Chapter 14

Hematopoietic and Hemolymphatic Disorders

Christopher Cebra
Margaret Cebra

ANSWERS AND EXPLANATIONS

1. The answer is 5 [I A 1 5]. Creatine phosphokinase (CPK) is released from degenerating muscle cells and reaches very high (diagnostic) levels in the serum. Nutritional myopathies are caused by deficiencies of vitamin E and selenium. These myopathies occur in foals, lambs, calves, piglets, and mature ruminants. Disease is uncommon in the selenium-rich areas of the North American plains. Losses are most commonly caused by clinical disease.

2. The answer is 1 [I B 3 a]. Pressure necrosis and ischemic myopathy occur when large animals are recumbent on hard surfaces for extended periods. Milk fever and obturator paralysis may cause cows to become recumbent but are not the result of recumbency. Fat cow syndrome is a ketotic condition of obese cows, and blackleg is a clostridial myositis unrelated to recumbency.

3. The answer is 2 [I B 4]. These are different manifestations of the same inherited susceptibility for excessive skeletal muscle metabolism in swine. Blackleg and malignant edema are clostridial diseases of ruminants.

4. The answer is 3 [I B 4 g (2)]. Test matings have been replaced by a polymerase chain reaction gene probe and the other choices do not pertain to porcine stress syndrome.

5. The answer is 1 [I C 1 b (1)]. The most common presentation of blackleg in cattle is sudden death of growing beef animals on pasture. Wounds often are not present (as opposed to malignant edema), and immunization is preventative.

6. The answer is 5 [I I A 3 b]. Although trauma may cause osteomyelitis, the most common cause is hematogenous spread from an infected process.

7. The answer is 4 [III A 1 c]. Fusobacterium necrophorum is a requirement for pasture foot rot (infectious pododermatitis) in cattle. Other organisms (e.g., Bacteroides melaninogenicus, Dichelobacter nodosus) may occasionally be recovered but are not necessary for disease. Actinobacillus pyogenes and Staphylococcus intermedius do not cause foot rot.

8. The answer is 2 [III A 4 b]. The clinical findings support a diagnosis of hairy heel warts (digital dermatitis).

9. The answer is 3 [III A 5 c (1)]. Interrupted feeding of high-grain diets causes bouts of rumen acidosis. This is thought to initiate the systemic hemodynamic changes that result in laminitis.

10. The answer is 1 [III B 1]. Thrush is a disease of the foot of the horse. It is a moist dermatitis of the frog that emits a sour, foul odor. In advance cases, thrush may cause lameness.

11. The answer is 5 [III B 2]. Diseases such as salmonellosis and endomycelitis may result in laminitis. Although laminitis may be irreversible in severe cases, early, vigorous therapy is often successful. Laminitis is diagnosed best by clinical findings, although radiology helps to provide prognostic information in more longstanding cases. Walking is controversial as a therapy but should not be considered in severe lameness. Although often a subclinical disease in cattle, the condition is more often clinical in horses.

12. The answer is 4 [III C 6]. The causative organism, Dichelobacter nodosus, causes the most significant clinical signs in affected sheep. The organism is susceptible to penicillin therapy. The disease occurs most commonly on pasture under conditions of moisture. Although straightforward to treat, this disease is difficult to eradicate because the organism is protected in the feet of carrier sheep. These carrier sheep are not lame.

13. The answer is 2 [III D 1]. Caprine arthritis-encephalitis (CAE) is prevalent across North America, Europe, and Australia. It produces a chronic, progressive arthritis, and there is no known treatment.

ANEMIA. Although anemia literally means "no blood," medically it refers to a state of inadequate oxygen transport by circulating hemoglobin. Anemia is rarely a primary disease and is usually a secondary problem related to trauma, infection, toxocosis, or another disease process.

A. Clinical evaluation of anemia

1. Clinical findings
   a. History. A complete history of the affected animal should be taken, including:
      (1) Anthelmintic and acaridical treatments and risk factors for infestation
      (2) Drug treatments or exposure to toxins
      (3) Dietary history (e.g., exposure to toxic plants and minerals)
      (4) Frequency of erythrocyte parasites in the region
      (5) Hemorrhage or other illnesses
   b. Clinical signs generally include weakness, lethargy, exercise intolerance, pallor of mucous membranes, and a loss of prominence of retinal or scleral vessels.
      (1) Chronic anemia. Poor growth and peripheral and ventral edema may be seen with chronic anemia, particularly if there is concurrent protein loss.
      (2) Severe anemia. Exertion can lead to tachycardia and tachypnea with severe anemia. If anemia is accompanied by a decrease in blood volume, tachycardia and poor jugular filling are common.
   c. Physical examination. The following should be noted during the physical examination:
      (1) Degree or presence of pallor
      (2) Degree or presence of icterus. It must be noted, however, that icterus can develop in the absence of hemolytic anemia—arotic horses frequently develop icterus due to alterations in bilirubin metabolism, and animals with porcine dermatitis also may develop icterus without hemolytic anemia.
      (3) Urine discoloration. Red urine can be caused by hematuria, hemoglobinuria, or myoglobinuria. Dark urine can result from these factors, as well as from a high bilirubin or methemoglobin content.
      (4) Fever. Often, animals with immune-mediated hemolytic and infectious conditions present with a fever. The absence of fever does not exclude these conditions.
      (5) Signs of internal or external blood loss (e.g., epistaxis, melena, hematuria, hematochezia, signs of shock).

2. Classification of anemia. Anemia can be classified by mechanism, regenerative response, red cell indices, and morphology.
   a. Mechanisms. There are four causes of anemia:
      (1) Egress of red blood cells (RBCs) from the vasculature (i.e., hemorrhage) can occur due to internal or external bleeding or parasitic ingestion. Peracute blood loss results in a loss of intravascular volume and possibly hypovolemic shock.
      (2) Destruction of RBCs (hemolysis)
         (a) Intravascular hemolysis occurs when damaged erythrocytes are lysed in the bloodstream.
         (i) Intravascular hemolysis can occur with some infections and toxins, osmotic damage, or with immunoglobulin M (IgM)-mediated hemolysis.
         (ii) Free hemoglobin is released into the blood, resulting in hemoglobinemia and hemoglobinuria (red urine).
(iv) Free hemoglobin can lead to secondary renal tubular necrosis.
(b) Extravascular hemolysis occurs when damaged erythrocytes are removed by the reticuloendothelial organs.
(i) Oxidative damage to hemoglobin, membrane changes due to drugs or infectious agents, and antibody binding (IgG) to the erythrocyte membrane are the most common causes of extravascular hemolysis.
(ii) Hemoglobin is metabolized by the reticuloendothelial cells to bilirubin and is not released into the peripheral blood.
(iii) Hyperbilirubinemia leads to jaundice and dark urine.

(3) Impaired production of RBCs can result from the suppression of bone marrow activity or the replacement of hematopoietic stem cells. Examination of bone marrow cells should reveal:
(a) A lack of hyperplasia of the precursor cells of the erythroid line
(b) Possibly a lack of megakaryocytes and myeloid precursor cells

(4) Impaired oxygen-carrying capacity of RBCs is extremely rare in large animals, but it is seen in cows with erythropoietic porphyria.

b. Regenerative response. The body's reaction to anemia is to increase erythrocyte production and release by the erythroid stem cells in the marrow. The direct stimulus for increasing erythrocyte production is erythropoietin, which is released into the blood by renal tubular cells in response to hypoxemia.

(1) Anemia can be classified as regenerative or nonregenerative, depending on the effectiveness of the marrow response.
(a) All anemias are initially nonregenerative, because it takes several days for marrow hyperplasia to occur.
(b) A strong regenerative response is more common after acute blood loss or in the presence of hemolytic anemia. A regenerative response is less likely when the anemia is caused by impaired production or chronic disease.

(2) Evidence of a regenerative response varies among large animal species.
(a) Ruminants and pigs can release large numbers of reticulocytes (i.e., immature erythrocytes) and other immature erythrocytes into the peripheral blood.
(b) Erythrocytes are larger than mature cells, resulting in anisocytosis and macrocytosis, and contain less hemoglobin per unit volume, resulting in hypochromasia.
(ii) The reticulocytes often contain DNA or RNA remnants, which are visible after staining as polychromasia (basophilic stippling).
(iii) The reticulocyte count adjusted for anemia can be used to test the effectiveness of the regenerative response. The adjusted reticulocyte count is calculated and interpreted as shown in Table 14-1.
(b) All large animal species should develop hyperplasia of erythroid precursor cells in the bone marrow. Lack of this reaction is strong evidence of a nonregenerative anemia.
(c) An increase in erythrocyte count over time is the best evidence that regeneration is occurring.

**TABLE 14-1. Calculating the Adjusted Reticulocyte Count**

| Reticulocyte count | PCV x 100 | Mean PCV for species
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A value of 20 or greater indicates a regenerative response.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A value of 15 or less indicates a nonregenerative response.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A value of 0-15 indicates an early or impaired response.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 14-2. Calculation of Red Cell Indices**

<table>
<thead>
<tr>
<th>MCV (fL)</th>
<th>MCH (pg)</th>
<th>MCHC (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV x 10</td>
<td>PCV x 10</td>
<td>Erythrocyte count (millions)</td>
</tr>
<tr>
<td>Erythrocyte count (millions)</td>
<td>Blood hemoglobin concentration (g) x 10</td>
<td>Blood hemoglobin concentration (g/dL) x 100</td>
</tr>
<tr>
<td>Erythrocyte count (millions)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**c. Red cell indices.** Calculation of the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) aids in the classification of anemia (Table 14-2).

1. **MCV.** The MCV of small ruminants is typically half that of cattle or horses. Normocytic, microcytic, and macrocytic refer to normal, low, and high MCV, respectively.
(a) **Microcytosis** occurs with iron deficiency and some immune-mediated hemolytic anemias.
(b) **Macrocytosis** occurs with maturation defects (e.g., cobalt or vitamin B 12 deficiency, some systemic diseases) or the release of immature erythrocytes into the peripheral blood, which is a normal regenerative response to anemia (particularly anemia due to acute blood loss or hemolysis).

2. **MCH decreases with most causes of anemia as a result of decreased erythrocyte count.** MCH may increase _in fact_ due to intravascular hemolysis because free hemoglobin in the blood is also measured.

3. **MCHC.** Normochromic, hypochromic, and hyperchromic refer to normal, low, and high MCHC, respectively.
(a) **Normochromasia** is common with nonregenerative anemia.
(b) **Hyperhemolysis** can accompany microcytosis (and low MCH) with iron deficiency or macrocytosis (with a normal to high MCH) with the release of immature erythrocytes into the blood as part of a regenerative response.
(c) **Hyperchromasia** can occur with intravascular hemolysis due to the measurement of free hemoglobin in the blood.

**d. Morphology.** Microscopic examination of a blood smear can be used to describe the size, shape, and staining characteristics of erythrocytes.

1. **Reticulocytosis** occurs when reticulocytes are released into the blood as part of the regenerative response to anemia. Reticulocytosis is seen only in ruminants and pigs, never in horses.
2. **Anisocytosis** refers to cells of varying sizes in peripheral blood. *Mild anisocytosis* is common in ruminants, but marked anisocytosis (due to macrocytosis and reticulocytosis) is usually a sign of a regenerative response. Anisocytosis may also be seen after a transfusion if the host and donor erythrocytes are different sizes.
3. **Basophilic stippling** (granulation) in erythrocytes stained with Romanowsky stain is the result of DNA remnants. This stippling is seen as part of the regenerative response in cattle and with chronic lead toxicosis. Howell-Jolly bodies are similar dark-staining nuclear remnants that are normally seen in horse erythrocytes and, thus, are of little value in determining regenerative response.
4. **Spherocytosis** refers to small erythrocytes that lack central pallor. Spherocytosis usually results from partial removal of the red cell membrane by reticuloendothelial cells and often accompanies extravascular hemolysis. Spherocytes
are difficult to identify in large animals because of the small size of normal erythrocytes.

(5) Heinz bodies are aggregates of hemoglobin that have undergone oxidative de-
naturation. Heinz bodies are visible as refractile bodies when stained with Roman-
owsky stain or as round, darkly staining peripheral bodies within erythro-
cytes when stained with new methylene blue stain.

(6) Methemoglobin is formed when the ferrous (Fe) form of hemoglobin is ox-
dized to its ferric (Fe3+) form. A small amount of methemoglobin is present normally and more is formed in some animals with oxidative injury (often in conjunction with Heinz body anemia). Methemoglobinemia and methemoglo-
binuria cause brown discoloration of the blood and urine, respectively.

(7) Erythrocyte aggregation can result from rouleaux formation or autoagglutina-
tion.
   a. Rouleaux are normal in horses and dissipate when diluted with saline.
   b. Autoagglutination is seen during inflammatory reactions and when eryth-
      rocytes are coated with antibody. Autoagglutinating erythrocytes do not disperse as readily with saline dilution.

3. Diagnostic plan and laboratory tests
   a. Blood work
      (1) Complete blood cell count (CBC) and morphologic examination. Anemia can be quantified by measuring the:
         a. Packed cell volume (PCV). The PCV, the percentage of blood volume oc-
            cupied by erythrocytes, can be determined by automated counter or cen-
            trifugation. Microcentrifugation may be necessary to adequately pack small ruminant erythrocytes.
         b. Blood hemoglobin concentration (Hb). Erythrocyte count
      c. Microcytic hypochromic anemia is suggestive of iron deficiency, whereas
         macrocytic hypochromic anemia is suggestive of a regenerative response
         (seen with acute blood loss or hemolysis). Normocytic normochromic
         anemia is seen before the regenerative response has started (2–4 days) or
         with nonregenerative anemia.
      d. Anemia with hypoproteinemia is suggestive of acute blood loss, whereas
         anemia with hyperproteinaemia is suggestive of an inflammatory reaction.
      e. Erythrocytes should be examined for morphologic abnormalities, regener-
         ative response, or parasites.
      f. Yellow plasma is seen with hyperbilirubinemia, whereas pink plasma is
         seen with hemoglobinemia. Whole blood may be dark brown with se-
         vere methemoglobinemia.
      g. Direct Coombs' test. Specific anti-immunoglobulin and anti-complement an-
         ti-bodies may be mixed with host erythrocytes. If host erythrocytes are coated
         with these factors, as often occurs with immune-mediated hemolysis, aggluti-
         nation may occur. The test is usually performed at body temperature (warm
         agglutination) for IgG and below body temperature (cold agglutination) for
         IgM. A Coombs' test cannot be performed on blood that autoagglutinates.
      h. Iron-binding capacity. Serum iron concentration and unsaturated iron-binding
         capacity can be measured. Both are low with anemia of chronic disease,
         whereas unbound iron-binding capacity is high with iron deficiency anemia.
   b. Fecal occult blood test detects the presence of blood peroxidase in feces and,
      therefore, helps identify gastrointestinal hemorrhage. Dietary factors in ruminants
      and small subclinical ulcerations affect the diagnostic value of this test. The sensi-
      tivity and specificity of this test has not been established for large animals. How-
      ever, test results can be used to raise or lower clinical suspicion of gastrointesti-
      nal bleeding.
   c. Urinalysis
      (1) Urine sediment should be examined for erythrocytes. If hematuria is present,
         urinary tract hemorrhage may be the source of blood loss.

(2) Tests may be performed to differentiate hemoglobin from myoglobin in red
urine. Hemoglobinuria is seen with hematuria or intravascular hemolysis.
(3) A high urine bilirubin concentration may be seen with hemolysis or liver dys-
function (or fasting in horses).

b. Bone marrow examination can be performed in order to examine the stem cell re-
sponse to anemia. Because horses do not get reticulocytosis, cytologic examina-
tion of marrow is the best way to determine if anemia is regenerative. Hyperplas-
ia of stem cell lines, particularly erythroid precursor cells, suggests a regenerative response.

B. Acute blood loss anemia

1. Clinical findings. Animals with rapid external blood loss may have obvious hemor-
rhage or ectoparasitism. With internal hemorrhage, the site of hemorrhage may not be obvious.
   a. Signs of anemia include pale pink to white mucous membranes, disappearance
      of visible capillary refill times, and prolonged capillary refill times.
   b. Animals with blood loss anemia also often have tachycardia, weak pulses, poor
      jugular filling, and cold extremities.
   c. Anemia with poor organ perfusion become weak and dull.

2. Etiology and pathogenesis
   a. Etiology. Rapid loss of blood from the vascular compartment can occur internally
      or externally. Blood loss can be caused by the rupture of a large, blood-filled vis-
      cera, vessel, spleen, heart, thrombocytopenia, a cloning defect factor, blood-
      sucking parasites, or severe ulceration of an epithelial membrane.
   b. Pathogenesis. Decreased intravascular volume and hemoglobin content result in
      low cardiac output and poor tissue perfusion. Severely affected animals develop
      hypovolemic shock and may die.

3. Diagnostic plan and laboratory tests
   a. Clinical findings suggest a diagnosis of blood loss anemia, particularly when ex-
      ternal hemorrhage is present.
   b. Blood work
      (1) With peracute blood loss, blood appears normal and has a normal PCV, total
         protein, and hemoglobin concentration.
      (2) With acute, subacute, or chronic blood loss anemia, blood appears thin and
         watery and has a low PCV, total protein, and hemoglobin concentration.
   c. After a few days of blood loss, there should be evidence of a regenerative re-
      sponse.

4. Therapeutic plan. Treatment is dictated by the degree, rapidity, and severity of blood loss.
   Efforts should be made to correct the cause of blood loss. Less aggressive inter-
   vention is required with gradual blood loss because of the animal's ability to com-
   pensate.
   a. Fresh whole blood is the best treatment
   b. Isotonic or hypertonic fluids should be given intravenously to restore vascular
      volume in patients with hypovolemic shock.
   c. Stress to the animal should be minimized.

C. Chronic blood loss anemia

1. Clinical findings
   a. Affected animals typically appear unthrifty, with poor body condition and hair
      coats. Pallor of mucous membranes may be present, but often is not remarkable.
   b. Animals with longstanding concurrent hypoproteinemia often develop edema of
      the ventrum and extremities.
   c. Severely affected animals are weak and lethargic and may die if stressed.

2. Etiology. Chronic blood loss can be caused by all of the causes of acute blood loss
   (see I 2). Parasitism and gastrointestinal ulceration are the two most com-
   mon causes in large animals. Because of the animal's ability to maintain circulatory
volume with chronic blood loss, hypovolemic shock is not seen. Clinical signs result from the decreased oxygen-carrying capacity of blood.

3. Diagnostic plan and laboratory tests
   a. Blood work. Determination of the PCV and hemoglobin concentration are necessary to diagnose chronic blood loss anemia. The regenerative response often is absent or poor, and there is occasionally hypochromasia and microcytosis compatible with iron deficiency.
   b. Identifying the cause of blood loss through fecal examination for endoparasites, visual inspection for ectoparasites, and endoscopic examination for gastric ulceration may be useful.

4. Therapeutic plan. Specific treatment for chronic blood loss anemia usually is not indicated. Iron supplements may be helpful. Efforts should focus on treating the cause of blood loss.

### Hemolytic anemia (HA)

1. HA of horses
   a. Infectious causes of HA
      (1) Babesiosis (piroplasmosis)
         (a) Clinical findings. Fever and icterus are common findings with both causative organisms, whereas hemoglobinuria is more common with Babesia equi than with Babesia caballi. Generalized signs seen are severe anemia and include weakness, anorexia, and depression. Eyelid swelling and naso-ocular discharges are common with severe disease.
         (b) Etiology and pathogenesis
            (i) Etiology. This disease is caused by the protozoan parasites 8. caballi and B. equi. Both organisms are predominately found in tropical and subtropical areas but potentially can be found anywhere within the ranges of their host, ticks. Both organisms live within erythrocytes; 8. caballi also has a lymphocytic stage.
            (ii) Pathogenesis. Babesia species are spread by Dermacentor, Hyalomma, and Rhipicephalus ticks. Vertical transmission in ticks occurs with B. caballi but not with B. equi. The parasites cause both intracellular and extravascular hemolysis, and most infected horses remain carriers for life.
   (c) Diagnostic plan and laboratory tests. Identification of Babesia in a blood smear examination from a horse with compatible clinical signs is diagnostic. B. caballi are large and pyriform, whereas B. equi/piroplasms are small and rounded. Multiple organisms can be found inside a single erythrocyte, occasionally forming the "Maltese cross" shape with B. equi. Serologic tests are also available.
   (d) Therapeutic plan. Imidocarb is the drug of choice to treat equine babesiosis. High doses are needed to treat B. equi and to prevent the carrier state with B. caballi. High doses (4 mg/kg body weight) have been associated with colics and death, particularly in donkeys.
   (e) Prevention. There is no vaccine for equine babesiosis. Tick control is essential to prevent the spread of the organisms.
   (f) Equine infectious anemia (EIA; swamp fever)
      (a) Patient profile. EIA only infects horses and other Equidae, regardless of age, breed, or sex. The disease is found worldwide.
      (b) Clinical findings. The clinical and hematologic manifestations vary depending on the virulence of the virus, host resistance factors, and environmental stressors. Ninety percent of acute and subacute episodes occur within the first year of infection. Recrudescence of clinical signs may occur in association with corticosteroid administration, stressors (e.g., transport, heavy work), intercurrent disease, or adverse environmental factors. There are three forms of clinical disease:
         (i) Acute form. Clinical signs include intermittent fever, depression, petechial hemorrhages, progressive weakness, weight loss, anemia, swelling of the legs, brisket and ventral abdomen, or sudden death.
         (ii) Subacute to chronic form. Clinical signs include recurrent episodes of fever, depression, anemia, icterus, lymphadenopathy, petechial hemorrhages, edema, and weight loss. Occasionally, there are neurologic alterations. Clinical signs usually occur within the first few months after infection.
         (iii) Chronic or inapparent form. There may be few clinical or hematologic signs. Occasionally, carrier animals have periodic fever or weight loss.
      (c) Etiology. EIA is caused by a lentivirus, which is a nononcogenic retrovirus that infects cells of the immune system.
      (d) Pathogenesis. EIA virus is host-specific and is transmitted from animal to animal through body fluids, particularly blood. Infected horses are carriers for life.
         (i) Transmission. Contaminated needles, syringes, and surgical or dental instruments may spread the disease. Horse flies and deer flies can also transmit infected blood to uninfected horses. The chance of spread of EIA virus via arthropod transmission is dependent on the distance between infected and uninfected horses, the number of vectors feeding on the horses, the amount of infected blood ingested, and other factors.
         (ii) Viral life cycle. The virus multiplies in lymphoid tissues throughout the body within monocytes and macrophage cells. The virus elicits brisk humoral and cellular immune responses. It incorporates into the host genome and is disseminated throughout the body. The virus escapes the host's immunosurveillance by remaining intracellular and by altering its surface glycoproteins to appear unrecognizable by surface neutralizing antibodies.
         (iii) Clinical manifestations. Many of the clinical manifestations of EIA infection are thought to be immune-mediated. Hepatitis, lymphadenopathy, and splenomegaly are caused by infiltrates of virus-infected mononuclear cells. Anemia results from the negative effects of the virus on hematopoiesis, viral hemagglutinin-mediated hemolysis and phagocytosis, and relative iron deficiency.
   (e) Diagnostic plan and laboratory tests
      (i) Clinical pathology. There may be a mild lymphocytosis and monocytosis during acute disease, but changes in the leukogram are inconsistent. Inapparent carriers may have a normal hemogram except for a marginally low erythrocyte count.
      (ii) Agar-gel immunodiffusion (ACID, Coggins) test is a highly specific and accurate indication of EIA infection. Test results may be negative in the first 10–14 days of disease. False-positive tests may occur in foals born to infected dams because of the absorption of antibodies from the colostrum.
      (iii) Competitive enzyme-linked immunosorbent assay (ELISA) is more sensitive but less specific than ACID.
      (f) Therapeutic plan. There is no effective treatment for EIA. State and federal regulations require that infected horses be reported. Only seronegative horses can be moved between states and internationally for participation in equestrian events.
      (g) Prevention. It is generally recommended (and may be required) to humanely destroy infected horses because even clinically normal chronic carrier horses pose a health risk to other horses. To avoid euthanasia, infected horses must be separated by at least 200 yards from healthy horses, and strict insect control must be practiced to ensure no transmission of disease. Strict attention to contaminated needles, syringes, or surgical instruments is also necessary.
b. Immune-mediated causes of HA

(1) Neonatal isoerythrolysis (NI)

(a) Epidemiology. In Thoroughbreds, NI occurs in approximately 1% of births. In Standardbreds, NI occurs in approximately 2% of births. The prevalence of NI is higher in mule foals (10%) because of the unique donkey erythrocyte antigen, which is present on donkey but not horse erythrocytes. Because mule foals are the product of a donkey sire and a horse dam, NI is possible in all such breedings, particularly if the dam has previously carried a mule foal.

(b) Clinical findings. The severity of clinical signs appears to relate to the amount of colostrum absorbed; therefore, vigorous foals are often the most severely affected.

(i) Foals are born healthy but develop progressive lethargy and weakness 24–36 hours postpartum after ingesting colostrum.

(ii) Mucous membranes are initially pale and later become icteric.

(iii) There may be hemoglobinuria and hemoglobinemia leading to death.

(iv) Other signs include rapid, shallow breathing followed by labored breathing, tachycardia, excessive yawning, and seizure-like activity.

(c) Etiology and pathogenesis. Coating of foal RBCs with maternal alloantibodies absorbed from colostrum causes RBC destruction.

(i) Blood group antigens. This condition can occur whenever the sire and foal share a blood group antigen that is not present in the mare. The Aa and Qa blood group antigens, as well as any unique donkey blood group antigen, appear to be strongly immunogenic and are responsible for most cases of NI.

(ii) Exposure in the mare. In order to have antibodies against these blood types in colostrum, the mare's blood must lack the antigen, and the mare must have been previously exposed to this antigen by blood transfusion, exposure to blood from a previous foal (usually sired by the same male) during parturition, or exposure to the foal's blood during gestation at placental pathology.

(iii) Exposure in the foal. When antibodies are absorbed from the colostrum into the foal's circulation, they attach to the foal's erythrocytes, leading to accelerated erythrocyte removal and destruction by reticuloendothelial cells.

(d) Diagnostic plan and laboratory tests

(i) Clinical pathology reveals anemia, hemoglobinemia, elevated bilirubin (mostly conjugated), and hemoglobinuria. Mule foals may also have thrombocytopenia. The leukogram should be evaluated to help eliminate sepsis as the cause of clinical signs.

(ii) Lytic or precipitation tests detect antibodies in the colostrum or the mare's serum against the foal's whole erythrocytes. The jaundiced foal's blood is tested for agglutination. The RBCs are washed and tested again. If it is positive, the test should be repeated closer to foaling if the results are equivocal.

(iii) Serum screening. If blood typing cannot be done before breeding or if a potentially incompatible match cannot be avoided, the mare's serum should be screened for the presence of antineutrophil antibodies within 30 days of foaling. This is done by mixing the mare's serum with the stallion's erythrocytes and looking for agglutination. This test can be repeated closer to foaling if the results are equivocal. If the test is positive, a JFA test should be performed before allowing the foal to nurse. If the JFA test is positive, colostrum from another source should be provided to the foal, or antibodies should be supplied by plasma transfusion from a suitable donor. When the foal can no longer absorb colostral antibody (usually by 48 hours postpartum), the foal can be allowed to nurse from the mare.

(2) Immune-mediated HA

(a) Clinical findings. Clinical signs, including fever and icterus, resemble those seen with parasitic immune-mediated hemolytic disorders (e.g., Babesiosis).

(b) Etiology and pathogenesis. Host antibodies and complement may bind to host erythrocyte membranes. This may result in intravascular hemolysis but more commonly leads to erythrocyte phagocytosis or partial phagocytosis by reticuloendothelial cells (extravascular hemolysis). This antibody binding may occur for two reasons: the alteration of the RBC membrane or an overzealous immune response. Charges in the membrane are more common and can result from:

(i) Intraerythrocyte parasites

(ii) Chronic bacterial and viral infections

(iii) Lymphosarcoma

(iv) Disorders of immune function (e.g., systemic lupus erythematosus, neonatal isoerythrolysis)

(v) Medications (particularly penicillin)

(vi) Idiopathic causes

(c) Diagnostic plan and laboratory tests. Spontaneous autoagglutination or a positive Coombs' test should be used to confirm immune-mediated hemolytic anemia. The JFA test should be performed before allowing the foal to nurse. If the JFA test is positive, colostrum from another source should be provided to the foal, or antibodies should be supplied by plasma transfusion from a suitable donor. When the foal can no longer absorb colostral antibody (usually by 48 hours postpartum), the foal can be allowed to nurse from the mare.

(d) Therapeutic plan. All prior medications should be discontinued.

(i) Immunosuppressive drugs. If an acute or chronic infectious condition can be ruled out, an immunosuppressive course of corticosteroids or cyclophosphamide can be initiated. The dosages of these drugs should be gradually reduced, and their administration should be discontinued within 1 month, if possible.

(ii) If a noninfectious disease state (e.g., lymphoma, systemic lupus erythematosus) is identified, treatment of the primary disease may result in the resolution of hemolysis.

(iii) Infectious diseases should be treated with the appropriate drugs, but classes of drugs that may have precipitated hemolysis should be avoided.

(iv) A blood transfusion is rarely necessary.

(c) Toxic causes of HA

(1) Oxidative injury (red maple leaf, onion, and phenothiazine toxicity)

(a) Patient profile. Red maple leaf toxicosis occurs in late summer and fall.
Any horse or pony is susceptible regardless of age, breed, or sex. Horses are less susceptible to onion toxicity than cattle, but they are more susceptible than sheep or goats. All horses are susceptible to phenothiazine toxicosis.

(b) Clinical findings

(i) Clinical signs. Polyneia, tachycardia, weakness, depression, anorexia, and cyanosis are common. Death may occur in 4–6 days.

(ii) Fever may be present during the hemolytic episode.

(iii) A brownish discoloration of blood and urine may occur with red maple leaf toxicosis.

(c) Etiology. Ingestion of onions or wilted, dry red maple leaves or the administration of phenothiazine sedatives or anthelmintics can lead to acute, hemorrhagic anemia.

(d) Pathogenesis. Oxidative denaturation of hemoglobin by n-propyl disulfide (an alkalioid) from onions, by an unknown toxin in red maple leaves (Acer rubrum), and by phenothiazines results in the production of Heinz bodies within RBCs. Red maple leaf toxicosis also causes methemoglobinemia.

(i) Onion toxicity. The alkalioid n-propyl disulfide depletes the intracellular enzyme, glucose 6-phosphate dehydrogenase, which maintains glutathione in its reduced state. When glutathione is oxidized, mixed disulfide linkages form between globin chains of hemoglobin and glutathione. These linked molecules precipitate within the cell, forming Heinz bodies.

(ii) Phenothiazines are also strong oxidizing agents.

(iii) Red maple leaf toxicosis. Erythrocytes containing Heinz bodies are removed from the circulation by the reticuloendothelial system (extravascular hemolysis), leading to anemia. With severe oxidative damage, some intravascular hemolysis can occur. There are two patterns of toxicity with red maple leaf toxicosis. The peracute form results from massive methemoglobinemia, causing marked tissue anoxia and sudden death. The hemolytic form is caused by continuous oxidative stress on RBCs, causing Heinz body anemia with subsequent intra- and extravascular hemolysis.

(e) Diagnostic plan and laboratory tests

(i) Clinical pathology. Anemia is present with all three diseases. Spherocytosis. Heinz bodies in peripheral blood, and elevated total bilirubin (mostly unconjugated) may also be seen. High MCHC and MCH, reticulocytosis, and increased RBCs with increased RBCs with polychromasia, Howell–Jolly bodies, or in Giemsa-stained smears as small, stippled. Erythrocytic enzyme, glucose 6-phosphate dehydrogenase, which maintains glutathione in its reduced state. When glutathione is oxidized, mixed disulfide linkages form between globin chains of hemoglobin and glutathione. These linked molecules precipitate within the cell, forming Heinz bodies.

(ii) Differential diagnoses. Other causes of hemolysis or methemoglobinemia should be eliminated.

(g) Therapeutic plan

(i) Eliminate red maple leaves or onions from the diet by moving the horse. Discontinue the use of phenothiazines.

(ii) Intravenous isotonic fluids are useful for diuresis, the correction of dehydration, electrolyte depletions, and acid-base abnormalities.

(iii) Whole blood transfusion may be necessary if the PCV is less than 12% and decreasing over time.

(iv) Dexamethasone may help stabilize erythrocyte membranes and reduce the risk of a transfusion reaction. Steroids must be used with caution because they may lead to laminitis.

(v) Ascorbic acid (125 mg/kg orally initially, followed by 50 mg/kg subcutaneously twice daily) has been used as an antioxidant for the treatment of red maple leaf toxicosis.

(2) Iatrogenic causes of HA. Several medications that are commonly administered to large animals cause hemolysis. Unless large amounts of the medication are administered, hemolysis is rarely clinically significant.

(a) Hypotonic solutions can cause osmotic lysis of RBCs when administered intravenously.

(b) Phenothiazine tranquilizers and anthelmintics cause oxidative injury to RBCs (see (D) (1)).

(c) Some concentrated drugs, notably tetracycline and dimethylsulfoxide (DMSO), cause hemolysis by an undescribed mechanism. To avoid this, these drugs should be diluted (less than 10% solution for DMSO) before intravenous administration.

2. HA of ruminants can also be categorized as intra- or extravascular. Each type leads to the characteristic abnormalities as discussed with horses (see (D) (1)).

(a) Infectious causes of HA

(1) Anaplasmosis

(a) Clinical findings are related to the immune-mediated loss of circulating erythrocyte mass. Calves under 1 year of age show few clinical signs. Severity of clinical disease increases with age, such that cattle older than 3 years often die of peracute disease. All of the following forms can occur in infected sheep and goats, but clinical disease is rare.

(i) Acute anaplasmosis is common in young adult cattle. Anemia, fever, tachycardia, tachypnea, weakness, depression, and icterus are seen. Blood appears thin, and mucous membranes appear pale.

(ii) Peracute anaplasmosis is more common in older cattle. Signs are similar to the acute disease, except that death often occurs before icterus develops.

(iii) Chronic anaplasmosis can follow acute infection and is characterized by ill-thrift and decreased production. The animal becomes a reservoir for the infection of herd mates.

(b) Etiology. The disease in cattle is caused by Anaplasma marginale marginale and Anaplasma marginale centrale of the order Rickettsiales. The disease in small ruminants is caused by Anaplasma ovis. These organisms are obligate intracellular parasites of erythrocytes.

(c) Pathogenesis

(i) Transmission. The organisms are spread by the passage of blood between animals. Chronically infected animals are carriers as reservoirs. Argasid and ixodid ticks, biting flies, and veterinary instruments are the most common means of transmission. Transmission is seasonal, based on the life cycle of the arthropod vectors. Experimental transplacental transmission has been documented.

(ii) Disease progression. After an incubation period of 2–7 weeks, parasites invade the erythrocytes (order Rickettsiales) when administered intravenously. These result in oxidative injury to RBCs with subsequent oxidative stress on RBCs, causing Heinz body anemia with subsequent intra- and extravascular hemolysis.

(iii) Necropsy. The blood smear reveals reticulocytosis, polychromasia, Howell–Jolly bodies, and basophilic stippling. Anaplasma may be visible on direct smear or as refractile bodies or in Giemsa-stained smears as small, round, purple bodies. A. marginale marginale are located at the periphery of erythrocytes, whereas A. marginale centrale are located toward the center.

(d) Diagnostic plan and laboratory tests. Because clinical signs are specific to hemolytic anemia but not anaplasmosis, laboratory tests can be used to confirm the diagnosis.

(i) Blood smears reveal reticulocytosis, polychromasia, Howell–Jolly bodies, and basophilic stippling. Anaplasma may be visible on direct smear or as refractile bodies or in Giemsa-stained smears as small, round, purple bodies. A. marginale marginale are located at the periphery of erythrocytes, whereas A. marginale centrale are located toward the center.

(ii) Serologic tests and DNA probes. Chronically infected animals have...
fewer visible rickettsia and may be better diagnosed by serologic
tests or DNA probes.

(e) Therapeutic plan. The three considerations of treatment include the resolu-
tion of acute parasitemia, maintenance of organ perfusion, and preven-
tion of the carrier state.

(i) Oral chlorotetracycline and parenteral oxytetracycline are the most
commonly used drugs to treat acute or chronic infection. Low-
concentrations of a tetracycline (usually chlorotetracycline) added to the
feed or water can be used to reduce morbidity during periods of
high transmission in endemic areas. Higher doses or longer treat-
ment courses are required to eliminate infection.

(ii) Although fluids or blood transfusions can be used to maintain organ
perfusion, these treatments are usually impractical.

(dii) Efforts should be made to minimize stress and exertion of severely af-
ected cattle until parasitemia is reduced and circulating erythrocyte
mass has been restored.

(f) Prevention. The control of vectors, reduction of parasitemia through the
continuous use of antimicrobial drugs, elimination of the carrier state, or
vaccination can be used to reduce the losses caused by anaplasmosis.

(2) Babesiosis (piroplasmosis) has been eradicated from North America.

(a) Patient profile. Cattle, goats, sheep, and swine may be affected.

(i) Cattle of all ages are susceptible to this disease, although calves be-
tween the ages of 2 and 9 months appear to be resistant. Offspring
of exposed dams are protected against clinical disease by maternal
antibody during the neonatal period. Exposed calves develop long-
lasting resistance to clinical babesiosis.

(ii) Bos indicus cattle and their calves appear to be more resistant than
other cattle.

(b) Clinical findings

(i) Clinical signs. FEVER is present for several days before other
signs appear. Anemia, depression, tachycardia, icterus, and weak-
ness are common. Hemoglobinuria helps distinguish babesiosis from
diseases characterized by extravascular hemolysis (e.g., anaplasmo-
sis). Neurologic signs (e.g., convulsions, somnolence) are common in the
hours before death.

(ii) Necropsy lesions. With anoxic organ damage, severe disease ensues,
and death is common. Necropsy lesions include icterus and dark,
swollen internal organs.

(c) Etiology. The disease is caused by protozoan parasites of the species Ba-
besia bigemina and Babesia bovis are the main pathogenic spe-
cies. These organisms are obligate intracellular parasites of erythrocytes.

(d) Pathogenesis

(i) Transmission between animals is by ticks. Boophilus species and Le-
odes ricinus are the most important tick vectors. Transovarial trans-
mission to the next generation of ticks plays a major role in the trans-
misssion to cattle.

(ii) After an incubation period of 2–3 weeks, the number of parasites
can increase enough to become clinically relevant. Intraerythrocytic
parasitism leads to extravascular hemolysis with hemoglobinemia and
hemoglobinuria ("redwater"). Babesia also releases toxins that cause vasodilation, increased vascular permeability, and erythrocyte
aggregation. These effects on the vascular system impair circulation, lead-
ing to tissue hypoxia and necrosis. Renal damage also results from
exposure to hemoglobin.

(e) Diagnostic plan and laboratory tests. Clinical signs and necropsy lesions
do not always make the diagnosis in an endemic area in a short period. Oxytetracyclines are probably the best drugs to
treat this infection. Other drugs have been used with mixed results.

(i) Hemogram evaluation should reveal anemia with evidence of a re-
generative response.

(ii) The parasites can be seen on Giemsa-stained smears and are seen at

single or paired large orvoid or pyriform organisms within erythro-
cytes. Organisms are more readily seen on smears of peripheral
blood (as opposed to jugular blood).

(dii) Serologic tests are also available.

(f) Therapeutic plan and prevention. A variety of babesicides are available
for the treatment of clinical disease. These include imidocarb, dimin-
azone, phenamidine, and amicarbalide. Imidocarb and diminazine can also
be used for short-term prophylaxis. Any treatment or prevention pro-
ocol should include provisions for tick control.

(3) Eperythrozoonosis. Eperythrozoon species, rickettsial parasites, are similar to
Anaplasma because these organisms stimulate immune-mediated hemolysis.
There are two principal species that affect ruminants and a third that affects
pigs.

(a) Eperythrozoon wenyoni

(i) Patient profile. Cows of all ages appear to be susceptible to infection
by this organism.

(ii) Clinical findings. Affected cattle typically have transient fever, lym-
phadenopathy, depression, and decreased milk production. Swelling
of the udder and hind legs is common in dairy cattle. Icterus is un-
common and mild when present.

(iii) Etiology. Although arthropod vectors are suspected, this has not
been proven. Most infections appear to result in minimal clinical dis-
ease, but some cattle show clinical signs of inflammation and hemo-
lytic anemia similar to those seen with acute anaplasmosis. Chronic
infections and a subclinical carrier state are thought to occur.

(iv) Diagnostic plan and laboratory tests. Diagnosis is made by identify-
ing the parasite on a peripheral blood smear examination. The organ-
ism is small, frequently round (but occurs in a variety of shapes), and
found within erythrocytes. The organism may be seen singly, in
clumps, or in a ring form. The ring form, together with a relatively
large number of free organisms in blood, helps differentiate this dis-
 ease from anaplasmosis.

(v) Therapeutic plan. Clinical signs usually resolve spontaneously in
7–10 days, except in immunocompromised or splenectomized cat-
tle. More rapid resolution is seen after the administration of a single
dose of a long-acting oxytetracycline or a 3-day course of a short-
acting oxytetracycline.

(b) Eperythrozoon ovis

(i) Patient profile. All ages of sheep appear to be susceptible to this or-
genism, but clinical disease is most common in young animals.

(ii) Clinical findings. Fever, depression, weakness, icterus, and hemoglobin-
uria are seen with severe disease. The more common manifesta-
tions are anemia, icterus, and death.

(iii) Etiology and pathogenesis. Other pathogen have been isolated from
sheep with ill-thrift syndrome. E. ovis is only one of several possi-
able etiologic agents. Ticks, lice, and mosquitoes are thought to be im-
portant vectors. Similar to E. wenyoni in cattle, E. ovis infection is
thought to result in minimal clinical disease in most affected sheep.

However, hemolytic anemia and the inflammatory response appear
to cause morbidity and mortality in some sheep.

(iv) Diagnostic plan and laboratory tests. Similar to E. wenyoni infection in
cattle, the diagnosis is made by identifying round or pleomorphic
organisms both within plasma and erythrocytes. Clumps, crosses,
and rings are a common finding.

(v) Therapeutic plan. Oxytetracyclines are probably the best drugs to
treat this infection. Other drugs have been used with mixed results.
In some cases, treatment failure may result from failure to identify an-
other primary pathogen.
(4) Leptospirosis
(a) Clinical findings and diagnostic plan. Leptospires are slender spirochaetes that require special laboratory techniques to stain and detect. Leptospires may be identified in body fluids (usually urine) by dark-field microscopy, immunofluorescence, or DNA hybridization. Single high (greater than or equal to 100:1 dilution) or a fourfold increase in paired samples on the microscopic agglutination tests are considered diagnostic.
(b) Etiology. Clinical disease is caused by serovars of Leptospira interrogans. Serovars hardjo and kenneewicki (formerly pomona) are responsible for disease in ruminants.
(c) Pathogenesis. A maintenance host (cattle for variant hardjo; wild mammals for variant kenneewicki) infects moist soil and pools of water. The organism may be ingested or penetrate intact skin. Acute disease coincides with the subsequent leptospiremia. Among other pathogenic mechanisms, cold-agglutinating IgM attaches to host erythrocytes, leading to intravascular hemolysis.
(d) Therapeutic plan. Intravenous fluid therapy should be initiated. Patients may require treatment for acute renal failure (see Chapter 15), disseminated intravascular coagulation [DIC; see II B 3 b (5)], or both. Antibiotic therapy includes penicillin initially, followed by dihydrostreptomycin or tetracycline therapy when renal function has returned to normal.

(5) Bacillary hemoglobinuria is very similar to Black's disease (see Chapter 5 III A 3).
(a) Clinical findings. Affected ruminants often are found dead due to peracute disease. Other affected animals are extremely depressed, walk with hunched backs, and are very sensitive to abdominal palpation. Normal bodily functions are reduced or absent. Tachycardia, tachypnea, and fever are common. Animals that survive more than 1 day may have icterus and hemoglobinuria, and icteric tissues are commonly found on postmortem examination.
(b) Etiology and pathogenesis. Clostridium hemolyticum is a large, spore-forming, gram-positive anaerobic rod. Spores survive in the environment for a long time, are ingested or inhaled, and are transported to the liver of ruminants. With hepatic injury, commonly due to fluke migration, spores germinate. Mature bacteria produce exotoxins, which cause local necrosis and intravascular hemolysis.
(c) Diagnostic plan and laboratory tests. Postmortem examination, revealing severe hepatic necrosis with infarcts, hemorrhagic exudates, and subcutaneous edema, is strongly suggestive of this disease. The organism may be found by bacteriologic culture or impression smear of liver lesions. Hemoglobinuria may also be present.
(d) Therapeutic plan. Treatment is rarely rewarding. If pursued, treatment should consist of large doses of penicillin and supportive care.
(e) Prevention. Vaccination with clostridial toxoids and fluke prevention are necessary.

(6) Yellow lamb disease
(a) Patient profile. This hemolytic disease has only been identified in lambs.
(b) Clinical findings. Affected lambs are depressed, weak, and often in distress. Anemia, icterus, and hemoglobinuria are common.
(c) Etiology and pathogenesis
(i) Etiology. Clostridium perfringens type A, the causative agent, is a large, spore-forming, gram-positive anaerobic rod. Spores survive for long periods in the soil, and the organism may inhabit the gut of healthy animals.
(ii) Pathogenesis. The organism proliferates in the gut and releases exotoxins. One of these exotoxins, the a-toxin, causes vasculitis and intravascular hemolysis due to phospholipase activity.
(d) Therapeutic plan. Most affected lambs die within 12 hours of the onset of clinical signs. Treatment with large doses of penicillin and supportive care can be attempted.
(e) Prevention. There is no toxoid useful in preventing this disease.

b. Immune-mediated causes of HA
(1) NI
(a) Patient profile. NI does not occur without human intervention in cattle, sheep, or goats. There is no breed or sex predisposition.
(b) Clinical findings. Clinical signs usually develop within 24–36 hours postpartum. Sudden loss of appetite and weakness are responsible. Death usually occurs within 24 hours. The animal may show anemia, tachycardia, and rapid or shallow breathing, which progresses to labored breathing.
(c) Etiology. This immune-mediated hemolytic crisis in neonates is associated with the ingestion of colostrum containing antibodies to the neonates' erythrocytes.
(d) Pathogenesis. Blood transfusion or the administration of whole erythrocyte vaccines (such as those against anaplasmosis and babesiosis) to breeding females may sensitize the dam to certain blood groups, most commonly in the A and F systems. If the blood types of the sire and offspring contain these antigens and the dam has produced alloantibodies against them, an immune-mediated hemolytic crisis may appear in the calf associated with successful passive transfer.
(e) Diagnostic plan and laboratory tests
(i) Clinical pathology reveals a low PCV, hypoprothrombinemia, and high (conjugated) bilirubin. In sheep, NI may be more of an extravascular hemolysis.
(ii) A direct Coombs' test should be performed.
(iii) Therapeutic plan. Treatment consists of blood transfusions or intravenous fluids.

(2) Bovine colostrum fed to sheep
(a) Patient profile. Disease is usually seen in lambs between the ages of 7 and 21 days that are fed bovine colostrum. No sex or breed predisposition has been reported.
(b) Clinical findings. Clinical signs include a sudden loss of appetite and weakness, without evidence of icterus or hemoglobinuria. Death may occur in less than 24 hours.
(c) Etiology. Immune-mediated destruction of sheep RBCs may occur because of antibodies directed against sheep blood group antigens, which are present in bovine colostrum.
(d) Pathogenesis. The presence of antibodies to sheep blood group antigens in bovine colostrum is a common occurrence. These antibodies are called "heterophile antibodies" and result from the production of antibodies to common cross-reactive antigens that are present on the surfaces of bacteria and protozoa. When bovine colostrum is fed to lambs, these antibodies bind to sheep RBCs and lead to extravascular destruction.
(e) Diagnostic plan and laboratory tests
(i) A direct Coombs' test with anti-sheep immunoglobulin and anti-bovine immunoglobulin may demonstrate immunoglobulin on the surface of RBCs.
(ii) Direct immunofluorescence may also demonstrate antibodies.
(iii) Clinical pathology reveals anemia, hypoprothrombinemia, icteric plasma, and hyperbilirubinemia (73% unconjugated). Hemoglobinemia or hemoglobinuria are usually not seen.
(f) Therapeutic plan. Whole blood transfusions or intravenous fluids may be necessary.

c. Toxic causes of HA
(1) Brassica species plants (e.g., kale, canola)
(a) Patient profile. Cattle appear to be more sensitive to Brassica plants than horses or small ruminants.
(b) Clinical findings. The severity of clinical signs relates to the duration and
dose of feeding the toxin. Because oxidant damage to erythrocytes usu-
ally results in extravascular hemolysis, only cows with a concomitant dis-
ease, which increases erythroctye fragility (postpartum hemoglobin-
uria), should have intravascular hemolysis and hemoglobinuria.

(i) Most affected animals exhibit pallor, weakness, decreased milk pro-
duction, dark urine, and mild to moderate icterus.

(ii) Neurologic signs and pulmonary emphysema are seen occasionally in
 cattle fed Brassica plants, but the mechanism is unknown.

(c) Etiology and pathogenesis

(i) The toxin content of Brassica plants increases as these plants mature
but is destroyed by heating or ensilage. Feeding these plants worsens
the hemolytic crisis seen with postpartum hemoglobinuria. [see I]

(ii) Brassica plants contain S-methyl cysteine sulfoxide, which is metabo-
lized by rumen bacteria to dimethyl disulfide. This toxin decreases
the activity of glutathione within erythrocytes, allowing disulfide
bonds to form between hemoglobin chains, resulting in Heinz body
formation. As erythrocytes containing Heinz bodies are removed by
the reticuloendothelial system, anemia develops.

(d) Diagnostic plan and laboratory tests. Feeding history, clinical signs, and
the identification of Heinz-body anemia are critical to making a diagno-
sis. Dimethyl disulfide concentration in blood or rumen fluid can be mea-
sured using gas chromatography.

(e) Therapeutic plan. The removal of animals from the feed and blood trans-
fusions for severely affected animals are the only treatments.

(2) Onion

(a) Patient profile and history. Cattle appear to be more sensitive to onions
than other farm animals. History of exposure to onions is important in es-
tablishing a diagnosis.

(b) Clinical findings. Affected animals can develop clinical signs within 1
week of being fed an all-onion diet.

(c) Pathogenesis. The toxic principle of onions is n-propyl disulfide, which
causes Heinz-body anemia by the same mechanism as Brassica plants
[see I D 2 c (1)]. S-methyl cysteine sulfoxide has also been reported to be
found in onions.

(d) Therapeutic plan. Treatment is the same as that for Brassica toxicity. [see I]

(e) Prevention. Clinical disease can be prevented by mixing onions with
other feedstuffs so that onions compose less than 25% of the dry matter
of the ration. However, cattle fed as little as 5% onions have laboratory
evidence of HA.

(3) Copper

(a) Clinical findings. Severely affected animals have icterus, hemoglobinuria,
weakness, and thin, watery blood. Vomiting and sudden death may also
be observed. If mucous membranes are not severely jaundiced, pallor
may be seen.

(b) Etiology and pathogenesis. Ingestion or injection of a toxic dose of cop-
p per can precipitate an acute episode of intravascular hemolysis. A similar
syndrome is seen in animals that are chronically overfed copper. It is
thought in this latter circumstance that hepatic saturation or another
stress leads to the massive release of liver copper stores into the blood.

(c) Diagnostic plan and laboratory tests. Feeding or treatment history and
clinical signs are strongly suggestive of this disease. For confirmation, cop-
per concentrations in blood, liver, and feed can be determined.

(d) Therapeutic plan. Except for supportive care, most treatments for copper
toxicosis are experimental.

(4) Nitrate and nitrite toxicosis

(a) Clinical findings

(i) Acute toxicosis. Clinical signs of acute nitrite toxicosis begin within
6 hours of ingestion of toxic feedstuffs. Animals display signs compatible
with severe anoxia, including weakness, depression, cyanosis,
and tachycardia. Animals die if 60%–75% of hemoglobin is oxi-
dized to methemoglobin (this usually occurs within 24 hours of inges-
tion). Gastrointestinal signs include salivation, diarrhea, and
vomiting.

(ii) Chronic toxicosis has been blamed for abortion and an increased vi-
tamin A requirement.

(b) Etiology. Cereal crops, Astragalus plants, other plants, and deep water
wells may accumulate nitrate, particularly in areas where nitrogenous fer-
tilizers are used heavily.

(c) Pathogenesis. Nitrate is reduced to nitrite in the rumen. Heat may also re-
duce nitrate, so that hay stacked in strong sunlight or heat-prepared feed-
stuffs may contain nitrates and cause toxicosis in nonruminants. Absorbed
nitrite oxidizes hemoglobin to methemoglobin and causes mild vasodila-
tion. These effects result in tissue anoxia and hemolysis. Nitrates also
are known to bind to hemoglobin to form Heinz bodies.

(d) Diagnostic plan and laboratory tests

(i) Clinical findings, history of exposure to nitrate-accumulating plants,
and inspection of blood for methemoglobinemia are strongly sugges-
tive of the disease.

(ii) A diphenylamine test can be performed on blood, urine, or feed (the
inside of the plant stalk or rod is best) to detect toxic nitrate levels.
Tests on animal tissue must be performed quickly because nitrite is not
converted to other compounds.

(e) Therapeutic plan. Methylene blue (1% solution) can be given to reduce
methemoglobin to hemoglobin. A single treatment (1–2 mg/kg of body
weight given intravenously) is usually sufficient in nonruminants, whereas
higher doses (up to 20 mg/kg) and repeated dosing (every 8 hours)
may be necessary in ruminants that have ingested large quantities of nitrates.

d. Other causes of HA

(1) Water intoxication

(a) Clinical findings. This is primarily a neurologic disease. Affected animals
show apparent blindness; a staggering gait, dullness, and head pressing.
Severely affected animals often have seizures and become comatose. He-
moglobinuria is seen in some cases.

(b) Etiology. Water intoxication occurs when free access to water is allowed
after a period of deprivation. The condition is more severe if the animal
has become dehydrated or is fed a high-sodium diet.

(c) Pathogenesis. With water deprivation, there is a gradual increase in the
plasma sodium concentration due to insensitive water loss and an inabil-
ity to excrete excess ingested salt. There is also a gradual increase in the
sodium concentration in the brain and cerebrospinal fluid (CSF), although
this occurs slowly because of the relative impermeability of the
blood–brain barrier to sodium. When the animal is re-exposed to water,
a rapid drop in plasma osmolality can cause osmotic lysis of RBCs and
rapid transfer of free water into the brain. These result in intravascular
hemolysis and cerebral edema, which lead to hemoglobinuria and neuro-
logic signs, respectively.

(d) Diagnostic plan and laboratory tests. Information concerning diet and ac-
cess to water helps confirm a diagnosis of water intoxication. Hemoglobin-
uria and the detection of a substantially higher CSF sodium concentra-
tion are also of diagnostic value. (There is usually a 10 mEq/L difference
between the CSF sodium concentration and the plasma sodium concen-
tration.)

(e) Therapeutic plan

(i) Treatment of comatose and seizing animals is rarely successful.

(ii) In less severely affected animals, the goal is to normalize the plasma
and CSF sodium concentrations without causing rapid shifts in
...
water. This can be accomplished through limited access to free water and slow administration of intravenous fluids. Fluids containing sodium concentrations close to that in normal plasma are preferable to 0.45% sodium chloride solutions. Administration of full-strength solutions is less likely to cause pathologic rapid decreases in plasma osmolality.

(2) Postparturient hemoglobinuria

(a) Patient profile. Cattle in the first 6 weeks of lactation are most susceptible. Herd outbreaks can occur, although the disease usually affects single cows.

(b) Clinical findings. Affected cattle have red urine, pale mucous membranes, absent scleral vessels, tachycardia, tachypnea, weakness, and decreased milk production. Clinical signs last several days, and icterus may be seen toward the end of the disease course. Tissue anoxia or renal damage can cause death.

(c) Etiology and pathogenesis

(i) Etiology. The cause of this disorder is unknown and may differ in different parts of the world.

(ii) Pathogenesis. Increased erythrocyte fragility in postpartum dairy cows leads to intravascular hemolysis, anemia, and hemoglobinuria. In North America, hypophosphatemia is thought to impair function of the Na+/K+ pump, causing erythrocyte lysis. In New Zealand, hypophosphatemia is thought to make erythrocytes more sensitive to the hemolyzing activity of oxidant-containing plants.

(d) Diagnostic plan and laboratory tests. Clinical findings aid in the diagnosis. Laboratory tests can be used to confirm hemoglobinuria and to investigate underlying mineral deficiencies.

(e) Therapeutic plan

(i) Blood transfusion. Severely affected animals should be transfused with fresh whole blood.

(ii) Fluids. If blood is unavailable, crystalloid fluids can be used to increase cardiac output and protect the kidneys against the toxic effects of hemoglobin.

(iii) Phosphorus or copper supplements can be administered, if indicated, and efforts should be made to avoid feeding oxidant-containing plants.

(f) Inherited congenital porphyria

(a) Clinical findings. Plasma and urine from affected animals are red or reddish brown. Photosensitization of unpigmented skin occurs in cattle exposed to direct sunlight. Teeth and bones may have a pink or brown discoloration and fluoresce red on exposure to ultraviolet (UV) light.

(b) Etiology and pathogenesis. Congenital porphyria appears to be an autosomal recessive defect of cattle. Similar diseases in people are caused by the insufficient activity of an enzyme in the pathway of heme synthesis. As a result, hemoglobin synthesis and RBC maturation are impaired, and porphyrins accumulate in body fluids and tissues. Anemia results both from impaired erythropoiesis and hemolysis. Porphyrin pigments are red or brown and act as photosensitizing agents.

(c) Diagnostic plan and laboratory tests. Clinical features are strongly suggestive of this disease.

(i) Histopathologic examination of bones and teeth reveals large amounts of porphyrin pigments. Porphyrin pigments may be identified in urine by spectroscopic examination.

(ii) Anemia is usually characterized by macrocytosis and anemia resembling iron deficiency anemia. Cobalt deficiency may be associated with fatal reactions.

(d) Therapeutic plan. Affected cattle should be shielded from direct sunlight. There is no other specific treatment.

3. Eperythrozoonosis of swine

a. Clinical findings. During the acute reaction, affected pigs are febrile and have a rapidly decreasing PCV.
(a) Etiology. Inadequate dietary cobalt results in inadequate ruminal vitamin B₁₂ production in ruminants. Horses require preformed vitamin B₁₂ in their diets.

(b) Pathogenesis. Vitamin B₁₂ is necessary in all large animal species for folate metabolism and is necessary in ruminants for gluconeogenesis from propionate. Deficient folate metabolism leads to impaired erythrocyte maturation.

(3) Diagnostic plan and laboratory tests. Diagnosis of cobalt deficiency can be established by measurement of vitamin B₁₂ concentrations in serum or liver tissue.

(4) Therapeutic plan. Supplemental vitamin B₁₂ can be given parenterally, or cobalt can be added to the diet.

2. Anemia of chronic disease

a. Overview. In addition to the effects of chronic disease, dysfunction of specific organs can lead to nonregenerative anemia.

(1) Cut function is necessary for the absorption of essential nutrients.

(2) Liver function is necessary for the proper distribution of nutrients.

(3) Liver and kidney function together are necessary for the adequate production of erythropoietin, the major stimulus for erythropoiesis.

b. Therapeutic plan

(1) Treatment efforts are usually directed toward the primary disease.

(2) Recombinant erythropoietin therapy may prove to be of some value in treating depression anemia in large animals.

3. Anemia secondary to organ dysfunction

a. Overview. In addition to the effects of chronic disease, dysfunction of specific organs can lead to nonregenerative anemia.

(1) The most common cause of loss of stem cell populations is crowding out through the proliferation of a neoplastic cell line. In all large animals, the most common neoplasm associated with marrow destruction is lymphoma.

(2) Suppression of stem cell hyperplasia, aplastic anemia, is most commonly an idiopathic reaction to a drug or toxin. Nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., phenylbutazone), synthetic estrogens, and bracken fern toxicity (in cattle) have been associated with aplastic anemia.

c. Diagnostic plan and laboratory tests

(1) Blood work. Anemias caused by suppression or replacement of bone marrow are usually normocytic and normochromic, with minimal evidence of a regenerative response.

(2) Cytologic examination of bone marrow. Because animals affected by these processes frequently have a chronic disease, differentiation between anemia secondary to bone marrow dysfunction or dysplasia and anemia of chronic disease is difficult and best achieved by cytologic evaluation of bone marrow.

(a) With anemia of chronic disease, the bone marrow contains numerous stem cells and frequently contains large iron stores, although evidence of active hyperplasia and maturation is less than expected.

(b) With anemia caused by crowding out of the marrow, stem cell lines are present in small numbers and another neoplastic cell line is also present.

(c) With suppression of bone marrow, stem cells are present, but evidence of hyperplasia and maturation is minimal.

d. Therapeutic plan

(1) When marrow suppression is suspected to be caused by a drug or toxin, the animal should be removed from the source of that drug or toxin.

(2) If marrow cells have been crowded out by neoplastic cells, chemotherapeutic agents may be administered to treat the neoplastic process.

(3) There are currently no specific therapeutic agents licensed for use in stimulating marrow hyperplasia in large animals. If nonerythroid cell lines [white blood cells (WBCs), platelets] are affected, fresh plasma or whole blood administration and prophylactic antibiotic administration may be beneficial.

(4) Treatments used in humans and small animals, including marrow transplants and administration of synthetic hormonal stimuli for marrow activity (colony stimulating factors) are currently impractical for use in large animals, but may be available in the future.

---

Hematopoietic and Hemolytic Disorders

1. Vasculitis

a. Equine purpura hemorrhagica (EPH)

(1) History. Typically horses with EPH have a history of respiratory infection 2–4 weeks before the onset of clinical signs. Respiratory infections may be caused by Streptococcus equi, Streptococcus zooepidemicus, or equine influenza virus.

(2) Clinical finding. This condition is characterized by fever and edema, primarily of the limbs and sometimes the head, ventral abdomen, thorax, and prepuce. Occasionally, horses are depressed. Lymphadenopathy may be found.

(3) Isolation of a respiratory pathogen from the upper respiratory tract or pharyngeal lymph node is supportive of a diagnosis.

b. Leukocytoclastic vasculitis

(1) History. Leukocytoclastic vasculitis is common in humans and small animals. Leukocytoclastic vasculitis is an immunologic vascular disease characterized by IgG and IgM deposition in vessel walls, with subsequent complement activation and chemotaxicant production. Infiltrating inflammatory cells release proteolytic enzymes that cause vessel-wall necrosis, with subsequent edema, hemorrhage, and infarction of supplied tissues.

(5) Death may occur.

(6) Therapeutic plan: Treatment is directed at removing the antigenic stimulus, reducing the immune response, reducing vessel wall inflammation, and providing supportive care.
(a) Edema can be minimized by hydrotherapy, the application of pressure wraps, and the administration of diuretics.
   (i) NSAIDs may reduce inflammation and provide analgesia.
   (ii) High doses of dexamethasone may be required initially.
   (iii) Antimicrobial therapy may reduce the incidence or severity of cellulitis and other septic sequelae.
   (iv) Intravenous fluids may be required to prevent dehydration.
(b) Isolation. Affected horses should be isolated for 4–5 weeks or until there are three negative nasal swab cultures.
(c) Prevention. There is no means of prevention other than avoiding exposure of previously sensitized horses to antigens such as S. equi.

Chapter b. Equine viral arteritis (EVA)

(1) Patient profile. The host range of EVA is restricted to equids. The disease is widely distributed in horse populations throughout the world. EVA infection is endemic in Standardbreds, although there does not appear to be any difference in susceptibility to infection between the Standardbred horses and other breeds.

(2) Clinical findings
   (a) Subclinical infections with EVA are very common, particularly in mares that are bred to carrier stallions. No carrier state has been demonstrated in the mare. Abortion with no other clinical signs can occur between 3 and 10 months’ gestation.
   (b) Clinical signs may include pyrexia (up to 41°C) that can last 2–9 days, depression, anorexia, lethargy, and edema (particularly of the hind limbs), stiffness of gait, nasal and lacrimal discharges, conjunctivitis, periarterial edema, and ventral edema involving the scrotum, prepuce, or mammary gland.

(3) Etiology. The causative agent is a non-arthropod-borne group of togaviruses in the genus Arterivirus. Only one major serotype of the virus has been recognized.

(4) Pathogenesis. Exposure to EVA may result in the development of clinical or inapparent infection, depending on the strain of virus involved, size of the virus challenge, the age and physical condition of affected animals, and environmental contamination. Except for the potential of abortion, mortality does not occur following infection with naturally occurring strains of EVA.
   (a) Transmission
      (i) Inhalation of infectious aerosolized particles is the primary means of transmission during outbreaks.
      (ii) Veneeral infection of a long-term carrier stallion represents the primary means whereby EVA is maintained in horse populations. Veneeral transmission to a susceptible mare can trigger an outbreak of the disease.
      (iii) Rarely, transplacental transmissions of EVA can occur when a pregnant mare is exposed to the virus during gestation. If infection occurs during late gestation, the fetus can acquire the infection. Infected foals are aborted after developing rapidly progressive fulminating interstitial pneumonia and a fibrinonecrotic enteritis.
   (b) Viral growth. Initial multiplication of the virus occurs in bronchial macrophages in the lung. Within 48 hours of infection, EVA disseminates to regional lymph nodes, and by the third day, viremia develops.
   (c) Disease progression. Characteristic vascular lesions first appear in the pulmonary blood vessels and later in the small arteries and veins throughout the body. The virus localizes in some epithelial sites, particularly the adrenal gland, seminiferous tubules, thyroid gland, and liver. The virus can persist in the reproductive tract long after it is no longer detectable in most body fluids.

(5) Diagnostic plan and laboratory tests. Both clinical and inapparent EVA infections often go undiagnosed due to limitations in available diagnostic capability and because the disease can be readily confused with other clinically similar respiratory diseases of horses.
   (a) Acute EVA. Confirmation of a diagnosis of acute EVA is based on viral isolation, corroborative serologic data, or both.
      (i) Serologic tests. Acute and convalescent sera samples should be taken 21–28 days apart. A fourfold rise in antibody titers is suggestive of an acute infection.
      (ii) Viral isolation can be done on nasopharyngeal swabs or washings, conjunctival swabs, and citrated, ethylenediamine tetraacetic acid (EDTA), or heparinized blood samples. Virus isolation can be attempted from placental and fetal fluids, placenta, lymphoreticular organs, lung, and other tissues.
   (b) Identifying carrier stallions can be done by serologic testing. Horses testing positive at a serum dilution of 1:4 or greater should be considered potential carriers of the virus. Isolation of the virus can be attempted from a semen sample. The virus is usually found in the sperm-rich fraction of the ejaculate.

(6) Therapeutic plan
   (a) There is no specific treatment for horses infected with EVA. Spontaneous recovery usually occurs within 4 weeks.
   (b) Symptomatic therapy, including rest, diuretics, and NSAIDs, may be helpful to counteract edema and pyrexia.

(7) Prevention
   (a) Vaccination. A modified-live vaccine appears to be safe and effective for stallions and nonpregnant mares. This vaccine is not recommended for pregnant mares or foals younger than 6 weeks of age.
      (i) Protection after vaccination lasts for at least 1–3 years. However, it does not prevent reinfection and limited replication of the challenge virus.
      (ii) Vaccinated horses cannot be distinguished from infected horses by serologic tests and, therefore, cannot be transported when a negative titer is required.
   (b) Isolation. In order to reduce the chances of introducing EVA into a group of susceptible horses, all horses returning from other farms, sales, or racetracks should be isolated for 3–4 weeks. In the event of an outbreak of EVA, the movement of breeding stock should be restricted. Selective vaccination may help curtail the spread of disease.
   (c) Control programs. Kentucky and New York are the only states that have formulated preventative and control programs for their respective Thoroughbred breeding industries.

(7) Hematopoietic and Hemolymphatic Disorders

(8) Equine ehrlichiosis (ehrlichiosis)

(1) Patient profile. There appears to be a seasonal incidence of infection, with most cases occurring during the fall, winter, and early spring.

(2) Clinical findings. Clinical signs vary according to the age of the affected horses.
   (a) In horses younger than 1 year old, fever may be the only sign.
   (b) In horses ages 1–3 years may develop fever, depression, limb edema, and ataxia.
   (c) Horses older than 3 years often are most severely affected. Clinical signs include anorexia, depression, severe limb edema, fever, mucosal petechial hemorrhages, and restricted movement.

(3) Etiology and pathogenesis
   (a) Etiology. The causative agent is Ehrlichia equi, a rickettsial organism.
   (b) Pathogenesis
      (i) The mode of transmission is unknown, but, in most cases, affected horses have been exposed to or infected with ticks.
Inherited coagulative disorders

a. Pathogenesis. All inherited clotting factor deficiencies affect the intrinsic pathway and, therefore, prolong the activated partial thromboplastin time (APTT) but not the prothrombin time (PT).

b. Therapeutic plan. Except for periodic transfusion with fresh plasma, specific treatments are not available.

c. Specific conditions

(1) Deficiencies in factors VIII, IX, XI, and prekallikrein have been described in horses.

(a) Factor VIII deficiency (hemophilia A) is sex-linked and recessive.

(b) Inheritance patterns for the other deficiencies are not known.

(2) Factor XI deficiency has been described in Holstein cows and is thought to have an autosomal recessive pattern of inheritance.

(3) Factor XII deficiency causes only slight bleeding tendencies.

Acquired coagulative disorders are usually related to a lack of production, consumption, or inhibition of clotting factors. Because multiple factors are affected, both the intrinsic and extrinsic pathways are impaired.

a. Inhibition of vitamin K-dependent factors

(1) Vitamin K reacts with the gamma-carboxyl group of factors II, VII, IX, and X to form a vitamin K-dependent carboxylase.

b. Clinical findings. The presence of vitamin K deficiency results in decreased clotting factors II, VII, IX, and X. Laboratory testing of factors II, VII, IX, and X confirms the diagnosis. Consistent with this, any laboratory testing abnormalities suggest the need for vitamin K repletion.

(ii) Pathogenesis. Vitamin K is synthesized by the normal gut bacteria and is therefore present in normally fed animals. If the animal is not consuming enough vitamin K or if the gut bacteria are not producing it, the animal will develop vitamin K deficiency.

(iii) Therapeutic plan. The treatment of vitamin K deficiency is to administer vitamin K1. The dosage needed is 4 mg/kg orally or IV, repeated every 3 to 4 hours, until clotting factor activity returns to normal. The dosage is individualized based on response to therapy.

Abnormal hemorrage from large vessels

1. Overview. This disorder almost always reflects a defect in the coagulation cascade and is, therefore, independent of platelet function. However, platelet dysfunction can be present and may contribute to bleeding tendencies.

a. Clinical findings. Clotting deficiencies can result in excessive bleeding after trauma or surgery, as well as from thracic cavities, hematemesis, hemothorax, hemopericardium, hemarthrosis, or bleeding from epithelial surfaces.

b. Etiology. Coagulopathies can be inherited or acquired. Acquired coagulopathies can result from toxins, infections, trauma, or neoplasms.
(2) Warfarin toxicosis
   (a) Patient profile. Pigs appear to be the most susceptible farm animal species because of their small size and eating behavior.
   (b) Clinical findings. Overt hemorrhage and rapid death may occur with massive dosages. Chronic exposure to smaller dosages causes a similar syndrome to moldy sweet clover.
   (c) Pathogenesis. Warfarin is related to dicumarol and also induces hypocoagulability by preventing the synthesis of the vitamin K-dependent clotting factors. Warfarin and related compounds are used as rodenticides.
   (d) Prevention. The source of the toxin should be determined to prevent subsequent exposure.

b. DIC is a disorder that may be characterized by widespread thrombosis, bleeding tendencies, or both.
   (1) Clinical findings. The most notable signs usually are referable to the primary disorder that triggers DIC.
      (a) Organ thrombosis may contribute to morbidity and mortality. Clinical signs of thrombosis include weakness, colic, oliguria, and neurologic defects.
      (b) Bleeding tendencies (coagulopathy) rarely result in overt hemorrhage but may result in mucosal petechiation, melena, renal hemorrhage, and prolonged bleeding from venipuncture sites.
   (2) Pathogenesis. The exact mechanism of DIC has not been described and may vary from case to case. It is generally accepted that a triggering insult leads to diffuse activation of the coagulation cascade. Triggering insults include:
      (a) Septis
      (b) Neoplasia
      (c) Vasculitis
      (d) Ischemia
   (3) Laboratory tests. Because DIC can be characterized by either hypercoagulation or hypocoagulation, tests of clotting function may be normal or abnormal. However, the finding of thrombocytopenia and prolonged clotting times is suggestive of DIC, as are findings of low plasma fibrinogen.
   (4) Diagnostic plan and laboratory tests. Because DIC can be characterized by either hypercoagulation or hypocoagulation, tests of clotting function may be normal or abnormal. However, the finding of thrombocytopenia and prolonged clotting times is suggestive of DIC, as are findings of low plasma antithrombin III concentrations with concurrent high fibrin degradation product concentrations.
   (5) Therapeutic plan. Many treatments have been proposed for DIC, but most have not been evaluated critically. Treatment of the primary disorder is essential.
      (a) Intravenous fluids help maintain organ perfusion and may decrease susceptibility to thrombosis.
      (b) Corticosteroids and heparin may be contraindicated because of their unpredictable effects on coagulation. Low doses of NSAIDs may be helpful in some cases when endothotoxin is thought to be an inciting factor for DIC.
      (c) Treatment is generally unsuccessful if there is evidence of a hypocoagulable state.
   c. Suppression. A lack of production of clotting factors is most common with severe chronic hepatic disease. Because factor VII has the shortest half-life, deficits in the extrinsic pathway are seen before there is overt hemorrhage. Animals with severe hepatic disease will have reduced blood coagulability, as measured by clotting assays and reduced plasma concentrations of most clotting factors, including fibrinogen. Coagulopathy is only one of many clinical signs seen in animals with severe chronic liver disease (see Chapter 5).
lymphadenopathy, signs of heart failure, exophthalmos, reproductive failure, anemia, and posterior paresis.

(d) Death usually occurs within 30 days of the onset of clinical signs.

(3) Etiology and pathogenesis
(a) Etiology. Bovine enzootic or adult lymphoma is caused by BLV, an oncogenic retrovirus.
(b) Pathogenesis. The virus infects and replicates in B cells and appears to be spread by the introduction of infected lymphocytes into a susceptible host. Repeated use of blood-contaminated equipment, including dehorning tools, hypodermic needles, and rectal sleeves, appears to be the major cause of transmission, although the virus can also spread transplacentally and possibly through biting flies and infected semen or milk.

(4) Diagnostic plan and laboratory tests. Because enzootic lymphoma is the most common internal neoplasm in cattle, finding a tissue mass in one or more of the above organs is strongly suggestive of this disease.
(a) Histopathology can confirm the diagnosis.
(b) Serologic tests, most commonly the AGID test, can be used to confirm BLV infection, but it must be remembered that most infected animals do not develop clinical disease. False-positive tests can occur in calves due to colostral antibody, and false-negative tests can occur in recently infected cattle and in periparturient cows.

(5) Differential diagnoses. Approximately 10% of cattle with lymphoma have lymphoid leukemia, which can be differentiated from persistent lymphosarcoma by the presence of immature cells.

(6) Therapeutic plan. Treatment is rarely attempted.

(7) Prevention of disease through reduced exposure to contaminated body fluids (sanitation of equipment) is vital. Serologic tests can be used to identify infected cattle for removal from the herd.

2. Equine lymphosarcoma. There are four different forms of equine lymphoma, with each form characterized by the accumulation of abnormal lymphocytes in a different location.

(a) Multicentric or generalized. Multiple internal organs and lymph nodes are affected, causing depression, weight loss, and anorexia. This is the most commonly reported form of lymphosarcoma in mature horses, but it can occur in horses of any age.

(b) Intestinal. Masses are most common in the bowel wall and abdominal lymph nodes without peripheral lymphadenopathy. This is the most commonly reported form in juvenile or young adult horses. Affected horses develop generalized ill-thrift due to nutrient malabsorption and protein-losing enteropathy.

(c) Mediastinal or thymic. Masses form in the cranial mediastinum and retropharyngeal lymph nodes, causing tachypnea, pleural effusions, and respiratory distress.

(d) Cutaneous. This may be the most common form of equine lymphoma, although it is not frequently reported. Affected horses develop multiple subcutaneous or dermal nodules of varying sizes. Spontaneous enlargement, regression, and growth are common. Nonaggressive forms can be present for years without morbidity, whereas aggressive forms lead to lymphadenopathy, internal metastasis, and death.

(b) Etiology. There does not appear to be an infectious etiology.
(c) Diagnostic plan and laboratory tests
(1) Biopsy. Diagnosis of any form of lymphoma is best made by histopathologic examination of a biopsy sample taken from a mass. Aspirates from masses are not as reliable. Masses can be found by external or rectal palpation or by thoracic radiographic examination.
(2) Abnormal lymphocytes also may be seen occasionally on examination of peripheral blood or thoracic or abdominal fluid.
IV. IMMUNE DEFICIENCY SYNDROMES

Immune deficiency syndromes of horses

1. Failure of passive transfer (FPT) is discussed in Chapter 18 IV.

2. Combined immune deficiency syndrome (CID)
   a. Patient profile. CID usually affects Arabian foals during the first few months of life as the maternal antibody wanes. As many as 25% of Arabian horses may be CID carriers.
   b. Clinical findings are associated with several diseases.
      (1) Infectious diseases. Chronic or recurrent pneumonia, enteritis, and sepsis are the most common infectious diseases associated with CID. These diseases can be caused by organisms not normally considered pathogenic.
      (2) Affected animals usually have persistent lymphopenia (less than 1000 cells/μL) and hypoglobulinemia, but CID also can be seen with other acute inflammatory conditions.
   c. Etiology and pathogenesis. CID is an autosomal recessive immunodeficiency of Arabian foals. The genetic defect has not been identified; affected foals appear to have a defect in stem cell maturation to both B and T cells.
   d. Diagnostic plan and laboratory tests. Because the parents of an affected foal are both carriers of the trait, care must be taken in establishing this diagnosis. Foals with CID have four characteristic findings:
      (1) Persistent lymphopenia
      (2) Absence of serum IgM either at birth before drinking colostrum or after 3 weeks of age (when the maternal antibody has been metabolized)
      (3) Absence of germinal centers and perivascular lymphoid sheaths in lymphoid tissue

3. Transient hypogammaglobulinemia
   a. Patient profile. Foals are most vulnerable in the first 3 months of life.
   b. Clinical findings. Chronic or recurrent infectious disorders are characteristic.
   c. Etiology and pathogenesis. There are few reports of this disorder, and it may often go unrecognized. When this disorder does occur, neonatal immunoglobulin synthesis does not begin early enough to replace metabolized colostral antibody. This immunodeficiency spontaneously resolves as the foal's antibody synthesis increases with time.
   d. Diagnostic plan and laboratory tests. Hypogammaglobulinemia with low concentrations of other classes of immunoglobulins is characteristic. Histopathologic examination of lymphoid tissue and lymphocyte function assays are normal.
   e. Therapeutic plan. Symptomatic treatment of infections is indicated. Immunoglobulin synthesis increases with time, making foals less susceptible to repeated infections.

4. Agammaglobulinemia
   a. Patient profile. This disease has only been reported in male Thoroughbred and Standardbred foals.
   b. Clinical findings. Chronic and recurrent infections are common.
   c. Etiology. A suspected defect in B-cell maturation leads to an absence of B cells and antibody production. Cell-mediated immunity is normal. That the disease only seems to occur in male Thoroughbred and Standardbred foals suggests X-linked inheritance.
   d. Diagnostic plan and laboratory tests. Although affected horses have normal blood lymphocyte counts, labeling demonstrates a lack of B cells. All classes of immunoglobulin are absent or found in very low concentrations. Tests of T-cell function are normal.
   e. Therapeutic plan. Symptomatic treatment of infections may be attempted. Affected horses may live for several years, whereas most other horses with congenital immunodeficiencies die as foals.

5. Selective IgM deficiency
   a. Patient profile and history. Animals of any age may be affected, but cases often occur in one of three groups of horses:
      (1) Foals that show signs similar to CID and die in the first year of life
      (2) Juveniles that show signs similar to agammaglobulinemia and die before adulthood
      (3) Adult horses, many of which have or develop lymphoproliferative disorders
   b. Clinical findings. Affected horses show signs of poor growth and chronic or remittent infection.
   c. Etiology. The cause of the disease is unknown. Some forms may be hereditary, but this has not been determined.
   d. Diagnostic plan and laboratory tests. Affected horses have persistently low serum IgM concentrations, with normal to high concentrations of other immunoglobulins. In most affected horses, lymphocyte function tests and lymphoid tissue histopathology are normal. Older horses should be examined for lymphosarcoma.
   e. Therapeutic plan. Symptomatic treatment of infection can be attempted, but most affected animals die within 1 year.

B. Immune deficiency syndromes of ruminants

1. FPT is discussed in Chapter 18 IV.

2. Bovine leukocyte adhesion deficiency (BLAD)
   a. Clinical findings
Chapter 3. Immunodeficiency induced by viral agents.

4. Etiology and pathogenesis. BLAD is an autosomal recessive immunodeficiency of Holstein calves. A point mutation in the CD18 gene leads to a defect in the Mac-1 surface glycoprotein, a B2 integrin, causing impaired leukocyte adhesion and migration in homozygotes.

b. Clinical findings. Affected animals have a dilute coat color and complete or partial ocular albinism. They suffer from chronic or recurrent pulmonary and gastrointestinal infection and typically grow poorly.

c. Diagnostic plan and laboratory tests. Young Holstein cattle with the mentioned clinical signs and laboratory abnormalities should be suspected as having BLAD. Additionally, histopathologic demonstration of the absence of neutrophilic infiltrates around bacterial foci is supportive. Definitive diagnosis can be made using a polymerase chain reaction test. This test identifies both heterozygous carriers and homozygotes.

d. Therapeutic plan. Most affected calves die within the first year of life. Antimicrobial drugs can be used to treat infections temporarily.

e. Prevention. Bulls used for stud should be tested as potential carriers. Efforts should be made to limit inbreeding.

3. Chediak-Higashi syndrome

a. Clinical findings. Affected animals have a dilute coat color and complete or partial ocular albinism. They suffer from chronic or recurrent pulmonary and gastrointestinal infection and typically grow poorly.

b. Etiology and pathogenesis. Chediak-Higashi syndrome is an autosomal recessive immunodeficiency of Hereford and Brangus calves. The defect leads to fusion and enlargement of granule-containing cells, including granulocytic leukocytes and melanocytes. This causes impaired immune function and abnormal coat color.

c. Diagnostic plan and laboratory tests. In addition to characteristic clinical features and abnormal tests of immune function, granulocytic leukocytes and melanocytes typically contain very large granules.

d. Therapeutic plan. Symptomatic treatment of infections is possible, but most affected animals die within 1 year.

4. Immunodeficiency induced by viral or bacterial infections

a. Clinical findings. Secondary immunodeficiency includes a broad spectrum of possible disease signs caused by the recrudescence of latent infections, as well as new infections. Clinical signs relate to the site and nature of the infection. Typically, secondary infections are recognized as the abrupt worsening in clinical condition. In some cases, the primary infection may be subclinical.

b. Etiology. Many infectious conditions cause secondary immunodeficiency by consuming or sequestering leukocytes, suppressing marrow production, or altering leukocyte function. Bovine viral diarrhea virus and sepsis are just two of many possible etiologies.

c. Diagnostic plan and laboratory tests. Bacteriologic and virologic culture techniques and serologic tests are used to identify both primary and secondary infectious agents.

d. Therapeutic plan. Treatment should be based on the nature and site of the secondary infection. If possible, the primary infection should also be treated.

5. Infestation with which intracellular parasite is LEAST likely to respond to treatment with oxytetracycline?

- Anaplasma marginale
- Babesia bigemina
- Eperythrozoon suis
- Ehrlichia equi
- Eperythrozoon wenyonii

6. Which one of the following statements is NOT typical of the regenerative response to anemia?

- Basophilic stipping in cattle
- Polychromasia in cattle
- Macrocytosis in pigs
- Reticulocytosis in horses
- Marrow erythroid stem cell hyperplasia in horses
1. The answer is 5 (III A 2 a (4)). Cutaneous lymphoma in horses may exist in a nonaggressive form. Affected horses often live for years, while clinical signs wax and wane. In contrast, almost all cattle with lymphoma die within 30 days of the first apparent clinical signs. Spontaneous regression of cutaneous lymphoma in cattle has been reported, but affected animals frequently die of metastatic tumor masses within 6 months.

2. The answer is 2 (III A 1 b (1)). Persistent lymphocytosis is composed of normal, non-neoplastic lymphocytes and is seen in a small subset (30%) of cattle infected with the bovine leukemia virus (BLV). It is an inconsistent finding in cattle with lymphoma. Persistent neutrophilia is the characteristic finding for cattle with the leukocyte adherence deficiency.

3. The answer is 4 (II A 1 b (2), (4)). Equine viral arteritis (EVA) is most commonly spread by aerosol or copulation with a carrier stallion. Insect transmission and immune-mediated hemolysis are characteristics of equine infectious anemia (EIA) but not viral arteritis. Viral arteritis is rarely fatal, and vaccination leads to antibody titers, which may preclude interstate or international transport.

4. The answer is 3 (II D 2 d (1) a, (d)), Water intoxication causes a rapid drop in plasma osmolality and osmotic intravascular hemolysis. Sodium concentration in the cerebrospinal fluid (CSF) is higher than that in the diluted plasma, leading to rapid movement of water into the brain, cerebral edema, and neurologic signs. Rapid administration of intravenous fluids can worsen clinical signs.

5. The answer is 2 (II D 2 a (2)). Oxytetracycline is an effective antibiotic against rickettsial organisms of the genus Anaplasma, Eperythrozoon, and Ehrlichia but is not effective against the protozoan parasite Babesia bigemina. Imidocarb is the most frequently used babesial drug.

6. The answer is 4 (II A 2 d (1)). Horses do not get reticulocytosis. In other large animal species, reticulocytosis, macrocytosis, polychromasia, and basophilic stippling all are seen in the peripheral blood of animals with regenerative anemia. In horses, the most common cause of erythroid stem cell hyperplasia in the bone marrow is often the only way to determine if anemia is regenerative.

7. The answer is 1 (I D 2 a (4)). Leptospirosis is caused by the ingestion or inhalation of organisms. Anthropic transmission is not thought to occur or to be of major importance. Bovine leukemia virus (BLV) is thought to be spread iatrogenically in many cases, but it can be isolated from biting flies. Anthropic transmission is thought to be the major route for Anaplasma, Eperythrozoon, and the equine infectious anemia (EIA) virus.

8. The answer is 8 (IV A 2 d). Combined immunodeficiency syndrome (CID) is caused by a defect in lymphocyte maturation, which leads to lymphopenia, low immunoglobulin production, abnormal function tests, and absence of germinal centers. Lymphadenopathy is not seen.

9. The answer is 3 (III B 2, 5, 6). The most likely diagnosis is caseous lymphadenitis. Efforts should be made to prevent the transmission of organisms to uninfected sheep and to decrease skin trauma. Identification and separation of infected sheep aids in the prevention of new cases. Anthropods are not thought to be important vectors.

10. The answer is 5 (II A 1 a, b). Clinical signs are compatible with vasculitis (as seen with EIA or EVA), immune-mediated anemia and thrombocytopenia, or purpura hemorrhagica. Purpura hemorrhagica can be diagnosed by a skin biopsy and may be exacerbated by exposure to streptococcal antigens.

11. The answer is 4 (II D 2 a (3) a, (b)). Of the important intraerythrocytic parasites, only Eperythrozoon organisms are found free in the plasma.