INTRODUCTION

• the hematopoietic system is composed of a wide range of lymphoid tissues and all the fixed and circulating blood cells originating from multipotent precursors cells in the bone marrow.
• for convenience it is often divided into discrete systems even though there are extensive interactions between these components (ie circulation of cells, soluble growth factors, etc).

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• some portions of the hematopoietic system are easily accessible to clinicians and their evaluations provide valuable information about the health status of the patient (eg blood smears and peripheral lymph node aspirates).
• in many cases antemortem laboratory evaluation of the blood (± lymph node and/or bone marrow aspirates) provides better information than necropsy in understanding diseases of the hematopoietic system.
• consequently many diseases affecting this system will be covered with more detail in Clinical Pathology courses.

MYELOID TISSUES

BONE MARROW & BLOOD CELLS

Normal Structure and Function

• hematopoiesis (= hemopoiesis): the process through which all blood cells are made.

Development of Hematopoiesis

• in the embryo, hematopoiesis begins as clusters of stem cells, called blood islands within the yolk sac.
• in the fetus, hematopoietic activity is found in the liver, spleen, thymus, lymph nodes and bone marrow.
• in neonates, hematopoiesis is confined primarily to the bone marrow involving both flat and long bones.
• as the animal grows, hematopoietic activity in the central areas of long bones regresses and is replaced by fat.
• in adults, most active hematopoiesis occurs in the flat bones (vertebrae, pelvis, skull, sternum, ribs) and in the extremities of the long bones (ie epiphyseal / metaphyseal regions) in the spaces between the spicules of cancellous bone; the medullary cavity in the diaphyseal region of adult long bones contains mostly fat (ie yellow marrow).
• in adults, when hematopoiesis occurs anywhere other than the bone marrow (usually the spleen), it is referred to as extramedullary hematopoiesis (EMH).
Basic Concepts of Hematopoiesis
- hematopoietic tissue is highly prolific; all blood cells are derived from a common multipotential hematopoietic stem cell capable of both self-renewal and further differentiation into committed stem cells.
- the cells undergo sequential divisions as they mature and the mature cells have different life spans (eg hrs for neutrophils, days for platelets, months for erythrocytes, and months to years for lymphocytes).
- the system is under exquisite local and systemic control by soluble stimulatory factors, including cytokines / hormones / growth factors, and can respond rapidly to stimuli.
- production and turnover of blood cells are balanced in health (steady-state kinetics).
- normally only mature cells are released into circulation; release of immature cells indicates stress or disease.

Examination of Bone Marrow
- bone marrow is located in multiple sites, but responds as a single tissue (whole-body homogeneity); the assumption is that a bone marrow sample taken anywhere in the body will represent the marrow as a whole.
- bone marrow samples are typically taken from the proximal femur and the iliac crest in dogs, from the proximal ribs in cattle, and from the sternum in horses.
- bone marrow examination is indicated for any abnormal hematology finding, such as:
  - unexplained cytopenias (any non-regenerative anemia).
  - maturation defects or morphologic abnormalities in blood cells.
  - suspected myeloproliferative diseases.
  - suspected malignancies that are metastatic to marrow.

Microscopic evaluation:
- microscopic evaluation of hematopoietic cells is performed on cytology samples (bone marrow smears/aspirates) and on histology samples (core biopsies).
- bone marrow smears/aspirates are interpreted by clinical pathologists and are the best samples for evaluating:
  - cellular morphology
  - ratio of white cell lineage to red cell lineage (myeloid:erythroid or M:E ratio), which gives a rough estimate of where the marrow’s replicative energies are directed.
- core biopsies are often interpreted by morphologic pathologists and are the best samples for evaluating:
  - bone marrow cellularity, which is measured as the ratio of adipose tissue to hematopoietic cells (altered ratios are seen with aplasia/hypoplasia or hyperplasia/neoplasia).
  - myelofibrosis - a rare disease in which there is a build up of fibrous (scar) tissue within the marrow cavity.
- please note: thorough evaluation of the bone marrow should include a CBC, a bone marrow aspirate and a bone marrow core.

Pathology of the Bone Marrow and Blood Cells (Alterations / Damage to Hematopoiesis)
- the end result is dependent on the type of cells damaged:
  - Multipotent stem cells: multiple cell lines affected.
  - Committed stem cells: one or more lines affected.
  - Differentiated cells: one cell line affected
- alterations in hematopoiesis are reflected in the peripheral blood as deficiencies or increases in different cell lines (such changes are apparent on a CBC and are therefore covered in clinical pathology).
- in the bone marrow, they are reflected as increased or decreased cellularity and/or alterations in the myeloid to erythroid ratio.
I - Bone Marrow: hereditary disorders
• most are reflected in the peripheral blood and will be covered in Clinical Pathology.
• eg’s: Bovine Leuocyte Adhesion Deficiency (BLAD) syndrome, Canine Cyclic Hematopoiesis (Gray Collie Syndrome), Chediak-Higashi syndrome, Pelger-Huet anomaly.

II - Bone Marrow: degeneration / necrosis
• since hematopoietic cells are in general very active metabolically, a variety of insults can affect their viability.
• main causes of bone marrow degeneration include:

  a) Radiation

  b) Toxins / Drugs: • antineoplastic / immuno-suppressive drugs • idiopathic drug toxicity • idiosyncratic drug reactions • toxic chemicals

  c) Infectious agents: • Feline parvovirus (panleukopenia) • Feline leukemia virus • Equine infectious anemia (EIA) • Canine parvovirus • Feline immunodeficiency virus

  d) Immune-mediated: • specific immune-mediated disorders, eg systemic lupus erythematosus (SLE). • altered surface cell antigens by drugs or infectious agents.

  e) Idiopathic: • in many cases the cause is not identified.

III - Bone Marrow: inflammation (covered in pathology of the skeletal system)
• myelitis usually occurs as part of localized suppurative osteomyelitis (inflammation of bone & medullary cavity)

IV - Bone Marrow: adaptations of growth

1) Bone Marrow Hypoplasia / Aplasia
• bone marrow hypoplasia (decreased proliferative activity) can be represented in one cell line (eg erythrocytic aplasia = aplastic anemia) OR multiple cell lines (eg aplastic pancytopenia).
• main causes of bone marrow hypoplasia / aplasia:
  ① Bone marrow suppression
    • estrogen in the dog; exogenous (therapeutic) or endogenous (eg Sertoli cell tumor).
    • anemia of chronic disease (cytokine release from some neoplasms, chronic inflammation, etc).
    • anemia of chronic renal disease (decreased erythropoietin, toxic depression of marrow).
  ② Lack of nutrients
    • inadequate iron, vitamin B12, folate, etc.
  ③ Endocrine dysfunction
    • eg hypothyroidism
  ④ Bone marrow degeneration / necrosis (see previous discussion)
• gross findings: usually characterized by increased yellow marrow (fat) and decreased red marrow.
• microscopic findings: - increased proportion of adipose tissue to hematopoietic cells (despite peripheral demand) - note: in the normal adult the red marrow is ~ 50:50 fat: blood cells.
2) Bone Marrow Hyperplasia
   • pathogenesis:
     - proliferation (hyperplasia) of hematopoietic cells in response to increased peripheral demand or
       hypofunction of blood cells.
     - one or multiple cell lines may be hyperplastic depending on the stimulus.

   a) Erythroid hyperplasia
     • response to decreased RBC number / function: eg anemia due to hemorrhage, immune or parasitic RBC
       destruction, etc.

   b) Megakaryocytic hyperplasia
     • response to decreases in platelet number / function: due to consumptive coagulopathies, immune-mediated
       destruction of platelets, etc.

   c) Myeloid (granulocytic or monocytic cell lines) hyperplasia
     • neutrophilia → response to most bacterial infections, tissue necrosis, etc.
     • eosinophilia → response to parasites, hypersensitivities, etc.
     • monocytosis → response to chronic infections, specific infectious agents, etc.

   • gross findings:
     - initially red marrow replaces yellow marrow (fat) at metaphyses and along endosteal surface of diaphysis.
     - with progression can occupy the entire marrow cavity (note: in young animals entire marrow is normally red).

   • microscopic findings:
     - proliferation of one or more cell lines, along with a shift toward immaturity in those cell lines; note: see
       associated decreased proportion of adipose tissue to hematopoietic cells (ie increased cellularity).
     - if severe can revert to extramedullary hematopoiesis (especially in spleen and liver).

3) Serous Atrophy of Bone Marrow Fat
   • see gelatinous transformation of marrow fat associated with starvation / malnutrition or chronic disease.

V - Primary Hematopoietic Neoplasia
   • primary hematopoietic neoplasia results from clonal expansion of hematopoietic cell types.
   • these tumors affect the bone marrow, the blood (leukemia, covered in clinical pathology) and the lymphoid tissues
     (lymph node, spleen, etc).

1) Common Features of Primary Bone Marrow Neoplasia
   a) Hypercellular marrow
     • reflects the uncontrolled proliferation of the neoplastic hematopoietic cells (but as mentioned below there is
       often ineffective hematopoiesis of other cell lines).

   b) Anemia
     • non-regenerative anemia due to ineffective erythropoiesis.
     • when the bone marrow occupied by neoplastic hematopoietic cells; due to competition for nutrients &/or space
       (myelophthisis) &/or inhibitory factors released from neoplastic cells.

   c) Thrombocytopenia, +/- Neutropenia
     • not present in all myeloproliferative diseases (same pathogenesis as anemia, see above).

   d) Leukemic cells in peripheral blood
     • immature stages of hematopoietic cells in peripheral blood are commonly seen in myeloproliferative disease.
     • one of the first laboratory findings which points to the diagnosis of leukemia / myeloproliferative disease.

   e) Splenic and hepatic involvement
     • myeloproliferative diseases often spread early to involve the spleen and liver.
     • animals may present with splenomegaly and/or hepatomegaly.
2) Lymphoproliferative vs myeloproliferative diseases
   • hematopoietic tumors are broadly divided into:

   a) Lymphoproliferative disease
      • neoplastic transformation of a lymphoid cell line (ie lymphocytes).

   b) Myeloproliferative disease
      • neoplastic transformation of one or more bone marrow cell lines (myeloid cells), including, granulocytes
        (neutrophils, basophils & eosinophils), erythrocytes, megakaryocytes & monocytes.

Primary Hematopoietic Neoplasia

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* these are covered in Clinical Pathology

VI - Lymphoproliferative Diseases
   • defined as a neoplastic proliferation of lymphocytes causing a spectrum of disease from pure lymphoid leukemia
      (= neoplastic lymphocytes primarily in bone marrow and circulation) to lymphoma (= neoplastic lymphocytes in
      lymph nodes / tissues / organs with relatively normal blood profile).
   • in the later stages of disease lymphoid leukemia will often invade tissues and lymphoma can involve marrow /
      circulating cells (ie leukemic lymphoma) - so separating these disease states from one another can be difficult; but
      in some case it can be important for prognosis and treatment options.

1) Leukemia (covered in Clinical Pathology)
   • leukemia refers to malignant hematopoietic neoplasms that originate in the bone marrow and typically have
     significant numbers of neoplastic cells in the blood.
   • leukemia can be lymphocytic (T-lymphocyte or B-lymphocyte in origin) or myeloid (erythroid, granulocytic,
     monocytic, or megakaryocytic in origin) and may be acute or chronic in nature.
   • chronic leukemias are characterized by well-differentiated cells and slowly progressive disease.
   • acute leukemias are characterized by poorly differentiated cells and an aggressive clinical course.

2) Lymphoma (lymphosarcoma)
   • **lymphoma is one of the most common malignant neoplasms in domestic animals**
   • it can be sporadic or have hereditary (eg porcine lymphoma) or viral (eg FeLV in cats, BLV in cattle) causes.

   a) Classification systems for Lymphoma
      • several classification systems exist, with classification by:
1. **Anatomical site** (subjective)
   - **multicentric**: generalized involvement of lymph nodes, +/- liver, spleen, marrow or other organs.
   - **alimentary**: nodular to segmental involvement of the GI tract, especially intestine.
   - **mediastinal / thymic**: involvement of the cranial mediastium / thymus.
   - **cutaneous**: both epitheliotropic (T-cell) and non-epitheliotropic (mostly B cell) forms.
   - **miscellaneous**: renal, ocular, cardiac, neural, etc.
   - **leukemic lymphoma**: when lymphoma invades marrow and occurs in blood (recall difficulty r/o lymphoid leukemia)

2. **Cellular morphology**
   - based on size, nuclear features, mitotic rate.
   - multiple classifications available based on the cytologic features of neoplastic lymphocytes
   - two prognostic assumptions of this method of classification are:
     - small cell lymphomas with low mitotic rates; slow progress and show poor response to chemotherapy.
     - large cell lymphomas with high mitotic rates; progress rapidly, but generally respond well to chemotherapy.

3. **Immunophenotype**
   - use immunohistochemistry to determine the origin of the lymphoblasts (B-lymphocyte: CD79a, T-lymphocyte: CD3 or non-T/B-lymphocyte).
   - in animals, B-cell lymphomas generally have better survival profiles and response to treatment when compared to T-cell lymphoma.

4. **Biologic behavior**
   - low-grade (indolent)
   - intermediate
   - high grade (aggressive)

5. **Histologic pattern**
   - diffuse versus follicular

b) **Clinical signs of lymphoma**
   - most common sign with lymphoma is painless enlargement (lymphadenopathy) of 1 or multiple lymph nodes.
   - multitude of additional signs are dependent upon the organ system involved, for example:
     - retrobulbar lymph node involvement may result in exophthalmos.
     - thymic lymphoma may induce jugular vein engorgement, dyspnea and/or esophageal obstruction.
     - enteric involvement may result in diarrhea, obstruction or melena.

c) **Lymphoma, gross findings**
   - affected lymph nodes are moderate to markedly enlarged, soft to firm, often bulge on cut surface and have a homogenous pale tan to white appearance, +/- focal areas of necrosis or hemorrhage.
   - nodes often firmly attached to surrounding tissue due to perinodal lymphocytic invasion & subsequent fibrosis.
   - lymphoma in other organs can cause:
     - diffuse organomegaly (usually splenomegaly / hepatomegaly)
     - single to multiple discrete tan nodules within the affected organ (heart, kidney)
     - localized to generalized thickening of the walls of tubular organs (intestine, stomach, uterus).

d) **Lymphoma, microscopic findings**
   - effacement of the normal histologic architecture due to proliferation of a homogeneous population of lymphocytes with variable degrees of anaplasia mitosis and apoptosis.
e) Lymphoma, other laboratory findings (variable)

- mild to moderate non-regenerative anemia
- lymphopenia or lymphocytosis or leukemia
- hypercalcemia (humoral hypercalcemia of malignancy)

f) Species Differences

① Canine lymphoma

- lymphoma is the most common canine hematopoietic neoplasia; often middle-aged and older dogs.
- no known viral causes of lymphoma in dogs (opposed to cats and cattle).
- most have a multicentric distribution (~ 85%), with prominent lymph node involvement and the majority are intermediate or high-grade tumors.
- other anatomic forms (decreasing order of frequency): alimentary, cutaneous, mediastinal (thymic) & miscell.
- alimentary form is often thought to be preceded by lymphoplasmacytic enteritis (inflammatory bowel disease).
- clinical signs may be referable to the organs involved, but often are nonspecific or absent at diagnosis; ninety percent of dogs with lymphoma have a normal leukogram.
- humoral hypercalcemia of malignancy is sometimes associated with canine lymphoma due to the production of parathyroid hormone-related peptide (PTHrP) by neoplastic cells in dogs.

② Feline lymphoma

- the most common malignant neoplasm of cats.
- anatomic forms (decreasing order of frequency): alimentary, multicentric, mediastinal (thymic) or miscellaneous (renal, ocular, etc).
- unlike dogs, there is often no peripheral lymph node involvement in cats and leukemia / bone marrow involvement are common in all forms.
- characterized by a short clinical course; ~75% of affected cats are dead within 8 wks of diagnosis if untreated.
- approximately 10-20% of cats with lymphoma are infected with Feline Leukemia Virus (FeLV).
- FeLV-associated lymphoma often affects young cats, and most commonly leads to mediastinal or multicentric T cell lymphoma (80% of young cats with mediastinal lymphoma are FeLV +).
- clinical signs are often non-specific and include weight loss, anorexia, poor grooming habits, or are referable to the affected organ system: diarrhea, vomiting, dyspnea.

③ Bovine Lymphoma

i) Enzootic bovine lymphoma (bovine enzootic leukosis)

- primarily a multicentric disease of adult cattle (average age 5-8 years old).
- caused by Bovine Leukemia Virus (BLV), an oncogenic retrovirus; once infection is established, it is lifelong.
- target cell for BLV is the B-lymphocyte; virus is transmitted by transfer of viral-infected lymphocytes; mostly horizontal by arthropods, natural breeding and accidental transmission by needles, ear tagging equipment, etc.
- ~30% of BLV-infected cattle develop non-neoplastic persistent lymphocytosis and of these less than 10% will go on to develop lymphoma (ie less than 3% of BLV infected cattle will develop lymphoma, and this is only if they are allowed to survive to the age of peak incidence of 6-8 years).
- dairy cattle are more commonly affected than beef cattle; likely due to management practices and average age.
- in addition to lymph nodes, commonly affected organs include heart (right atrium especially), abomasum, uterus, vertebral canal, kidneys, and the retro-orbital space.
- clinical signs depend on the organ involved but can include lymphadenopathy, diarrhea, vagal indigestion, congestive heart failure, and posterior paresis/paralysis.
- BLV may cause lymphoma in sheep and goats and causes widely disseminated tumors.
ii) Sporadic bovine lymphoma
- occurs in young cattle and not associated with BLV infection.
- there are three forms of sporadic lymphoma:

  Calf form
  - multicentric lymphoma in calves (from birth to about 6 months of age).
  - see symmetrical lymph node enlargement, often with leukemia and bone marrow involvement; kidney, liver
    and spleen are also often affected.

  Juvenile/thymic lymphoma
  - lymphoma of the mediastinal area, typically seen in yearling (mostly less than 2 yrs) beef breeds.
  - characterized by large cranial thoracic/lower cervical masses, respiratory distress, and weight loss.

  Cutaneous form
  - usually 2 to 3 yr-old cattle.
  - see plaque-like, round raised skin lesions, often with ulceration; typically on the head, sides, and perineum.
  - lesions may wax and wane and animals may survive for 12 – 18 months.
  - ultimately there is deep organ involvement indistinguishable from multicentric lymphoma.

4 Porcine lymphoma
- lymphoma is considered to be the most common neoplasm of swine.
- a familial (autosomal recessive) form of multicentric lymphoma is seen in Large White pigs.
- usually in swine < 1 year old; females more than males.
- lesions are usually multicentric (eg visceral lymph nodes, spleen, liver, stomach, intestine, kidney, and bone
  marrow involvement are common) or mediastinal.

5 Equine lymphoma
- has a lower incidence than in cats, cattle and dogs.
- multicentric lymphoma is the most common form; however cutaneous / subcutaneous, alimentary, abdominal,
  splenic, and leukemic forms also occur.
- is often intermediate or low grade and frequently is of mixed cell type (B &T lymphocytes)

3) Plasma cell tumors

1 Cutaneous plasmacytoma
- solid tumor of plasma cells originating in the skin (esp pinna or digits) or mucous membranes.
- occur in mature animals, most frequently dogs (rarely in cats).
- usually a solitary benign lesion (surgical excision is often curative); occasionally they are more aggressive.
- histo: - composed of dense sheets of a uniform population of well-differentiated plasma cells or may have
  marked anisocytosis and anisokaryosis (anaplastic plasmacytoma).
  - amyloid is produced in a small percentage of tumors.

2 Extramedullary plasmacytoma
- solid tumor of plasma cell origin arising in sites other than the bone marrow and skin.
- rare tumors; occur more often in dogs (Cocker Spaniels are predisposed) than in other species (cat and horse).
- most often arise in the gastrointestinal tract; also occur in the trachea, spleen, kidney, uterus, etc.
- grossly the tumor may be multinodular or cause thickening of the organ wall.
- tend to be more aggressive than cutaneous plasmacytoma with occasional metastasis to the lymph nodes.
Multiple myeloma (Plasma cell myeloma)

- relatively uncommon in domestic animals; seen most often in dogs and cats.
- malignant tumors of plasma cell origin arising within the bone marrow; neoplastic plasma cells (derived from one clone) secrete immunoglobulins or immunoglobulin fragments of one class leading to hyperproteinemia due to hyperglobulinemia (hypergammaglobulinaemia)
- clinical signs: - includes lameness, ill-defined pain and lethargy.
  - paraplegia can occur due to direct spinal cord compression by protrusion of tumor masses into the vertebral canal or secondary to a pathologic vertebral fracture.
  - clinically often slowly progressive and neoplastic cells may metastasize to spleen, liver, lymph nodes & kidneys.
- gross: - sections of affected bone exhibit multiple dark-red soft / gelatinous tissue nodules filling areas of bone resorption / lysis (~ 2/3 of dog cases have radiographic “punched out” lesions in skeleton*).
  - lesions often multifocal & can be found in any hematopoietically active bone, but most common in vertebrae.
- histo: - increased numbers of neoplastic plasma cells in the bone marrow*; some cases well-differentiated.
- other: - hypergammaglobulinaemia is detected by serum protein electrophoresis as a monoclonal spike in the gamma globulin fraction (monoclonal gammopathy*); this can lead to hyperviscosity syndrome (sludging of blood cells, hypotension and shock) &/or renal amyloidosis &/or hemorrhage due to secondary platelet dysfunction.
  - cytopenias (due to myelophthisis).
  - hypercalcemia* (due to osteoclastic activity in the bone lesions = osteolysis).
  - light-chain (Bence-Jones) proteinuria*; Bence-Jones proteins are free immunoglobulin light chains which pass through the glomeruli into urine – detected using electrophoresis and immunoprecipitation.
- diagnosis of multiple myeloma is often based on a minimum or 2 or 3 of these findings.

VII - Myeloproliferative Diseases

1) Myeloid Leukemia (covered in Clinical Pathology)
- erythroid, granulocytic (neutrophilic, eosinophilic, basophilic), monocytic, or megakaryocytic in origin

2) Myelodysplastic Diseases (covered in Clinical Pathology)
- group of myeloid proliferative disorders characterized by ineffective hematopoiesis.
- rare in veterinary medicine: most often seen in FeLV-infected cats.

3) Histiocytic Neoplasia/Proliferative Disorders
- histiocytic proliferative diseases occur most commonly in dogs.
- canine proliferative histiocytic diseases include a wide range of disorders which vary in clinical behavior.
- this group of disorders includes the following:
  ① Cutaneous histiocytoma (covered in Dermatopathology)
    - common benign (often spontaneously regress) tumors of the skin of dogs; arise from Langerhans cells.
    - especially in young dogs (mostly less than 4 years of age).
2 Canine Reactive Histiocytosis (cutaneous and systemic reactive histiocytosis)
- canine reactive histiocytosis is either limited to the skin (cutaneous histiocytosis) or simultaneously affects the skin and other organs (systemic histiocytosis).
- considered an immunoregulatory disorder rather than true neoplasia; often respond to immunotherapy.
- the cell of origin is thought to be an activated dermal/interstitial dendritic cell (ie antigen presenting cell).
- cutaneous histiocytosis is characterized by multifocal skin masses which can wax and wane or slowly progress.
- Bernese Mountain dogs are predisposed to developing the systemic form which often involves the skin, peripheral lymph nodes, ocular/nasal mucosa, lungs, liver and spleen.

3 Histiocytic Sarcoma & Disseminated Histiocytic Sarcoma (malignant histiocytosis)
- rare malignant tumors of histiocytic (macrophage/dendritic cell) origin which occur most often in dogs.
- breed predilections include Bernese Mountain dogs, Rottweilers and Flat-coated Retrievers.
- localized histiocytic sarcoma:
  - start as solitary masses occurring most often in periatrictural regions or in the skin / subcutis; however other primary sites have been reported (eg spleen, lymph nodes, liver); grow rapidly and will metastasize.
- disseminated histiocytic sarcoma (malignant histiocytosis):
  - is an aggressive multisystemic disease characterized by the presence of multiple tumor masses in several organ systems, esp. spleen, lung, liver, bone marrow, lymph nodes, CNS, rarely skin / subcutis, etc.
  - this disease (esp disseminated form) has a guarded to poor prognosis & often responds poorly to chemotherapy
- histo: - composed of atypical histiocytes (may arise from dendritic cells or less often from macrophages).
  - those from macrophages may be avidly hemophagocytic causing rapidly progressive anemia (= hemophagocytic histiocytic sarcoma).

4) Mast cell tumors
- not technically a myeloproliferative disease.

a) Cutaneous mast cell tumors (covered in Dermatopathology)

b) Systemic mastocytosis (= visceral mast cell tumors)
- rare, occurring most commonly in cats with the 2 most common forms being splenic and intestinal.
- splenic form: - splenomegaly is evident (difuse or nodular), can metastasize to liver, bone marrow, lungs, etc.
  - microscopically see effacement of the splenic architecture by dense sheets of mast cells.

VIII - Secondary Hematopoietic Neoplasia
- secondary neoplasia of the bone marrow is the result of metastasis of non-marrow origin neoplastic cells to the bone marrow: eg. carcinomas (mammary, prostatic etc), sarcomas (hemangiosarcoma, malignant melanoma etc).

IX - Myelophthisis
- myelophthisis = the replacement of hematopoietic tissue within the bone marrow by abnormal tissue.
- usually replaced by fibrous tissue (myelofibrosis) or malignant cells.
- may be reflected in the peripheral blood as pancytopenia.

MONOCYTE-MACROPHAGE SYSTEM (MMS)
- the monocyte-macrophage system cells are of bone marrow origin and include blood monocytes and monocytes that have migrated and differentiated into fixed macrophages in connective tissue throughout the body and within vascular beds of specific organs, such as the spleen (sinusoidal and splenic cord macrophages), lymph nodes (sinus histiocytes), liver (kupffer cells), lung (pulmonary intravascular and intra-alveolar macrophages), and brain (resident and perivascular microglial cells).
LYMPHOID SYSTEM

LYMPH NODES
Normal Structure and Function
- Lymph nodes are oval to bean shaped organs which are distributed throughout the body along lymphatic vessels (“in-line” filters → all lymph filtered by at least one lymph node prior to returning to blood).
- The lymph nodes help co-ordinate and direct the body’s immune response, via immune cells (B & T lymphocytes, macrophages, and dendritic cells).
- Constantly responding to antigenic stimuli, even in the absence of clinical disease.
- Lymph nodes are divided into an outer cortex, inner cortex and medulla (note, in swine this arrangement is reversed, ie cortex is in the center of the node and the medulla is at periphery).
  - The outer cortex, includes follicular structures (primary follicles) which, when antigenically stimulated, develop into secondary follicles (ie have a pale-staining germinal center and a surrounding mantle zone); populated mostly by B lymphocytes, but also some macrophages and dendritic (antigen-presenting) cells.
  - The inner cortex (paracortical region) contains primarily T lymphocytes.
  - The medulla contains medullary cords (mostly macrophages, B cells & plasma cells) and medullary sinuses (with macrophages that can phagocytose foreign material and bacteria).
- Lymph circulation: lymph enters via afferent lymphatic vessels → subcapsular sinuses → trabecular sinuses → medullary sinuses → efferent lymphatics → thoracic duct (note: slow flowing lymph can percolate through the cortical meshwork and interact with macrophages / APC’s (antigen presenting cells) / lymphocytes for possible immune response).
- Recirculation of lymphocytes from the blood: lymphocytes from the blood (predominately T cells) can bind to specialized high endothelial venules in the paracortex (via specific endothelial / leukocyte adhesion molecules) → into lymph node → can leave lymph node via efferent lymphatic.

PATHOLOGY OF THE LYMPH NODES
- Two basic changes can be appreciated grossly: the lymph nodes may be increased in size or decreased in size.
- The differentials for these two changes are listed in the following table:

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<th>Enlarged Lymph Nodes</th>
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<td>Lymphadenitis</td>
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<td>Lymph node hypoplasia</td>
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Miscellaneous Lymph Node Pathology
1) Hemorrhage
   - Can originate within the lymph node or the tissues drained by the node → red discolouration.
   - With time: accumulation of hemosiderin-laden macrophages (hemosiderosis) → brown discolouration.

2) Anthracosis
   - Retention of carbon within phagocytes, especially in the medullary cords → black discolouration
   - Common in the pulmonary nodes of dogs living in industrial areas, humans that smoke tobacco, etc.
Small Lymph Nodes:

1) Lymph Node Atrophy / Degeneration

- causes:
  ① senile atrophy – seen in aged dogs, cats and primates.
  ② cachexia / malnutrition atrophy – common, especially old sheep and goats with dental attrition.
  ③ many viral infections can cause degeneration of lymph nodes; (lymphocytolysis = direct lymphocyte necrosis).
    - eg’s, feline panleukopenia (parvovirus), canine parvovirus, canine distemper virus, bovine viral diarrhea virus, feline immunodeficiency virus (FIV).
    - with chronicity, can often result in lymph node atrophy.
  ④ toxins / drugs (eg chemotherapy) / irradiation.

- gross: lymph nodes are decreased in size
- histo: - overall reduced cellularity / lymphoid depletion.
  - with toxins / chemotherapy / viral infections, there is often lymphocytolysis in the germinal centers.

Large Lymph Nodes:

- lymphadenopathy or lymphadenomegaly = lymph node enlargement of unknown or unspecified cause.
  - can be localized or generalized:
    - local enlargement usually reflects a pathological process limited to the drainage area
    - generalized enlargement seen with sepsis, certain infectious diseases (tuberculosis, brucellosis) & lymphoma

1) Lymph Node Hyperplasia

- hyperplastic changes lead to lymph node enlargement (lymphadenopathy)
- hyperplastic changes may involve lymphoid tissue (antigenic stimulus) &/or cells of the monocyte-macrophage system (eg sinus histiocytosis)
- lymph node hyperplasia is a common reactive lesion; it can be localized or generalized, and occurs in response to presentation of foreign material / antigen or in response to circulating interleukin levels.
- a classic example of reactive hyperplasia is in local lymph nodes draining a site of local infection or vaccination.
- reactive hyperplasia also occurs during early lymphadenitis; but hyperplastic changes in the lymphoid cell population are often obscured by the infection / inflammatory response.

- gross: - moderate enlargement of affected lymph nodes, may bulge on cut section.
- histo: - proliferation of the lymphoid follicles with prominent germinal centers, increased T-cells in the paracortex & increased plasma cells in medullary cords (note, overall tissue architecture is maintained)

2) Lymphadenitis

- lymphadenitis = an inflammatory response to an infectious agent within the node (note; be able to differentiate this from reactive lymphoid hyperplasia in which the node is immunologically reactive, but free of local infection).

i) Acute lymphadenitis

- usually the result of a regional lymph node draining a site of inflammation and subsequently becoming infected.
  - eg’s: - infection of the tracheobronchial lymph nodes accompanying pneumonia
    - infection of the mesenteric lymph nodes accompanying enteritis
    - infection of the supramammary lymph nodes accompanying mastitis
  - with sepsis, many nodes will be involved.

- gross: - affected lymph nodes are enlarged / swollen, soft, moist, hyperemic, and often bulge on cut surface.
  - swelling is due to edema, exudate and proliferation of the lymphoid / monocyte-macrophage system (MMS) components of the node.
  - exudates are usually serous, but may be hemorrhagic or suppurative.
ii) Chronic lymphadenitis
- characteristic features are increased size and firm texture due to fibrosis; lymph node may become irregularly shaped, dry and indurated (hardened) with prolonged inflammation.

a) Chronic suppurative lymphadenitis (lymph node abscessation)
- swollen lymph node with a necrotic / pus filled center in response to pyogenic bacteria.
- can have fistulous tract draining to the skin surface.

1 Equine strangles
- *Streptococcus equi* subsp. *equi* causes inflammation of the upper respiratory tract and results in abscesses in the mandibular, retropharyngeal, and parotid lymph nodes.

2 Porcine jowl abscess
- *Streptococcus porcinus* colonizes the oral cavity and tonsils and spreads to the regional lymph nodes (usually the mandibular lymph node).

3 Streptococcal adenitis in dogs
- *Streptococcus spp* (Lancefield’s group G) can cause minor endemics in kennels.
- usually transient and characterized by pharyngitis, fever, conjunctival discharge, and enlargement of the submaxillary nodes with abscessation.

4 Caseous lymphadenitis
- common disease of sheep and goats caused by *Corynebacterium pseudotuberculosis*.
- this agent is also responsible for ulcerative lymphangitis of horses and cattle and pectoral abscesses in horses.
- in sheep, the organism usually penetrates the body via cuts (eg shear wounds) or rarely by inhalation and drains to the regional lymph nodes.
- in young sheep the disease tends to be confined to the superficial lymph nodes, of which the cervical (prescapular) and subiliac (prefemoral) are most frequently affected.
- in goats, it often affects the lymph nodes of the head, and neck and may be acquired through the buccal mucosa in addition to skin wounds.
- in both species can be slow spread of disease to produce abscesses in internal organs, eg lung, liver, spleen, etc.
- gross: - chronic suppurative inflammation and caseous necrosis of the lymph nodes.
  - concentric laminations within these areas (when present) are considered characteristic of the disease; they are the result of progressive necrosis and reformation of a connective tissue capsule.

b) Granulomatous lymphadenitis
- may be nodular or diffuse; characterized by large, firm solid nodes that may exhibit areas of caseous necrosis and/or discrete granulomas with mineralization, eg’s:

1 Nodular (focal to multifocal) granulomatous lymphadenitis
- *Mycobacterium bovis* (bovine tuberculosis)
  - initially in regional lymph nodes (eg tracheobronchial lymph nodes in the case of pulmonary tuberculosis) but can become disseminated, ie affecting lymph nodes throughout the body.
  - gross: enlarged lymph nodes with single to multiple (coalescing) pale caseous nodular lesions (often with gritty / mineralized centers); confluence of multiple lesions may produce locally extensive to generalized (diffuse) involvement of the node.
  - histol: nodular aggregates of epithelioid macrophages, multinucleated giant cells, fewer lymphocytes and plasma cells surrounding central regions of necrosis +/- mineralization and acid-fast bacilli.
- *Mycobacterium avium* subsp. *paratuberculosis* (Johne's disease)
  - several non-caseating granulomas in the mesenteric lymph nodes (associated with granulomatous enteritis).
- *Actinobacillus lignieresii* (wooden tongue of cattle)
  - often submaxillary / parotid node involvement.
- migrating parasitic larvae

2) **Diffuse granulomatous lymphadenitis** (generally enlarged, dry firm nodes)
- Porcine Circovirus type-2 (PCV-2)
  - in postweaning multisystemic wasting syndrome (PMWS) typically see granulomatous lymphadenitis with large botryoid (“bunch of grapes”) intracytoplasmic viral inclusions within macrophages.
- Histoplasmosis
  - *Histoplasma capsulatum* (a dimorphic fungus) is a facultative intracellular pathogen of macrophages (therefore disease is characterized by diffuse involvement of the mononuclear phagocyte system)
  - worldwide distribution, especially Mississippi, Ohio and St Lawrence River valley.
  - infections are from soil (especially where pigeons or bats congregate) by ingestion/inhalation of dust.
  - affects dogs more often than cats.
  - **gross:** see enlarged lymph nodes, spleen and liver; due to marked proliferation of macrophages in the spleen, lymph nodes, liver, lungs and intestine
  - **histo:** see clusters of very small yeast (3-5 um in histo sections) within the macrophages.
- *Blastomyces dermatitidis* and *Cryptococcus neoformans*
  - affects regional lymph node draining the primary affecting areas (often lungs, skin, etc)

iii) **Resolution of lymphadenitis**
- Acute → Resolves by Healing → Full Recovery
- Acute → Progresses to Chronic → Residual scarring or permanent loss.

3) **Neoplasia**

1) **Primary Neoplasia**
- lymphoma: *see previous discussion of primary neoplasia of the hematopoietic system*

2) **Secondary neoplasia (metastatic)**
- lymph node metastasis is most commonly seen with carcinomas (eg mammary, squamous cell, prostatic), malignant melanomas (especially of the oral cavity of dogs) and mast cell tumors.
- **gross:** the lymph nodes may be enlarged.
- **histo:** there may be few cells within the peripheral/medullary sinuses or there may be variable effacement of the normal node architecture by neoplastic cells.
- lymph node involvement is one basis for the clinical staging of tumor malignancy (ie prognostic indicator):
  - Stage 0: no palpable regional lymph nodes or nodes appear normal.
  - Stage 1: lymph node(s) draining area are palpably enlarged, but still freely movable.
  - Stage 2: fixed, palpably enlarged, regional lymph nodes.
SPLEEN

Normal Structure
- the spleen, located in the left cranial abdominal region, is covered by a fibromuscular capsule and the parenchyma is incompletely dissected by trabeculae.
- histologically, the splenic parenchyma consists of red pulp and white pulp.
- red pulp consists of fenestrated sinusoids (vascular spaces) and splenic cords (reticular cells/fibers) which support macrophages, lymphocytes, plasma cells and blood cells (granulocytes, platelets, rbc’s).
- white pulp consists of periarteriolar lymphoid sheaths (= PALS, which are T cells), appended lymphoid nodules (B cells) and a peripheral marginal zone (rich in phagocytic macrophages and dendritic cells).

Normal Function
- just as the lymph nodes filter lymph, the spleen filters blood.

1) Red Pulp
   - removal of foreign material, microorganisms and senescent or altered erythrocytes by splenic macrophages via phagocytosis (ie part of the monocyte-macrophage system).
   - storage of mature erythrocytes in some species (eg horse); spleen size may decrease by contraction of the fibromuscular capsule / trabeculae to release stored blood into circulation in response to hypovolemia, or epinephrine stimulation (note, barbiturate administration relaxes the splenic muscular tissue and results in a spleen engorged with blood)
   - extramedullary hematopoiesis (EMH) is found in the red pulp under certain circumstances in the adult; EMH in red pulp is normal in the fetus and neonate and also in adults of some species (eg rodents, mink).

2) White Pulp (secondary lymphoid organ)
   - plays a role in the immune response, see production of B lymphocytes and plasma cells to produce antibody and memory lymphocytes.
   - the response starts in the red pulp where macrophages / dendritic cells trap and process blood-borne particles / viruses / bacteria / protozoa and present them as processed Ag to lymphocytes (T and B cells) → production of antibody, memory cells, etc.
   - note, splenectomized animals are more susceptible to hemoparasites, eg Mycoplasma haemofelis.

I - Miscellaneous Disorders of the Spleen

1) Siderofibrosis of the splenic capsule (= siderotic nodules or Gamna-Gandy bodies)
   - common incidental finding in aged dogs, likely represent residual effects of prior hemorrhage.
   - gross: granular, white to yellow-tan deposits are present in the splenic capsule (especially at margins).
   - histo: accumulations of hematoidin (yellow pigment), hemosiderin / iron (golden-brown pigment), mineral (blue staining granules) and fibrosis within the affected capsule.

2) Splenic amyloidosis
   - in animals, the most common form of amyloidosis is “secondary amyloidosis”, which is associated with the deposition of amyloid protein AA (an acute phase protein) secondary to chronic inflammation.
   - gross: splenomegaly (not always), beige to orange discoloration, +/- firm prominent white pulp areas.
   - histo: there is deposition of amyloid around follicular arteries (detected with Congo red stain).
3) **Splanic contraction**
- due to contraction of smooth muscle in the capsule/trabeculae which can be induced by catecholamine release, circulatory failure (shock), and acute splenic rupture.
- **gross**: small spleen, wrinkling of the capsular surface, dry on cut surface
- sometimes see incomplete contraction of the spleen due to failure of contraction of the smooth muscle in some areas; grossly appears as numerous variably sized, dark red to black, raised, soft, blood-filled areas with intervening depressed areas (may be indistinguishable from acute splenic infarcts - see below).

4) **Splanic lymphoid necrosis** (for information only)
- acute viral infections can result in lymphocytolysis within splenic lymphoid tissue (white pulp); eg panleukopenia in cats, parvovirus in dogs, pseudorabies in pigs, BVD in bovines, EVR in horses, etc
- splenic lymphoid necrosis may also be seen as a result of stress (increased glucocorticoids), toxins, etc.

5) **Hemosiderosis / hemosiderin deposition** (for information only)
- normally a small amount of hemosiderin (storage form of iron) is present within macrophages in the spleen (due to normal red blood cell turnover).
- increased deposition (called hemosiderosis) suggests increased erythrocyte destruction / decreased erythrocyte half-life; most commonly seen in hemolytic anemias (eg IMHA = immune-mediated hemolytic anemia).
- **gross**: - the spleen appears brown to black.
- **hists**: - macrophages within the red pulp contain abundant golden-brown, granular cytoplasmic pigment.

II - **Circulatory disturbances of the Spleen**

1) **Active hyperemia**
- seen with acute systemic infection, eg bacterial sepsis.

2) **Passive congestion**
- caused by disturbances in systemic and portal circulation; can be seen with shock (vascular pooling), barbiturate administration (especially horses, dogs), and hemolytic anemia.
- not common in animals with right heart failure because the liver buffers much of the back blood pressure.
- **gross**: - the spleen is enlarged/swollen and red-purple to black because of increased amounts of blood (unoxygenated) and oozes blood on cut surface.
- **histo**: - sinuses are dilated & contain rbc’s; germinal centers are widely separated & the trabeculae are thinned.

3) **Splanic Infarction - due to thrombosis or embolism**
- thrombosis and infarction:
  - seen with diseases causing vascular damage, eg certain viruses (Classical swine fever), bacterial sepsis.
  - with hypercoagulable states, eg nephrotic syndrome, IMHA, steroid therapy/Cushings, neoplasia, pancreatitis.
  - splenomegaly (of any cause) makes the spleen prone to thrombosis and infarction.
- embolism and infarction: is usually the result of septic emboli, eg endocarditis of the left heart.
- **gross**: - acutely, infarcts are discrete, slightly raised, dark red areas usually located at the margins of the organ.
  - over time (chronicity) they become depressed, pale and firm (due to fibrosis)
4) Splenic rupture
- most often seen in dogs and cats; can be primary due to trauma (eg hit by car) or may occur secondary to splenomegaly or splenic neoplasm (eg, hemangiosarcoma, lymphoma) which causes thinning of the capsule.
- the result may be death by exsanguination or healing by scarring
- occasional following rupture there may be seeding of splenic explants on peritoneal/serosal surfaces (‘slenosis’); grossly see one or more small red nodules in the omentum which microscopically appear as normal splenic tissue (note, histology often required because grossly they look very similar to seeding metastasis of hemangiosarcoma).

5) Splenic hematoma
- splenic hematoma is one of the more common canine splenic “masses”.
- usually the result of trauma; often associated with nodular hyperplasia or splenic vascular neoplasia.
  - **gross**: red nodular mass(es), bloody consistency, often very large.
  - **histo**: histopathology is necessary to rule-out underlying neoplasia (esp hemangiosarcoma).

6) Torsion of the spleen
- torsion of the spleen, with or without torsion of the stomach, occurs mainly in pigs and dogs.
- if the whole spleen is twisted around gastroplenic ligament, there is severe congestion and hemorrhagic (venous) infarction due to occlusion of the splenic vein; may lead to hemodynamic shock.
  - **gross**: splenomegaly, blue-black in colour, and often folded back on itself (C-shaped).

III - Inflammation of the Spleen

1) Acute splenitis
- occurs with bacterial septicemia (sepsis).
  
  a) Multifocal splenitis
   - in some septicemias, spleens are of relatively normal size with multifocal small (1 to 2 mm diameter) foci of necrosis / suppurative infiltrates.
   - **gross**: small white foci scattered throughout the spleen; similar lesions often present in lymph nodes & liver.
     - slightly larger older lesions may resemble granulomas.

  ❄️ Tularemia (*Francisella tularensis*)
   - tularemia is found world-wide (except for Australia and Antarctica) and is common in wild rodents.
   - it can affect most species, and is an important zoonosis* (can cause severe systemic disease in humans).
   - the organism can penetrate intact skin and mucous membranes, but is also infective by ingestion, inhalation and inoculation by biting insects and ticks.

  ❄️ Yersiniosis (*Yersinia pseudotuberculosis*)
   - esp wild rodents and birds; can affect many species

  b) “Septicemic” (diffuse) splenitis
   - in other septicemias there is marked splenomegaly → spleen is soft, dark and engorged with viscous blood.

  ❄️ African swine fever

  ❄️ Erysipelas
3) **Anthrax** (due to *Bacillus anthracis*)

- in horses, pigs & dogs, localization to the throat or intestine is more common and may be fatal before invasion of the blood occurs (note, dogs and pigs acquire infection by eating infected carcasses).
- in ruminants tends to be a brief septicemic disease.
- with sepsis, the blood swarms with vegetative organisms; these form spores when exposed to air.
- spores of *Bacillus anthracis* may survive for decades in certain soil types and ruminants are frequently infected following soil excavation (probably via ingestion of contaminated food or water, inhalation or entry through traumatized mucous membranes).
- following infection there is a lymphangitis and local lymphadenitis.
- sepsis ensues and bacterial toxins (edema factor, protective antigen, lethal factor) are secreted resulting in increased capillary permeability, impaired coagulation, and injury and inactivation of phagocytes.
- **gross:** in cattle, the characteristic finding is a carcass that bloats and autolyzes rapidly with blood oozing from body orifices.
  - internally there is marked splenomegaly, multiple hemorrhages and edema of the soft tissues.
  - the blood is thick and dark (frequently described as tarry or jam-like) and is either not clotted or the clots are very soft and friable.
  - in pigs and dogs, splenomegaly is not characteristic; they tend to have pharyngeal inflammation with cervical lymphadenitis or localized necrotizing enteritis.
- *you are not supposed to necropsy animals suspected to have died from anthrax!*
- in suspect cases diagnosis should be based on the identification of organisms in blood smears - usually from “nicking” ear or tail; these bacilli have a distinct capsule that stains pink with old methylene blue.

2) **Granulomatous splenitis**

- multiple pale nodules or diffusely swollen / firm spleen (grossly may be difficult to differentiate from neoplasia).
- causes include: *Mycobacterium bovis* (Tuberculosis - nodules), *Brucella* spp, systemic mycotic diseases (eg Histoplasmosis and Blastomycosis) and *Leishmania*.

3) **Splenic abscesses**

- not common and can be caused by a variety of organisms: eg’s *Trueperella* (*Arcanobacterium*) *pyogenes* in cattle, *Rodococcus equi* in horses.

IV - Disturbances of Growth

- **splenomegaly** = enlarged spleen.

1) **Aplasia, malformations**

- these tend to have little pathological significance.

2) **Atrophy**

- grossly there is decreased size and weight with a thick wrinkled capsule; histologically see lymphoid depletion.
- causes include old age (dog, horse) or prolonged cachexia (note, a contracted spleen can look grossly similar).

3) **Nodular hyperplasia**

- common incidental finding in aged dogs.
- cause is unknown, however they may predispose to splenic hematomas.
- **gross:** - single or multiple raised nodules, gray to reddish pink or variegated red and white.
  - usually < 2 cm, but can reach >5 cm in diameter.
- **histo:** - unencapsulated nodules are composed of aggregates of lymphoid tissue, +/- extramedullary hematopoiesis (EMH), separated by congested red pulp.
4) Lymphoid hyperplasia
- hyperplasia of lymphoid follicles and PALS in response to blood-borne antigens/chronic antigenic stimulation.
- **gross**: lymphoid follicles are visible as 1-3 mm white foci scattered throughout the spleen.

5) Hyperplasia of monocyte/macrophage population (Hypersplenism)
- **hypersplenism** = a spleen that is overactive in cell destruction.
- any cause of splenomegaly has the potential to stimulate the phagocytic population of the spleen to proliferate, filling all available splenic space.
- often leads to phagocytic hyperactivity (hypersplenism), with resultant anemia and/or thrombocytopenia.
- hyperplasia of the macrophages can also be caused by infectious agents, usually intracellular pathogens of macrophages (eg *Histoplasma, Leishmania*).

6) Extramedullary hematopoiesis (EMH)
- in response to increased demand (eg anemia, infection) there is proliferation and maturation of normal erythroid and/or myeloid and/or megakaryocytic cell lines in the red pulp of the spleen (expansion of marrow production).
- note, EMH is normal in fetuses and neonates.

V - Neoplasia
- in dogs, nodular tumors must be differentiated from hematomas & nodular hyperplasia; often requires histology / cytology.

1) Primary Neoplasms

a) Lymphoproliferative Diseases *(see previous section)*
- with lymphoma / lymphoid leukemia may see nodular or diffuse splenomegaly; +/- coexisting lymphadenomegaly or lymphoid leukemia.

b) Myeloproliferative Diseases *(see previous section)*
- most myeloproliferative diseases will involve the spleen and liver as the disease progresses.

c) Mast Cell Tumor *(see previous section)*
- diffuse splenomegaly (+/- nodular surface), most common in aged cats.

d) Hemangioma
- benign tumor of endothelial cell origin.
- **gross**: single, soft, nodular, dark red mass.
- **histo**: - composed of cavernous blood-filled spaces lined by well-differentiated endothelium.

e) Hemangiosarcoma
- malignant tumor of endothelial cell origin.
- most common malignant neoplasm of canine spleen (German shepherds predisposed).
- **gross**: single to multiple, discrete to coalescing, dark red masses in the spleen (+/- metastasis)
- **histo**: blood filled vascular spaces lined by anaplastic endothelial cells.
- **sequelae**: splenic hematomas, rupture leading to internal hemorrhage & death, “seeding” the peritoneal cavity (ie neoplastic implants on visceral surfaces; rule-out splenosis), widespread metastasis.

f) Others
- fibrosarcoma, leiomyoma / leiomyosarcoma, fibrohistiocytic nodules / malignant fibrous histiocytoma.
2) Metastatic (secondary) Neoplasms
- metastases in the spleen (as single or multiple nodules) are not as common as expected; the functional efficiency of the sinusoidal macrophages are thought to prevent the establishment of metastatic foci.

The following two tables include important differentials for splenomegaly and splenic nodules:

<table>
<thead>
<tr>
<th>Diffuse splenomegaly with a bloody consistency “Bloody Spleen” (ie due to congestion)</th>
<th>Diffuse splenomegaly with a meaty consistency “Meaty Spleen” (ie due to proliferation of cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Septicemia (eg Anthrax, Salmonella)</td>
<td>Septicemia (eg Salmonella)</td>
</tr>
<tr>
<td>Acute Hemolytic disease</td>
<td>Hemolytic disease</td>
</tr>
<tr>
<td>Splenic torsion</td>
<td>Neoplasia (eg lymphoma, mast cell tumor, histiocytic sarcoma)</td>
</tr>
<tr>
<td>Barbiturate anesthesia or euthanasia**</td>
<td>Granulomatous disease (Histoplasmosis)</td>
</tr>
<tr>
<td>Shock (vascular pooling)</td>
<td>Amyloidosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Splenic nodules with a bloody consistency</th>
<th>Splenic nodules with a firm consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>Nodular hyperplasia</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Primary Neoplasia (eg lymphoma, histiocytic sarcoma, leiomyoma)</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>Metastatic (secondary) Neoplasia</td>
</tr>
<tr>
<td>Acute splenic infarct</td>
<td>Abscess</td>
</tr>
<tr>
<td>Incompletely contracted area of spleen</td>
<td>Granuloma</td>
</tr>
</tbody>
</table>

THYMUS

Normal Structure and Function
- the thymus is a white to tan, lobulated organ, found in the anterior mediastinal region of most mammals.
- ruminants and pigs have a large cervical lobe which extends along the cervical trachea.
- composed of epithelial tissue (from endodermal branchial pouches) and lymphoid tissue (T lymphocytes).
- it is divided into lobules, each lobule having a cortex (immature T cells) and a medulla (mature T cells).
- the thymus provides the necessary microenvironment required for T lymphocytes to proliferate and mature.
- bone marrow derived pre-T lymphocytes arrive via the blood and enter the cortex.
- cortex: - the blood-thymus barrier (epithelial reticular cells and endothelium) isolates the numerous immature T cells from circulating Ag’s.
  - more than 95% of these developing cells are removed (clonal deletion of self reactive cells) → survivors move to the medulla and become CD4+ (helper) or CD8+ (cytotoxic) T cells → migrate via blood to T cell areas of lymphoid tissues (eg paracortex of lymph nodes, PALS of spleen, etc).
- the thymus is large at birth and begins involution at or near puberty (although it remains active throughout life); the involuting organ is gradually replaced by loose connective tissue and fat.
I - Miscellaneous Disorders of the Thymus

1) Lymphocytolysis / Thymic atrophy
• lymphocytolysis in the thymus (as in other organs) is caused by:
  ① Malnutrition
  ② Drugs/Toxins: glucocorticoids, cytotoxic/chemotherapeutic drugs, lead, mercury, PCB, etc.
  ③ Viral infections: Equid herpes virus-1, Feline leukemia virus, Feline immunodeficiency virus, Feline panleukopenia virus, Canine distemper virus, Hog cholera virus, Bovine viral diarrhea virus.
• results in varying degrees of immunodeficiency (ie secondary / acquired immunodeficiency); see increased severity of infectious diseases and an increased susceptibility to opportunistic pathogens (eg normally low or non-pathogenic microorganisms, eg *Pneumocystis carinii*).
• thymic atrophy is normal with advancing age.

2) Thymic aplasia / hypoplasia
• aplastic or hypoplastic thymic disorders occur with loss or functional impairment of T cells and impaired cell-mediated immunity → primary / congenital immunodeficiency.
• many deficiencies involve failure of both T and B cells (= combined immunodeficiency) with morphologic changes including lymph node hypoplasia, lack of splenic white pulp, and thymic hypoplasia.
  - eg SCID (severe combined immunodeficiency) foals, mice, dogs (eg Jack Russell terriers, Basset hounds)
  ① SCID foals (for information only)
    • a combined immunodeficiency syndrome seen in roughly 2% of Arabian-bred foals, with an autosomal recessive mode of inheritance.
    • SCID foals are normal at birth, but usually develop a range of opportunistic infections starting by as early as 10 days of age and are usually dead within 5 months.
    • respiratory infections most common, esp with adenovirus, Pneumocystis carinii and opportunistic bacteria.
    • affected animals are profoundly lymphopenic.
    • gross: - small spleen, lymph nodes and thymus and often have secondary bronchopneumonia.
    • histo: - reduced cellularity of the lymphoid tissue of the thymus, lymph nodes, and spleen.

3) Thymic hemorrhage/hematoma
• occasionally seen in dogs; ie sudden death due to hypovolemic shock resulting from massive thymic mediastinal hemorrhage.
• variety of causes implicated, eg trauma (HBC), ruptured aortic aneurysms, ingestion of anticoagulant rodenticide.

II - Neoplasia

1) Thymic (mediastinal) lymphoma (see also primary hematopoietic neoplasia)
• a T-cell neoplasm of usually younger animals (calves, cats, dogs).
• in cats: have a wide age distribution, ie 1-10 years (often associated with FeLV).
• in cattle: yearlyings, usually beef (no known viral association).
• gross: - large space occupying mass in the cranoventral mediastinum (may see dyspnea).
  - thoracic effusion is common and thoracic aspirates are often used for diagnosis.
• histo: - sheet-like infiltrates of neoplastic lymphocytes.
2) Thymoma:
• less common than lymphoma; mostly in dogs, sheep and goats.
• tend to be slow-growing, heavily encapsulated tumours that rarely metastasize.
• gross: large space occupying mass in the cranioventral mediastinum (may see dyspnea).
• histo: neoplastic proliferation of thymic epithelial elements and varying amounts of non-neoplastic lymphoid tissue.
• sequelae: - in dogs and humans can result in a paraneoplastic syndrome of myasthenia gravis (ie autoimmune attack of the acetylcholine receptors of the neuromuscular junction).
  - in cats may cause a cutaneous paraneoplastic syndrome (ie, feline thymoma-associated exfoliative dermatitis).

OTHER SECONDARY LYMPHOID ORGANS
• includes tonsils, pharyngeal lymphoid follicles, mucosal-associated lymphoid tissue (MALT)
• note MALT includes BALT (bronchial), GALT (gut), and Peyer's patches.
• pathology:
  - see a range of pathologic processes similar to that of lymph nodes.
  - some degree of constant stimulation/inflammation is not surprising since they tend to occur on mucosal surfaces and serve as immunologic sentinels for the body.
  - often the portal of entry for pathogens, eg Mycobacterium avium subsp. paratuberculosis, Listeria, Salmonella.
  - note, lymphoma may arise from MALT (especially in aged cats and dogs); MALT lymphoma tends to be low-grade, of B-cell origin, and is thought to arise in a background of chronic inflammation.

BURSA OF FABRICIUS (for information only)
• located along the dorsal aspect of the cloaca; like the thymus it atrophies as the bird matures.
• in birds, it is the location of proliferation, maturation and removal of self-reactive B cells.
• a specific viral infection of chickens, Infectious Bursal Disease (IBD), causes severe damage to the bursa in young chicks and results in immunodeficiency.
• lymphoid leukosis (due to avian leukosis virus) is a neoplastic proliferation of B cells, which involves many organs, including the bursa.