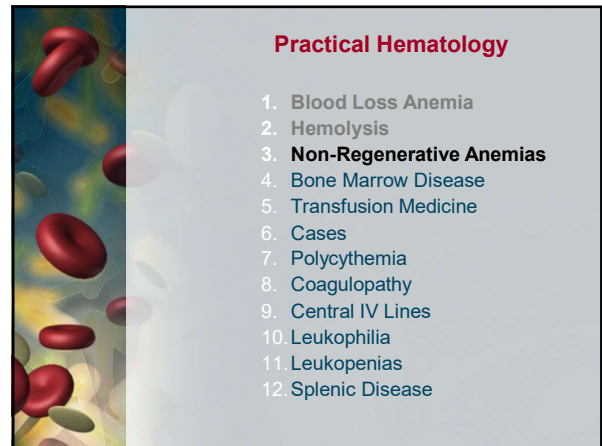


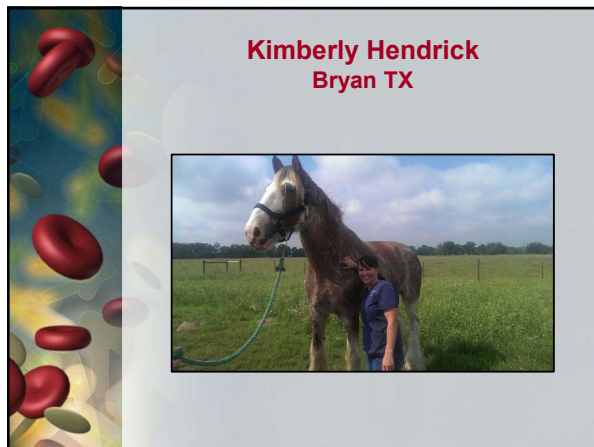
## Practical Hematology Non-Regenerative Anemias

Wendy Blount, DVM  
February 2017


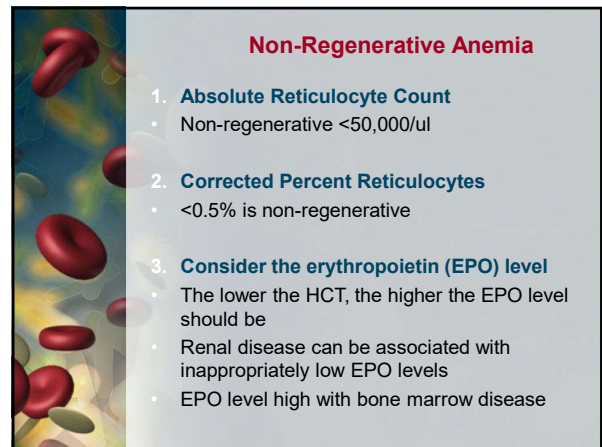


### Practical Hematology

1. Blood Loss Anemia
2. Hemolysis
3. **Non-Regenerative Anemias**
4. Bone Marrow Disease
5. Transfusion Medicine
6. Cases
7. Polycythemia
8. Coagulopathy
9. Central IV Lines
10. Leukophilia
11. Leukopenias
12. Splenic Disease

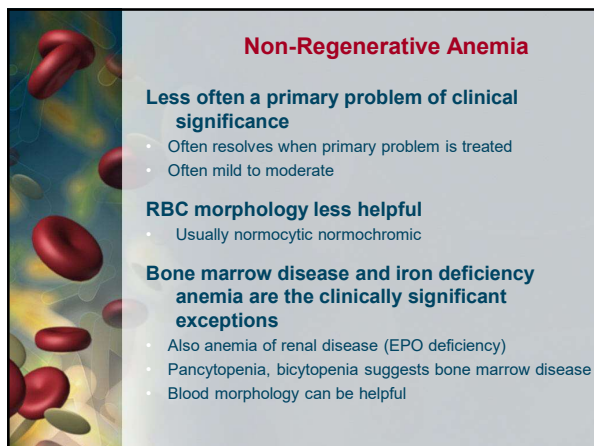


### Kimberly Hendrick Bryan TX

### Non-Regenerative Anemia

1. **Absolute Reticulocyte Count**
  - Non-regenerative <50,000/ul
2. **Corrected Percent Reticulocytes**
  - <0.5% is non-regenerative
3. **Consider the erythropoietin (EPO) level**
  - The lower the HCT, the higher the EPO level should be
  - Renal disease can be associated with inappropriately low EPO levels
  - EPO level high with bone marrow disease



### Non-Regenerative Anemia

**Less often a primary problem of clinical significance**

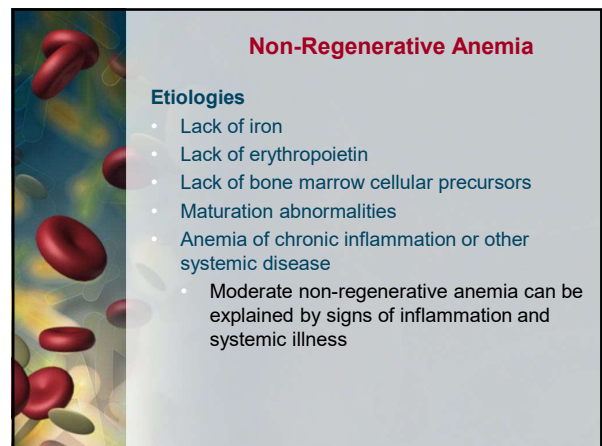
- Often resolves when primary problem is treated
- Often mild to moderate

**RBC morphology less helpful**

- Usually normocytic normochromic

**Bone marrow disease and iron deficiency anemia are the clinically significant exceptions**

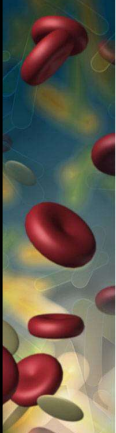
- Also anemia of renal disease (EPO deficiency)
- Pancytopenia, bicytopenia suggests bone marrow disease
- Blood morphology can be helpful



### Non-Regenerative Anemia

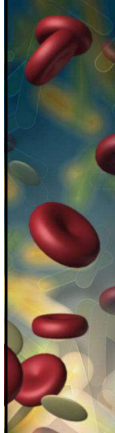
**Etiologies**

- Lack of iron
- Lack of erythropoietin
- Lack of bone marrow cellular precursors
- Maturation abnormalities
- Anemia of chronic inflammation or other systemic disease
  - Moderate non-regenerative anemia can be explained by signs of inflammation and systemic illness



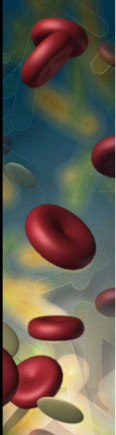
### Non-Regenerative Anemia

- **EPO has four effects on bone marrow:**
  1. Stem cells differentiate to erythroid
  2. Decreases RBC maturation time
  3. Increases Hb per RBC
  4. Premature release of reticulocytes from bone marrow to blood



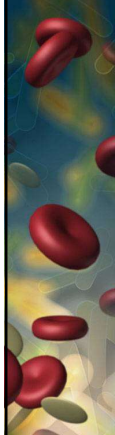
### Diagnostics for Nonregenerative Anemia

- Make sure anemia has been present for at least 1 week before assessing regenerative response
- Bone Marrow Sampling
- EPO levels
- Iron testing
- Blood Morphology – IDA, infectious organisms, leukemias



### Lack of Erythropoietin

- **Renal Disease**
  - Lack of EPO production
  - shortened RBC lifespan, bone marrow suppression and GI blood loss can also contribute
  - Look for concurrent IDA
- **Endocrinopathy (mildly low EPO)**
  - Hypothyroidism – most common
  - Addison's disease
  - Growth hormone deficiency



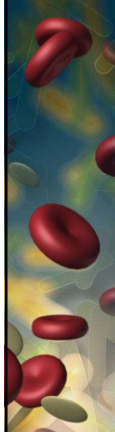
### Renal Disease – Poor EPO Production

- **Bone Marrow**
  - Normal
  - Increased hemosiderin if ACID
  - Or decreased iron stores if IDA
- **Iron Panel**
  - Usually normal
  - IDA also possible
- **EPO levels**
  - Normal to modestly reduced
  - Lower in cats with CRF than in dogs
  - Respond well to EPO therapy
- Uremic toxins suppress bone marrow activity (PTH)



### Renal Disease – Poor EPO Production

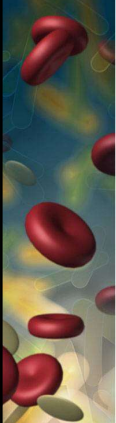
- **Treatment**
  - Treat renal disease
  - Human recombinant erythropoietin (extralabel)
    - 100 U/kg SC 3x weekly until PCV low-normal, then 1-2x weekly
    - Procrit®, Epogen®
    - Reserve for HCT <25% in dogs and <20% in cats
    - Correct iron deficiency first if present
    - Takes a few weeks to a few months for antibodies to develop
    - Sudden severe anemia may mean antiEPO antibodies have developed (25%)
      - Transfuse and stop EPO
    - Darbopoietin – only 10% secondary PRCA



### Anemia of Chronic Liver Disease

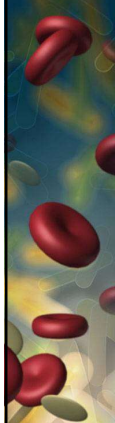
**Compounded by coagulopathy and blood loss, especially in cats**

- **RBC Morphology**
  - Abnormal lipid metabolism – acanthocytes, target cells, leptocytes, codocytes
  - Microcytosis in dogs with PSS
- **Bone Marrow** - variable
  - ± Erythroid hypoplasia due to reduced synthesis of nutrients for hematopoiesis
- **Iron panel**
  - Increased hepatic iron, ± low serum iron
  - Normal TIBC, UIBC
- **EPO levels** - variable



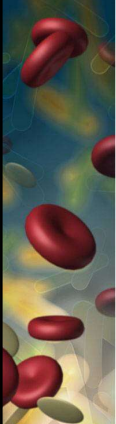
### Endocrinopathy

- Decreased tissue oxygen consumption causes moderately low EPO levels
- **Bone Marrow**
  - normal
- **Iron panel**
  - Serum iron decreased
- **EPO levels**
  - modestly reduced
- **Anemia resolves after 3-4 months of thyroxine therapy**
  - Less common with Addison's



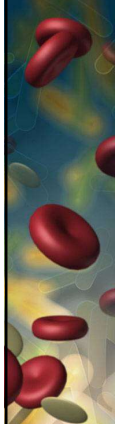
### Iron Deficiency Anemia

- **IDA becomes non-regenerative only if chronic blood loss is prolonged and severe, or if diet is lacking in iron**
- **Mother's milk contains little iron**
  - Neonates susceptible to non-regenerative IDA due to parasitism
- **Tissue iron stores depleted**
  - Liver, spleen, bone marrow
  - Soluble – ferritin
  - Insoluble – hemosiderin
- **Plasma transport to RBC Hb**
  - Transferrin (TIBC) increased
  - Copper helps transport iron across cell membranes



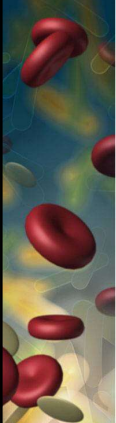
### Iron Deficiency Anemia

- **Iron metabolism**
  1. Absorbed from food in the GI tract
  2. Held on intestinal epithelial cells by ferritin
    - Sloughed or absorbed, based on need
  3. Absorbed into blood and carried by transferrin (measured as TIBC)
  4. Stored in the tissues as soluble ferritin
    - Mostly in the liver



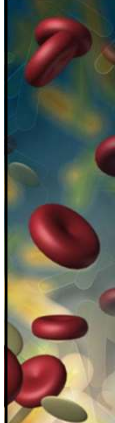
### Iron Deficiency Anemia

- **Blood Smear**
  - Microcytic (<60 fl), hypochromic (MCHC <32 g/dl)
  - nRBC
- **CBC**
  - Decreased MCV, MCH, MCHC
- **Iron stores – Definitive Diagnosis**
  - Serum iron & ferritin markedly decreased
  - Transferrin/TIBC normal to increased
  - Increased UIBC
  - decreased transferrin saturation (% = serum iron/TIBC)
    - Normal 20-60%; IDA <10%
- **Bone marrow**
  - Depleted iron stores
  - mild erythroid response
- **EPO levels**
  - increased



### Iron Deficiency Anemia

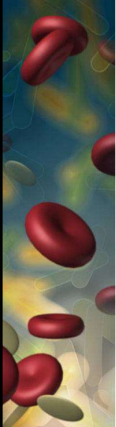
- The most common causes of iron deficiency anemia are chronic GI blood loss and flea anemia
- Blood loss anemia is first strongly regenerative, then non-regenerative as IDA develops
- Anemia varies from mild to severe
- Poikilocytosis and hypochromasia are typical
- Hypoproteinemia often present
- Anemia won't budge until iron is supplemented, even if chronic blood loss is corrected
- Rapid improvement within a week or two supplementing iron



### Differential Diagnosis

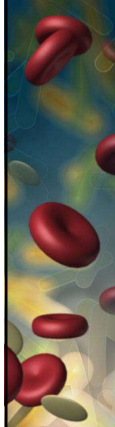
#### Microcytic anemia

- **Microcytic but not hypochromic**
  - Akita, Shiba Inu, Chow chow
  - Puppies
  - **Dyserythropoiesis of Springer Spaniels** (polymyopathy, cardiac)
  - Chloramphenicol toxicity
- **Iron deficiency anemia**
  - Hypochromic (low MCHC)
  - Microcytic (low MCV)
- **Copper Deficiency**
- **Liver disease**
  - Especially portasystemic shunt



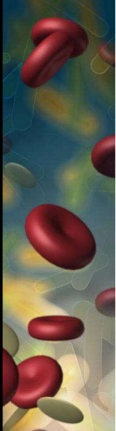
**Anemia of Chronic Inflammatory Disease**

- Mild-moderate anemia (can be severe in cats)
- **The most common anemia in small animals**
- Can develop within 7-10 days
- Iron is sequestered in the macrophages, so not available for RBC production
  - Physiologic metabolic response to deprive infectious organisms of iron
  - Apolactoferrin secreted by neutrophils
  - Chelated iron, especially at low pH of inflammation
- Macrophages have lactoferrin receptors that internalize the chelated iron
- Results in diversion of iron from ferritin (soluble) to hemosiderin (insoluble)



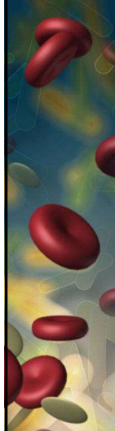
**Anemia of Chronic Inflammatory Disease**

- Activated macrophages remove RBC from circulation
- Fever shortens RBC lifespan
- Iron panel
  - Serum iron normal to decreased
  - Ferritin normal to increased
  - Transferrin/TIBC normal to decreased
- Bone marrow
  - **Increased hemosiderin in macrophages**
  - Lack of marked erythroid response
  - Myeloid hyperplasia



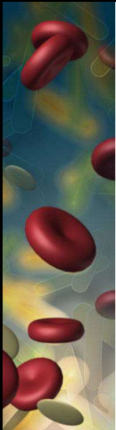
**Anemia of Chronic Inflammatory Disease**

- EPO levels
  - Normal to decreased
- Treatment
  - Treat underlying problem
  - Iron administration is of little help, and can make matters worse:
    - Chronic overdose - liver failure, GI distress/fibrosis
    - Acute overdose - pulmonary edema, shock
    - Repeated transfusion can cause chronic overdose
  - EPO administration of little help



**Non-Regenerative IMHA (NRIMHA)**


- Iron stores
  - normal
- Bone marrow
  - Maturation arrest at affected stage
  - May see other bone marrow problems: dyserythropoiesis, hematomphagocytic syndromes, myelofibrosis, bone marrow necrosis
  - Can do immunologic staining for definitive diagnosis
- Etiology
  - Immune mediated destruction of erythroid stem cells later than PRCA
- Treatment
  - Immunosuppression as for IMHA

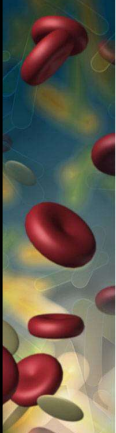


**Pure Red Cell Aplasia (PRCA)**

- Severe anemia – PCV <10-20%
- Sometimes spherocytes and stomatocytes
- Iron stores - normal
- Bone marrow
  - Nearly absent erythroid precursors
- Etiology
  - FeLV, FIV, parvovirus infection
  - Immune mediated destruction of earliest erythroid stem cells
- Treatment
  - Immunosuppression as for IMHA

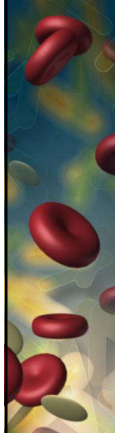
**Mark Jousan  
Center TX**





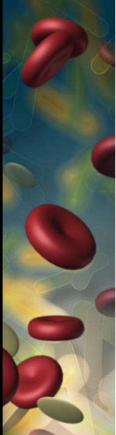
## Aplastic Anemia

- **Pancytopenia**
  - often preceded by leukocytosis for several weeks
  - Neutropenia first
  - then thrombocytopenia
  - then anemia
- **Etiology**
  - Estrogen toxicity
    - Iatrogenic
    - Sertoli cell or granulosa cell tumor
  - Drugs
    - AZT, antineoplastics, azathioprine, phenylbutazone, sulfas, fenbendazole, quinidine, thiacetarsamide, phenobarbital, cephalosporins
    - Cats – propylthiouracil, methimazole, griseofulvin
    - Dobermans –
    - Dogs with bute toxicity rarely recover



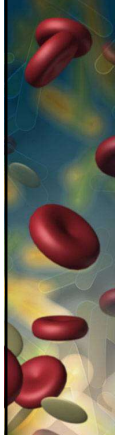
## Aplastic Anemia

- **Etiology**
  - Chloramphenicol causes mild, reversible nonregenerative anemia in dogs
  - Infection
    - Ehrlichia (also immune mediated)
    - Bacterial endotoxins, Aflatoxin B
    - Parvovirus
  - DIC (necrosis)
  - Idiopathic
- **Bone marrow**
  - Hypocellular bone marrow despite spicules, except plasmacytosis
  - May have myelonecrosis
  - Often need bone marrow histopath to confirm



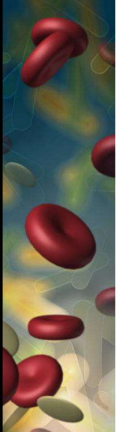
## Aplastic Anemia

- **Treatment**
  1. Discontinue bone marrow toxins
  2. Doxycycline 5-10 mg/kg PO BID x 3 weeks
  3. 1 week later - if that fails, immunosuppression
    - Prednisone 1 mg/lb/day
    - If not effective after 1-2 weeks, increase to 2 mg/b/day x 1-2 weeks & start azathioprine
    - Then as for resistant IMHA
  4. Prophylactic antibiotics
  5. Avoid injury that can risk bleeding
  6. Transfuse to buy time for bone marrow response
- **WBC recover first, then platelets, then RBC**



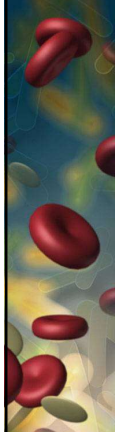
## Aplastic Anemia

- **“Panic Numbers”**
  - Weekly rechecks until near normal range
  - If stable and above panic numbers, continue treatment
  - If numbers falling or below panic thresholds, add/increase immunosuppression
- **1.** PCV <15% - transfuse, start EPO
- **2.** Neutrophils 1,000-1,500/ul – amoxicillin x 14d
- **3.** Neutrophils <1,000/ul – amoxi + quinolone
- **4.** Neutrophils <500/ul – start GCSF, treat sepsis
- **5.** Platelets <50,000/ul at risk for hemorrhage
  - If no vasculitis, often don't bleed unit <10K/ul
- **6.** Platelets <10,000/ul – vincristine 0.02 mg/kg IV

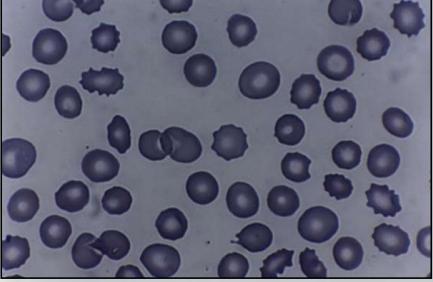


## Myelophthisic Disease

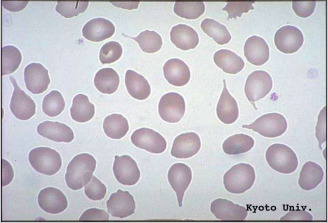
- **Bone marrow has been replaced by something else**
  - Tumor cells
  - Fungal granuloma
  - Fibrous tissue
  - fat
- **Hemogram**
  - Normocytic, normochronic anemia
  - nRBC



## Myelophthisic Disease



## Myelophthisic Disease



Kyoto Univ.

- Budding fragmentation, dacryocytosis
- Large platelets or megaplatelets
- Degenerative left shift

## Myelophthisic Disease

- **Myelofibrosis**
  - neoplasia
  - Chronic severe hemolytic anemia
    - Congenital anemia
  - Idiopathic myelofibrosis
    - Nonregenerative anemia and thrombocytosis
    - Organomegaly due to EMH
    - Left shift in all 3 cell lines
- Can not diagnose on bone marrow aspirate
  - Need bone marrow core biopsy

## Myelophthisic Disease

- **Bone Marrow Neoplasia**
  - May or may not be associated with leukemia
    - Neoplastic cells in peripheral blood
  - Neoplastic cells often found elsewhere
    - Liver, spleen, lymph nodes
  - Myeloproliferative neoplasia
    - Granulocytes and monocytic
    - "non-lymphoid leukemia"
  - Lymphoproliferative Neoplasia
- Clinical Signs
  - Bone pain
  - Fever, infection, leukopenia
  - Anorexia, lethargy, vomiting, diarrhea
  - May progress to anemia and thrombocytopenia

## Myelodysplasia

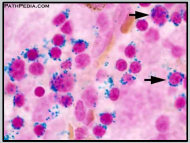
- **Also known as...**
  - Refractory anemias
    - RARS – Refractory Anemia with Ringed Sideroblasts
    - RAEB – Refractory Anemia with Excess Blasts
  - Refractory Cytopenias
    - RCMD – Refractory Cytopenias with Multiineage Dysplasia
  - Preleukemia (**can progress to acute leukemia**)
    - Subacute leukemia
  - Dysmyelopoiesis (due to toxicity)
  - Myelodysplastic Syndrome (MDS)

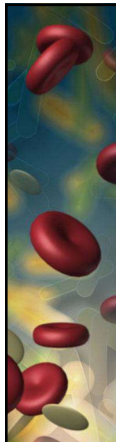
## Myelodysplasia

- **Many blast cells in the affected line (5-20%)**
- **But they don't mature in the usual way, due to acquired genetic mutation**
  - maturation arrest – atypical (dysplastic) morphology of RBC precursors
  - Hyperplastic bone marrow with 5-20% blasts
- **Etiology**
  - drug induced - chloramphenicol
  - FeLV, FIV
  - Idiopathic, immune mediated

## Myelodysplasia

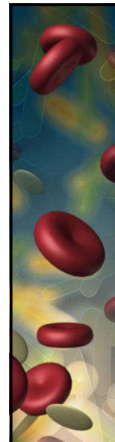
- **Siderocytes, Sideroblasts**
  - Contain Pappenheimer bodies – iron granules
  - Resembles basophilic stippling
  - Prussian Blue stains Pappenheimer bodies, but not RNA of basophilic stippling
  - RARS – Refractory Anemia with Ringed Sideroblasts
- **Treatment**
  - EPO





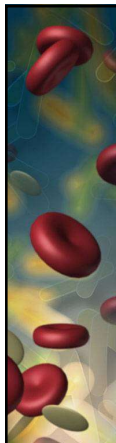
## Congenital Dyserythropoiesis

- **English Springer Spaniels**
  - Bone marrow - dyserythropoiesis
  - Polymyopathy
  - Cardiac disease
  - Hemogram – poikilocytosis
    - spherocytes, schistocytes, dacryocytes, codocytes, vacuolated RBC
- **Giant Schnauzers**
  - Vitamin B12 malabsorption
  - Chronic non-regenerative anemia and neutropenia
  - Hemogram – anisocytosis, MCV normal, poikilocytosis
    - macrocytes, schistocytes, acanthocytes, elliptocytes, keatocytes, hypersegmented segs, giant platelets
- **Poodles**
  - Dyserythropoiesis (PK deficiency like disease), hemolysis, macrocytosis



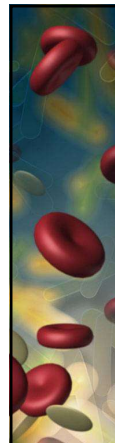
## Folate Deficiency

- **hemogram**
  - Macrocytosis (increased MCV)
- **B12 deficiency anemia not observed in dogs and cats, except Giant schnauzers**
- **Etiology folate deficiency**
  - Distal small intestinal disease
  - Prolonged TMPS administration
  - Increased requirements during pregnancy
- **Treatment**
  - Treat small intestinal disease
  - Supplement if giving TMPS for more than 30 days
  - Supplement during pregnancy



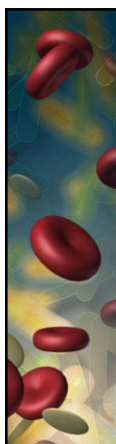
## Feline Leukemia

- **Causes anemia in numerous ways**
  - ACID by susceptibility to pathogens
  - Pure red cell aplasia
  - Aplastic pancytopenia (NRIMHA)
  - Hemolytic anemia due to hemoplasmas
  - IMHA
  - Myelodysplasia
  - Myelofibrosis
  - Hemophagocytic syndrome
- **You can't treat FeLV anemia intelligently without a bone marrow sample**
- **Hemogram**
  - Often macrocytic (>52 fl), normochromic
  - Megaloblastic rubricytes
  - **Usually non-regenerative**



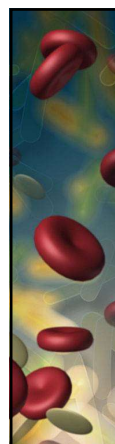
## Macrophage Proliferative Disorders

- **Hemophagocytic Syndrome**
  - Benign proliferation of macrophages
  - Causes cytopenias
  - Idiopathic or secondary to chronic antigenic stimulation:
    - IMHA, ITP
    - Chronic infection
    - Myelodysplastic syndromes
    - neoplasia
- **Malignant Histiocytosis**
  - Aggressive histiocytic neoplasia that results in death within weeks to months



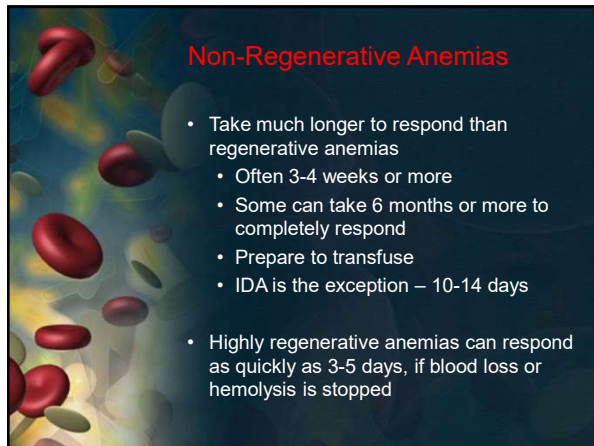
## Treating FeLV Anemia

- **If myelodysplasia (pancytopenia possible)**
  - EPO 100 U/kg SC 3x weekly until PCV low-normal, then 1-2x weekly
  - Prednisone 1-2 mg/lb/day, and taper over 60-90 days or more
  - Relapse common with taper
- **If regenerative anemia**
  - Prednisone 1-2 mg/lb/day, and taper over 60-90 days or more
  - Doxycycline 5-10 mg PO BID x 3 weeks
- **Antibiotics for infection, or if Neutrophils <1000-1500/ul**
- **Check for & treat histoplasmosis (form)**
- **Screen for lymphoma**
  - Imaging, CSU PARR on EDTA marrow (form)



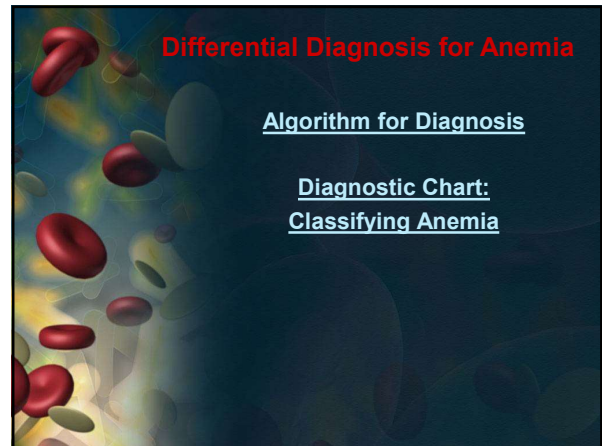
## Treating FeLV Anemia

- **Can live 2-4 years**
- **If lymphoma, prognosis worse**
- **Acts of desperation**
  - **Various herbal immunostimulants**
  - Baypamun®
  - Immunoregulin®
  - Feline Interferon (Verbagen Omega®)
  - Interferon (RoferonA®)
  - Transfer Factor®



## Non-Regenerative Anemias

- Take much longer to respond than regenerative anemias
  - Often 3-4 weeks or more
  - Some can take 6 months or more to completely respond
  - Prepare to transfuse
  - IDA is the exception – 10-14 days
- Highly regenerative anemias can respond as quickly as 3-5 days, if blood loss or hemolysis is stopped



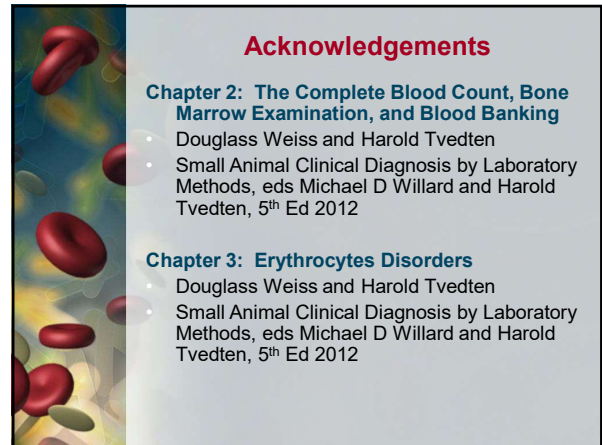
## Differential Diagnosis for Anemia

Algorithm for Diagnosis

Diagnostic Chart:  
Classifying Anemia



## Merry Holmes Vann Coldspring TX



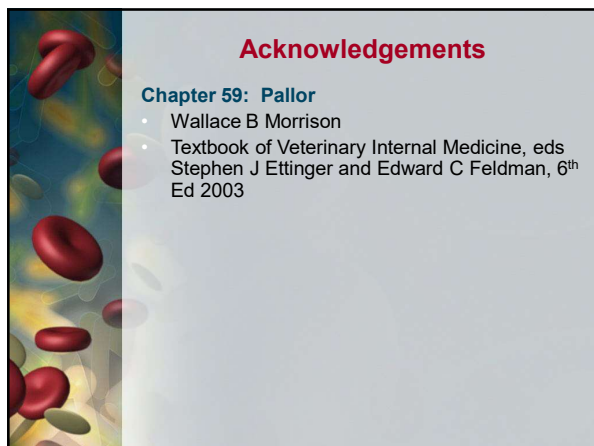
## Acknowledgements

**Chapter 2: The Complete Blood Count, Bone Marrow Examination, and Blood Banking**

- Douglass Weiss and Harold Tvedten
- Small Animal Clinical Diagnosis by Laboratory Methods, eds Michael D Willard and Harold Tvedten, 5<sup>th</sup> Ed 2012

**Chapter 3: Erythrocytes Disorders**

- Douglass Weiss and Harold Tvedten
- Small Animal Clinical Diagnosis by Laboratory Methods, eds Michael D Willard and Harold Tvedten, 5<sup>th</sup> Ed 2012



## Acknowledgements

**Chapter 59: Pallor**

- Wallace B Morrison
- Textbook of Veterinary Internal Medicine, eds Stephen J Ettinger and Edward C Feldman, 6<sup>th</sup> Ed 2003