Anemia is defined as a decrease in the red blood cell (RBC) mass. In practical terms it can be defined as a decrease in the packed cell volume (PCV) or hematocrit (HCT), the hemoglobin (Hb) concentration, or the RBC count below reference interval (RI) for the species. In the context of this lecture, PCV and HCT are used interchangeably. In special circumstances, anemia is diagnosed in a given patient with a HCT that has decreased over time even though it may remain within reference values. For example, Greyhounds and other sighthounds rarely have HCT < 50%, so an anemic Greyhound may have a HCT within the RI for the dog. Because the RIs reflect the actual status in 95% of the feline and canine population, occasionally, an “abnormal” value is indeed normal for a particular animal, prompting a needless evaluation in search of other abnormalities. Please remember that anemia does not constitute a primary diagnosis; therefore every effort should be made to identify its cause.

When interpreting the HCT, Hb concentration, or RBC count, the clinician should keep in mind that in some situations these values are above (e.g., sighthounds) or below (e.g., puppyhood, pregnancy) the RI for the species. From a practical standpoint, when evaluating the erythroid series, you do not need to assess all the values in the CBC because several of them provide identical information. For example, the HCT, Hb concentration, and RBC count provide the same type of information (i.e., an increase in the number of RBCs usually results in an increased HCT and Hb concentration, and vice versa). Thus when evaluating the erythron in a CBC, I use the HCT as an indirect index of the RBC mass (or number).

The main clinical manifestations of anemia in cats and dogs include pale or icteric mucous membranes, lethargy, exercise intolerance, pica (in cats), and decreased overall activity; in dogs, pica is mainly associated with pure red cell aplasia (PRCA). These clinical signs can be acute or chronic and can vary in severity; the duration of the clinical signs may not reflect the mechanism of anemia. For example, “acute” clinical signs are common in cats with chronic anemia; most cats with chronic anemia compensate by shifting the oxyhemoglobin dissociation curve to the right, thus releasing oxygen to the tissues more readily. Therefore cats are clinically stable until their HCT level gets below a specific percent and they develop “acute” signs. Owners may also detect some of the adaptive changes to anemia, such as tachycardia or an increased precordial beat. Following are several important questions to ask the owner of an anemic cat or dog:

- **Is the pet currently receiving any medication?** Certain drugs can cause hemolysis, gastrointestinal blood loss, or bone marrow hypoplasia.
- **Have the owners detected any blood loss or dark (tarry) stool?** Gastrointestinal tract bleeding from a tumor or a gastric ulcer can lead to iron deficiency anemia (IDA).
- **Have the owners noticed any fleas?** Severe flea infestation can cause IDA.
- **Has the cat recently been tested for feline leukemia (FeLV) or feline immunodeficiency virus (FIV) infections?** Retroviruses can cause bone marrow hypoplasia, myelodysplasia, or leukemias, leading to cytopenias.
- **Has the owner noticed any ticks on the dog?** Ehrlichiosis can cause bone marrow hypoplasia; babesiosis can cause hemolysis.
- **Has the dog been in a fight with a pitbull?** Babesia gibsoni infection causes signs similar to those of immune-mediated haemolytic anemia, and it is transmitted by pitbull bites.
- **Has the pet been vaccinated recently?** Modified live vaccines can cause bleeding as a result of platelet dysfunction or thrombocytopenia, or they may be associated with immune-mediated hemolysis.
- **Has the dog received any “shots” for mismating recently?** Estrogen derivatives can cause bone marrow aplasia or hypoplasia.

In addition to these questions, a detailed travel and pharmacologic history should be obtained. Certain infectious diseases associated with anemia used to have a geographic distribution (e.g., babesiosis in the southeastern part of the United States); however, global warming and world wide travel have extended the range of most of these infectious agents. In addition, dogs frequently travel throughout the United States; thus, the geographic disease distribution is becoming less common.

When evaluating a patient with pallor, first one must determine whether it is due to hypoperfusion or anemia (i.e., not every patient with pale mucous membranes is anemic). The simplest approach is to evaluate
the HCT and the capillary refill time (CRT). Dogs and cats with cardiovascular disease and hypoperfusion usually have normal HCT values and additional clinical signs, whereas symptomatic anemic dogs have low HCT; in addition, anemic dogs and cats almost always have hyperkinetic pulses. Dogs and cats with congestive heart failure rarely have dilutional anemia caused by intravascular fluid retention. The CRT may be difficult to evaluate in anemic patients because of the absence of contrast from the pallor.

The clinician should also look for petechiae, ecchymoses, and evidence of deep bleeding in animals with pallor. These findings are suggestive of a platelet or clotting factor deficiency (as seen in animals with Evans syndrome, disseminated intravascular coagulation [DIC], or acute leukemias), resulting in blood loss anemia. Jaundice is common in dogs (but not in cats) with haemolytic anemia; in these patients, the color of the gums is “white on yellow”, as opposed to “white on pink”, because the HCT is low. In our clinic, most dogs with jaundice have hemolysis, whereas most cats with jaundice have liver disease.

Particular attention should be paid to the lymphoreticular organs, such as the lymph nodes and spleen, because several disorders associated with anemia may also result in lymphadenopathy, hepatosplenomegaly, or both. Abdominal radiographs in a dog with intravascular hemolysis may show metallic foreign bodies in the stomach, a potential source of zinc that frequently results in RBC lysis. Abdominal ultrasonography may reveal diffuse splenomegaly with a mottled texture in dogs with anemia due to immune-mediated hemolysis, or in those with lymphoma, leukemias, or malignant histiocytosis.

The degree of anemia may be helpful in establishing its cause. To this end, anemias are graded according to HCT level as follows:

<table>
<thead>
<tr>
<th></th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>30%-36%</td>
<td>20%-24%</td>
</tr>
<tr>
<td>Moderate</td>
<td>18%-29%</td>
<td>15%-19%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;18%</td>
<td>&lt;14%</td>
</tr>
</tbody>
</table>

For example, if an anemic dog or cat has severe anemia, certain causes (e.g., bleeding, anemia of chronic disease, anemia of renal disease, IDA) can immediately be ruled out because none of those mechanisms is likely to result in such a severe decrease in the HCT; therefore the patient most likely has hemolysis or a bone marrow disorder (see below). The severity of the clinical signs usually also correlates with the pathogenesis of the anemia. For example, a dog or cat with severe anemia and mild to moderate clinical signs more likely has a chronic anemia (e.g., bone marrow disease); acute causes of severe anemia (e.g., hemolysis) result in clinical signs of marked severity because the adaptive compensatory changes have not yet occurred.

As part of the evaluation of a patient’s HCT, the plasma should be examined for evidence of icterus (yellow), hemolysis (pink or red), or both (i.e., port wine colored plasma) and the protein content should be determined with a refractometer. The microhematocrit tube should be carefully inspected for evidence of autoagglutination and a saline slide agglutination test should be performed (see below). A blood smear should be evaluated to detect morphologic changes that may point the clinician toward the cause of the anemia. Blood smear evaluation provides relevant clinicopathologic information in most patients with anemia.

A common issue that comes up often is whether a general practicing veterinarian should do CBCs in-house or send them to a referral laboratory. The recent introduction of accurate, user-friendly, benchtop hematology analyzers has revolutionized the practice of small animal hematology. Currently, over half of the practices in the US have their own analyzers. Most of these instruments are user-friendly, trouble-free, and provide accurate results. However, when values are outside the RI or are flagged, the clinician or technician should evaluate a blood smear from the patient in question. Indeed, the blood smear constitutes the easiest, cheapest quality control for the instrument.
New benchtop analyzers frequently provide a graphic depiction of the cell distribution (dot plot, histogram, or cytogram). Depending on the instrument, these dot plots provide clinically relevant information regarding cell size, distribution, presence of reticulocytes, left shift, nucleated red blood cells, and other cell characteristics.

Once it has been established that the patient is anemic, it should be determined whether the anemia is regenerative or nonregenerative. This is accomplished by obtaining a reticulocyte count during a routine CBC (some of the in-house analyzers, such as the LaserCyte and ProCyteDx from IDEXX Laboratories, Westbrook, Maine, provide reticulocyte counts), by obtaining a reticulocyte count from the reference laboratory, or simply by evaluating a blood smear for the presence of polychromasia. Visual evaluation of the RBC dot plot allows easy classification of the anemias as regenerative or nonregenerative. This reflects the pathogenesis of the anemia, thereby dictating the most logical diagnostic and therapeutic approach.

In brief, regenerative anemias always stem from extra-marrow causes because the presence of reticulocytes or polychromatophilic RBCs (i.e., immature RBCs) in the circulation is a clear indication of a functional bone marrow. Regenerative anemias can result only from hemolysis or blood loss. Nonregenerative anemias can be caused by bone marrow or extra-marrow disorders, such as erythroid hypoproliferation, chronic inflammatory disease, and chronic kidney disease; obviously, anemias due to acute hemorrhage or hemolysis are nonregenerative for the first 48 to 96 hours. Although IDA is traditionally classified as nonregenerative, most dogs with chronic blood loss leading to iron deficiency display a mild to moderate degree of regeneration, and the RBC indices are different than in other nonregenerative anemias (see below). Therefore I prefer to classify IDA in a separate category. Regenerative anemias are usually acute, whereas nonregenerative anemias are either peracute (i.e., blood loss or hemolysis of less than 48 hours’ duration) or, more often, chronic.
During the initial clinical evaluation of an anemic patient, examination of the blood smear or dot plots usually suffices to determine whether the bone marrow is responding appropriately to the anemia (i.e., whether the anemia is regenerative or not). Several pieces of information can be acquired during the examination of a good-quality, properly stained blood smear, including the RBC size and morphology, the presence of autoagglutination, the approximate numbers and morphology of white blood cells and platelets, the presence of nucleated RBCs, the presence of polychromasia (indicative of regeneration), and the presence of RBC parasites. The clinician or technician should perform this cursory evaluation of the blood smear; a blood sample should be submitted to a diagnostic laboratory for further analysis and evaluation by a clinical pathologist if the diagnosis is still uncertain after evaluating the blood smear. This evaluation should be conducted under oil immersion lens in a monolayer field, in which the erythrocytes are in a single layer and 50% of the cells are touching.

A CBC and a reticulocyte count in an anemic patient provide more absolute data by which to assess the degree of regeneration. However, the information presented below must be used cautiously because the number of reticulocytes should increase proportionally to the decrease in the HCT. For example, a reticulocyte count of 120,000/µL or a pHCT of 30% but not for one with an HCT of 10%. Interestingly, with the advent of automated analyzers that provide reticulocyte counts, it became apparent that up to 10% of dogs with normal HCT have “high” reticulocyte counts. We now know that excitement causes release of reticulocytes, likely from the spleen, into systemic circulation. Hence, an excited dog, will likely have a higher reticulocyte count than a “calm” one. Overall, normal dogs had cats with a normal HCT have <100,000 reticulocytes/µL, and most of them have between 10,000 and 50,000/µL. As discussed above, when evaluating dot plots from a LaserCyte or ProCyteDx (IDEXX Laboratories, Westbrook, ME), the presence of a large reticulocyte “cloud” is almost always associated with regeneration.

The following points generally hold true:

1. If the RBC indices are macrocytic and hypochromic, the anemia is most likely associated with the presence of high numbers of reticulocytes (which are larger and contain less Hb than mature RBCs); therefore the anemia is likely regenerative. However, a variable proportion of regenerative anemias
are normocytic normochromic, or normocytic hypochromic.

2. If the reticulocyte count is $>120,000/\mu\text{L}$ or 4% likely regenerative.

As part of the evaluation of a patient with regenerative anemia, it is beneficial to determine the serum or plasma protein concentration because blood loss usually results in hypoproteinemia and hemolysis does not.