IMPORTANT TERMS related to Hematopoietic System

Hematopoiesis: Hematopoiesis is the production of blood cells (myeloid cells, erythroid cells, platelets and lymphocytes).

RBC Life Spans (the length of time that RBCs circulate in the blood) vary depending on species and is related to body weight and metabolic rate. The RBC life span in routine domestic species is about **70 days (2 month) in Cats,** to approx **100 days (4 month) in dogs)** to **150 days (6 month) in Horses and Cattle**.. When erythrocytes reach the end of their life span, they are destroyed in a process termed *hemolysis*. n healthy animals, about 1% of RBCs are removed from circulation each day due to normal aging and damage

Neutrophils are produced daily and normally have a **Circulating Lifespan** of <24 hours in humans and 10-11 hours in Horses.

Platelets Life Span: The normal lifespan of platelets in dogs (and presumably other species) is around **5-7 days**.

Anisocytosis: a term that denotes variation in **SIZE** of Erythrocytes (RBC)
Change in size: This includes macrocytes and microcytes

Poikilocytosis: a term that denotes variation in **SHAPE** of Erythrocytes (RBC).
Change in shape: This includes Acanthocytes, Drepanocytes, Eccentrocytes, Echinocytes, Elliptocytes, Keratocytes, Poikilocytes, Pyknocytes, Schistocytes, Spherocytes, Stomatocytes, Target Cells.

Hyperchromasia: a term that INCREASED Intensity of STAINING.
Change in color: This includes hypochromasia, polychromasia, and ghost cells

RBC G*hosts* represent cells that have ruptured in the circulation, losing their hemoglobin. The remaining red blood cell membranes are then seen as “ghosts”. Ghost red blood cells represent red blood cell lysis (Hemolysis).

Basophillic Stippling or Puntate Basophilia: represents the spontaneous aggregation of ribosomal RNA in the cytoplasm of erythrocytes. These aggregates stain, and hence RBCs are visible containing blue-staining granules scattered throughout. Seen in (i) Regenerative Anemia, and (ii) Lead Poisoning

Heinz Bodies: Precipitation of hemoglobin which may then coalesce to form intracellular inclusions known as heinz Bodies. This is due to distortion of the tertiary structure of the hemoglobin molecule, due to oxidation of exposed sulfhydryl groups on hemoglobin (forming of disulfide bonds). It can be seen in Healthy CATS, however Heinz Bodies are found **Oxidant-Induced Hemolytic Anemia**.

Howell Jolly Bodies: (also called micronuclei) are small fragments of non-functional nucleus which were not extruded , when the erythrocyte left the bone marrow. Usually the erythrocyte contains only a single Howell-Jolly body, which appears as a **blue, perfectly round inclusion.** It can be seen in (i) cases of Regenerative Anemia, (ii) Erythroid Dysplasia and (iii) in Healthy Cats & Horses also

Cabot Rings: Cabot rings are **thin, thread like rings - or "figure eight"shaped inclusions in the RBCs, which are probably remnants of microtubules from the mitotic spindle**. Are rare, and their presence indicates a defective erythrocyte production, especially in (i) Pernicious Anemia and (ii) Lead Poisoning

Rouleaux: are **clumps of RBCs that look like stacked plates**. They usually form as a result of abnormal quantities of certain proteins (immunoglobulin, fibrinogen) in the blood. Its a non-specific indication of some underlying Pathology.

Purpura: is accumulation of blood, under the skin due to spontaneous rupture of capillaries.

Porphyrias: are a group of hereditary disorders in which porphyrins accumulate in the body because of defective heme synthesis

Macrocyte:

Spherocytes

Drepanocytes

Left Shift

Band cells

ANAEMIA

DEFINITION:

Anemia – is a condition in which hemoglobin (Hb) concentration and/or red blood cell (RBC) quality / numbers are Lower Than Normal and insufficient to meet an individual's physiological needs. Body does not have enough healthy red blood cells (quality/numbers) to transport enough oxygen to the tissues. So, Anemia *is* also defined as **a decreased Hematocrit (HCT) or Hemoglobin**.

Packed cell volume (PCV), which is readily measured in clinical practice, can be used as a surrogate for hematocrit (a calculated value from the mean cell volume and red blood cell [RBC] count) and hemoglobin concentration.

Strictly speaking, Anaemia is defined as a **reduction in circulating red blood cell mass**.

However, in clinical practice, anaemia is defined by more measurable variables such as:

- Red blood cell (RBC) count
- Haemoglobin (Hb) concentration in blood
- Haematocrit – Cell volume when packed

Clinical Features are dependent on the **absolute degree / severity of Anaemia** & **RATE** of decline in Hb concentration.

Anemia is therefore characterized mainly by (i) Severity, (ii) RBC Indices and (iii) Regenerative Response. This characterization is useful in helping to determine the mechanism and cause of an anemia.

RED CELL INDICES play a vital role in classification of anemia. In well equipped laboratories, these parameters are provided by the automated analyzers. The important red cell indices are as follows:

- ✓ **Mean Corpuscular Volume** or MCV is defined as the **volume of the average red blood cell** expressed in **femtoliters (fl).** It deermines the **Size of RBC**.
- ✓ **Mean Corpuscular Haemoglobin** or MCH is the **average mass of hemoglobin per red cell** expressed in picograms. It is derived based on the hemoglobin and the RBC count.
- ✓ **Mean Corpuscular Haemoglobin Concentration** or MCHC is the measure of the **Concentration of Hemoglobin in a given volume of packed red cells** and is expressed as gram per Liter (g/L). This is a derived value from Hb and PCV (or MCV and RBC). It deermines the **Colour of RBC**.
- ✓ **Red Cell Distribution Width** or RDW is a measure of **variation of red cell size or Anisocytosis**. It can be expressed either as a coefficient of variation (CV) (%) of the RBC volume or as the standard deviation (in **femtoliters fL**).

Anemia causes clinical signs referable to decreased red hemoglobin pigment (e.g., pale mucous membranes), decreased oxygen-carrying capacity (e.g., depression, lethargy, weakness, and exercise tolerance), and decreased blood viscosity (e.g., heart murmur). Hb concentration is commonly used in the assessment of Anaemia. Nowadays, hemoglobin estimation is being correlated to understand the severity of anemias and so many define Anemia as **reduction of Haemoglobin (Hb) less than the lower limit of the reference range for a particular age**. This is being practiced in human medicine. It is important to understand that anaemia is a **manifestation of an underlying problem**, not a diagnosis in itself. Its recognition warrants further investigation to establish the underlying cause.

CLASSIFICATION OF ANAEMIA

Anaemia are classified on the basis of:

I. **Basis of ETIOLOGY**: based on etiology, its classified into 3 categories
   i. DysHemopietic - Due to decreased RBC production-reduction or failure of production (Hematopietic),
   ii. Hemolytic - Increased RBC destruction, and
   iii. Hemorrhagic – due to intra / extra vascular blood loss

II. **Basis of MORPHOLOGICAL** approach, that categorieses based upon the:
   A. Size of RBC [(i) Microcytic, (Ii) Normocytic, and (iii) Macrocytic) and
   B. Amount of Hemoglobin [(i) Hypochromic, (ii) Normochromic, and (iii) Hyperchromic

Particulars	**Amount of Haemoglobin** (in RBCs)	**Size of RBCs**	**Remarks**
Morphological Presentation of ANEMIA	Less Hb- **HYPOCHROMIC**	Smaller size - **MICROCYTIC**	
	normal Hb- **NORMOCHROMIC**	Smaller size - **NORMOCYTIC**	**Nonregenerative Anemia** (too few reticulocytes)
	High Hb- **HYPERCHROMIC**	Larger size - **MACROCYTIC**	

III. Nowadays, classifying anemia as (i) Regenerative or (ii) Nonregenerative is clinically useful because it provides information about the mechanism of disease;

- **Regenerative Anemia** indicates hemorrhage or hemolysis,
- whereas erythroid hypoplasia or aplasia causes **Non-regenerative Anemia**

The hallmark of regenerative anemias, except in horses, is ***Reticulocytosis*** (i.e., increased numbers of circulating reticulocytes [immature erythrocytes]), which is evident as ***polychromasia*** on a routinely stained blood smear. Reticulocytosis indicates **increased bone marrow erythropoiesis** and release of erythrocytes before they are fully mature.

Reticulocytosis is an appropriate marrow response to anemia and **is often seen with hemorrhage or hemolysis**. On a CBC a strong regenerative response may produce an **increased** mean cell volume (MCV) and **decreased** mean cell hemoglobin concentration (MCHC) because reticulocytes are larger in size and have a lower hemoglobin concentration than mature erythrocytes.

If **nucleated RBCs** (nRBCs) are present as part of a regenerative response, they should be in low numbers relative to the numbers of reticulocytes. However, the presence of circulating nRBCs is not in itself definitive evidence of regeneration and may signify **Dyserythropoiesis** (e.g., lead poisoning or bone marrow disease) or Splenic Dysfunction.

HORSES are an exception to this classification scheme because they do not release reticulocytes into circulation. But definitive determination of regeneration in a horse requires demonstration of erythroid hyperplasia via bone marrow examination

TYPES OF ANAEMIA – based on Etiology

DYSHEMOPOIETIC ANEMIA

This group have all those type of Anemia, where there is DEFECT in the Formation / Synthesis of RBCs.

1. **Diminished Stroma Protein Formation**:
    a) Dietary deficiency of *External Factors*: COBALT, Cyanocobalamin-Vit B12; deffciency of Vit B12 seem mostly in Ruminants. It is synthesized by rumin microorganisms, using Cobalt essentially.Vit B12 is essential for synthesis of DNA/RNA in RBCs and its defficincy can cause arrest of maturation of prorubricyte & metamyelocytes. So larger nuclei is seen but Hb synthesis is normal. Macrocytes results and gives rise to **Macrocytic Anemia**.
    b) Dietary deficiency of *FOLIC ACID*: required for maturation (sp. Nuclei) of erythroblasts. As maturtion slows down, gives rise to **Macrocytic Anemia**.
    c) Deficiency of *Intrinsic Factors*: few intrinsic factors released from GIT mucosa help in absorption of Vit B12. Their absence may result, reduced B12 absorption, therby causing Anemia (B12 def-cause **Macrocytic Anemia**)
    d) Failure to *store Erythrocyte Maturation Factor*: certain hematinic/maturation factors like B12 etc are stored in Liver. So Diseases of Liver could lead to failure of its storege, leading to Anemia.
    e) Hypopituitarism: Anterior pituitary has influence over erythropoiesis.

2. **Diminished HEMOGLOBIN Formation**: (Blood picture is Normocytic-Hypochromic converting to **Microcytic**-Hypochromic)
    a) Dietary deficiency of IRON: (i) due to deficient intake (pigs); (ii) Dfective absorption: excessive phosphorus / phytic acids- form insoluble iron complex-that excretes thru feces; (iii) Increased requirements: in young growing animals.; all usually leads to **Microcytic Anemia**
    b) Dietary deficiency of COPPER: .It acts as catalyst in utilization of iron in Hb formation; leads to iron deficiency anemia, causes **Microcytic Anemia**.
    c) Dietary deficiency of ASCORBIC ACID (Vit.C): facilitate reduction of Fe+++ to Fe++ for easy absorption and utilization. Also in folic acid utilization.
    d) Dietary deficiency of PYRIDOXINE: required for utilization of Iron in hemoglobin synthesis.
    e) Dietary deficiency of NICOTINIC ACID: Role in cell respiration, so deficiency affects respiration (oxidative metabolism) in immature RBCs
    f) Dietary deficiency of RIBOFLAVIN: role is synthesis of protein for synthesis of hemoglobin

g) Dietary deficiency of THYROXINE: along with Vit-C, required for conversion of Folic acid to Folinic acid

3. **TOXIC Inhibition**: here Marrow is normal but unable to utilize hematinics; (Blood picture is Normocytic-to- Microcytic; with no regenerative forms)
    a) Chemical Poisons: (i) Nitrogen mustard (is Cytotoxic); (ii) Antimetabolites like 6-mercaptopurines (are folic acid antagonists); (iii) Antibiotics like Suplhonamides, Stretomycin etc; (iv) Toxic Metals like Arsenic, Bismuth etc; (v) Other chemical like hair dyes, insecticides etc
    b) Chronic Interstitial Nephritis: in advanved cases, Uremia occurs which suppresses erythropoietic cells.
    c) Oesophagostomiasis: causes 'pimply gut' disease, reduces absorption and leads to multiple deficiencies; Anemia
    d) Chronic Infections: like TB, Brucellois etc ; few affect Hb synthesis and other lead to defficiency of iron etc
    e) Ionizong Radiations: leads to ealy effects on leupoiesis. Then Thrombocytopenia leads to hemorrhages and damage to vasular endothelium; Anemia follows.

4. **APLASTIC ANEMIA**: occurs due to **Aplasia of Bone marrow**, becoming severly inactive. Anemia picture is **Normochromic** and **Normocytic**. No Regenerative forms are present. It is of two types
    a) Primary or Idiopathic: rare
    b) Secondary:
        i. exhaution due to Chronic Hemorrhages (GiT ulcers, blood sucking worms; neoplasms; defficiencies;
        ii. Toxic: due to ionising radiations, Chemicals poisonings as in toxic inhibiton but for a longer duration & at higher dose
        iii. Metabolic: this form of Aplastic anemia, occurs in baby piglets-born to sows, suffering from protein malnutrition during pregnancy (def of Vit B12, Fe, folic acid etc).

5. **MYELOPHTHISTIC ANEMIA** (Leuco-Erythroblastic Anemia): Here **Replacement of Bone marrow by other tissues takes** place. In such, immature forms granulocytes are seen in peripheral blood. Also k.a. Leuco-Erythroblastic Anemia. It is seen in:-
    a) Secondary metastais of other tumours to Bone marrow (lymphatic leukemia in dogs/cats)
    b) Osteodystrophies : (myeloid tissue replaced by connective tissue)
    c) Primary Tumours of reticulo-endothelial systems: (Nieman-Picks disease)

HEMOLYTIC ANEMIA

In this group, '**intravascular' destruction** of RBCs occurs. Anemia is **Normochromic/Macrocytic** that becomes **Hypochromic/Microcytic** as iron stores are used up/exhausted. Many Regenerative forms are seen. Bone marrow is active, while RBCs show increased fragility and Spherocytosis.

Hemolytic Anemia could lead to clinical outcomes like Jaundice, increased deposition of Hemosiderine crystals; Hemoglobinuria

Hemolyic Anemia is caused by the following:

1. **Abnormal Auto-Antibodies**:
    a) Primary or idopathic
    b) Secondary due to:
        i. Malignant disease : like lymphatic neoplasms, ovarian tumours etc
        ii. Collagen Disease (auto-immune): like dissseminated lupus erythematosis (DLE)
        iii. Viral Diseases: *eg.* infectious mononucleosis

2. **Abnormal Iso-Antibodies**: Due to presence of certain hemolysins in plasma (intravascular hemolysis) that may be due to (i) incompatible blood trasfusion, (ii) injection of blood products; (iii) pregancy- antigen of foetus blood pass to dams (not having similar antigens) – icterus neonatorum

3. **Toxic** (partly also Toxic Dyshemopoietic):
    a) **Chemicals**:
        i. Copper Poisoing : Cu is poorly excreted, so toxicity overloads the liver resulting in hemolysis - jaundice & hemoglobinuria etc (such toxicity can be due to fodder treated with copper containing fungicides; or heavy dose of water containing Copper sulphate; or over licking of Salt-licks containg high CuSO4; etc)
        ii. Onion Poisoning: in cattle & sheep; toxic principle is **n-propyl disulphide**. Symptoms of hemolytic anemia with hemoglobinuria and icterus. Carcass smell like onions.
        iii. Castor Seed Poisoning: '**Ricin**' found in castor seeds causes Hemolysis
        iv. Phenothiazine poisoning (drug sensitivity): in higher doses, it is Hemolytic in Horses causing hemolytic anemia; hemoglobinuria alongside nephritis and hepatitis.
        v. Naphthalenes:
        vi. Lead:
        vii. Hypersensitivity: to certain drugs like sulphanilamides, quinine etc

b) **Post-Parturient Hemoglobinuria** (PPH): also k.a. post-parturient hemoglobinemia. Seen in dairy animals after parturiton and is associated with **Hypo-Phophatemia** (defficiency)

c) **Infections**: like
   i. Protozoa: Anaplasmosis, Babesiosis, Hemobartonellosi, Eperythrozoonoses, Ehrlichia canis
   ii. Bacterial: leptospirosis, Clostridial infections, Streptococci etc
   iii. Viruses: Equine Infectious Anemia

d) **Hypersplenism**: Spelnomegaly with icterus

e) **Cold Hemoglobinuria** in calves: eating excess of frozen/cold foage or water – cardian insuffciancy & pulmonary oedema folowed with hemolytic anemia 7 hemoglobinuria.

HEMORRHAGIC ANEMIA

In this group, '**extravascular' destruction** of RBCs occurs, where blood loss is greater than the production.

The nature and type of hemorhhagic anemia is determined by (i) **Amount** of blood loss, (ii) **Rate** at which blood is lost, and (iii) **Diet** controlling the balance between loss and production

Various types of Hemorrhagic Anemia are as following:

1. **Acute hemorrhagic Anemia**: due to Sweet clover poisoning, Warfarin poisoning, Bracken Fern poisoning (contain Thiaminase- which destroy Thiamin vitamin B1; acute throbocytopenia-hemorrhages-anemia)

2. **Chronic Hemorrhagic Anemia**: due to
   i. Blood sucking worms like Hemochus, Fasciola flukes, Bunstomum in cattle/sheep; Strongyles in Horses; Ancylostomes in Dogs
   ii. Ectoparsites-like Ticks, lice and fleas
   iii. Protozoa- like Coccidiosis in dogs
   iv. Hemorrhagic diseases : eg. Chronic bovine Hematuria
   v. Others-like GIT ulcers, vascular tumours etc

3. **Purpura and Hemorhhagic Diseases**: Purpura is accumulation of blood, under the skin due to spontaneous rupture of capillaries.

   A. Vascular Disorders
   i. Purpuric infections: *eg.* HS or Anthrax disease infection; injury to vessels by toxins-endothelium damage
   ii. Allergic purpura or purpura hemorrhagica: *eg.* Post-infection toxemia in Stragles Disease (Horse)- No thrombocytopenia seen, but injury to endothelium of vessels.

iii. Congential purpura: in foetus – due to iso-agglutinins aginst platelets, pass from mother to foetus-thrombocytopenia (destruction)

iv. Vit-C deffciency: increases cappilay permeability, hemorrhages

B. Impaired Clotting mechanisms

i. Thrombocytopenia

Primary / Idiopathic Throbocytopenia : unknown cause-autoantibodies to platelets

Secondary Throbocytopenia : (1) Damage to Bone marrow by Chemicals like Nitrogen mustard, benzol, antimetabolites; or by Individual Sensitivity – to drugs like quinine, Streptomycin, Ergot etc; or by Animal Toxins like snake venom, extensive burns : or by Physical agents-like ionizing radiation, heat strokes; or by Infections like Septicimea;

ii. Other Coagulation Defects

- Hemophilia
- Prothrombin deficiency: mostly due to impaired formation,
  - due to Liver Diseases;
  - Deficiency of Vitamin-K or its impaired absorption;
  - Poisoning by Dicoumarin and Warfarin: Sweet Clover contains Coumarins, that converts to Dicoumarol, & it is powerful anti-coagulant, antagonises Vit-K, depresses formation of Prothrobin and many clotting factors. Resulting in extensive hemorrhages, followed by Anemia. Warfarin is used as Rodenticide and has function as dcoumarol, causing hemorrhages
  - Presence of Circulating anticoagulants: like heparin excess etc
- Presence of Circulating anticoagulants: like heparin excess etc, preventing conversion of prothromin to thrombin, resulting into bleeding

iii. Unknown Etiology

- Mouldy Corn Poisoning (cattle/swine):
- Epitaxis in Horses: mostly after strenous exercise in some horses

OTHER IMPORTANT SHORT NOTES / DEFINITIONS

PERNICIOUS ANEMIA / also known as **Addison's Anemia** is usually caused due to (i) Iron Defficiency or (ii) due to defficiency of Vitamin B12. RBCs are **hypochromic and macrocytic**. RBCs are larger and immature. Synthesis of hemoglobin is slowed due to protein defficiency.

MEGALOBLASTIC ANEMIA: It is caused by lack of Folic Acid-another RBC maturation factor. Here also the RBCs are hypochromic and macrocytic (magaloblastic), but RBCs are not immature here, rather due to defective DNA synthesis, the size is large & may be unable to pas out of bone marrow too.

SIDEROBLASTIC ANAEMIA is characterised by **defective protoporphyrin synthesis**. This can be due to congenital or acquired causes:

- **Congenital**: deficiency of amino-levulinic acid synthetase (ALAS; rate-limiting enzyme)
- **Acquired**: alcoholism, lead poisoning, vitamin B6 deficiency (co-factor for ALAS)

In sideroblastic anaemia, there is nothing wrong with the iron component of haemoglobin. The iron is stuck waiting around because the **lack of protoporphyrin** prevents the formation of **haem**. This results in iron building up in mitochondria, creating the pathognomonic ringed **Sideroblasts.**

SICKLE CELL ANAEMIA: occurs due to an **autosomal recessive mutation** in the **beta-globin chain** of haemoglobin, causing valine to replace glutamic acid.

Intravascular haemolysis may occur due to the deformed **sickle shape** of the RBC, but the spleen has predominant role in **extravascular haemolysis** of the misshapen cells.

Investigation findings in **sickle cell anaemia** include:

- Reticulocyte count: increased due to compensation by the bone marrow for intravascular/extravascular haemolysis
- Serum Uric Acid: increased due to lysed RBCs
- In Blood Film - **Sickling** of erythrocytes and features of hyposplenism including target cells and **Howell-Jolly bodies**

MICROANGIOPATHIC HAEMOLYTIC ANAEMIA: In this case, RBCs are destroyed because of **structural issues with the Vasculature**, such as microthrombi, prosthetic

heart valves and aortic stenosis. Sometimes the RBCs get torn on these protruding structures, creating visibly distinct **SCHISTOCYTES**

APLASTIC ANEMIA *(Aplastic Pancytopenia)*

Aplastic anemia, or more accurately aplastic pancytopenia, is a rare condition characterized by **aplasia or severe hypoplasia of all hematopoietic lineages in the bone marrow** with resulting cytopenias.

The term aplastic anemia is a misnomer because affected cells are not limited to the erythroid lineage. Many of the conditions reported to cause aplastic anemia do so only rarely or idiosyncratically; more frequently, they cause other hematologic or nonhematologic abnormalities.

ERYTHROPOIETIC PORPHYRIAS. Porphyrias are a group of hereditary disorders in which porphyrins accumulate in the body because of defective heme synthesis.

Inherited enzyme defects in hemoglobin synthesis have been identified in Holstein cattle, and Siamese cats, resulting in erythropoietic porphyria. Accumulation of **toxic porphyrins in erythrocytes** causes **hemolytic anemia**, whereas accumulation of **porphyrins in tissues and fluids** produces discoloration, including red-brown teeth, bones, and urine

Because of the circulation of the **photodynamic porphyrins in blood**, these animals have lesions of **photosensitization** of the Nonpigmented skin.

Pelger-Huët Anomaly. Pelger-Huët anomaly (PHA) is a condition of hyposegmented granulocytes due to a lamin B receptor mutation. In Pelger-Huët anomaly the **nuclei of neutrophils, eosinophils, and basophils fail to segment**, resulting in band-shaped, bean-shaped, or round nuclei

Chédiak-Higashi Syndrome. Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive defect in the **Lysosomal Trafficking Regulator (LYST) Protein**. The defective LYST protein **results in granule fusion in multiple cell types**, including granulocytes, platelets, and melanocytes, as well as abnormal cell function. Individuals with Chédiak-Higashi syndrome have impaired cellular innate immunity because of neutropenia, impaired leukocyte chemotaxis, and impaired killing by granulocytes and cytotoxic lymphocytes. Seen in Hereford, Brangus Cattle and Persian cats.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC): Disseminated intravascular coagulation is a syndrome characterized by continuous activation of both coagulation and fibrinolytic pathways and is also known as consumptive coagulopathy. It is not a primary disease, but rather a secondary complication of many types of underlying disease, including severe inflammation, organ failure, and neoplasia

Scott's Syndrome. An inherited thrombopathy in which platelets lack normal procoagulant activity, has been recognized in German shepherd dogs.

A classic sequela of hemolytic anemias in general is ***hyperbilirubinemia***, which is an increase in the plasma bilirubin concentration.

Intravascular hemolysis is grossly evident as **pink-tinged plasma or serum**, termed *hemolysis* or *hemoglobinemia*
Ghost cells are ruptured red blood cell membranes devoid of cytoplasmic contents and they indicate **Intravascular Hemolysis**

Spherocytosis and autoagglutination are hallmarks of immunemediated hemolytic anemia

In sheep with copper toxicosis, hemoglobinuric nephrosis, frequently described as **gunmetal-colored kidneys with port wine–colored urine**, is a classic postmortem lesion.

Bovine Anaplasmosis causes anemia mainly by **immune-mediated extravascular** hemolysis.

Leptospirosis causes hemolytic disease that includes (i) immune-mediated (immunoglobulin M [IgM] cold agglutinin) Extravascular Hemolysis and (ii) enzymatic (phospholipase produced by the organism) Intravascular Hemolysis.

***Clostridium perfringens* type A** - produces hemolytic α-toxin, which also has phospholipase C activity AND it causes **Intravascular Hemolytic Anemia** in lambs and calves—a condition known as yellow lamb disease, or enterotoxemic jaundice because of the characteristic **icterus.**

Equine Infectious Anemia causes anemia by both Immune-Mediated Hemolysis and decreased Erythropoiesis **Hemolysis is typically extravascular** but may have an intravascular component during the acute phase.

Cytauxzoonosis. Cytauxzoonosis is a severe, often fatal disease of **DOMESTIC CATS** caused by the protozoal organism, ***Cytauxzoon felis***.

Disease is relatively common in during summer months. *C. felis* is transmitted by a tick vector, *Dermacentor variabilis*, which is probably essential for infectivity of the organism.

Cytauxzoonosis has a **schizogenous phase within macrophages** throughout the body (especially liver, spleen, lung, lymph nodes, and bone marrow) that causes systemic illness. These schizont containing **macrophages enlarge and accumulate within the walls of veins, eventually causing vessel occlusion, circulatory impairment**, and tissue hypoxia.

Later in disease, merozoites released from schizonts enter erythrocytes, resulting in an **Erythrocytic Phase** of infection. On blood smear evaluation, signet ring–shaped erythrocytic inclusions (piroplasms) may be observed during the erythrocytic phase of disease (differentiate with babesiosis)

Infected domestic cats often have Nonregenerative Anemia.

Other Features on the Blood Film Appearance that prompt Further Investigation and are associated with Anemia are as below:

Film features	Cause	Investigation
Target cells	Iron deficiency anaemia Haemoglobinopathies	Ferritin Haemoglobinopathy testing (HPLC/Hb Electrophoresis)
Elliptocytes or pencil cells	Iron deficiency anaemia Haemoglobinopathies	Ferritin Haemoglobinopathy testing (HPLC/Hb Electrophoresis)
Spherocytes	Hereditary Spherocytosis Autoimmune haemolysis lack of protoporphyrin	DAT BGAB (Blood group) Eosin 5 maleimide (E5M)
Fragmented red cells	Haemolysis	Platelet count Bilirubin, Reticulocyte count Urea + Creatinine Coagulation profile
Bite and blister cells	G6PD deficiency	G6PD assay
Nucleated red blood cells	Bone marrow infiltration Haemolysis	Consider bone marrow examination Thalassaemia testing (HPLC/Hb Electrophoresis)
Sickle cells	Sickle Cell Anaemia	Haemoglobinopathy testing (HPLC/Hb Electrophoresis)
Tear drop cells	Bone marrow infiltration Vitamin B12 deficiency	May need Bone Marrow examination Active vitamin B12
Schistocytes	structural issues with the Vasculature Microangiopathic Haemolytic Anaemia	Markers of vascular injury