Anemia is a reduction below normal in the total red blood cell (RBC) count, packed cell volume, or hemoglobin concentration and a consequent decrease in oxygen-carrying capacity and delivery to tissue. Anemia is not a diagnosis in itself but is rather a sign of an underlying disease process. Classification of anemia using RBC indices and a reticulocyte count helps in determining whether the anemia is regenerative or nonregenerative. Regenerative anemias involve normal bone marrow production of RBC (erythrocyte) precursors and result from blood loss or hemolysis. Nonregenerative anemias result from impaired RBC production by the bone marrow. This distinction limits the etiologic possibilities. This article focuses on the differential diagnosis of nonregenerative anemia in cats. A companion article discusses diagnostic approaches and treatment options.

Red Blood Cell Physiology
A thorough knowledge of RBC physiology is essential to the approach to anemic patients. The process of erythropoiesis depends on the hormone erythropoietin. Erythropoietin is a highly glycosylated glycoprotein with a peptide core of 18 kDa and a mature molecular weight of 30 kDa. It is made primarily in the kidneys. Although the exact site of synthesis has not been determined, in situ hybridization studies implicate the peritubular interstitial cells of the renal cortex. The stimulus for erythropoietin synthesis is renal hypoxia, which triggers increased erythropoietin production within minutes to hours. The maximum rate of erythropoietin production is reached within 24 hours after the onset of hypoxia. However, there may not be a detectable increase in the peripheral RBC count for approximately 5 days.

After release from the kidneys, erythropoietin is transported to the bone marrow and (to a lesser degree) spleen. At these locations, it stimulates the proliferation and maturation of erythroid progenitor cells. Erythropoietin is very specific to erythroid progenitor cells, primarily colony-forming unit–erythrocytes, and has little effect on other cells. In addition to promoting erythropoiesis, erythropoietin facilitates hemoglobin synthesis and stimulates the release of RBCs and reticulocytes into the circulation.

In healthy adult cats, erythropoiesis occurs in the bone marrow of the axial skeleton (Figure 1). In cases of prolonged anemia or bone marrow dysfunction, erythropoiesis can also occur in extramedullary sites such as the spleen, liver, and lymph nodes. However, this latter type of erythropoiesis may not be effective. In cases of severe anemia, the bone marrow can increase its RBC production six- to eightfold in an effort to maintain a normal RBC count.

At a Glance
- Red Blood Cell Physiology
- Feline RBC Morphology and Life Cycle
- Etiologies

Abstract: Nonregenerative anemia in cats results from the inability of the bone marrow to respond appropriately to a peripheral deficiency in RBCs. There are many causes of nonregenerative anemia, including primary diseases of the bone marrow and systemic diseases that have secondary effects on the bone marrow. The prognosis is variable: some etiologies are reversible, whereas others may be chronic or fatal.

A companion article, “Feline Nonregenerative Anemia: Diagnosis and Treatment,” is also available on CompendiumVet.com.
Feline RBC Morphology and Life Cycle

Feline RBCs are different from those of other domestic species in that they exhibit moderate anisocytosis and lack central pallor. Blood smears from healthy cats may have a moderate number of rouleaux and Howell-Jolly bodies (Figure 2). Cats are more susceptible to oxidative RBC damage and Heinz body formation than other species because they have eight weak sulfhydryl groups on their hemoglobin molecules (versus two in most other species), and their hemoglobin tends to dissociate easily from tetramers to dimers. In addition, the nonsinusoidal feline spleen is inefficient at removing RBCs that contain Heinz bodies.

Healthy feline RBCs are released from the bone marrow and circulate for approximately 73 days. They are then broken down and recycled by the mononuclear phagocyte system of the spleen, liver, and bone marrow. Daily, immunologic and nonimmunologic mechanisms remove about 1.3% of circulating RBCs in healthy adult cats.

Etiologies

Acute Blood Loss

Anemia may be nonregenerative in the early phases of blood loss, before a peripheral reticulocyte response develops. Immediately following hemorrhage, the hematocrit may be normal, reflecting a loss of RBCs and plasma in equal proportions. However, a shift of water from the interstitial to the intravascular space ensues within 12 to 24 hours (more quickly with volume resuscitation). The result is a decrease in the hematocrit and the total protein level. At this point, the RBCs will likely appear normal in morphology, and anemia is normocytic and normochromic. As hypoxia stimulates the release of erythropoietin, reticulocytes are formed and released from the bone marrow, and the anemia becomes regenerative 4 to 5 days after acute blood loss.

Inflammatory Disease

Chronic inflammatory disease is the most common cause of anemia in veterinary patients, occurring with conditions such as infection, trauma (bony or soft tissue), immune-mediated disease, and neoplasia (focal or disseminated). The resulting anemia, anemia of inflammatory disease (AID), is usually mild to moderate, normocytic, normochromic, and nonregenerative.

The pathogenesis of AID is multifactorial, but a key mediator is hepcidin, a type 2 acute-phase protein that is produced by the liver in response to inflammatory stimuli. Specifically, interleukin-6, which is produced early during host defense, induces hepcidin synthesis. Hepcidin inhibits iron export from duodenal enterocytes and macrophages, resulting in decreased iron absorption and the accumulation of iron in macrophages. This reduces the serum iron level and results in decreased iron availability, which is thought to be a protective mechanism to deprive infectious agents of iron but can also decrease the iron available for erythropoiesis. Hepcidin production is decreased in hypoxic or iron-deficient states.

Studies in cats with experimentally induced sterile abscesses indicate that decreased RBC survival plays a large role in the early stages of AID. While the pathogenesis of decreased RBC survival is not fully understood, one theory is that macrophages may increase the clearance of RBCs with surface alterations.
Three components of decreased erythropoiesis are involved in AID:

- Inappropriately low secretion of erythropoietin. In AID, erythropoietin levels are insufficiently increased relative to the degree of anemia. 
- Decreased response of the bone marrow to erythropoietin. This is likely related to the actions of cytokines, particularly tumor necrosis factor, which has been shown to suppress erythropoiesis in laboratory animals and decrease the development of RBC precursors.
- Iron-limited erythropoiesis. Because less iron is available for erythropoiesis, there is a corresponding decrease in RBC production.

Cats tend to develop AID within 2 to 3 days of the onset of the inflammatory process, and the hematocrit drops by an average of 8%. 

Renal Disease
The association between progressive renal disease and anemia is well recognized in animals. There are four main components to the pathogenesis of anemia associated with renal disease. The most important is a deficiency in erythropoietin. Renal disease inhibits the ability of the kidneys to increase erythropoietin production in response to hypoxia. Thus, patients with renal disease have decreased erythropoietin levels relative to their degree of anemia. The second component involves the suppressive effects of uremic toxins on the bone marrow. These effects appear to be confined to the erythroid cell line, as leukocytes and platelets do not seem to be similarly suppressed. The third component, blood loss, is often overlooked as a cause of anemia in patients with renal disease. Bleeding can occur chronically from the GI tract, skin, and other sites due to qualitative platelet dysfunction induced by uremic toxins and to GI ulcers caused by the effects of uremia on the GI mucosa. The fourth potential component is shortened RBC survival due to mild hemolysis.

Renal disease most often causes a normocytic, normochromic, nonregenerative anemia. Initially, the anemia is often mild, but as renal function declines and the hematocrit drops, it can become severe enough to necessitate blood transfusion. Bone marrow cytology may reveal erythroid hypoplasia with an increased myeloid:erythroid ratio.

Feline Leukemia Virus
FeLV can induce anemia in cats by causing bone marrow suppression, myelodysplastic syndromes, neoplasia (lymphoma or leukemia), or a secondary immune-mediated hemolytic anemia (IMHA). There are three FeLV subgroups (A, B, C); infection with subgroup C is most often associated with nonregenerative anemia secondary to bone marrow suppression. The virus is believed to affect RBC precursors near the stem cell level, as suppression of other cell lines can also be seen with this disease. Erythropoietin levels can be increased in anemic cats with FeLV, but ferrokinetic studies and bone marrow cultures have revealed decreased erythropoiesis and an impaired response of the bone marrow to anemia. All strains of FeLV undergo cell-associated viral replication and can stimulate IMHA. In a survey of 21 cases of feline IMHA, 52% were positive for FeLV. A condition known as panleukopenia-like syndrome can occur in cats with FeLV infection and is characterized by leukopenia, anemia, thrombocytopenia, and enteritis with destruction of intestinal crypt epithelium.

Photomicrograph of a cytologic preparation of blood from a healthy cat showing rouleaux (arrows). (Wright–Giemsa stain, 100×.)

QuickNotes
Chronic inflammatory disease is the most common cause of anemia in feline patients.
The anemia seen with FeLV infection is most often mild to moderate and normocytic–normochromic or macrocytic–normochromic, with reticulocytopenia. The macrocytosis is thought to result from skipped mitoses during erythropoiesis.21 Megaloblastic anemia has been associated with FeLV infection and carries a poor prognosis.25 Some cats with FeLV have a regenerative hemolytic anemia.

**Immune-Mediated Hemolytic Anemia**

IMHA occurs in cats less frequently than in dogs. It can be primary (idiopathic) or secondary to infectious diseases such as mycoplasmosis or FeLV, toxins, medications, neoplasia, and systemic lupus erythematosus.24 Hemolysis in cats with IMHA is complement mediated and extravascular; no cases of intravascular hemolysis have been reported in feline patients.26 Approximately 50% of feline IMHA patients have nonregenerative anemia.24,26

**Pure Red Cell Aplasia**

Pure red cell aplasia is a rare syndrome that is characterized by severe nonregenerative anemia with a lack of RBC precursors in the bone marrow, despite normal leukocyte and platelet counts. Pure red cell aplasia can be primary (idiopathic) or secondary to FeLV infection, most likely with subgroup C, which can impair maturation of erythroid progenitors.20 Primary pure red cell aplasia has been reported in nine cats, all with severe normocytic, normochromic to hypochromic anemia and hematocrits ranging from 6% to 15%.27 The leukocyte and platelet counts of these patients were within the normal reference range. Bone marrow aspiration revealed normocellular to hypocellular marrow in most cases, and small, mature lymphocytes were found to account for 12% to 45% of the total marrow cells. Three of six cats had positive direct Coombs test results in a subsequent study.28

**Myeloproliferative Syndromes**

Myeloproliferative disorders are interrelated dysplastic and neoplastic conditions that originate from clonal transformation of nonlymphoid stem cells and their progeny.29,30 This group of disorders includes myelodysplastic syndrome (MDS), acute and chronic myeloid leukemias, and acute undifferentiated leukemia. A discussion of leukemia is beyond the scope of this article. Dysmyelopoiesis is a general term referring to bone marrow disorders that originate in the hematopoietic stem cells and result in a reduction of one or more types of circulating blood cells. The anemia is most often nonregenerative and can be macrocytic and normochromic as well. MDS is considered preleukemic because it can progress to acute myelogenous leukemia. However, due to severe cytopenia, MDS is often lethal without progression to leukemia. FeLV infection is a well-known cause of MDS in cats; approximately 80% of cats with MDS test positive for FeLV.29 In recent years, the incidence of MDS in cats has been declining, likely due to increased awareness and vaccination for FeLV.29,31

**Other Infectious Diseases**

*Mycoplasma haemofelis,* “*Candidatus Mycoplasma haemominutum,*” and *Cytauxzoon felis* directly infect RBCs, often causing hemolytic anemia due to extravascular hemolysis that occurs secondary to antibody-mediated RBC destruction.32 Such anemias are usually regenerative, but nonregenerative anemia can be observed in cases of cytauxzoonosis.32

*Mycoplasma Infection*

*Hemobartonella* spp have been reclassified as hemotropic mycoplasmas (hemoplasmas) based on phylogenetic evidence and 16S ribosomal RNA gene sequences.33 Two species of mycoplasma infect cats in the United States: *M. haemofelis* (Ohio organism or large form) and *"Candidatus Mycoplasma haemominutum*” (California organism or small form). These organisms do not infect other species. *M. haemofelis* and “*Candidatus Mycoplasma haemominutum*” are gram-negative, epacellular RBC parasites. They may be rod-shaped, ring-shaped, or spherical and may exist individually or in chains (Figure 3). The anemia associated with Mycoplasma infection occurs via direct RBC damage and (more importantly) immune-mediated RBC injury, as suggested by positive Coombs test results.34 Macrophages in the spleen, liver, lungs, and bone marrow cause extravascular hemolysis. Intravascular hemolysis has been infrequently reported.35 The anemia varies from mild to severe, and icterus usually is not observed. If the hematocrit drops acutely, the anemia may appear nonregenerative. In most cases, the anemia is regenerative.
Feline Nonregenerative Anemia: Etiologies

by the time clinical signs are observed. Some patients present with severe hemolytic anemia from acute *Mycoplasma* infection; others may have a more chronic course.

Results of studies with cats experimentally infected with both *Mycoplasma* spp have shown that more severe clinical abnormalities and anemia result from infection with *M. haemofelis*.36,37 This has led to speculation that *M. haemofelis* may be more pathogenic than “*Candidatus Mycoplasma haemominutum*.” *Mycoplasma* spp may exist without causing clinical disease in healthy cats.

Cytauxzoonosis

*C. felis* is a tick-borne protozoon that causes disease (usually fatal) in domestic and exotic cats in the central southern and southeastern United States. The natural reservoir host is the North American bobcat, *Lynx rufus*. Transmission of *C. felis* is by the American dog tick, *Dermacentor variabilis*. Infected domestic cats tend to have outdoor access and most often present with clinical disease between May and September.38,39

The life cycle of *C. felis* begins with schizonts that develop in mononuclear phagocytes. The schizont-containing phagocytes line the vascular lumens of almost all organs and can lead to vessel occlusion. The schizonts divide and develop merozoites (buds) that eventually fill the entire host cell. Merozoites exist in phagocytes for 1 to 3 days before they can be observed in RBCs.40 The cell ultimately ruptures, releasing the merozoites to invade RBCs. Parasitemia results in a mild to moderate nonregenerative anemia as well as neutropenia, thrombocytopenia, and icterus that is often profound. Clinically infected cats often present with a fever that progresses to hypothermia.

Domestic cats are believed to be an accidental host of this parasite, as the course of disease is short and the outcome nearly always fatal. In contrast, bobcats, which are believed to be carriers, can be either asymptomatic or show mild clinical disease.52

Iron Deficiency

Iron exists in the body as hemoglobin (the most common form), myoglobin, labile iron, tissue iron, and transport iron. Each molecule of hemoglobin has four atoms of iron, representing 0.34% of its total weight. Each milliliter of RBCs contains 1.1 mg of iron.41

Iron-deficiency anemia can be the result of total body iron depletion, which in young animals can result from parasitism (ectoparasites or endoparasites) or repeated blood sampling. Flea-bite anemia tends to be most severe in young kittens that develop iron deficiency secondary to blood loss combined with low iron stores at birth.42 Iron deficiency is uncommon in adult cats.9 However, conditions resulting in chronic gastrointestinal (GI) blood loss (e.g., ulceration, neoplasia, endoparasitism) can cause iron deficiency. Other possible etiologies, although rare in cats, include genitourinary disease (e.g., transitional cell carcinoma) and diseases resulting in thrombocytopenia. Iron-deficiency anemia has also been documented in cats that are frequently used as blood donors.12,43

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The anemia associated with iron deficiency can range from mild to life threatening. Early on, the anemia is often regenerative and is characterized by anisocytosis, polychromasia, and reticulocytosis. Subsequently, it can progress to become nonregenerative, characterized

#### QuickNotes

All cats with nonregenerative anemia should be tested for FeLV because anemia is an important sign of infection.
by a lack of reticulocytes and by microcytosis. Other laboratory findings in feline patients with iron deficiency may include poikilocytosis, leptocytosis, RBC fragmentation, and thrombocytosis.14

Nutritional Deficiency
Nutritional deficiency anemias are rarely seen in veterinary medicine today because of the improved quality of commercial pet foods and increased owner awareness of nutritional requirements. Such anemias are most likely to occur as a result of error (such as feeding an improperly balanced homemade diet) or a GI problem affecting nutritional absorption.

A normocytic, normochromic, nonregenerative anemia can be seen in severely malnourished cats due to deficiencies in protein, calories, vitamins, or minerals.45 Although iron deficiency is a well-documented cause of nonregenerative anemia in animals, most cases of iron-deficiency anemia are not nutritional in origin. However, iron depletion can occasionally occur in young, nursing kittens because milk is low in iron. An anemia characterized by anisocytosis and poikilocytosis has been detected in a family of giant schnauzers with congenital selective intestinal cobalamin malabsorption,46 but anemia has not been reported in cobalamin-deficient cats.

Conclusion
The etiologies of feline nonregenerative anemia are numerous. Formulating an appropriate and effective plan for the anemic patient requires a thorough understanding of feline RBC physiology. Although determining the underlying cause of anemia is the first step in managing these cases, the course of the disease may be chronic and require frequent monitoring.

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References
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1. Is/are an abnormal morphologic finding in feline RBCs.
   a. Moderate anisocytosis
   b. Rouleaux
   c. Howell-Jolly bodies
   d. Central pallor

2. In severe anemia, which organ is not capable of extramedullary erythropoiesis?
   a. spleen
   b. kidney
   c. liver
   d. lymph nodes

3. Patients with late-stage iron-deficiency anemia typically do not have
   a. hypochromia
   b. microcytosis
   c. reticulocytes
   d. poikilocytosis

4. Which mechanism does not contribute to AID?
   a. blood loss
   b. decreased iron availability
   c. decreased RBC survival
   d. relative erythropoietin deficiency

5. Which statement accurately describes AID?
   a. The anemia is often severe, requiring blood transfusion.
   b. The anemia is often regenerative initially, progressing to a nonregenerative anemia.
   c. Patients often have an absolute iron deficiency.
   d. The anemia is most often normocytic, normochromic, and nonregenerative.

6. Anemia of renal disease is not caused by
   a. erythropoietin deficiency.
   b. blood loss.
   c. decreased RBC survival.
   d. bone marrow resistance to erythropoietin.

7. Which statement is true regarding IMHA in cats?
   a. The hemolysis seen in cats with IMHA is only extravascular.
   b. Thromboembolic complications are common.
   c. It is always secondary to another condition.
   d. Cats with IMHA rarely have a nonregenerative anemia.

8. FeLV infection is not associated with anemia that is
   a. megaloblastic.
   b. hemolytic and regenerative.
   c. macrocytic and nonregenerative.
   d. microcytic and regenerative.

9. A nonregenerative anemia associated with Mycoplasma infection could indicate
   a. bone marrow suppression secondary to Mycoplasma infection.
   b. insufficient time for regenerative response to develop.
   c. concurrent FeLV infection.
   d. b or c

10. Which statement is false with regard to cytauxzoonosis?
    a. In domestic cats, the disease is nearly always fatal.
    b. D. variabilis transmits the pathogen.
    c. The anemia is usually regenerative.
    d. Domestic cats are believed to be an accidental host of the causative parasite.