PERIPHERAL SMEARS
The Primary Diagnostic Tool

The Anemias

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Microcytic Anemias

1. **Abnormalities in Fe metabolism**
   - **Fe ↓**
   - **Anemia of chronic disease – Due to insufficient erythropoiesis, trapping of iron needed for Hgb synthesis, and decreased RBC survival**
     - **neoplasms**
     - **Infection**
     - **Other chronic diseases i.e. Rheumatoid arthritis, SLE, etc**
2. **Abnormalities in porphyrin metabolism (blockage of heme synthesis)**
   - **Lead poisoning**
   - **Congenital sideroblastic anemia**
3. **Thalassemia and other Hgbs with abnormalities in globin synthesis**
4. **Congenital, i.e. Atransferrinemia and acquired, i.e. Idiopathic pulmonary hemosiderosis**

Etiology of Fe Deficiency

- **Decreased dietary iron intake**
- **G.I. Bleeding, bleeding associated with idiopathic pulmonary hemosiderosis, colonic neoplasms, peptic ulcers, gastrectomy, and hiatal hernia**
- **Pregnancy - combination of diversion of Fe to fetus, blood loss at delivery, and lactation amounts to approximately 900 mgs. This is equivalent to approximately 2 liters of blood in regards the content of iron. Approximately 30 mgs of Fe alone is used monthly in lactation**

Etiology of Fe Deficiency con't

- Malabsorption - rare, except after GI surgery, (i.e. subtotal gastric resection) and in the malabsorption syndromes
- Intravascular Hemolysis, with hemoglobinuria, i.e. PNH
- Dialysis. There are 2 possible causes
  - trapping of blood in the dialyzing equipment
  - microcytic anemia also occurs as a result of poisoning the dialysate with aluminum, inhibiting heme synthesis
- Growth spurts in adolescents, and growth demands in infants and children

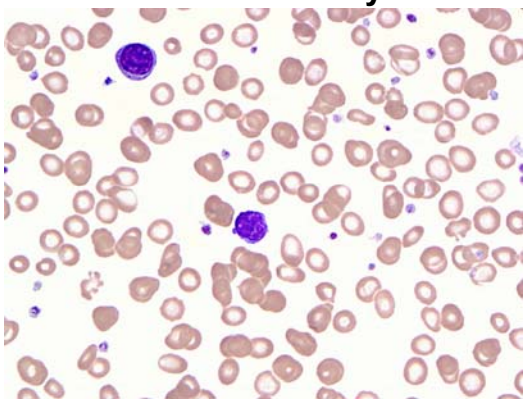
Iron Deficiency Anemia

- Progression of Fe deficiency goes through 3 pathways
  - Fe depletion - earliest stage of Fe ↓. Storage Fe reduced or absent (from the RE cells, i.e. liver and BM). Results in ↓ serum ferritin levels; however serum Fe, PCV, and Hgb is relatively normal. RDW may only be slightly elevated (↑14)
  - Fe ↓ without anemia - (Fe deficient erythropoiesis) Has reduced or absent storage of Fe, low serum Fe and transferrin saturation, but no forthright anemia. Depletion of Fe stores occurs as Hgb levels fall to ↓ 11 gm/dL in women and ↓ 13 gm/dL in men. Hgb concentration and RBC morphology still normal. MCV in the low 80 fL range. Microcytosis starts at ≤ 10 gm/dL in women, and ≤11gm/dL in men
  - Fe ↓ anemia has decreased or absent Fe stores, low serum Fe, low transferrin, high TIBC, and a low Hgb and PCV. Hypochromia now develops at ↓ 10 gm/dL, with MCHC falling below 32.0

ATRANSFERRINEMIA

- Marked ↓↓ in TIBC
- A rare condition, but without transferrin, the primary system for the delivery of Fe to the bone marrow cannot function
- Results in severe impairment of heme synthesis, causing severe microcytic hypochromic anemia
- Can be treated with normal plasma or purified transferrin. Massive transfusions are not desired, because of increased Fe overloading

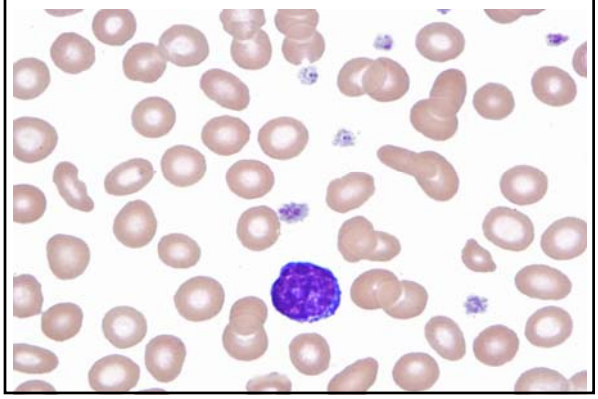
Iron Deficiency



Anemia of Chronic Disease

- In chronic diseases Fe gets trapped in the histiocytes, and is not readily released for utilization
- Researchers suggest the anemia results from a "hematological stress syndrome", which may be due to iron sequestration by histiocytes and activation of the lymphocytes
- Cellular injury, such as that seen in infection, neoplasms or inflammation may be the cause of the cellular activation
- Rarely are patients with ACD hypochromic. However, only about 10% of the cases with ACD are microcytic, therefore, impairment of Fe metabolism does not seem to be the entire explanation

Anemia of Chronic Disease



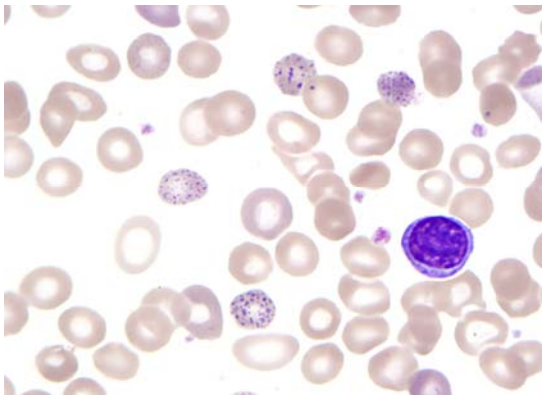
Heavy Metal Poisoning Etiology

- Lead interferes with several enzymes needed for Heme synthesis, i.e. delta aminolevulinic acid synthetase and ferrochetalase
- Causes
  - Adults - Occupational hazard, ingestion with lead laden dishes or glasses
  - Children – Ingestion, mostly of leaded paint
- Major tissues affected are
  - Kidney - reversible
  - Blood - reversible
  - CNS - occasionally irreversible
- Lead-line often present. This is a blackish rim of lead sulfide on the gums directly over the teeth

Heavy Metal Poisoning

- Microcytic normochromic mild anemia with high RDW
- Platelets normal
- Increased reticulocytes (polychromatophilia), often >10%
- Coarse basophilic stippling due to inhibition of pyrimidine 5' – nucleotidase activity, resulting in precipitated ribosomal RNA

Heavy Metal Poisoning



Thalassemia Traits

- Microcytosis occurs in Thalassemia trait because of reduction or deletion of globin chain synthesis (1-4 α genes on chromosome 16 = α thal; 1-2 β genes on chromosome 11 = β thal)
- Characterized by varying amounts of target cells, tear drops, and basophilic stippling
- Confusion with Fe ↓ by peripheral smear should only occur early in the iron deficient patient
- Thalassemia looks hypochromic, is not. Note MCHC usually normal, unless concurrent Fe ↓

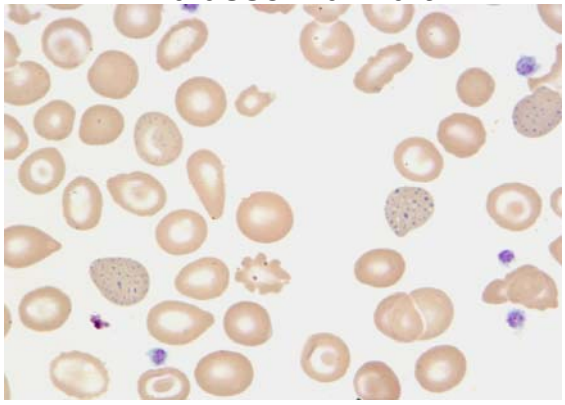
Differences between Fe ↓ and Thalassemia trait

	Iron def.	Thal minor
• RBC	< 5.50x106/µL	>5.50x106µ/L
• MCV	< 70 fl (can be low as < 50 fl)	< 70 fl > 55 fl
• MCHC	< 31.5 g/dl	> 31.9 g/dl
• RDW	increased (usually > 17)	normal (<14)
• BASO. STIPP.	absent	present

Hgb E – A Thalassemic like Hgb

- Hgb E is the most common thalassemia-like anemia in the USA today
- Has a reduced rate of synthesis due to a mutation of the ß chain
- Heterozygotes produce a picture similar to thalassemia trait, i.e. a microcytic normochromic anemia with variable numbers of targets, tears and basophilic stippling
- The cells are not as microcytic as in ∂ or ß thalassemia minor, the MCV usually falling between 70 - 80 fL. Target cells are present

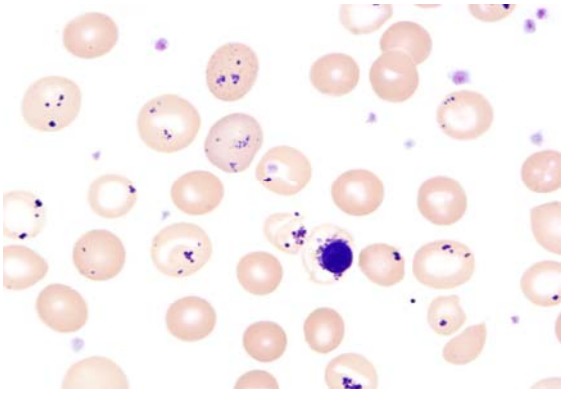
Thalassemia Trait



Congenital Sideroblastic Anemia

- ↑ iron storage and sideroblastic Fe
- Large numbers of bone marrow ringed sideroblasts, resulting in varying numbers of microcytic hypochromic red cells, containing Pappenheimer bodies
- 2 types of sideroblastic anemia
  1. Acquired - Primary (RARS) or Secondary to drugs, toxins such as alcohol, or cancer
  2. Inherited (Pyridoxine responsive or refractory))
     Fe loaded mitochondria enlarged and distorted ^{3}. Possible deposits are mostly insoluble ferric phosphate. Fe in ferric form CANNOT be inserted into protoporphyrin ring
     Reason that microcytosis, resulting from sideroblastic anemia, is placed in the group of, "disorders of porphyrin synthesis"

Congenital Sideroblastic Anemia



LABORATORY TESTS IN THE EVALUATION OF THE MICROCYTIC ANEMIAS

	MCV	MCHC	RDW	FE	TIBC	FERRITIN	FEP	BMFe
FE ↓	↓	↓	↑	↓	↑	↓	↓	↓
ACD	N↓	N↓	N↑	↓	↓	N↑	↑	↑ in histiocytes
THAL	↓	N	N	N	N	N	N	N
SA	↓(conj.) ↑(acq)	N↓	↑	↑	N↓	↑		+ in ring forms

FE = iron; ACD = anemia of chronic disase; THAL = thalessemia; SA = sideroblastic anemia; MCV = mean corpuscular volume; MCHC= mean corpuscular hemoglobin concentration; TIBC=total iron binding capacity; FEP=free erythrocyte protoporphyrin; BMFe= bone marrow iron

MACROCYTIC ANEMIAS

- **Macrocytic anemia should be listed under 2 different categories**
  - **Oval macrocytes**
  - **Round macrocytes**
- **Oval macroyctes indicate impaired or abnormal DNA synthesis**
  - **Megaloblastic anemia**
  - **Myelodysplastic syndrome**
  - **CDA (congenital dyserythropoietic anemia – types I, III, IV)**
- **Round macrocytes indicates increased or impaired growth patterns**
  - **Increased reticulocytosis**
  - **Liver disease**
  - **Alcohol with or without liver disease**
  - **Aplastic anemia**
  - **Hypothyroidism**

MEGALOBLASTIC ANEMIA

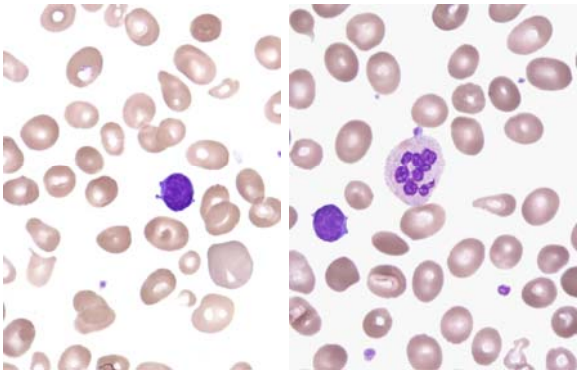
(B12 or Folate deficiency or Absence of Intrinsic Factor ⟶ PA)

- **Result of impaired DNA synthesis caused by a deficiency in the coenzyme forms of folate and B_{12}**
- **The maturing megaloblastic RBCs do not synthesize enough DNA per unit time of maturation for normal mitosis**
- **Leads to an increased number of cells in "S" phase**
- **Cytoplasm's RNA synthesis does not depend on B_{12} and folate, there is asynchrony of cytoplasm to nucleus maturation causing "megalocytosis in all proliferating cells**

MEGALOBLASTIC ANEMIA

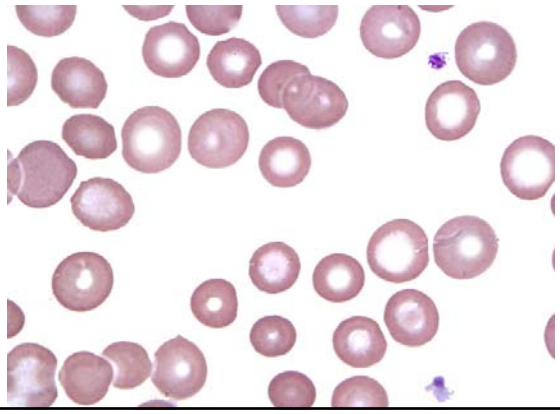
- Presents with pancytopenia
- Oval macrocytes and tear drops, a direct result of dyserythropoiesis
- Bizarre microcytes
- Hypersegmented PMNs, which are the last sign of impaired DNA synthesis to appear, not the first as has been postulated

MEGALOBLASTIC ANEMIA

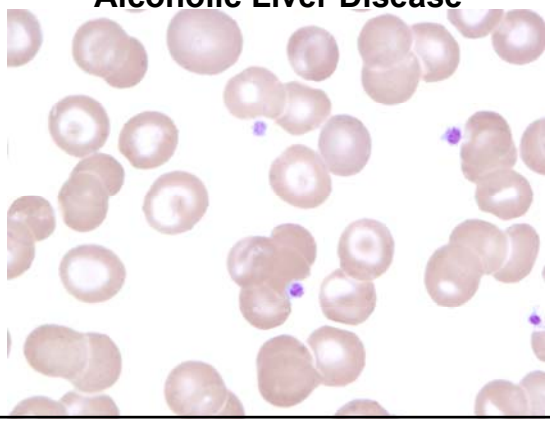


ROUND MACROCYTOSIS

Alcohol Abuse



Alcoholic Liver Disease



Hemolytic Anemia

- Definition of hemolytic anemia is a decreased RBC life span, usually under 10 days
- There are 2 types of hemolysis
  - Extracorpuscular – usually acquired
    Something is wrong with the environment in which the RBCs circulate
  - Intracorpuscular – usually Inherited
    Something is inherently wrong with the RBC itself
    - Membrane of the RBC
    - The Hgb molecule of the RBC

Characteristics of Hemolytic Anemia

One or more of the following is usually present

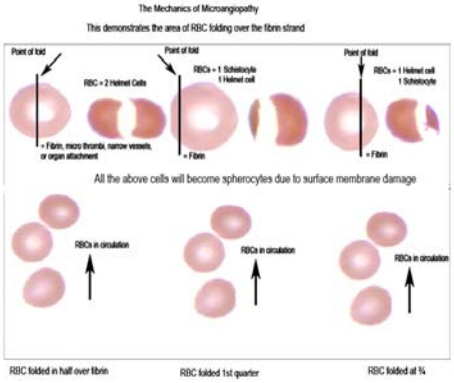
- **Macrocytosis - due to increased reticulocytes which is demonstrated by increased polychromatophilia**
- **Increased spherocytes**
- **Poikilocytes, according to type of anemia, i.e. sickle cells, bite cells, etc**
- **NRBCs - especially in a hemolytic crisis**
- **Reactive thrombocytosis**

Extracorpuscular Anemia

- **Microangiopathic anemia (MAP)**
- **Hypersplenism**
- **Drug induced oxidative hemolysis**
- **Autoimmune hemolysis**

MAP Anemias

- **Consumptive coagulapathies usually occurs when outside forces produce thromboplastin like material, which instigates the clotting and de-clotting mechanism**
- **This causes DIC which utilizes all clotting factors including consumption of platelets**
- **Marked thrombocytopenia in non-consumptive MAP anemias is usually a result of mechanical destruction of RBCs and trapping of platelets, i.e.TTP**
- **TTP shears RBCs with a hyaline like material plugging up vessels. The hyaline is very sticky and tends to trap the platelets, as opposed to consumption**



Common Disorders Associated with MAP

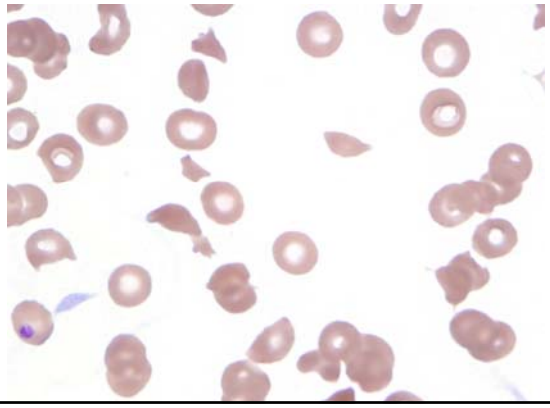
Consumptive	Non consumptive
Septic DIC, i.e. meningococcemia	"Warring Blender" Syndrome (heart valve in origin
Pre/Post Eclampsia (HELLP syndrome)	Thrombi Thrombocytopenia Purpura (TTP)
Placenta Abruptia	Cyclosporin therapy
Cavernous Hemangiomas	Malignant hypertension
	Cancer, mostly in small vessels

- All consumptive coagulapathies are thrombocytopenic
- Not all non consumptive coagulapathies are thrombocytopenic

Causes of MAP con't

- Some patients on cyclosporin or TK 506 get nephrotoxic reaction (cyclosporin or TK 506 toxicity) by forming small hyaline masses in the small capillaries of the kidney, resulting in a TTP - like syndrome
- HELLP syndrome is probably initiated by a hypertensive attack in pre-eclamptic patients causing eventual DIC
- "Waring blender" syndrome caused by a small nick or protrusion in teflon valves that rip and shear RBCs as they pass. Platelets not affected
- The toxin of certain bacteria produce a thromboplastin like phenomenon initiating massive DIC

MAP Anemia



Drug Induced Oxidative Hemolysis

- In class III variant, which has only moderate or mild decrease in G6PD activity, ingestion of some drugs will give a "bite-cell" anemia. This then is an intracorpuscular problem caused by an extracorpuscular accident
- There is a defective oxidative burst resulting from the lack of NADH and NADPH
- If a patient is anemic, therapeutic doses of an oxidant drug can cause hemolysis even if no G6PD deficiency exists
- Patients who are not anemic may develop oxidative hemolysis if given greater than therapeutic doses of an oxidant, even if no G6PD deficiency exists

Drug Induced Oxidative Hemolysis

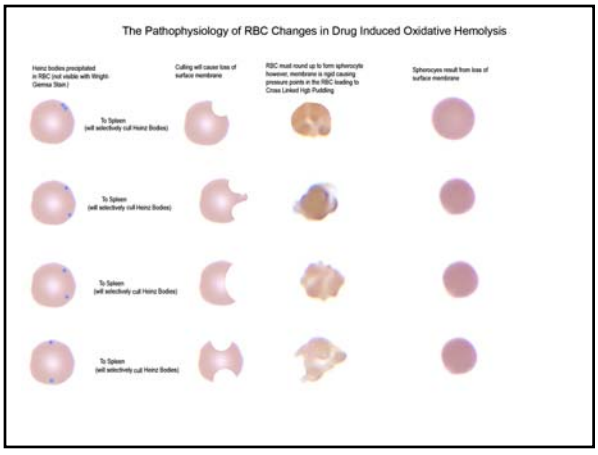
- Ingestion of certain oxidant reduction drugs causes cleaving of Fe^{+3} from O2-(superoxygen) leaving Fe^{+} (methemoglobin) and O_2ö (supraoxide, a weak oxidant)
- The O_2ö joins with H_2O_2 (normally found on RBCs) creating free Hgb (from the supraoxide) and OH^0 (from the H_2O_2), a very strong oxidant
- Results in precipitation of Heinz bodies, which is precipitated Hgb on the RBC surface
- Heinz bodies are removed by the spleen in a pitting action leaving "bite cells" and spherocytes after undergoing a "pressure-like" push on the RBC membrane, causing "cross linked Hgb puddling"

Drug Induced Oxidative Hemolysis

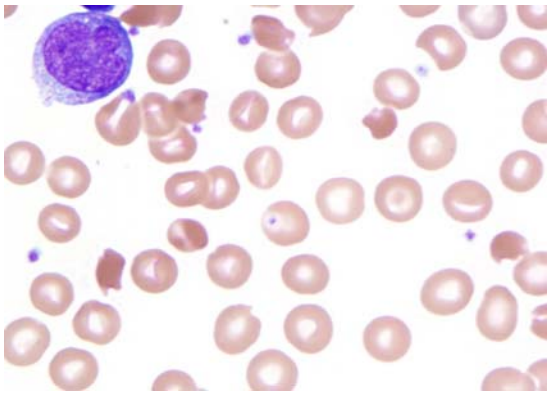
- Some common drugs that cause this defect are
  - Pyridium and Lasix
  - Sulfonamide and the sulfone drugs
  - Phenylhydrazine
  - Nitrofurantoin
  - Methylene blue
  - Dapsone
  - Naphtho
  - Aldomet

Other Enzyme Deficiencies in the Hexose Monophosate Shunt

- 99% of all deficiencies in the HMPS are of the G6PD deficiency type
- Several other enzyme deficiencies of the HMP shunt have been noted, although their numbers are small. They include
  - Defective biosynthesis of GSH
  - γ Glutamylcysteine synthetase deficiency
  - Glutathione synthetase deficiency
  - Glutathione reductase deficiency
  - Glutathione peroxidase deficiency



Drug Induced Oxidative Hemolysis



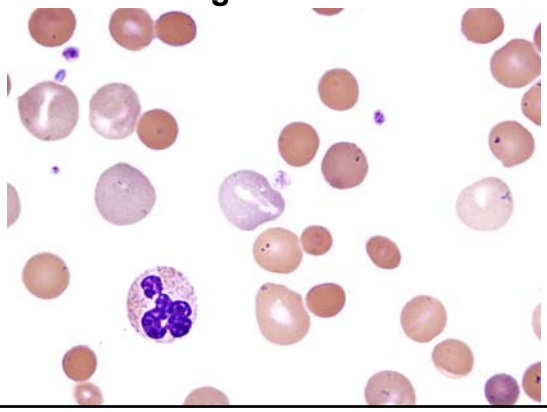
Autoimmune Hemolytic Anemia (AIHA)

- Mechanism causing RBC destruction is by coating of the RBCs with either IgM antibodies and complement, or with IgG
- AIHA can be idiopathic (IdHA), but the majority is associated with some underlying disease
- The proof of AIHA is in a positive direct Coombs test (autoantibody mediated hemolysis) and a positive indirect Coombs (with negative direct) in patients with alloantibody, i.e. pre-stimulation with either transfusion or pregnancy

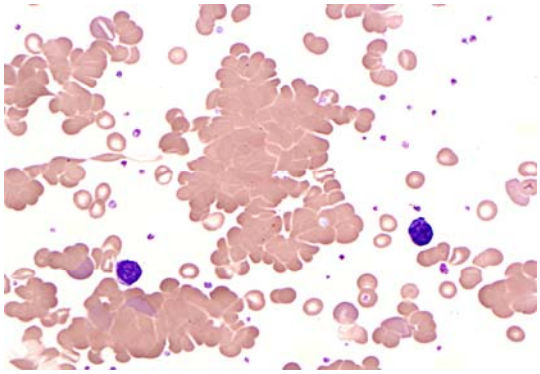
(AIHA) con't

- 2 types of AIHA
  - Warm: IgG coating of the RBCs resulting in many spherocytes. Associated with
    - Lymphoproliferative disorders, benign or malignant, account for over half the cases of 2^0 AIHA
    - Post viral syndromes
    - Idiopathic
    - Drugs, i.e., penicillin
  - Cold: IgM coating of the RBCs resulting in autoagglutination. Associated with
    - Mycoplasma pneumonia
    - Lymphoproliferative disorders, benign or malignant, account for over half the cases of 2^0 AIHA
    - Idiopathic
    - Drugs

IgG AIHA



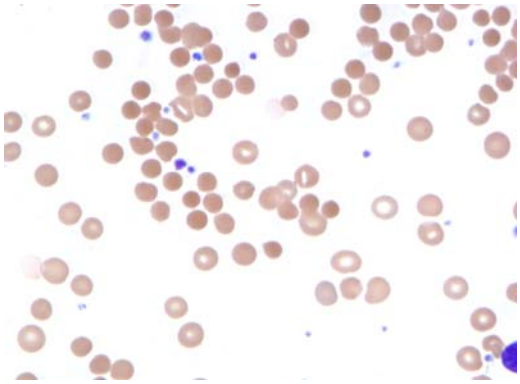
AIHA IgM



CLOSTRIDIUM INFECTION

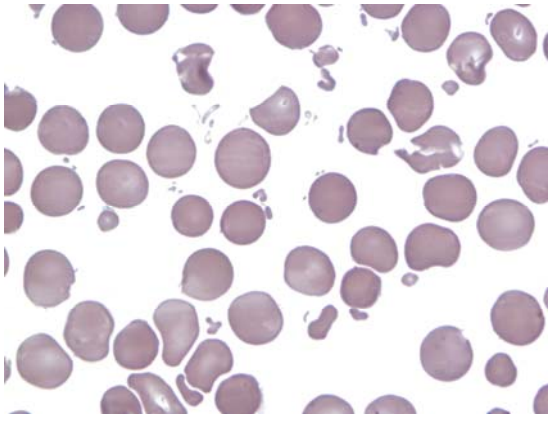
- Clostridial gas gangrene: a highly lethal necrotizing soft tissue infection of skeletal muscle caused by toxins- and gas-producing Clostridium species
- Clostridia are gram-positive, anaerobic, spore-forming bacilli
- Left shifted granulocytosis is common
- Profound anemia results from severe DIC, producing high numbers of spherocytes. The *clostridial* hemolysin is an α -toxin, which hydrolyzes phospholipids in RBC membranes.

CLOSTRIDIAL RBC CHANGES



Severe Burns

- Heat will denature Spectrin
- Severe burns will cause a marked intravascular hemolysis
- Many schistocytes, spherocytes and “dribbled” Hgb present on the peripheral smear
- Spherocytes will remain for many days after the initial burn due to damage to RBCs in the bone marrow



Intracorpuscular

- Membrane defects:
  - Congenital Spherocytosis
  - abetalopoproteinemia
  - Congenital Ovalocytosis
- Enzyme deficiencies
  - G6PD
  - Pyruvate Kinase
- Abnormal Hgb Structure
  - SS disease, SC disease, CC disease
  - Other hemoglobinapathies
- Anemia Associated with Impaired Globin Chain Synthesis
  - Thalassemia and other related conditions
  - Unstable Hgbs

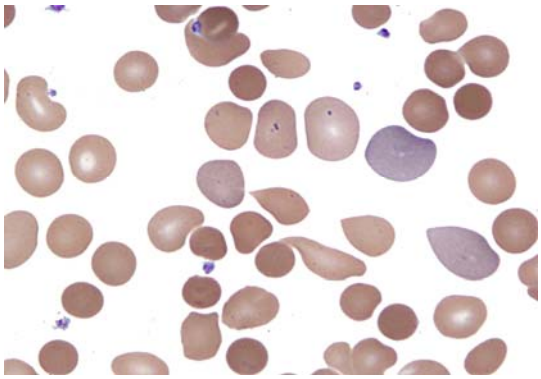
Congenital Spherocytosis

- Cause of this defect is a decrease in the amount of normal spectrin, protein 4.1 deficiency, and sometimes a deficiency of ankyrin 11
- Number of spherocytes varies in affected newborns from approximately 3% to 30%, Spherocyte percentages of little value in diagnosing this disorder
- Diagnositic test is Osmotic Fragility. If positive, splenectomy advised at the proper age
- Best clue to use in detection of a hemolytic condition in the neonate is retics >17%

RETICULOCYTE VALUES

Normal newborns	approximately	5-6%
ABO incompatibility	approximately	10-12%
Congenital spherocytosis		> 17%

Congenital Spherocytosis



A-abetalopoproteinemia

- Disorder clinically characterized by fat malabsorption
- Serum triglyceride level is < 300 mg/L, cholesterol levels are <500 mg/L and there is a total absence of apolipoprotein B
- Plasma cholesterol, triglycerides and phospholipids are markedly reduced [14]
- These patients usually suffer from vitamin deficiencies of the fat-soluble vitamins A,D,E, and K

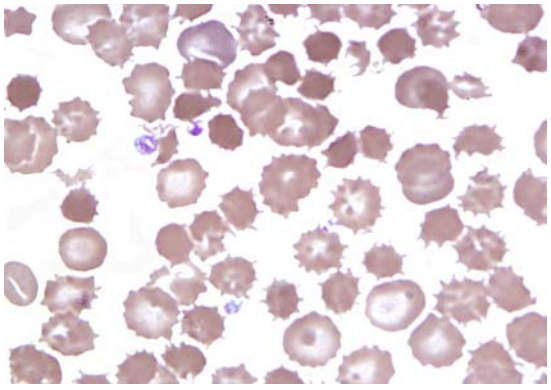
A-betalipoproteinemia

- Approximately 80% acanthocytes on smear
- These patients usually suffer from vitamin deficiencies of the fat-soluble vitamins A,D,E, and K
- anemia seen is mild, with retics approximately 7-9%
- Mild hemolytic anemia is a result of the RBCs lack of deformability and reformability, probably due to increased surface membrane cholesterol with normal total phospholipids

Other Causes of Acanthocytes

- Premature infants undergoing hyperallementation
- Severe cases malnutrition, i.e. anorexia nervosa
- Liver disease
  - Alcoholic cirrhosis
  - End stage liver disease
  - Some liver carcinomas

A-betalipoproteinemia



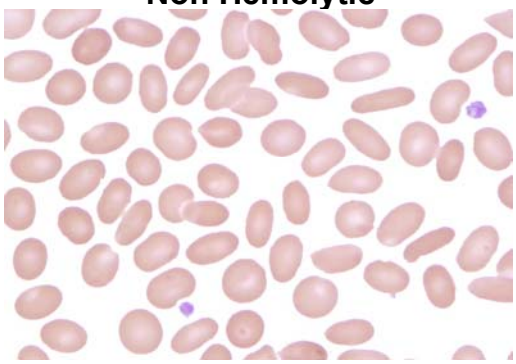
Congenital Ovalocytosis

- Probably caused by a decrease in one of the RBC surface proteins, spectrin
- Spectrin is a high molecular weight protein responsible for maintaining the normal cell shape and deformability
- In the ovalocyte, there is also an increase in bipolar cholesterol
- 2 types of hereditary ovalocytosis
  - Non-hemolytic
  - Hemolytic variant
    - Pyropoikilocytosis - homozygous
    - Hemolytic ovalocytosis - heterozygous

Congenital Ovalocytosis Non Hemolytic

- Benign condition
- Mild red cell destruction is well compensated
- Patients present with 50 - 70% ovalocytes
- All other parameters are normal

Congenital Ovalocytosis Non Hemolytic



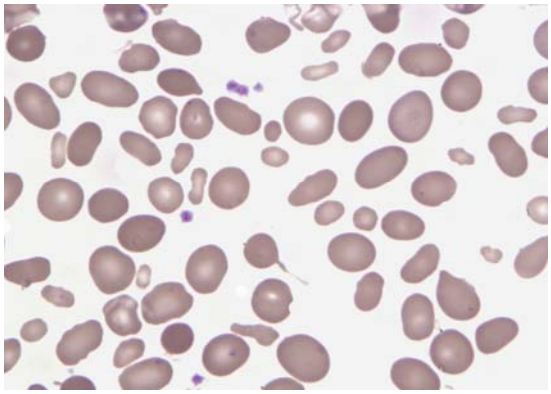
Pyropoikilocytosis

- Can be a severe hemolytic anemia
- Many distorted microspherocytes, schistocytes, polychromatophilic cells, and ovalocytes
- Normal RBCs rupture their cytoskeletal membranes at 49°C
- Patients with congenital Pyropoikilocytosis denature protein at 45°C

Pyropoikilocytosis

- Variety in the degree of hemolysis from patient to patient, depending on the severity of spectrin deficiency
- Severe cases have a morphology that is almost 90% spherocytes and schistocytes
- The presence of many macro ovalocytes may be observed in severe cases, due to rapid RBC turn over resulting in folate depletion
- Therapy is splenectomy, which ameliorates some of the hemolysis, but not the majority, as in congenital spherocytosis

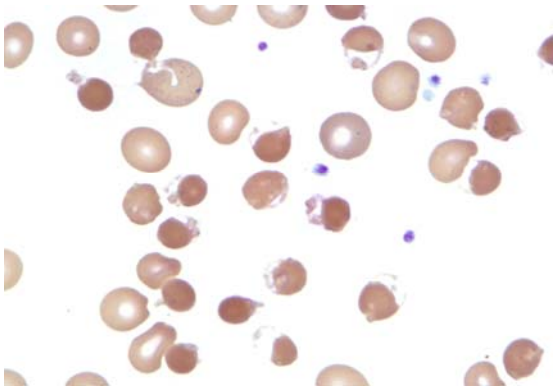
Pyropoikilocytosis



Enzyme Deficiencies

- Class I and II deficiency of G_6PD
  - Extremely low G_6PD activity
  - Suffer with interminable non-spherocytic hemolytic anemia, caused by the production of Heinz bodies – denatured HGB
  - In extreme cases of oxidative hemolysis, there is intravascular hemolysis, with Heinz bodies being "squeezed" out of cell membrane
  - Contributors to hemolysis in G_6PD-deficient patients are infections, or Fava beans (Favism) - found in the Mediterranean variant) in class II variant of G_6PD deficiency

G_6PD Deficiency



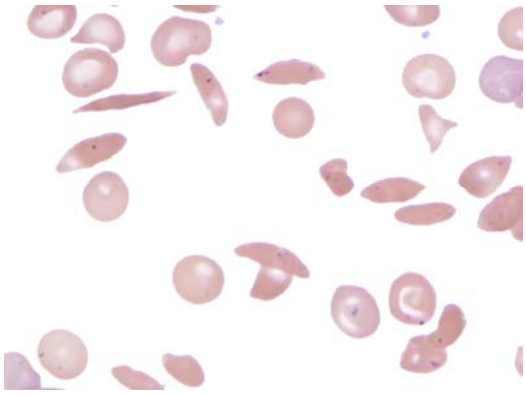
ABNORMAL HEMOGLOBIN STRUCTURE

- Most common finding in this hemolytic type, with few exceptions, is target cells. The most common hemolytic types are
  - Sickle Cell Anemia
  - Hgb SC Disease
  - CC Disease
  - Others in this category not diagnosable by peripheral smear

Sickle Cell Anemia

- Macrocytic, due to increased retics, normochromic anemia
- Increased numbers of target cells, nucleated RBCs, polychromatophilia, and sickle cells
- Howell-Jolly bodies increase in number with each hemolytic crisis, due to splenic atrophy from multiple splenic infarcts
- Leukocytosis and reactive thrombocytosis often elevated as a result of infection, and as a secondary reaction to extreme marrow erythroid hyperplasia

SS Disease



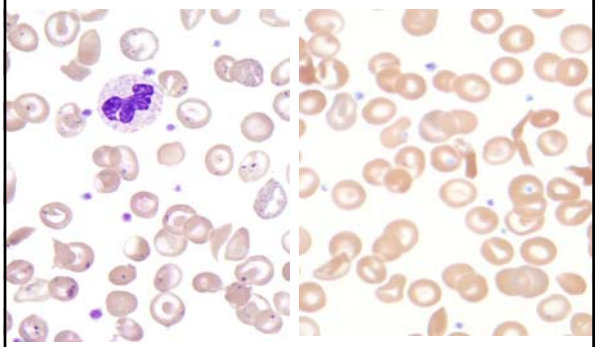
SC Disease

- Normocytic normochromic anemia, not usually a severe hemolytic anemia. If sickle crisis does occur, can be more severe than the crisis associated with SS
- Presence of at least 40-60% target cells and few sickle cells
- Indeterminate numbers of blister cells
- Rare to high numbers of intra-erythrocytic "C" crystals

CC Disease

- Mild, chronic hemolytic anemia
- 60-80% target cells
- Mildly increased retics, blister cells, and "C" crystals. “C” crystals are birefringent tetrahedral crystals that strongly absorb Soret light
- The heterozygote of Hgb AC is non symptomatic and clinically normal

SC CC



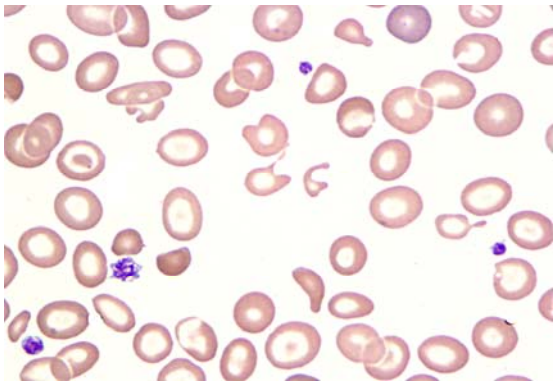
ANEMIA ASSOCIATED WITH IMPAIRED GLOBIN CHAIN SYNTHESIS

- Unstable Hgbs
  - Hemoglobin H disease
  - Others (Hgbs Hammersmith, Köln, Zurich, Ann Arbor, Gun Hill, Philadelphia, Bethlehem, and Constant Spring, Bristol etc.)
- β Thalassemia major
- E β Thalassemia

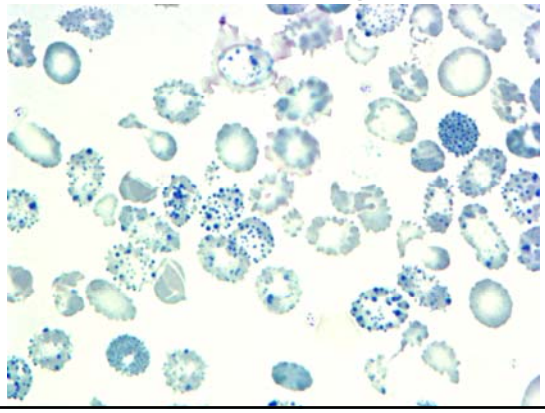
Hgb H

- Hemoglobin results because of a deletion of 3 of the 4 ∂ genes
- Hgb is an unstable Hgb
- Microcytic hypochromic anemia, with increased numbers of target cells, tear drops and basophilic stippling
- Spherocytes and some schistocytes are also present, giving a dimorphic picture. With BCB stain, Hgb H precipitates out and gives a golf ball appearance

Hgb H



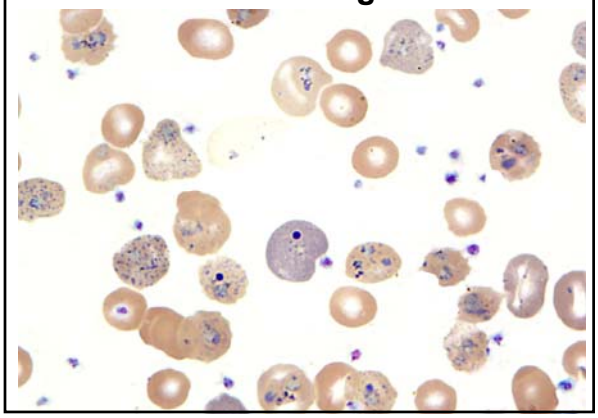
BCB Stain for Hgb H



Unstable Hgbs

- Autosomal dominant. Usually treated with splenectomy if severe hemolysis is present
- Causes denatured Hgb or Heinz bodies, which are larger than those found in G6PD deficiency. Unstable Hgb usually arises when there is an alteration in the sequence of amino acids in one of the globin chains
- On occasion, precipitated Hgb may be seen in the RBC with Wrights-Giemsa stain
- Tests to prove the presence of unstable Hgbs are the Heinz body test, heat denaturation test, and isopropanol precipitation test.

Unstable Hgbs



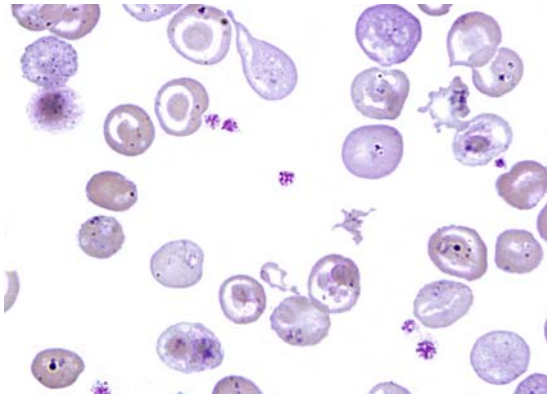
Thalassemia Major and E-β Thalassemia Morphology similar

- Patients present with severe hepatosplenomegaly. In time they develop marked skeletal abnormalities
- Splenectomy is the standard course of treatment to ameliorate some of the hemolysis
- Patients are maintained on an adequate transfusion program with chelation therapy to minimize excess iron overload. But iron overload, leading to cardiomyopathy, is common
- Bone marrow transplant is the only guaranteed cure

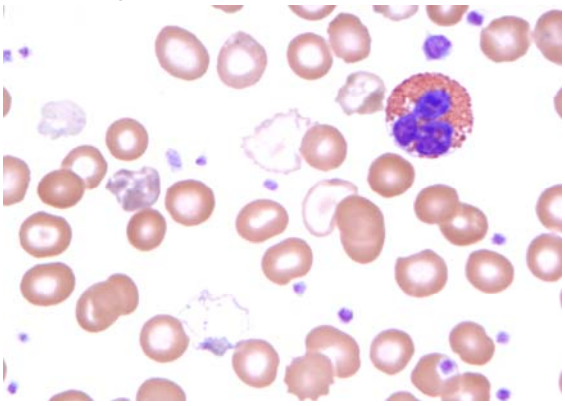
Thalassemia Major and E-β Thalassemia

- Severe microcytic hypochromic anemia
- Marked increase in basophilic stippling, bizarre microcytes (some as small as 2-3μ), many tear drops, a marked increase in polychromatophilia, leukocytosis with a severe left shift (blasts may be seen
- Many normoblasts
- Classic example of ineffective (but not dysplastic) erythropoiesis with increased extramedullary hematopoiesis

Thalassemia Major and E-β Thalassemia



Thal Major S/P Multiple Transfusions



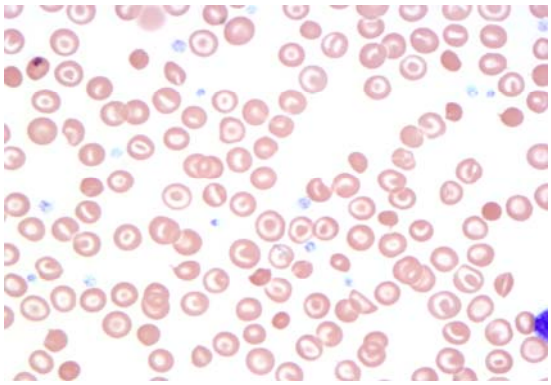
Homozygous E

- Hemoglobin E is the most common abnormal hemoglobin identified in the state of California on newborn screening. It is common in Laos, Cambodia and Thailand
- Hemoglobin E is the result of a ß-chain mutation (AÆG) in codon 26 changing glutamine Æ lysine
- This creates a new splice site which competes with the normal splice site causing decreased production of an unstable hemoglobin.

Homozygous E CON'T

- Hgb E disease (Hgb EE) causes a hypochromic microcytic (Hgb ~10; MCV ~ 60) anemia with many up to 90% targets and some basophilic stippling.
- Individuals who have Hgb EE do not have significant anemia and do not require special care except that they should not be treated with iron for anemia.

Hgb EE



Congenital Dyserythropoietic Anemia

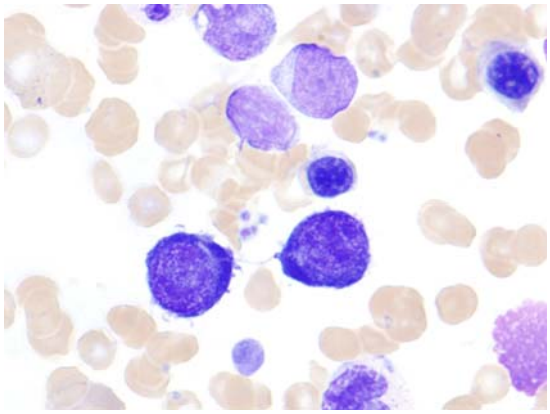
- The CDAs are a group of hereditary anemias characterized by ineffective erythropoiesis, erythroid multinuclearity, refractory anemia and secondary iron overloading
- Probably caused by a disturbance in the erythroid development, resulting in an alteration of the normal diploid genome in the erythroid precursor
- Peripheral smears are usually macrocytic, although normocytic anemias have been reported, usually in CDA II
- Increased numbers of macro ovalocytes, especially in types I and III, with normal to slightly increased polychromatophilia. Granulocytes, lymphocytes, and platelets are normal

CDA

- Oval macrocytes are associated with dyserythropoiesis, as seen in megaloblastic anemias and the myelodysplastic syndromes
- The marrow erythrogenesis is megaloblastoid with marked erythroid hyperplasia
- Even though ineffective erythropoiesis typifies the CDA patient, RBC survival of mature reds in the blood is usually normal
- Genetics is Recessive

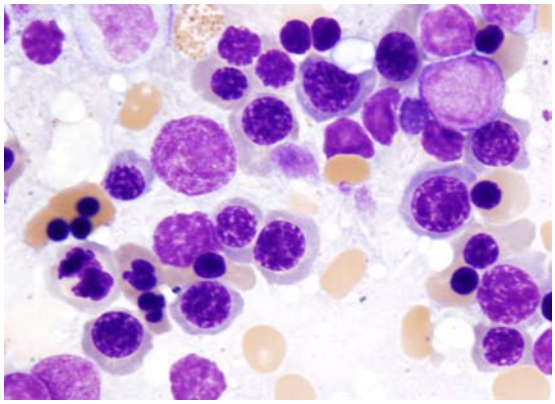
CDA I

- Type I This type shows three types of multinuclearity
  - Nuclear bridging. i.e. binucleate megaloblastoid cells, joined together with a fine strand of nuclear material.
  - Giant cells with 2 irregular shaped nuclei, without bridging, which probably represents abnormal or incomplete nuclear division
  - 2 nuclei, in which neither has the same size, structure, or stainability
  - Mild to moderate anemia with macro ovalocytes. On occasion, Cabot rings are found



CDA II

- Type II - Hempas type. The most common of the CDAs.
  - Hempas stands for Hereditary erythroblastic multinuclearity positive for acidified serum (Hams test). The multinuclearity is only seen in the late erythroblasts, beyond the basophilic stage of maturation. There is also a double cell membrane found on EM that reflects an excess of endoplasmic reticulum
  - There is a moderate amount of size variation, and chromasia, with an occasional spherocyte seen
  - Reticulocytes may be slightly increased
  - The bone marrow shows much (approximately 10-31%) multinuclearity in the more mature erythroblasts, with 2 or more nuclei.
  - Pseudo-Gaucher cells are commonly found
  - Often requires transfusion eventually causing iron overloading



CDA III

- One of the rarest types of CDA
- Giant megalocytes are present in the peripheral blood
- Bone marrow is characterized by extreme multinuclearity, with up to 12 nuclei seen in one erythroblast
- These bizarre multinucleated cells have been referred to as "gigantoblasts"

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