: Osmotic Fragility Test
  - Tx: Splenectomy after Syo

- **Pyropoikilocytosis**

### Diagnosis
- spherocytes, polychromasia/reticulocytosis/NRBC
- Direct/Indirect Coombs (15% negative)
  - Direct = pt’s Ags (mix pt’s RBCs w/ pre-made IgM against IgG/C3 = if pt’s RBC have IgG and/or C3 on them then agglutination occurs)
  - Indirect = pt’s Abs (mix pt’s serum w/ pre-made RBCs that have IgG/C3 on them = if pt has IgM against IgG and/or C3 then agglutination occurs) NB + indirect Coombs can be seen after transfusions, pregnancy, etc

### Treatment
- treat underlying cause
- steroids NOT effective rather consider plasma exchange
- treat underlying cause
- first try glucocorticoids then rituximab then IVIG then splenectomy

### Enzyme Defect Anemias

- **Mechanism**
  - 1° G6PD Deficiency (X-linked)
    - Episodic w/ the following precipitating oxidizing agents: Fava beans, infection (most common), drugs (sulfas, cipro, anti-malarials, probenecid, methylene blue, aspirin et al), naphthalene (moth balls)
    - Mechanism: iron of Hgb oxidizes from Fe2+ to Fe3+ (met hemoglobin) and precipitates forming Heinz Bodies → Heinz bodies bind to membrane reducing flexibility → RBCs slow down in reticuloendothelial system allowing for macrophages to feel for Heinz bodies below RBC surface and take “bites” out of them → when there is increased oxidative stress (precipitants above) more Heinz bodies are produced → more deformity → more destruction
    - A-Variant (AA, Middle Eastern) mild b/c partial absence of enzyme such that only old RBCs are affected, usually precipitated by drugs
    - B-Variant (Mediterranean, Middle Eastern) severe b/c complete absence of enzyme, usually precipitated by Fava beans
    - VERY common like millions of people in the world
    - Dx: check G6PD levels when pt is not experiencing a hemolytic episode b/c the cells that have lowest levels of G6PD have lysed while those that have higher levels are still circulating resulting in a false negative
    - G6PD: bite RBC with Heinz Bodies
    - Tx: remove oxidant stressor, oxygen, transfusions

- **EM Pathway**
  - 2° Pyruvate Kinase Deficiency (AR)
  - 3° Hexokinase Deficiency (AR)
    - chronic w/ no precipitating agents

### Membrane Defect Anemias

- **Mechanism**
  - 1° Hereditary Spherocytosis
    - AD mutation in membrane proteins (ankyrin, spectrin, et al) that afford shape, strength, and stability → membrane become unstable → loss of membrane but not contents → spherocyte shape w/ hyperchromia → less deformable and more permeable to Na putting metabolic strain on cell b/c of the increased ATP required to maintain gradients → extravascular hemolysis in spleen b/c has smallest vessels in body and lowest glucose/oxygen content b/c of sluggish blood flow resulting in even less ATP, usually a chronic mild anemia that is dx in adulthood
    - Dx: Osmotic Fragility Test
    - Tx: Splenectomy after Syo

- **Pyropoikilocytosis**

- **2° Paroxysmal Nocturnal Hemoglobinuria (PNH)**
  - Acquired mutation of the PIG-A gene resulting in failure to express cell membrane anchor proteins (CD55 - Decay Accelerating Factor, CD59 - Homologous Restriction Factor) that normally DECREASES complement mediated destruction of RBCs → unusual susceptibility to complement mediated (Coomb’s Negative) lysis of RBCs, WBCs, and platelets (pancytopenia) occurring at night b/c of lower O2 and higher pH which activates complement pathway → extravascular hemolysis, infection, bleeding (25% of mortality), arterial/venous thromboemboli esp Budd-Chiari Syndrome (50% of mortality), 10% r/o AML, aplastic anemia, MF
    - Dx: Ham’s Test (cells are incubated in acidified serum which triggers complement pathway resulting in lysis which is increased if pt has PNH), Sugar Water Test (cells are incubated in sucrose solution which triggers complement pathway resulting in lysis which is increased if pt has PNH), Flow Cytometry of anchored proteins (CD55/59) (has replaced the tests above)
    - Tx: Steroids for acute Tx and chronic w/ Steroids, Androgens, AC, HSCT and eculizimab (Soliris) monoclonal Ab that inhibits terminal complex-mediated hemolysis