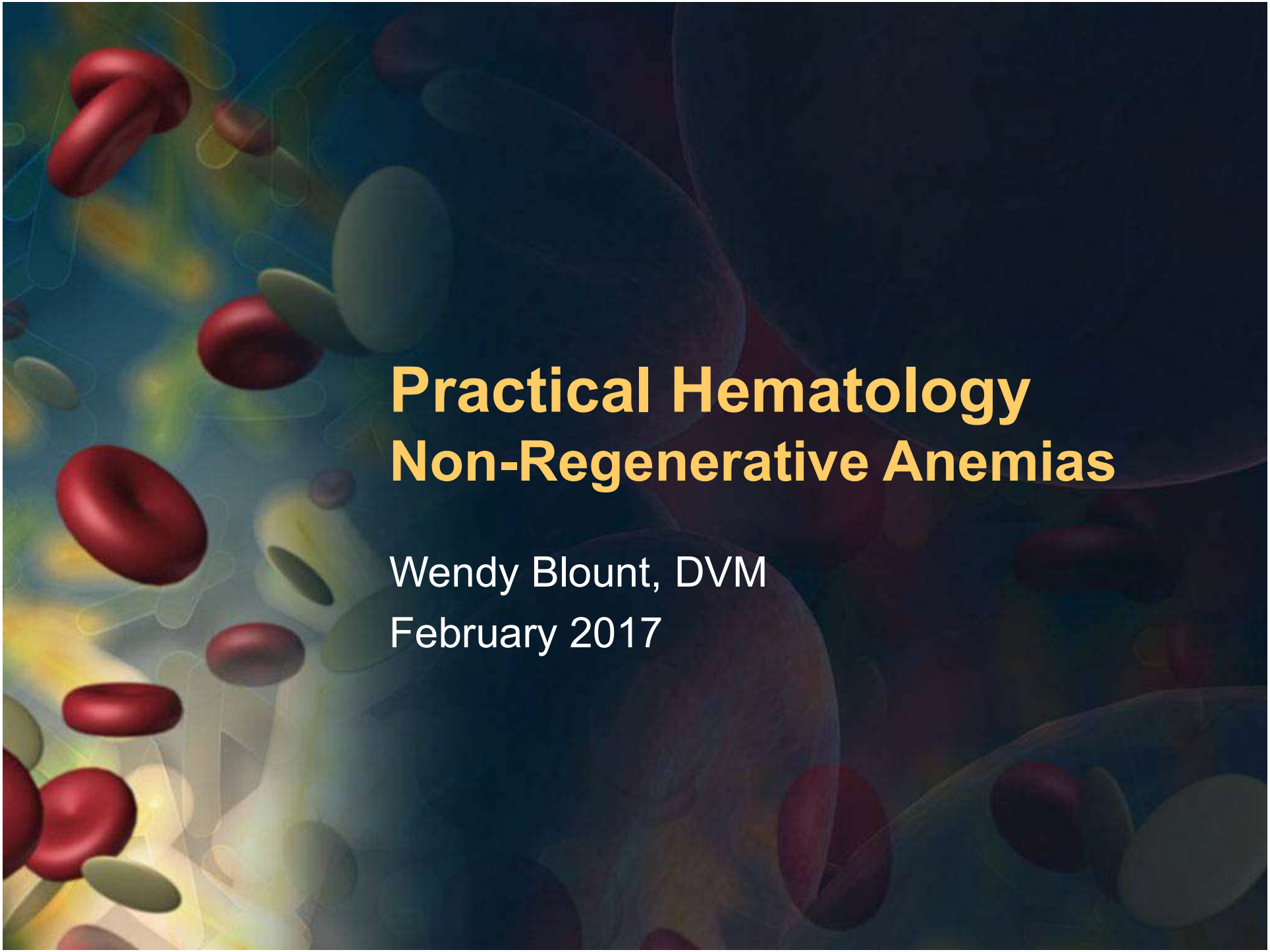
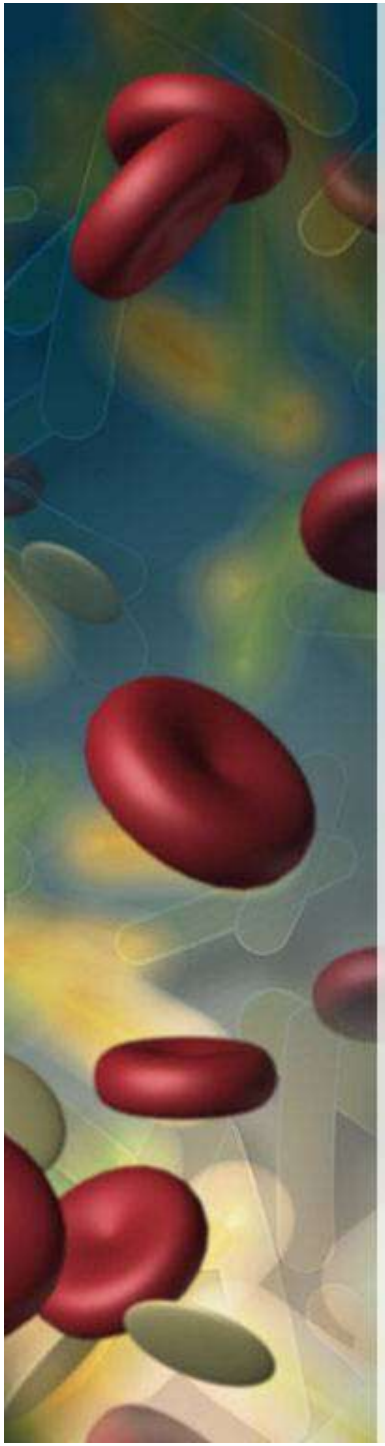


Practical Hematology
Non-Regenerative Anemias

Wendy Blount, DVM

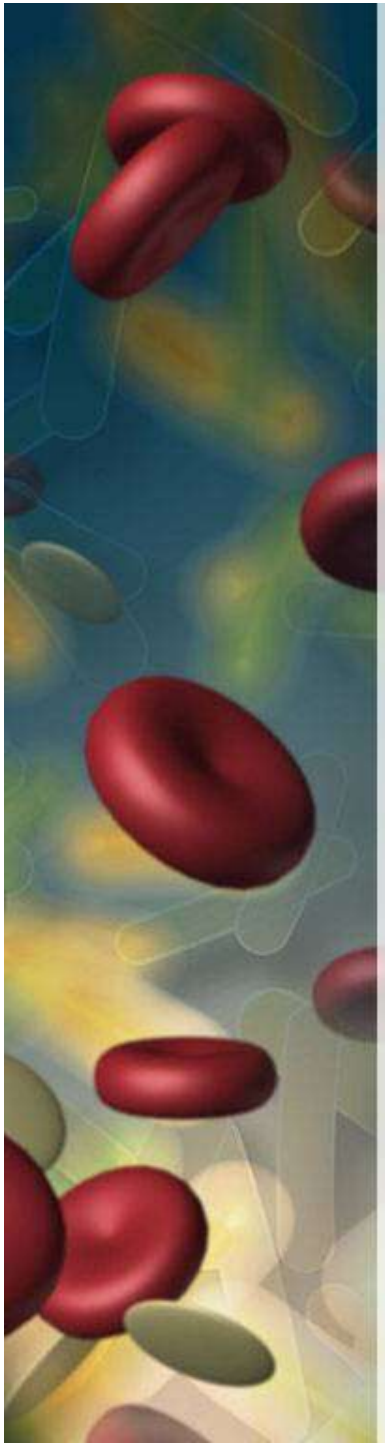
February 2017



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

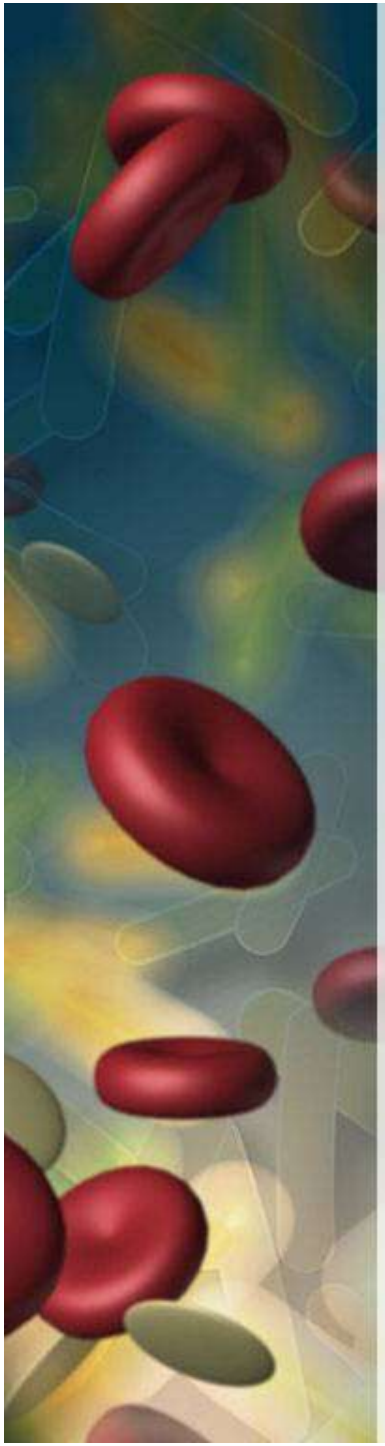


Non-Regenerative Anemia

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

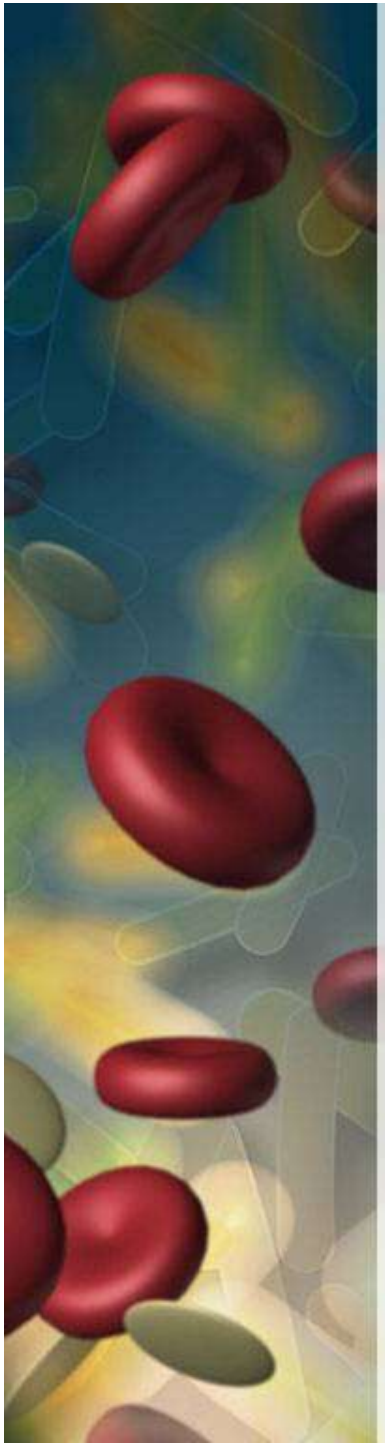
- Often resolves when primary problem is treated
- Often mild to moderate

RBC morphology less helpful

- Usually normocytic normochromic

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

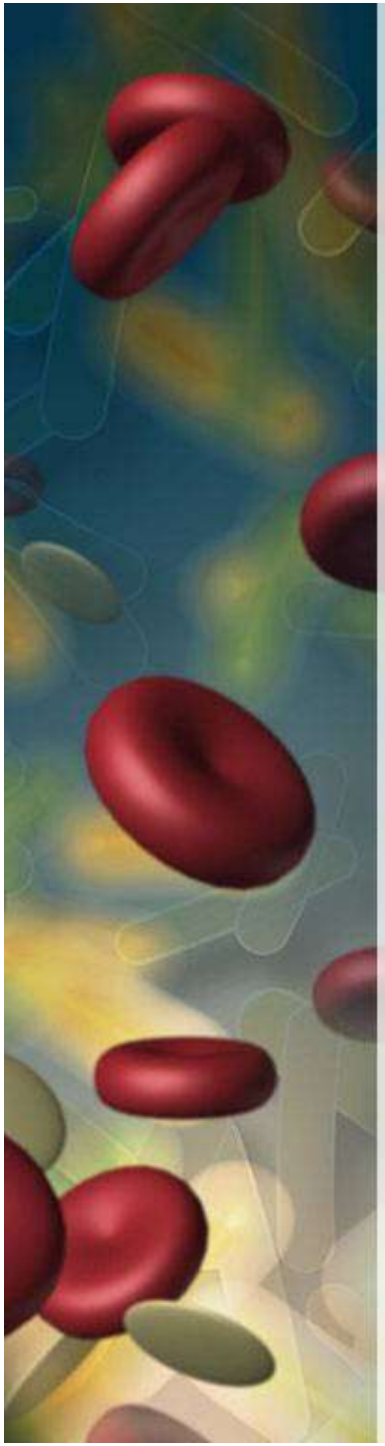
- Also anemia of renal disease (EPO deficiency)
- Pancytopenia, bicytopenia suggests bone marrow disease
- Blood morphology can be helpful



Non-Regenerative Anemia

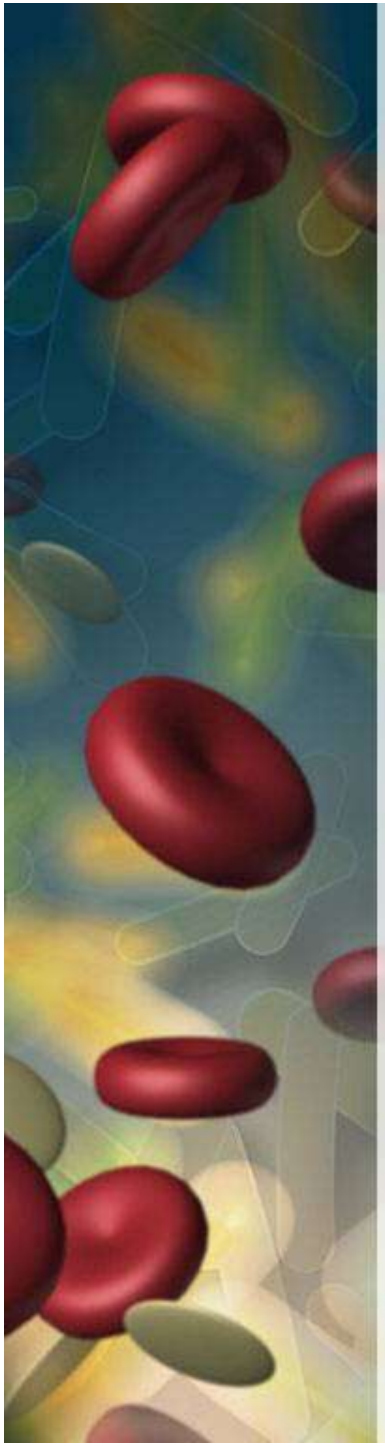
Etiologies

- 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



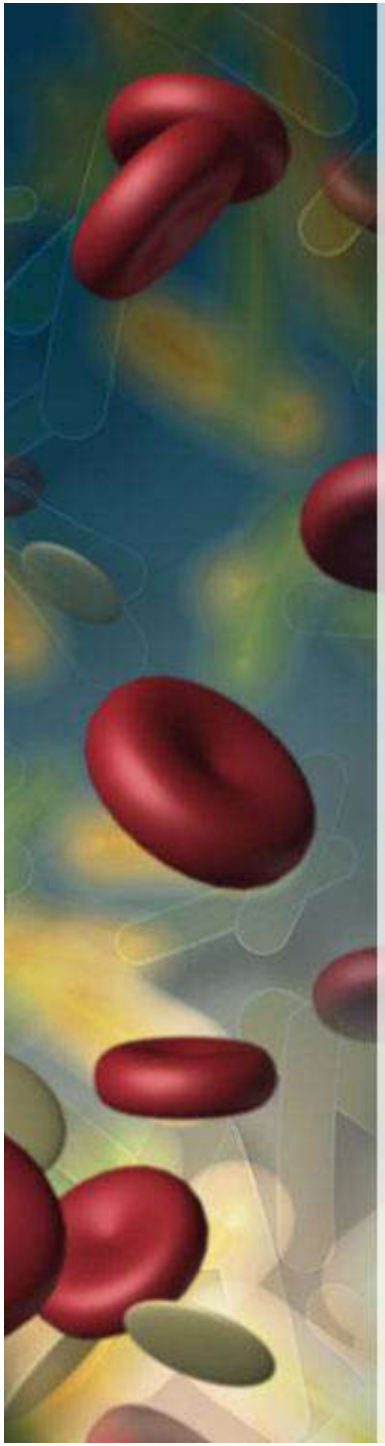
Non-Regenerative Anemia

- **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



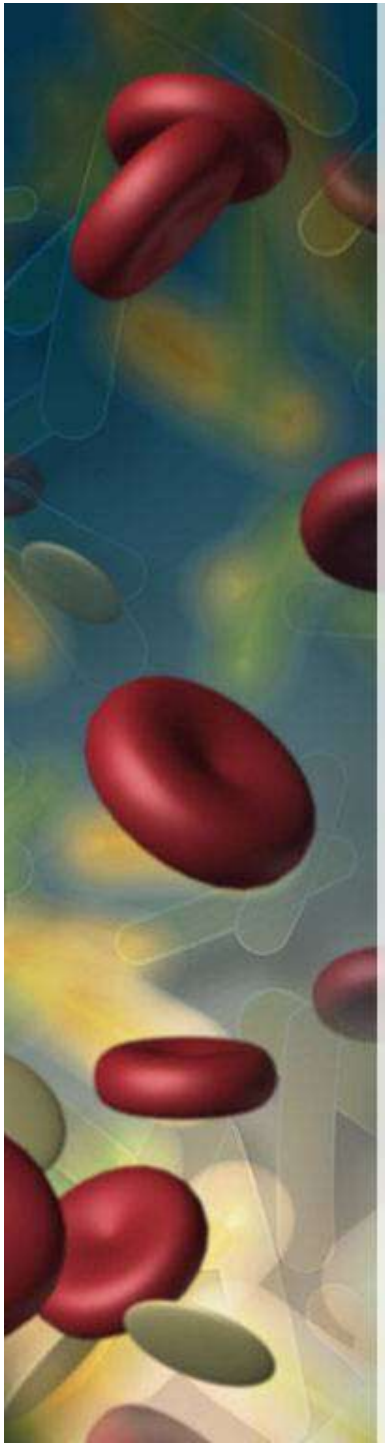
Diagnostics for Nonregenerative Anemia

- 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



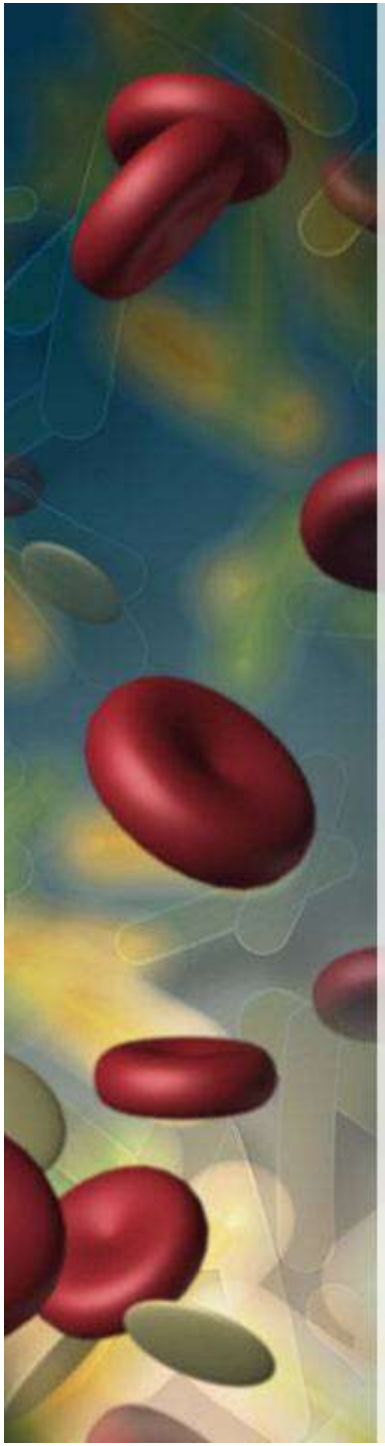
Lack of Erythropoietin

- **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



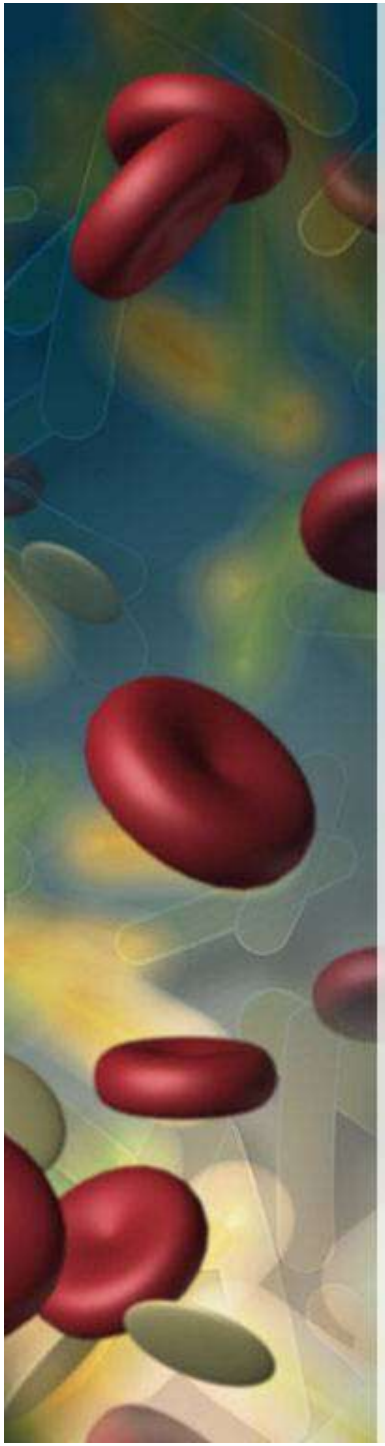
Renal Disease – Poor EPO Production

- **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

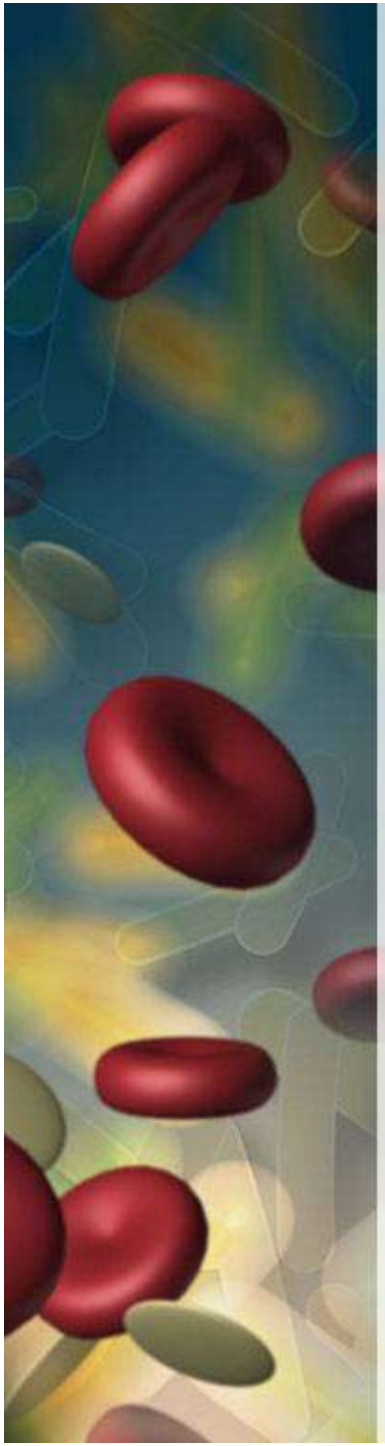
- **Treatment**
  - Treat renal disease
  - Human recombinant erythropoietin (extralabel)
    - 100 U/kg SC 3x weekly until PCV low-normal, then 1-2x weekly
    - Procrit®, Epogen®
    - Reserve for HCT <25% in dogs and <20% in cats
    - Correct iron deficiency first if present
    - Takes a few weeks 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

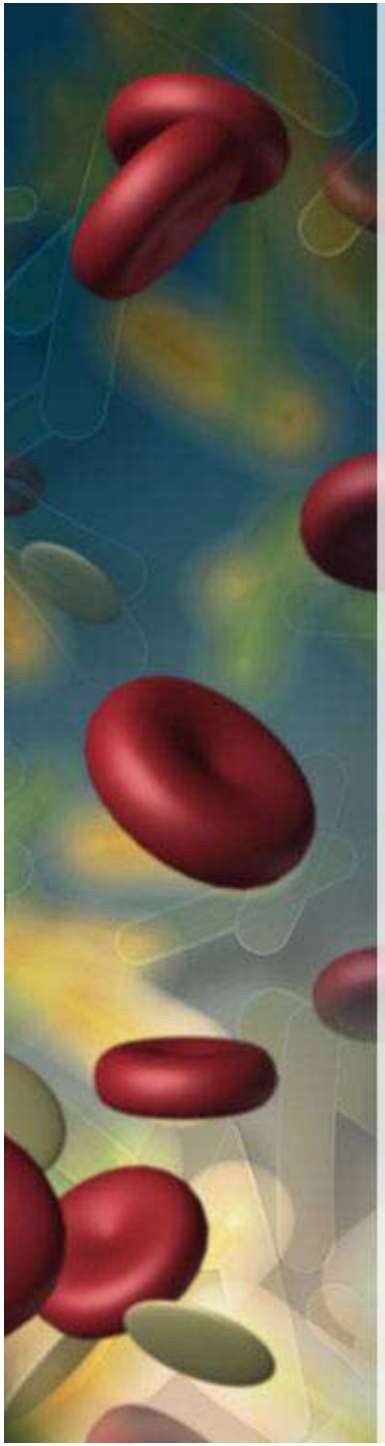
Compounded by coagulopathy and blood loss, especially in cats

- **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



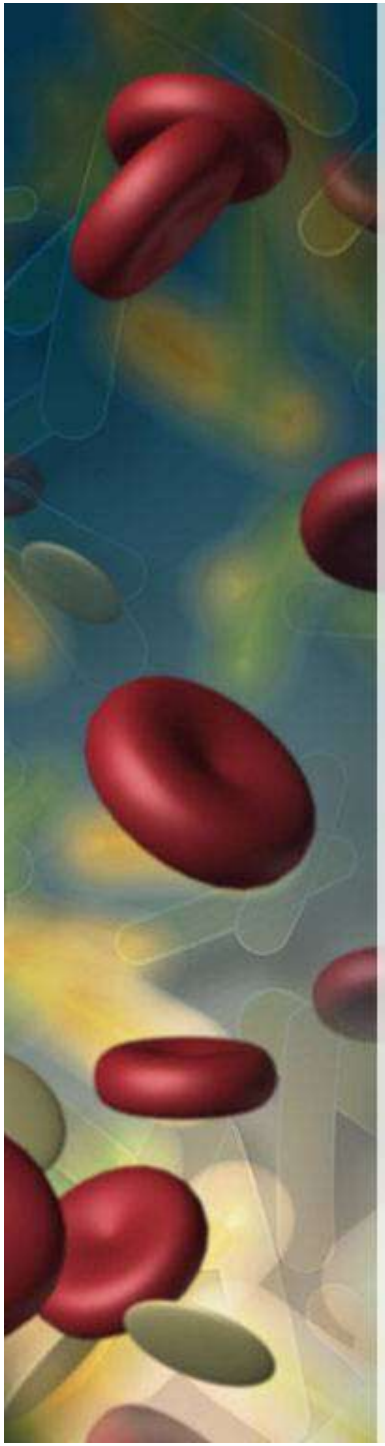
Endocrinopathy

- **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

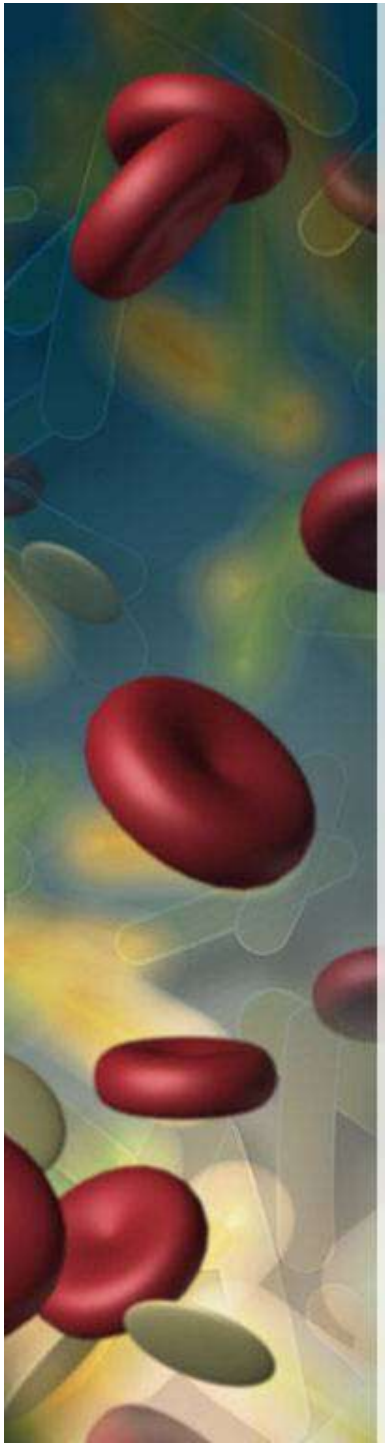
- **Iron metabolism**

1. Absorbed from food in the GI tract

2. Held on intestinal epithelial cells by ferritin
   - Sloughed or absorbed, based on need

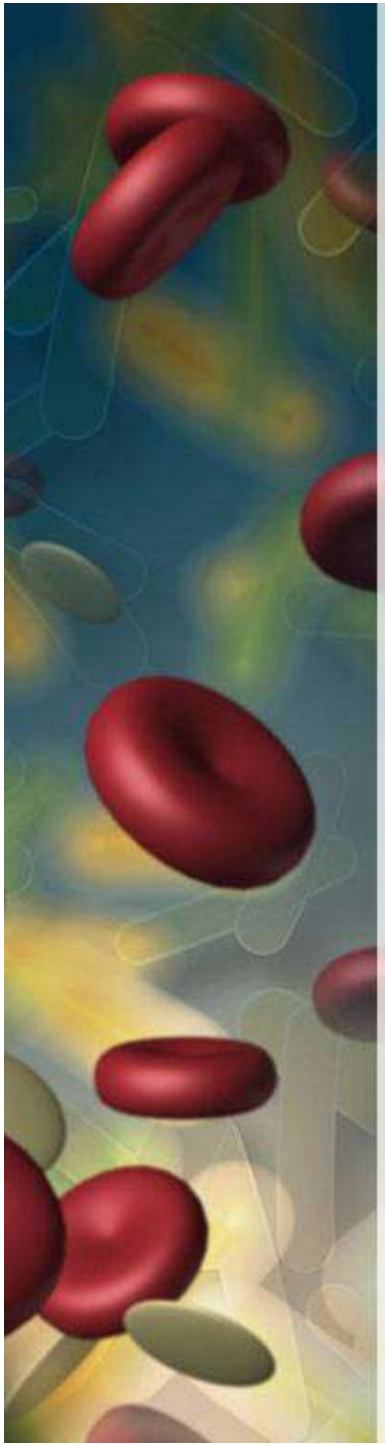
3. Absorbed into blood and carried by transferrin (measured as TIBC)

4. Stored in the tissues as soluble ferritin
   - Mostly in the liver



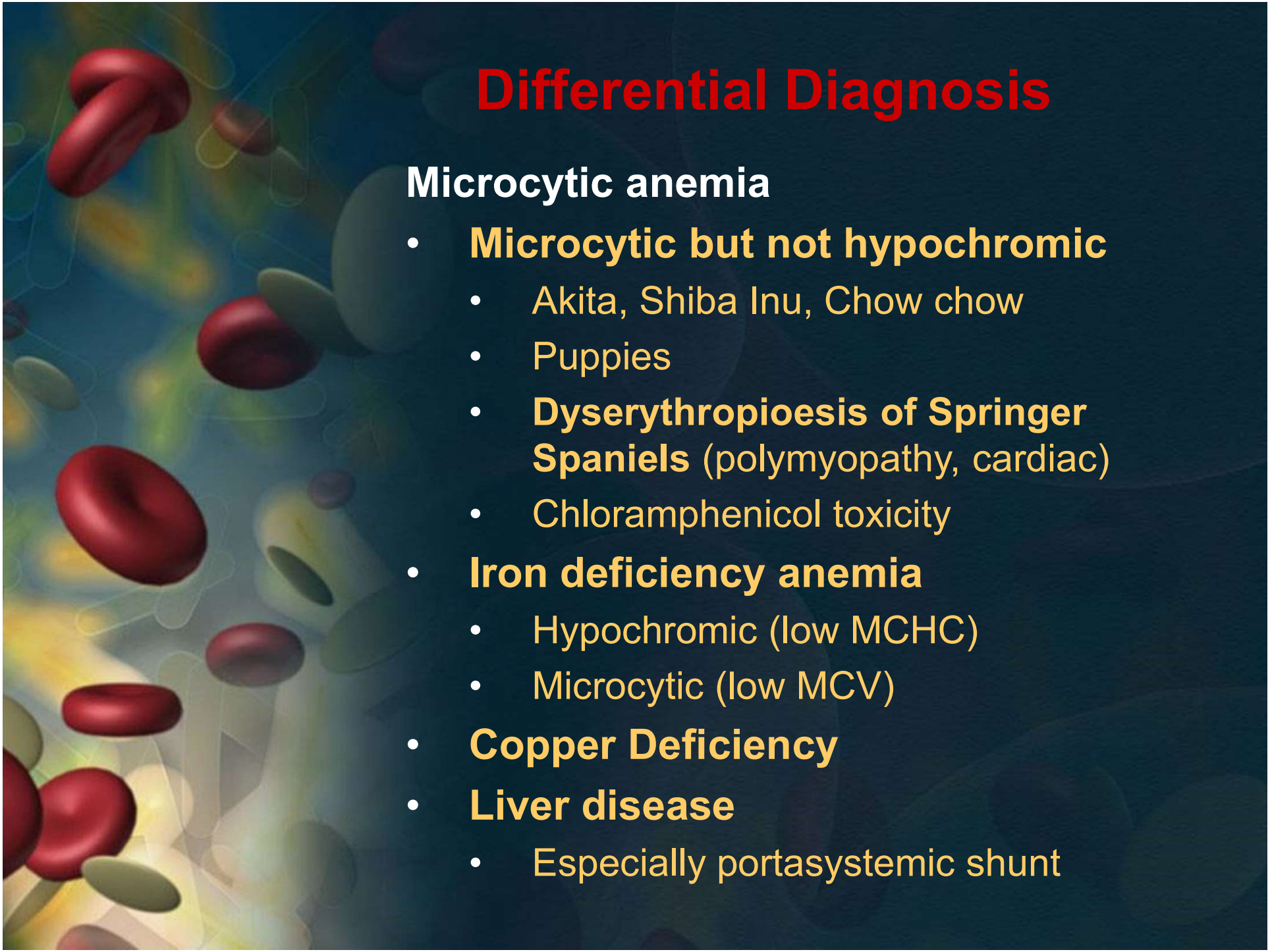
Iron Deficiency Anemia

- **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

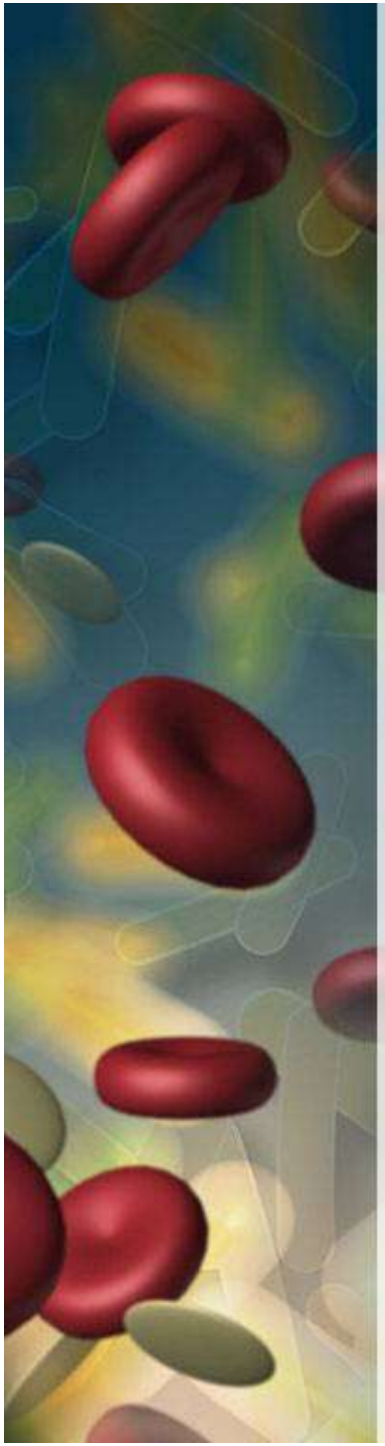
- The most common causes of iron deficiency anemia are chronic GI blood loss and flea anemia
- Blood loss anemia is first strongly regenerative, then non-regenerative as IDA develops
- Anemia varies from mild to severe
- Poikilocytosis and hypochromasia are typical
- Hypoproteinemia often present
- Anemia 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

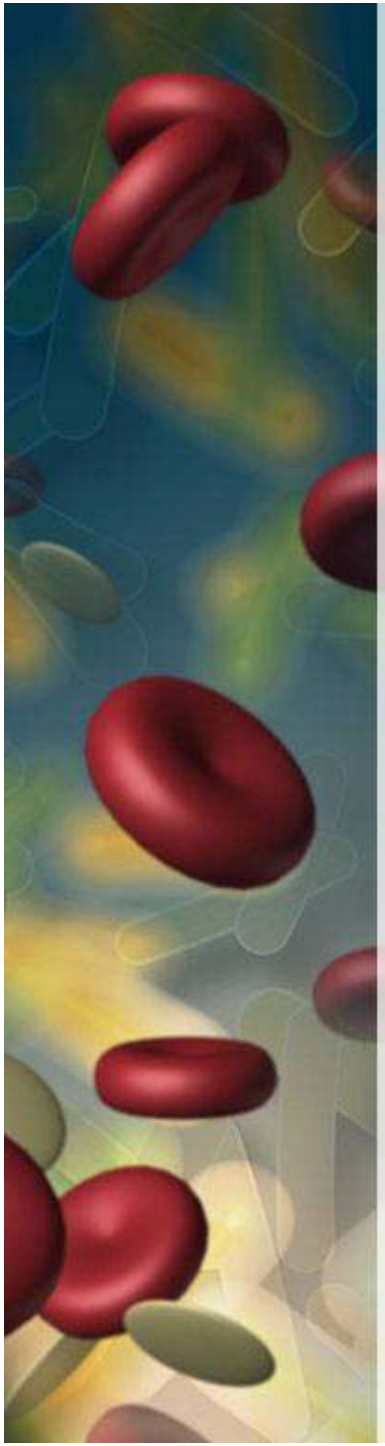
Microcytic anemia

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



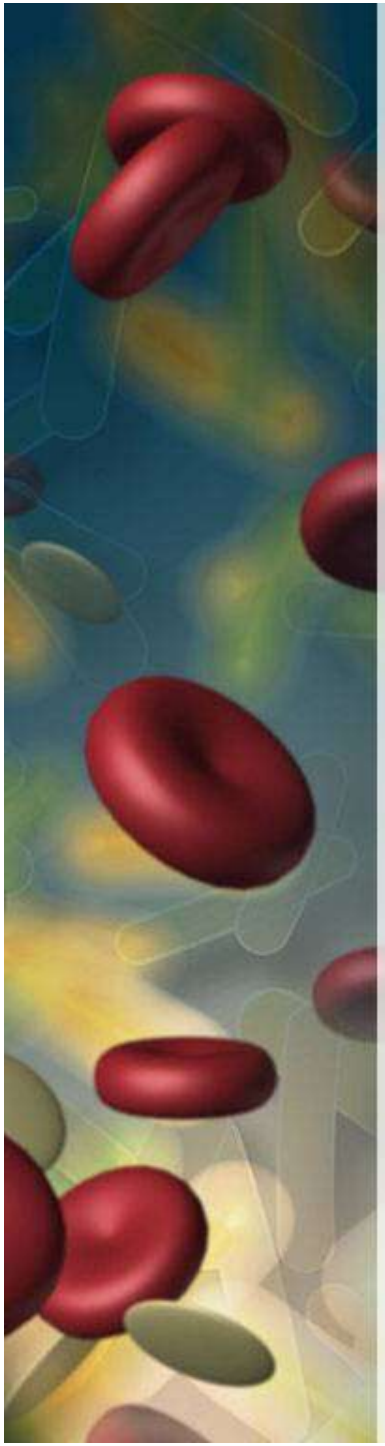
Anemia of Chronic Inflammatory Disease

- **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)



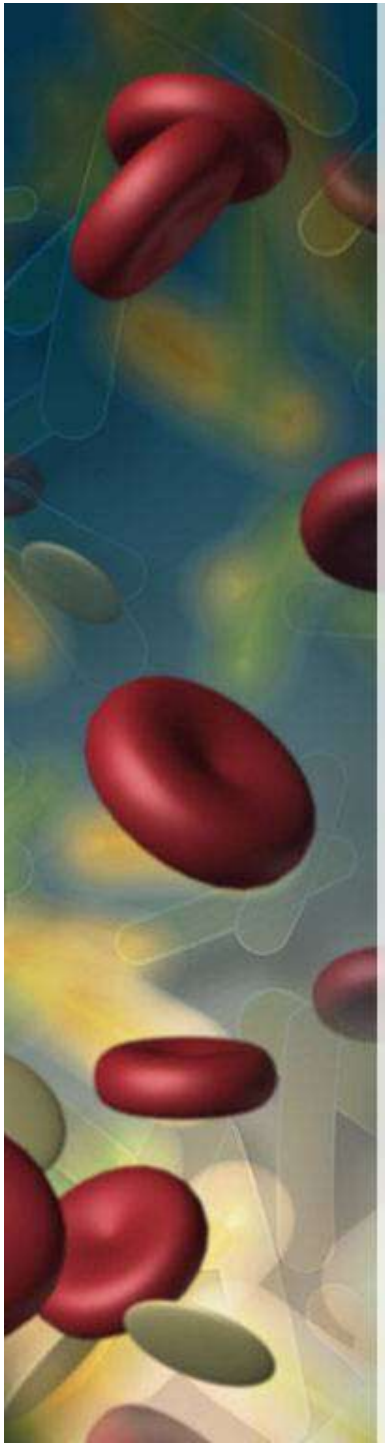
Anemia of Chronic Inflammatory Disease

- **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



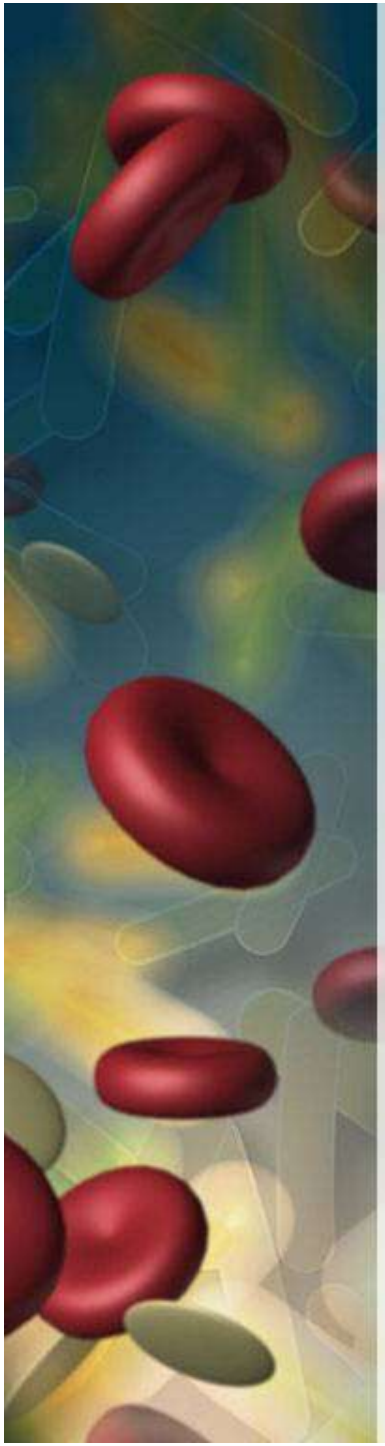
Anemia of Chronic Inflammatory Disease

- **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)

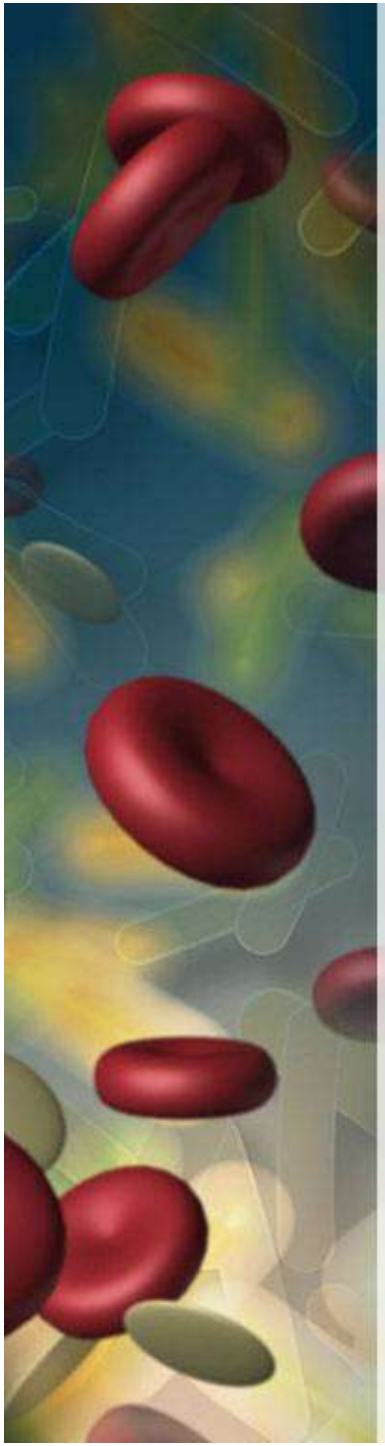
- **Iron stores**
  - normal
- **Bone marrow**
  - Maturation arrest at affected stage
  - May see other bone marrow problems: dyserythropoiesis, hematophagocytic syndromes, myelofibrosis, bone marrow necrosis
  - Can do immunologic staining for definitive diagnosis
- **Etiology**
  - Immune mediated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



Pure Red Cell Aplasia (PRCA)

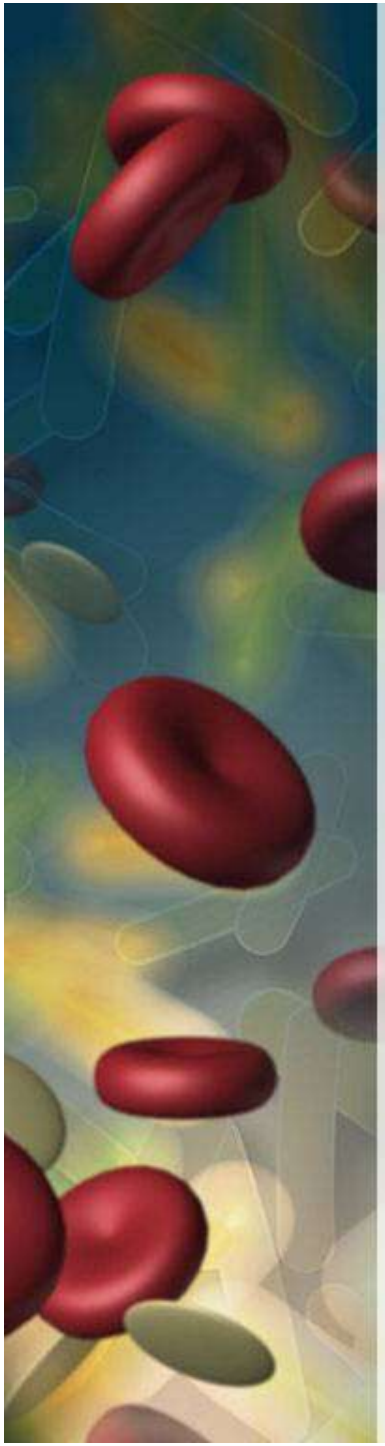
- **Severe anemia – PCV <10-20%**
  - Sometimes spherocytes and stomatocytes
- **Iron stores -** normal
- **Bone marrow**
  - Nearly absent erythroid precursors
- **Etiology**
  - FeLV, FIV, parvovirus infection
  - Immune mediated destruction of earliest erythroid stem cells
- **Treatment**
  - Immunosuppression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

Mark Jousan
Center TX



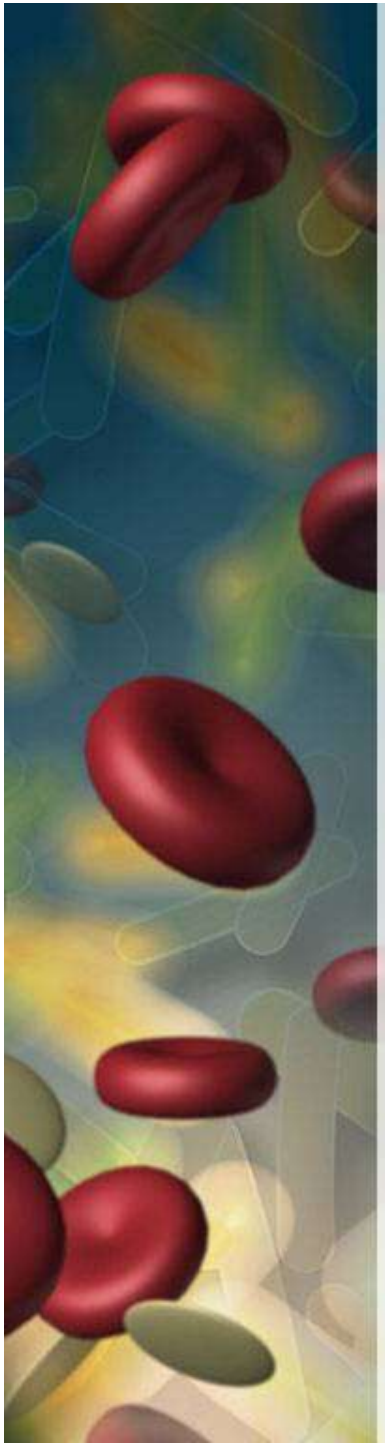
Aplastic Anemia

- **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, thiacetarsemide, phenobarbital, cephalosporins
    - Cats – propylthiouracil, methimazole, griseofulvin
    - Dobermans – predisposed to sulfa toxicity
    - Dogs with bute toxicity rarely recover



Aplastic Anemia

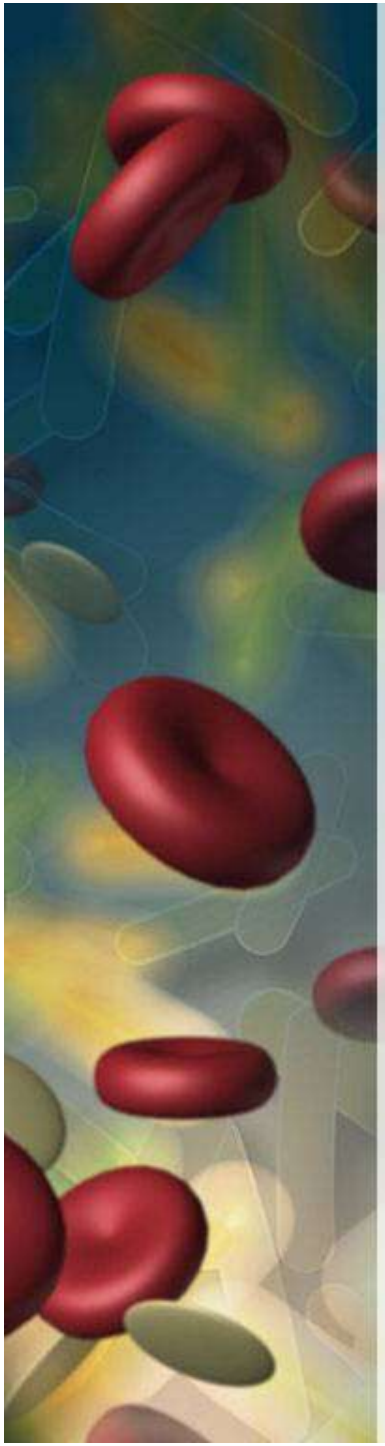
- **Etiology**
  - Chloramphenicol causes mild, reversible nonregenerative anemia in dogs
  - Infection
    - Ehrlichia (also immune mediated)
    - Bacterial endotoxins, Aflatoxin B
    - Parvovirus
  - DIC (necrosis)
  - Idiopathic
- **Bone marrow**
  - Hypocellular bone marrow despite spicules, except 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

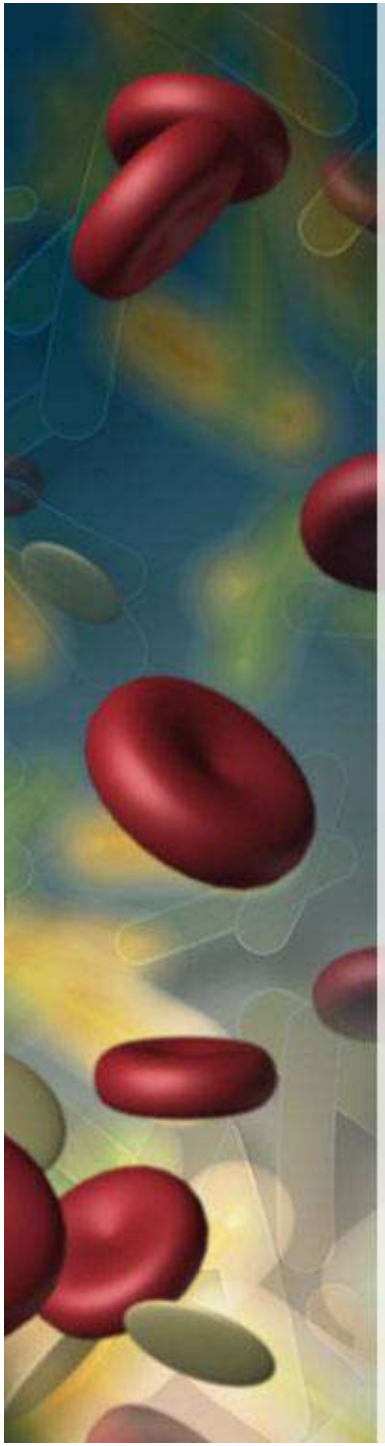
WBC recover first, then platelets, then RBC



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

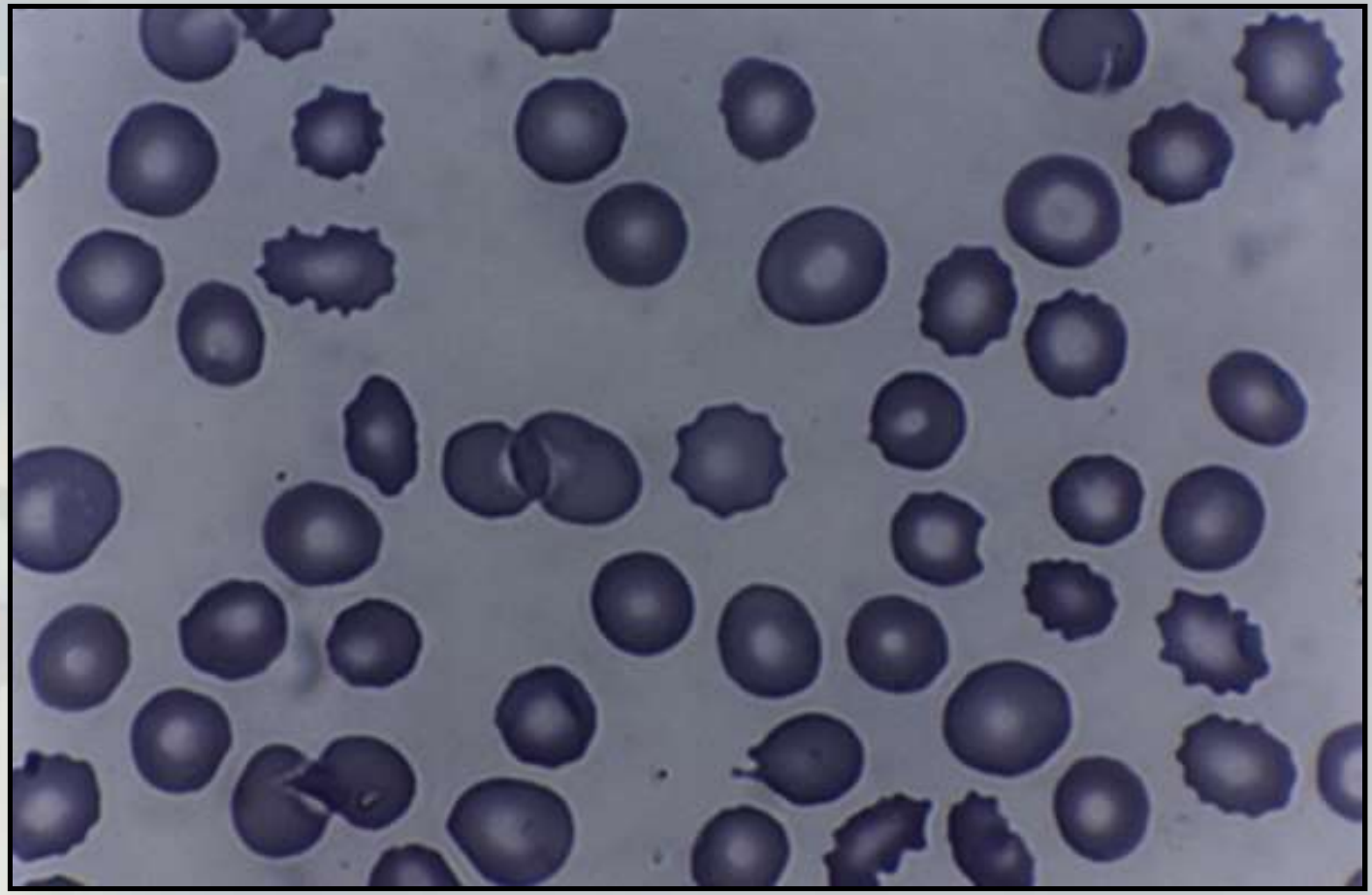
1. PCV <15% - transfuse, start EPO
2. Neutrophils 1,000-1,500/ul – amoxicillin x 14d
3. Neutrophils <1,000/ul – amoxi + quinolone
4. Neutrophils <500/ul – start GCSF, treat sepsis
5. Platelets <50,000/ul at risk for hemorrhage
   - If no vasculitis, often don't bleed unit <10K/ul
6. Platelets <10,000/ul – vincristine 0.02 mg/kg IV



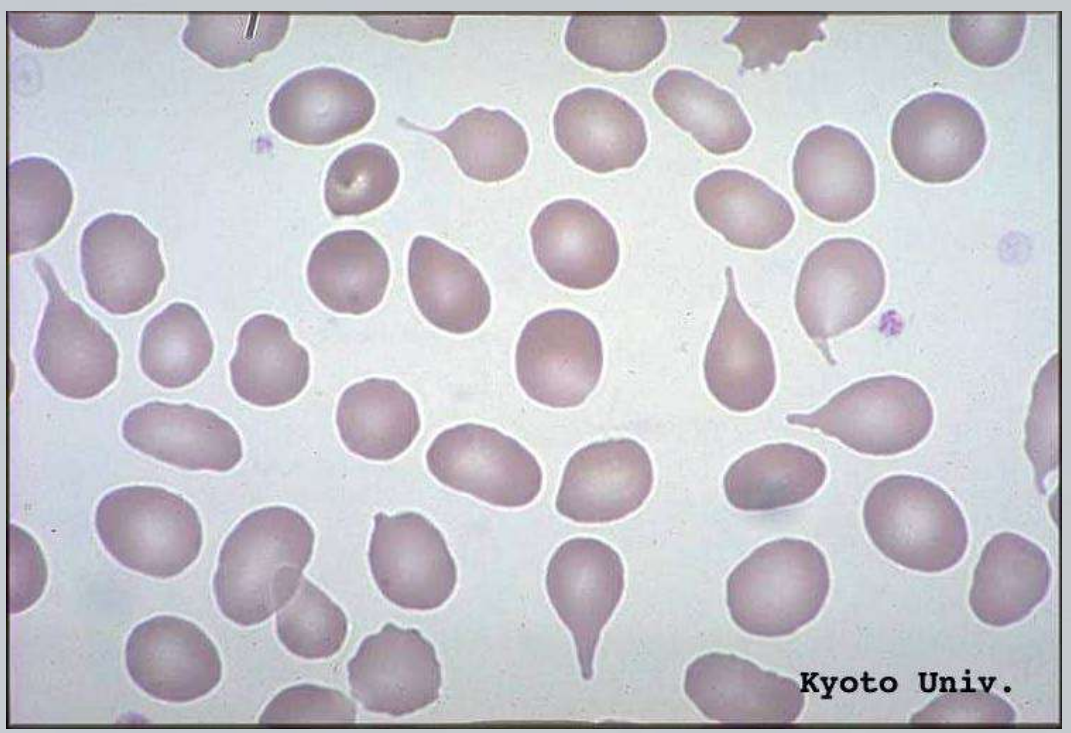
Myelophthisic Disease

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

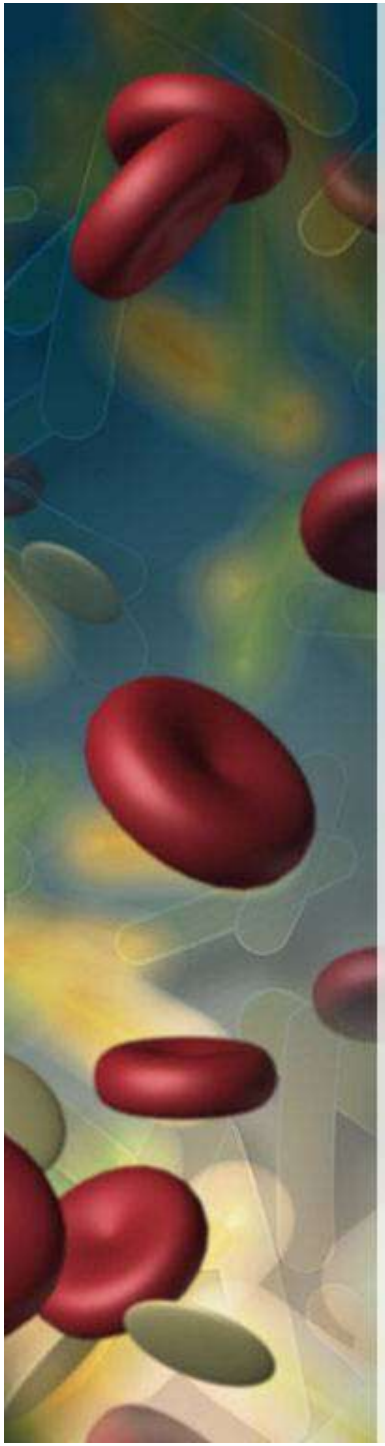
Myelophthisic Disease



Myelophthisic Disease

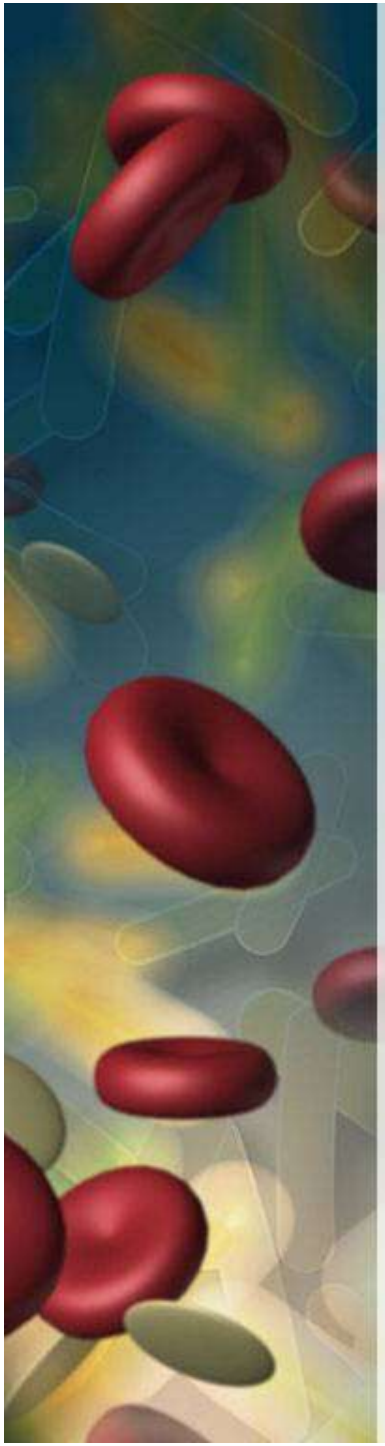


- Budding fragmentation, dacryocytosis
- Large platelets or megaplatelets
- Degenerative left shift



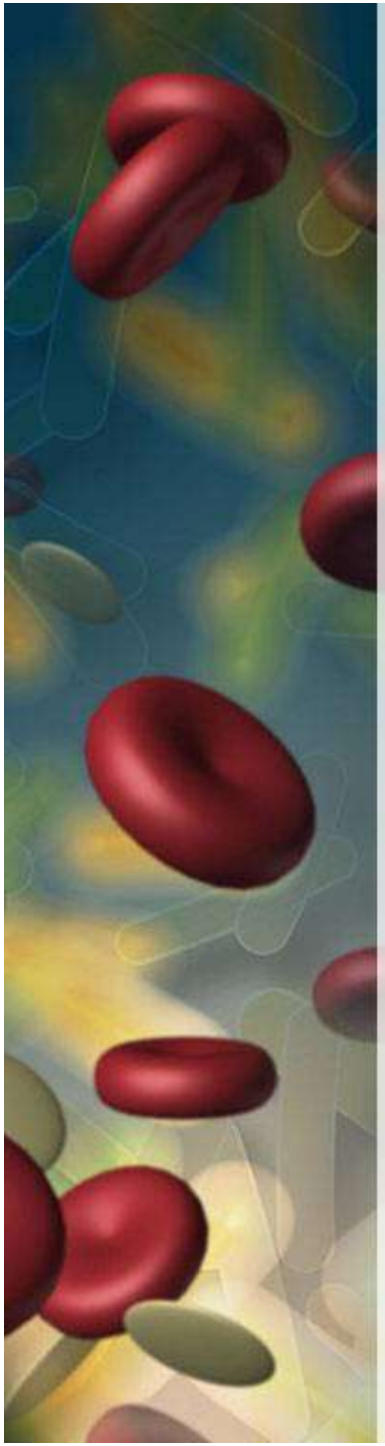
Myelophthisic Disease

- **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



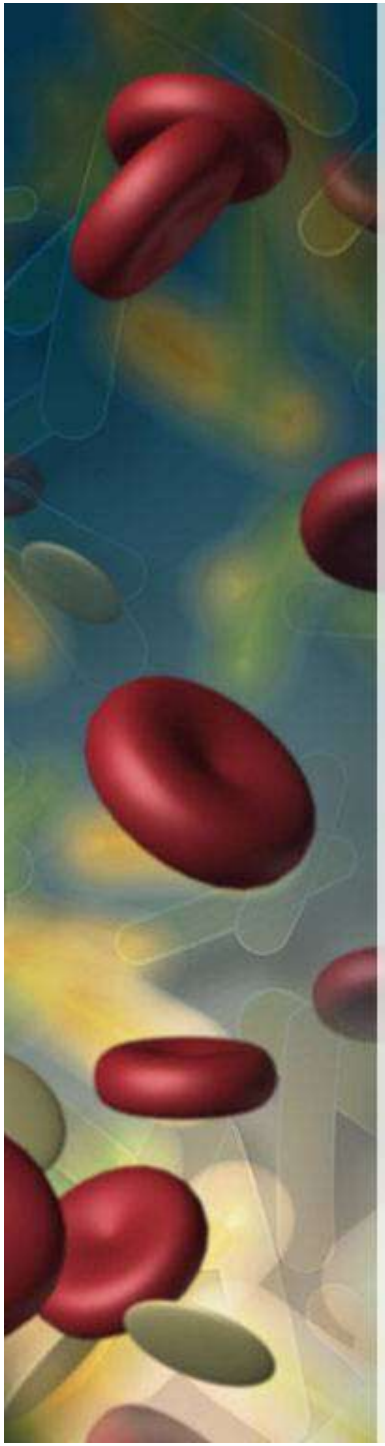
Myelophthisic Disease

- **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 Multilineage Dysplasia
  - Preleukemia (**can progress to acute leukemia**)
  - Subacute leukemia
  - Dysmyelopoiesis (due to toxicity)
  - Myelodysplastic Syndrome (MDS)

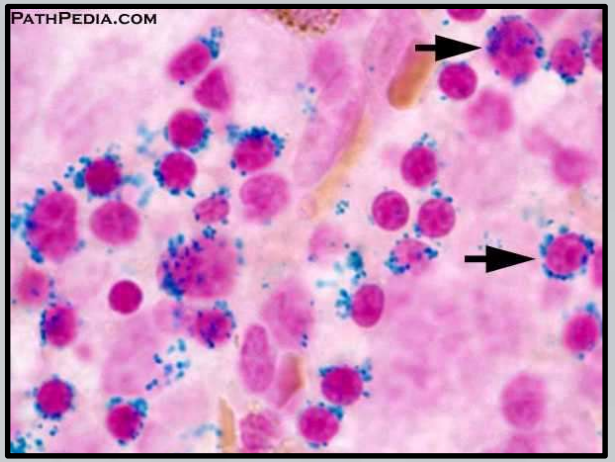


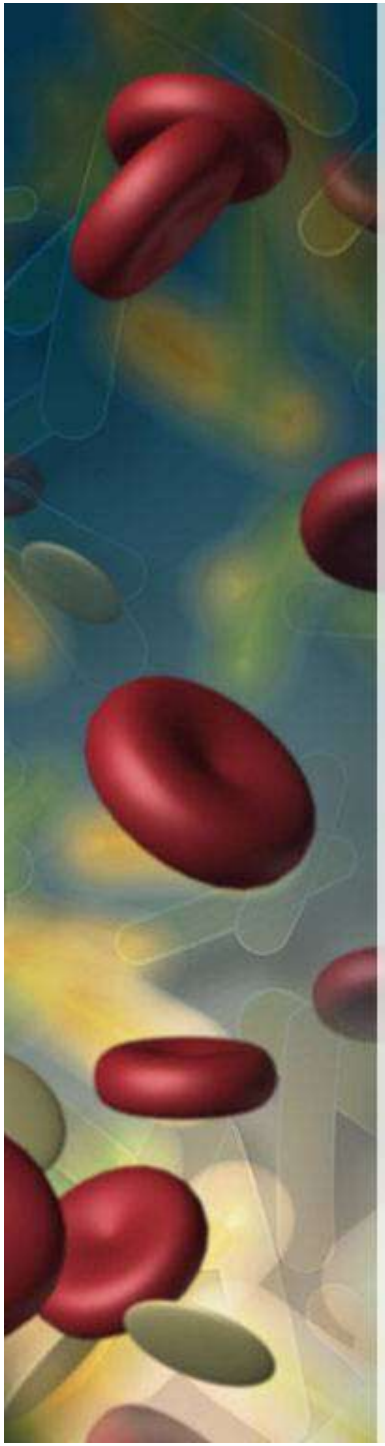
Myelodysplasia

- **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

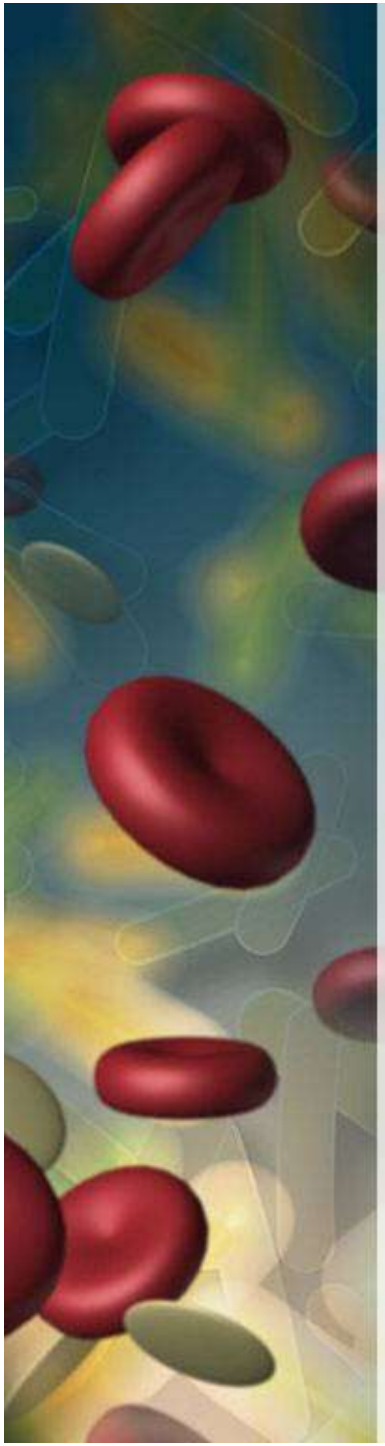
- **Siderocytes, Sideroblasts**
  - Contain Pappenheimer bodies – iron granules
  - Resembles basophilic stippling
  - Prussian Blue stains Pappenheimer bodies, but not RNA of basophilic stippling
  - RARS – Refractory Anemia with Ringed Sideroblasts
- **Treatment**
  - EPO





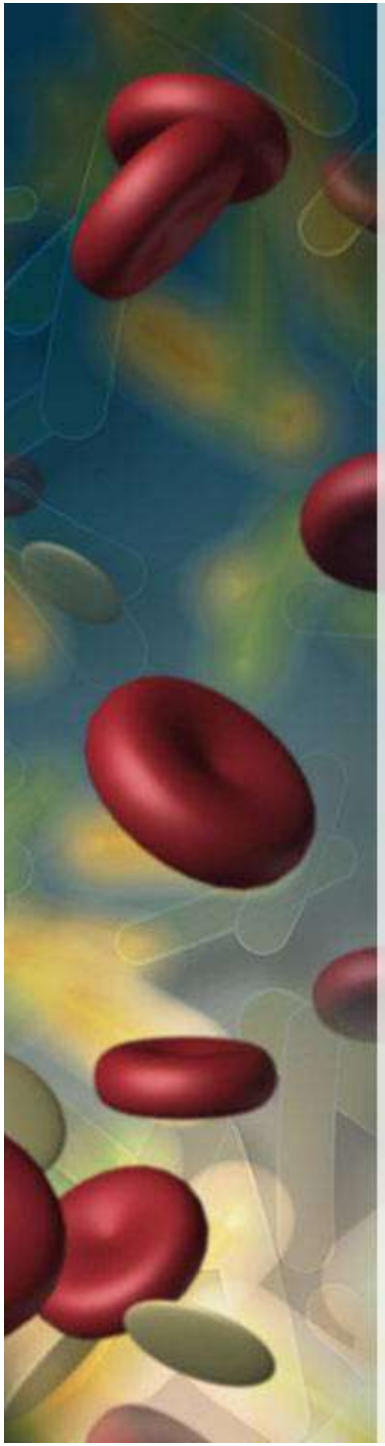
Congenital Dyserythropoiesis

- **English Springer Spaniels**
  - Bone marrow - dyserythropoiesis
  - Polymyopathy
  - Cardiac disease
  - Hemogram – poikilocytosis
    - spherocytes, schistocytes, dacryoctyes, 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

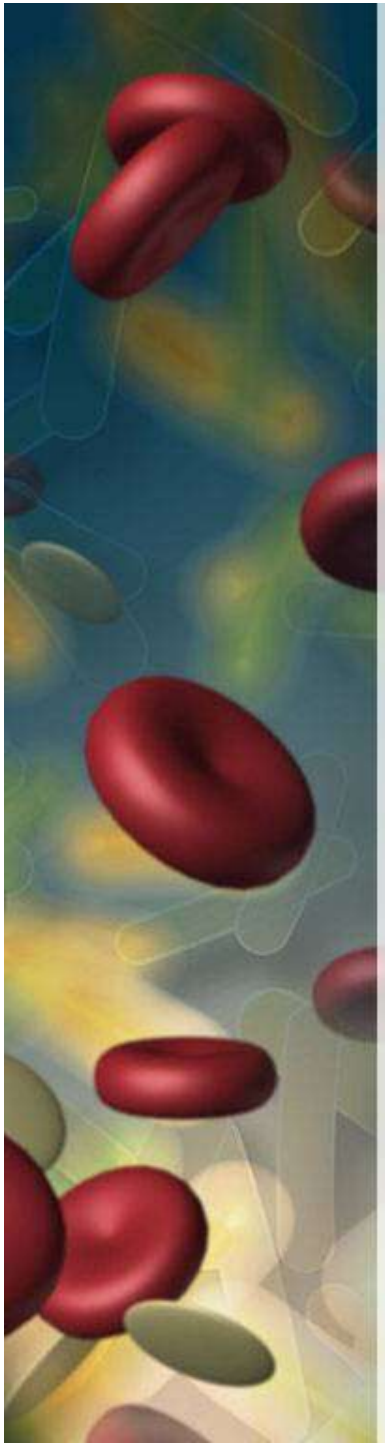


Feline Leukemia

- **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

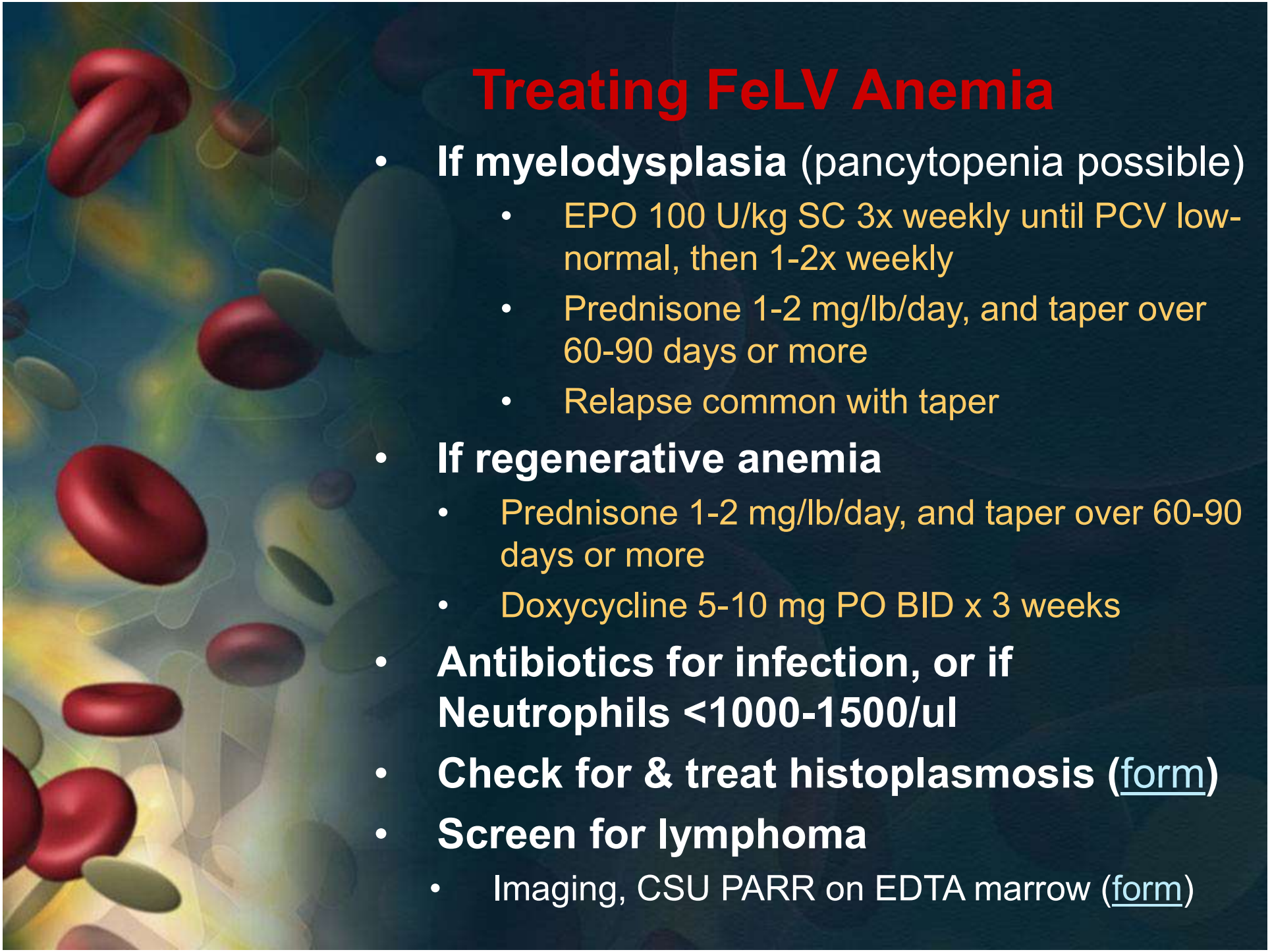
You can't treat FeLV anemia intelligently without a bone marrow sample

- **Hemogram**
  - Often macrocytic (>52 fl), normochromic
  - Megaloblastic rubricytes
  - **Usually non-regenerative**



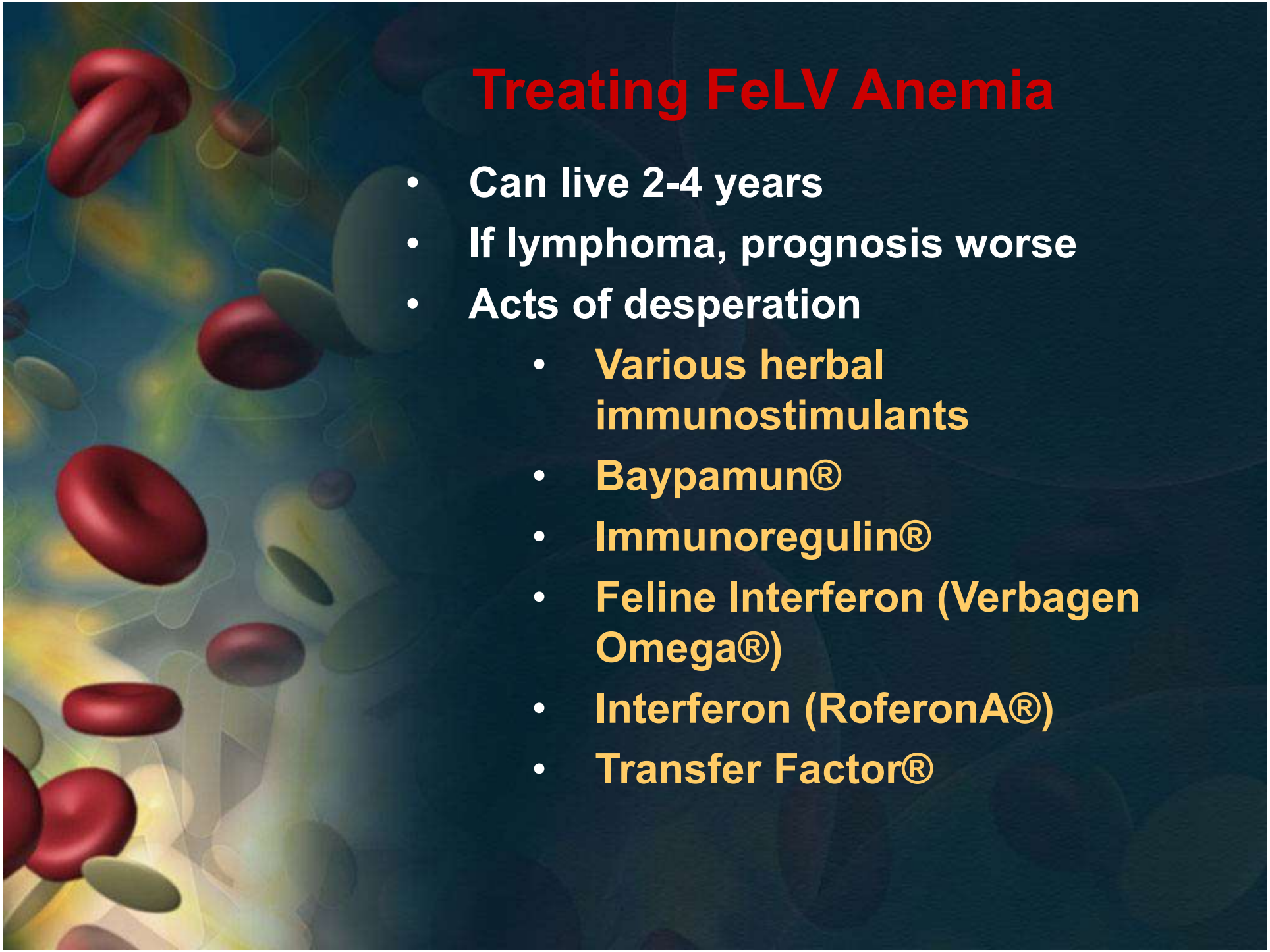
Macrophage Proliferative Disorders

- **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



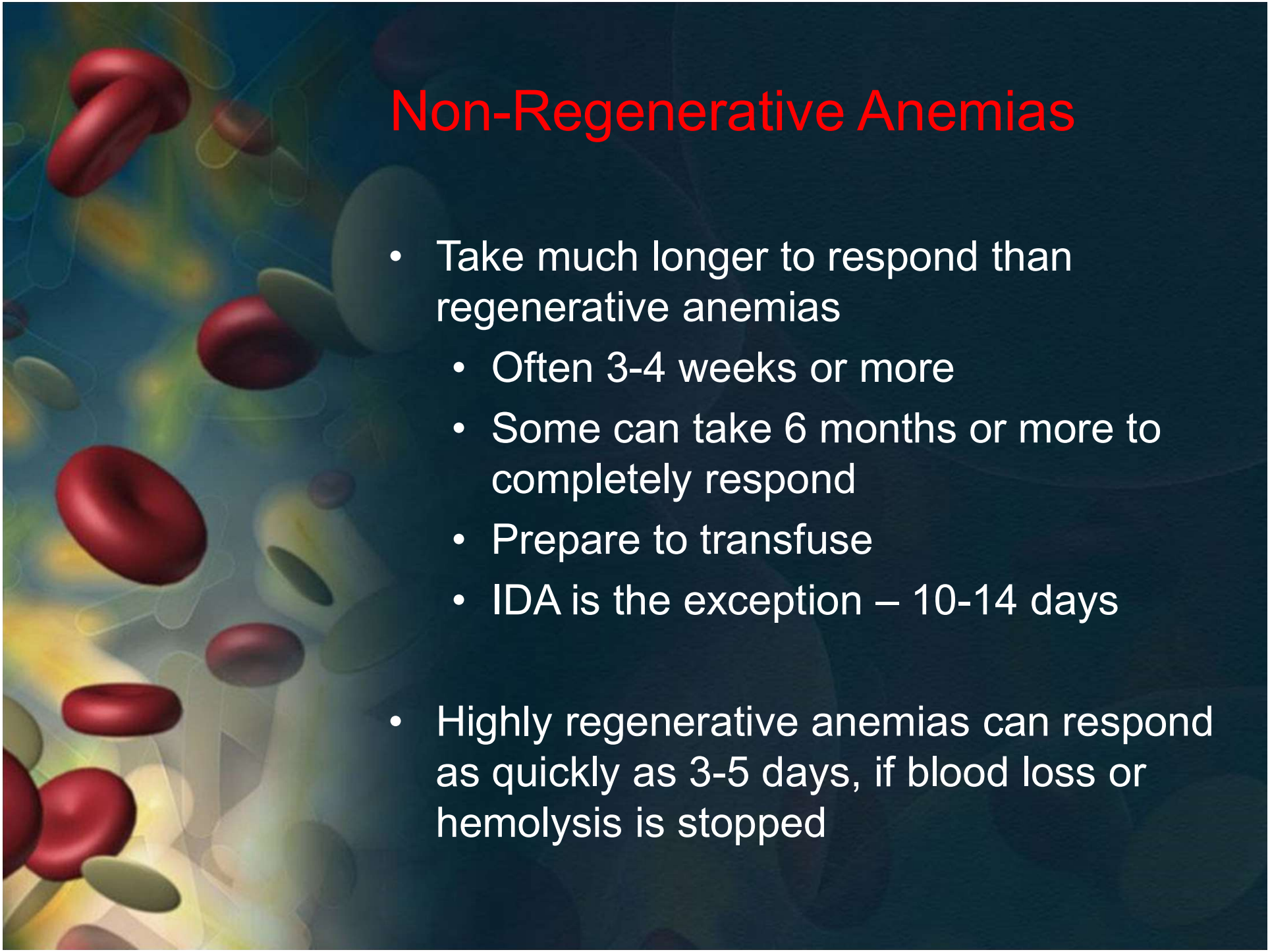
Treating FeLV Anemia

- **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

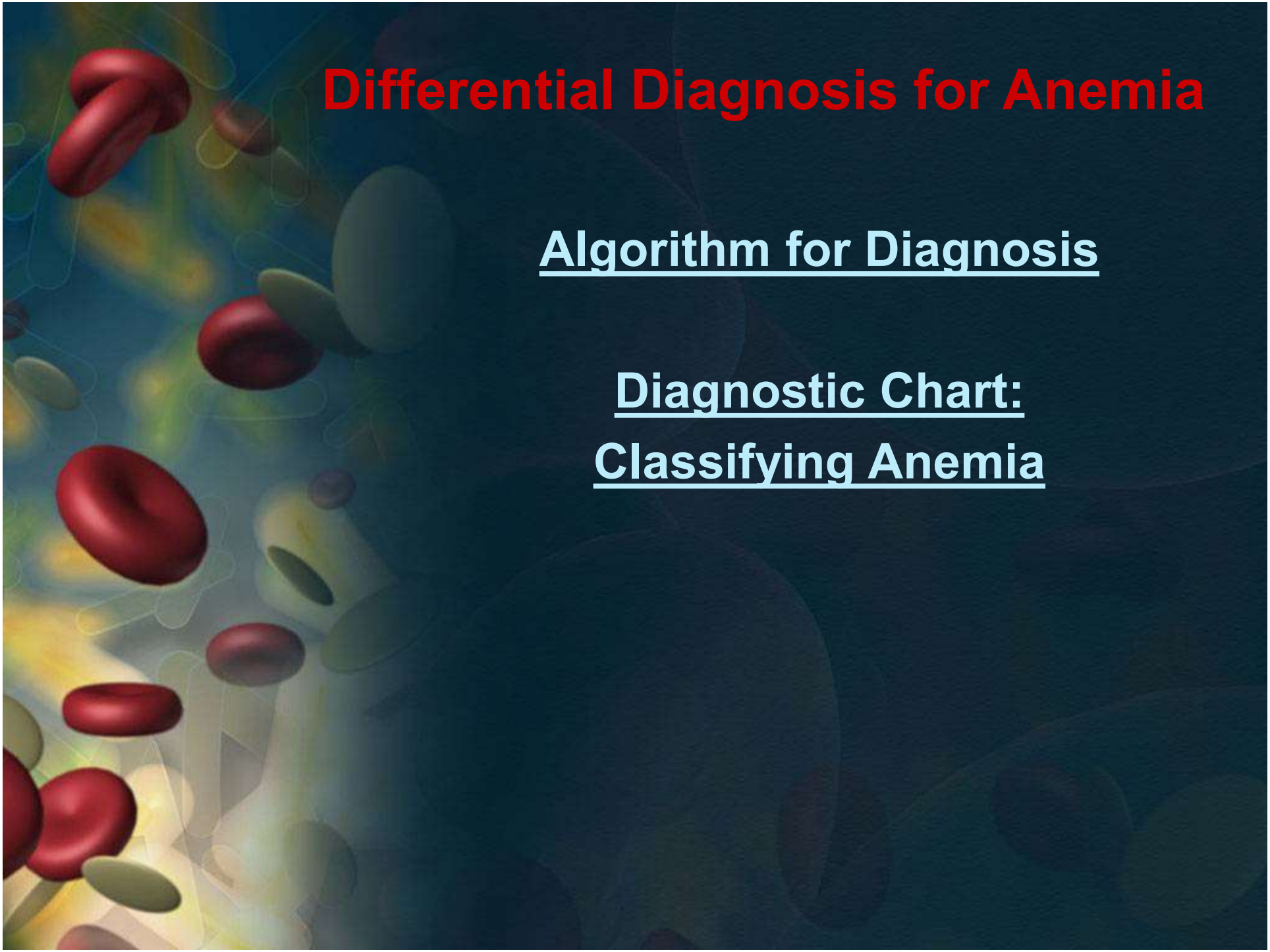
- Can live 2-4 years
- If lymphoma, prognosis worse
- Acts of desperation
  - Various herbal immunostimulants
  - Baypamun®
  - Immunoregulin®
  - Feline Interferon (Verbagen Omega®)
  - Interferon (RoferonA®)
  - Transfer Factor®



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

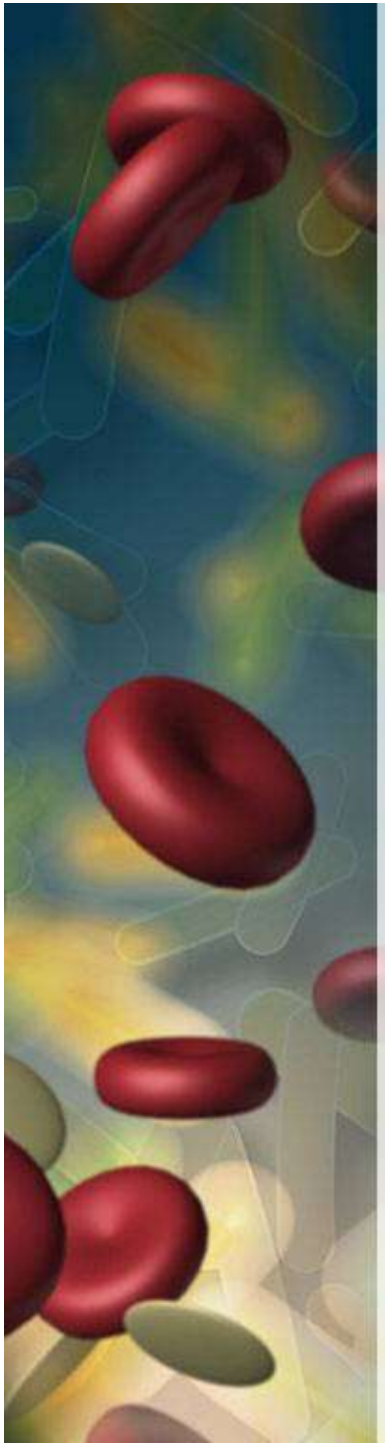
Differential Diagnosis for Anemia



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, 5th Ed 2012

Chapter 3: Erythrocytes Disorders

- Douglass Weiss and Harold Tvedten
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Acknowledgements

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