INTRODUCTION
The hematopoietic system is composed of a wide range of lymphoid tissues and all the fixed and circulating blood cells originating from pluripotent 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):

<table>
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<tr>
<th>Myeloid Tissues</th>
<th>Lymphoid tissues</th>
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<tbody>
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<td>Bone Marrow</td>
<td>Lymph node</td>
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<tr>
<td>Blood cells</td>
<td>Spleen</td>
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<td>Monocyte-macrophage system</td>
<td>Thymus</td>
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<td>Accessory lymphoid tissues (MALT, tonsils)</td>
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Some portions of the hematopoietic system are easily accessible to clinicians and 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 AND BLOOD CELLS

Normal Structure and Function
Definition of 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 (ie change from red marrow to yellow marrow in diaphyseal regions). 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 the long bones contains mostly fat. In adults, when hematopoiesis occurs anywhere other than the marrow (usually the spleen), it is referred to as extramedullary hematopoiesis.

Basic Concepts in Hematopoiesis

- Hematopoietic tissue is highly prolific; all blood cells are derived from a common pluripotential 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 limited life spans.
- The system is under exquisite local and systemic control by soluble stimulatory factors, including: cytokines / hormones / growth factors, and can respond rapidly to various 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 certain abnormal hematology findings:

- Unexplained cytopenias (any non-regenerative anemia)
- Maturation defects or morphologic abnormalities in blood cells
- Suspected myeloproliferative diseases

Examination is also indicated to evaluate for malignancies 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 hematopoietic cells to adipose tissue (altered ratio is seen with aplasia/hypoplasia or hyperplasia/neoplasia)

Please note: thorough evaluation of the bone marrow should include a CBC, a bone marrow aspirate and a bone marrow biopsy.

Pathology of the Bone Marrow and Blood Cells (Alterations / Damage to Hematopoiesis)

The end result is dependent on the type of cells damaged:
  - Pluripotent 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 therefore are 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

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
   - Idiosyncratic Drug Reactions
   - Idiopathic drug toxicity
   - Toxic chemicals

C) Infectious agents
   - Feline parvovirus (panleukopenia)
   - Canine parvovirus
   - Feline leukemia virus (FeLV)
   - Feline immunodeficiency virus (FIV)
   - Equine infectious anemia (EIA)

D) Immune-mediated
   - Specific immune-mediated disorders, eg systemic lupus erythematosus (SLE)
   - Altered surface cell antigens caused 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 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:

A) Bone marrow suppression
- Estrogen in the dog; exogenous (therapeutic) or endogenous (Sertoli cell tumor)
- Anemia of chronic disease
- Anemia of chronic renal disease

B) Lack of nutrients
- Inadequate iron, vitamin B12, folate, etc

C) Endocrine dysfunction
- Hypothyroidism

D) Bone marrow degeneration/necrosis (see previous section)

Gross findings: characterized by increased yellow marrow (fat) and decreased red marrow. Microscopic findings: increased proportion of adipose tissue to hematopoietic cells (despite peripheral demand). Please note: in a normal adult the marrow is ~ 50:50 fat: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: due to hemorrhage, immune or parasitic RBC destruction, anemia, etc

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

C) Myeloid 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.

Microscopic findings: Proliferation of one or more cell lines, along with a shift toward immaturity in those cell lines. If severe, it can revert to extramedullary hematopoiesis (especially in spleen and liver).

3) Bone Marrow Atrophy?
- The term atrophy (decrease in cell size) is seldom used to describe bone marrow.
- An exception is a condition referred to as **serous atrophy of fat** = gelatinous transformation of fat within the marrow due to catabolism of fat associated with starvation from malnutrition or chronic disease.

V) Primary Hematopoietic Neoplasia**
Primary hematopoietic neoplasia results from clonal expansion of hematopoietic cell types. These tumours affect the bone marrow, the blood (leukemia: to be covered in clinical pathology) and the lymphoid tissues (lymph node, spleen, etc.)

Common Features of Primary Bone Marrow Neoplasia:
- **Hypercellular marrow:** reflects uncontrolled proliferation of the neoplastic hematopoietic cells.
- **Anemia:** non-regenerative anemia due to ineffective erythropoiesis. When the bone marrow is occupied by neoplastic hematopoietic cells there is competition for nutrients &/or space (myelophthisis). Additionally, inhibitory factors may be released from neoplastic cells.
- **Thrombocytopenia +/- Neutropenia:** not present in all myeloproliferative diseases.
- **Leukemic cells in peripheral blood:** immature stages of hematopoietic cells in peripheral blood are commonly seen in myeloproliferative disease. This is one of the first laboratory findings which points to the diagnosis of leukemia / myeloproliferative disease.
- **Splenic and hepatic involvement:** myeloproliferative diseases often spread early to involve the spleen and liver. Animals may present with splenomegaly and/or hepatomegaly.

Hematopoietic tumours are broadly divided into:
- **Lymphoproliferative disease:** neoplastic transformation of a lymphoid cell line -lymphocytes
- **Myeloproliferative disease:** neoplastic transformation of one or more bone marrow cell lines (myeloid cells), including: granulocytes (neutrophils, basophils, and eosinophils), erythrocytes, megakaryocytes and monocytes

<table>
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<td><strong>Lymphoproliferative Diseases</strong></td>
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<td>Lymphoid leukemia*</td>
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<td>Plasma Cell Tumours</td>
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*Please note, these are covered in Clinical Pathology and will not be covered here.*
Va) 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).

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 cases can be important for prognosis and treatment options.

1). Lymphoid 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.
- Lymphoid leukemia is lymphocytic (T-lymphocyte or B-lymphocyte) in origin and may be acute or chronic in nature

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

A) Several classifications systems exist, with classification by:
   a) Anatomical site
   - 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 mediastinum / 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 in separating from lymphoid leukemia).

b) Cellular morphology
   - Based on size, nuclear features, mitotic rate
   - Multiple classifications available based on the cytologic features of neoplastic lymphocytes (used to correlate tumor type with best treatment method).
   - Two prognostic assumptions of this method of classification are:
     - Small cell lymphomas with low mitotic rates: slowly progress and show poor response to chemotherapy.
     - Large cell lymphomas with high mitotic rates: progress rapidly but respond to chemotherapy.

c) Immunophenotype
   - Use immunohistochemistry to determine the origin of the lymphoblasts (B-lymphocyte: CD79a, T-lymphocyte: CD3, or non-T/B-lymphocyte) and their stage of differentiation.
• In animals: B-cell lymphomas generally have better survival profiles and response to treatment when compared to T-cell lymphoma*

d) Biologic behavior
- Low-grade (indolent)
- Intermediate
- High grade (aggressive)

e) Histologic pattern
- Diffuse versus follicular

B) Clinical signs of lymphoma:
- Most common sign of lymphoma is painless enlargement (lymphadenopathy) of one to 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 lymphoma often results in diarrhea, intestinal obstruction or melena.

C) Lymphoma, gross findings:
- Affected lymph nodes are moderately to markedly enlarged, soft to firm, often bulge on cut surface and have a homogenous pale tan to white appearance (sometimes with focal areas of necrosis or hemorrhage). Often the nodes are firmly attached to surrounding tissue due to peri-nodal invasion and subsequent fibrosis.
- Lymphoma in other organs can cause diffuse organomegaly (usually splenomegaly/hepatomegaly), single to multiple discrete tan nodules within any affected organ, or 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 degree of anaplasia, mitosis, and apoptosis.

E) Species Differences:
  a) Canine lymphoma:
  Lymphoma is the most common canine hematopoietic neoplasia. Affected animals are often middle-aged and older. Clinical signs are often nonspecific or absent at diagnosis. Ninety percent of dogs with lymphoma have a normal leukogram. Most have a multicentric distribution (about 80 - 85%) with prominent lymph node involvement and the majority of cases are intermediate or high-grade tumors. Other forms include alimentary, cutaneous, mediastinal (thymic), and miscellaneous. The alimentary form is often thought to be preceded by lymphoplasmacytic enteritis (Inflammatory Bowel Disease - IBD). There are no known causes of lymphoma in dogs and no known viral associations. Hypercalcemia of malignancy is sometimes associated with canine lymphoma due to the production of parathyroid hormone-related peptide (PTHrP) by neoplastic cells.
b) Feline lymphoma:
This is the most common malignant neoplasm of cats. In decreasing order of frequency, the
tumors may be alimentary, multicentric, mediastinal (thymic) or miscellaneous (renal, ocular,
etc). Unlike dogs, there is often no peripheral lymph node involvement in cats and leukemia
and bone marrow involvement are common in all forms. Feline lymphoma is characterized
by a short clinical course - approximately 75% of affected cats are dead within 8 weeks 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.

c) Bovine Lymphoma:
i) Enzootic bovine lymphoma (bovine enzootic leukosis): This is primarily a multicentric
disease of adult cattle (average age 5 – 8 years old). In addition to the lymph nodes, the
commonly affected organs include the heart (right atrium), abomasum, uterus, and the
vertebral canal. Clinical signs depend on the organ involved but include lymphadenopathy,
diarrhea, vagal indigestion, congestive heart failure, and posterior paresis/paralysis. The
etiologic agent is Bovine Leukemia Virus (BLV), an oncogenic retrovirus. The virus is
transmitted by transfer of viral infected lymphocytes; mostly horizontal by arthropods,
natural breeding and accidental transmission by needles, ear tagging equipment, etc. Once
infection is established, it is lifelong. The target cell for BLV is the B-lymphocyte.
Approximately 30% of BLV-infected animals develop non-neoplastic persistent
lymphocytosis and, of these, less than 5% develop lymphoma. Dairy cattle are more
commonly affected than beef cattle; likely because of management practices and average age.
BLV may cause lymphoma in sheep and goats and causes widely disseminated tumours.

ii) Sporadic bovine lymphoma: Occurs in young cattle and is not associated with BLV
infection. There are three forms of sporadic lymphoma:
• Calf form - multicentric lymphoma in calves from 3 to 6 months of age. Symmetrical
  lymph node enlargement, often with leukemia and bone marrow involvement. Kidney,
  liver and spleen are often affected.
• Juvenile/thymic lymphoma - mediastinal lymphoma, usually yearling beef breeds.
  Characterized by large cranial thoracic/lower cervical masses, respiratory distress, and
  weight loss in cattle less than 2 years of age.
• Cutaneous form – usually 2 to 3 yr-old cattle. Characterized by plaque-like, round raised
  skin lesions, often with ulceration. Typically located 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.

d. Porcine lymphoma:
Lymphoma is considered to be the most common neoplasm of swine. The lesions are usually
multicentric (visceral lymph nodes, spleen, liver, stomach, intestine, kidney, and bone
marrow involvement are common) or mediastinal and affected animals are often less than
one year old. Females are affected more often than males. A viral cause (C type viruses) has
been suggested, but not substantiated. A familial form of multicentric lymphoma has been described in Large White pigs (autosomal recessive heritability).

e. Equine lymphoma: Has a lower incidence than in cats, cattle and dogs. Multicentric lymphoma is the most common form. Cutaneous, subcutaneous, alimentary, abdominal, splenic, and leukemic forms also occur. Lymphoma in horses is often intermediate or low grade and frequently is of mixed cell type (B lymphocytes and T lymphocytes). Concurrent leukemia is not uncommon.

3) Plasma cell tumours
A. Plasmacytoma
a. Cutaneous plasmacytoma: Solid tumour of plasma cell originating in the skin. Occur in mature animals, most frequently dogs (rarely in cats). Form soft dome-shaped masses which frequently affect the pinna and digits. Usually a solitary benign lesion; surgical excision is often curative. Less often they are more behaviorally aggressive. Microscopically, masses are composed of solid sheets of round cells; may be composed 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 tumours.

b. Extramedullary plasmacytoma: Solid tumour of plasma cell origin arising in sites other than the bone marrow and skin. These are rare tumours which occur more often in dogs (Cocker Spaniels are predisposed) than in other species (cat and horse). Most often arise in the gastrointestinal tract but may also occur in the trachea, spleen, kidney, uterus, etc. Grossly the tumour may be multinodular or cause thickening of the intestinal wall. Tend to be more aggressive than cutaneous plasmacytoma with occasional metastasis to the lymph nodes.

B. Multiple myeloma (plasma cell myeloma)*
Relatively uncommon in domestic animals; seen most often in dogs and cats. These are malignant tumours of plasma cell origin arising within the bone marrow. The neoplastic plasma cells (derived from one clone) secrete immunoglobulins or immunoglobulin fragments of one class leading to hypergammaglobulinemia. Hypergammaglobulinemia is detected by serum protein electrophoresis as a monoclonal spike in the globulin fraction (monoclonal gammopathy*). It can lead to hyperviscosity syndrome (sludging of blood cells, hypotension, and shock). Other findings can include myelophthisis/cytopenas, hypercalcemia* (due to osteoclastic activity in the bone lesions), and light-chain (Bence-Jones) proteinuria*. Bence Jones proteins are free immunoglobulin light chains which pass through the glomerulus into urine – they are detected using electrophoresis and immunoprecipitation.

Gross lesions: Sections of affected bone exhibit multiple dark-red soft / gelatinous tissue nodules filling areas of bone resorption / lysis. Approximately 2/3 of dog cases have radiographic “punched out” lesions in skeleton*. Lesions can be found in any hematopoietically active bone, but are most common in the vertebrae.

Histology: Masses composed of sheets of neoplastic plasma cells in the bone marrow*.
**Clinical signs:** 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. The clinical course is often slowly progressive and neoplastic cells may metastasize to spleen, liver, lymph nodes and kidneys.  

(*Diagnosis of multiple myeloma is often based on a minimum or 2 or 3 of these findings*)

**Vb) Myeloproliferative Diseases**

1) **Myeloid Leukemia** (covered in Clinical Pathology)
- Erythroid, granulocytic, 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:
   A. **Cutaneous histiocytoma** (covered in Dermatopathology)

   B. **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). It is considered an immunoregulatory disorder rather than true neoplasia; with lesions responding (somewhat) to immunosuppressive therapy. The cell of origin is thought to be an activated dermal dendritic cell (an antigen presenting cell). Disease is characterized by multifocal skin masses which wax and wane. Bernese Mountain dogs are predisposed to developing the systemic form which often involves the skin, peripheral lymph nodes, ocular/nasal mucosa, liver, spleen etc.

   C. **Histiocytic Sarcoma/Disseminated Histiocytic Sarcoma (malignant histiocytosis)**
   Rare malignant tumours of histiocytic origin which occur most often in dogs. Breed predilections include Bernese Mountain dogs, Rottweilers and Flat-coated Retrievers. Histiocytic sarcomas may occur as solitary nodules or as multiple lesions that rapidly disseminate in most instances. Solitary masses often arise in the subsynovium of the joints or in the subcutis; however other primary sites have been reported (spleen, lymph nodes, etc.). Disseminated histiocytic sarcoma (malignant histiocytosis) is an aggressive multisystemic disease characterized by the presence of multiple tumour masses in several organ systems; primary sites include spleen, lung, bone marrow, lymph nodes, skin and subcutis. This disease (especially the disseminated form) has a guarded to poor prognosis and often responds poorly to routine chemotherapy. Masses are composed of atypical histiocytes; these tumours may arise from dendritic cells or less often from macrophages. Those arising from macrophages may be avidly hemophagocytic causing rapidly progressive anemia (= hemophagocytic syndrome).

4) **Mast cell tumours** (often not included in myeloproliferative disease)
   A) **Cutaneous mast cell tumours** (covered in dermatopathology)
B) Alimentary mast cell tumours (covered in pathology of the alimentary system)

C) Systemic mastocytosis/visceral mast cell tumours*
Primarily affects the hematopoietic system, especially the spleen. Most commonly occurs in cats. Grossly splenomegaly is evident (diffuse or nodular). Microscopically there is effacement of the splenic architecture by dense sheets of mast cells. Mast cells can be identified on histology by using toluidine blue staining. Other viscera which may be affected include the intestine and liver.

VI) Secondary Bone Marrow 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).

VII) 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

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MONOCYTE MACROPHAGE SYSTEM (MMS) *(for your information only)*
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 (in swine this arrangement is reversed with the cortex at the center and the medulla at the 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 by macrophages and dendritic cells.
  - The inner cortex (paracortical region) contains primarily T lymphocytes.
  - The medulla contains medullary cords (mostly macrophages, B cells and plasma cells) and medullary sinuses (surrounded by macrophages which phagocytose foreign material/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 / Antigen Presenting Cells / lymphocytes for possible immune response).

Modified from: Pathologic Basis of Veterinary Disease
• 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 → leave lymph node via efferent lymphatic if no contact with antigen.

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>
<th>Small Lymph Nodes</th>
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<td>Lymphadenitis</td>
<td>Lymphoid atrophy</td>
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<td>Lymphoid Hyperplasia</td>
<td>Lymph node degeneration</td>
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<td>Hyperplasia of</td>
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<td>Primary neoplasia</td>
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<td>Metastatic neoplasia</td>
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Small Lymph Nodes:
I) Lymph Node Atrophy/Degeneration
• Senile atrophy – seen in aged dogs, cats and primates
• Cachectic atrophy – common, especially old sheep and goats with dental attrition
• Toxins
• Chemotherapy/Irradiation
• Many viral infections cause degenerative changes of the lymph nodes – such as direct lymphocyte necrosis (lymphocytolysis)
  o Egs. feline panleukopenia virus, canine parvovirus, canine distemper virus, bovine viral diarrhea virus, feline immunodeficiency virus
  o With chronicity, often results in lymph node atrophy
• Gross: Lymph nodes are decreased in size
• Histology: Overall reduced cellularity/lymphoid depletion. With toxins/chemo/viral infections, there is often lymphocytolysis in the germinal centers

Enlarged Lymph Nodes:
*Lymphadenopathy or lymphadenomegaly = lymph node enlargement of unknown or unspecified cause.
• Can be localized or generalized:
  o Local enlargement usually reflects a pathological process limited to the drainage area
  o Generalized enlargement is seen with sepsis, certain infectious diseases (tuberculosis, brucellosis), and with lymphoma

II) Inflammation (Lymphadenitis)
Lymphadenitis = an inflammatory response to an infectious agent within the node (be able to differentiate this from reactive lymphoid hyperplasia in which the node is immunologically reactive but free of local invasion).
Lymphadenitis can be acute or chronic:

1) **Acute lymphadenitis**
   - Usually the result of a regional lymph node draining a site of inflammation and subsequently becoming infected. Examples:
     - Infection of the tracheobronchial lymph nodes in pneumonia
     - Infection of the supramammary lymph nodes in mastitis
     - Infection of the mesenteric lymph nodes with enteritis
     - 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 components of the node.
     - Exudates are usually serous, but may be hemorrhagic or suppurative.

2) **Chronic lymphadenitis**
   - Characteristic features are increased size and firm texture due to fibrosis; lymph node may become irregularly shaped, dry and indurated with prolonged inflammation.

   A) **Chronic suppurative lymphadenitis (ie. lymph node abscess):** Swollen lymph node with a necrotic / pus- filled center (can have fistulous tract draining to the skin surface), in response to pyogenic bacteria.

     - **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.

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

     - **Streptococcal adenitis in dogs:** *Streptococcus sp* *(Lancefield group G)*. Occurs in minor endemics in kennels. Characterized by pharyngitis, fever, conjunctival discharge, and enlargement of the submaxillary nodes with abscessation. Usually transient.

     - **Caseous lymphadenitis:** Common disease of sheep and goats caused by *Corynebacterium pseudotuberculosis*. The etiologic 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 (shear wounds) or rarely enters the body by inhalation and drains to the regional lymph nodes. In young animals 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 there may be slow spread of disease with time to produce abscesses in the internal organs (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

- **Nodular (focal to multifocal) granulomatous lymphadenitis:**
  - *Mycobacterium avium* subsp. *paratuberculosis* (Johne’s disease)
  - Several non-caseating granulomas in the mesenteric lymph nodes
  - *Mycobacterium bovis* (bovine tuberculosis)*
    - Single to multiple discrete white to yellow nodules with central caseous necrosis
    - Initially in regional lymph nodes (e.g., trachobronchial lymph nodes in the case of pulmonary tuberculosis) but can become disseminated affecting lymph nodes throughout the body
  - **Gross:** Enlarged lymph nodes with single to multiple (coalescing) pale caseous nodular lesions. Often have gritty (mineralized) centers.
  - **Histology:** Nodular aggregates of epithelioid macrophages, multinucleated giant cells, fewer lymphocytes and plasma cells surrounding central regions of necrosis +/- mineralization. Acid-fast bacilli are located in lesions.
    - *Actinobacillus lignieresi* (wooden tongue)
    - Migrating parasitic larvae

- **Diffuse granulomatous lymphadenitis:** Generally see enlarged, dry firm nodes
  - Porcine Circovirus type-2* (PCV-2) – granulomatous inflammation with large botryoid intracytoplasmic viral inclusions within macrophages.
  - *Histoplasma capsulatum* is a facultative intracellular pathogen of macrophages. Therefore disease is characterized by diffuse involvement of the mononuclear phagocyte system.
    - Marked proliferation of macrophages in the spleen, lymph nodes, liver, lungs and intestine → enlarged lymph nodes, spleen and liver
  - *Blastomyces dermatitidis* and *Cryptococcus neoformans*
    - Affects regional lymph node draining the affecting areas (skin, lungs, etc)

III) Lymph Node Hyperplasia

- **Hyperplastic changes lead to lymph node enlargement (lymphadenopathy)**
- **Hyperplastic changes may involve lymphoid tissue (lymphoid hyperplasia) and/or cells of the monocyte-macrophage system (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.
- One classical example of reactive hyperplasia is seen in local lymph nodes draining a site of local infection or a site of vaccination.
- **Reactive hyperplasia also occurs during early lymphadenitis, but changes in the lymphoid**
cell population may be obscured by the infection / inflammatory response.

- **Gross**: Moderate enlargement of affected lymph nodes, may bulge on cut section.
- **Histologically**: Proliferation of the lymphoid follicles with prominent germinal centers, increased T-cells in the paracortex, and increased plasma cells in the medullary cords.

**IV) Neoplasia**

1) **Primary Neoplasia – Lymphoma**: *See primary neoplasia of the hematopoietic system*

2) **Secondary Neoplasia (metastatic)**

Lymph node metastasis is commonly seen with carcinoma (mammary, squamous cell, prostatic, etc), malignant melanoma (especially of the oral cavity of dogs) and mast cell tumors. Grossly, the lymph nodes may be enlarged. Histologically there may be few cells within the peripheral/medullary sinuses or there may be 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, which is located in the left cranial abdomen within the omentum, is covered by a fibromuscular capsule and the parenchyma is incompletely dissected by trabeculae.
- Histologically, the splenic parenchyma consists of **white pulp** and **red pulp**:
  - **White pulp** consists of periarteriolar lymphoid sheaths = PALS (T cells), appended lymphoid nodules (B cells), and a peripheral marginal zone (rich in phagocytic macrophages and dendritic cells)
  - **Red pulp** consists of fenestrated vascular spaces and splenic cords (reticular cells/fibers) supporting macrophages, lymphocytes, plasma cells and blood cells (granulocytes, platelets, red blood cells).

**Function**: Just as the lymph nodes filter lymph, the spleen filters blood:

- **Red Pulp**
  - Removal of foreign material, microorganisms, and senescent or altered erythrocytes by splenic macrophages via phagocytosis (→ part of the monocyte macrophage system).
  - Storage of mature red blood cells 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.
  - 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 (rodents, mink).
• **White Pulp (secondary lymphoid organ)**
  • Plays a role in the immune response, with 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 antigen $\rightarrow$ T and B cells $\rightarrow$ production of antibody, memory cells, etc.
  • Note: splenectomized animals are more susceptible to hemoparasites, eg *Mycoplasma haemofelis*.

I) **Miscellaneous diseases**

1) **Splenic lymphoid necrosis**
  • Acute viral infections can result in lymphocytolysis within splenic lymphoid tissue (white pulp).
    - Panleukopenia in cats, Parvovirus in dogs, Pseudorabies in pigs, BVD in cattle, etc
  • Spleenic lymphoid necrosis may also be seen as a result of stress (increased glucocorticoids), toxins, etc.

2) **Siderofibrosis of the splenic capsule (= siderotic nodules or Gamma-Gandy bodies)**
  • Very common incidental finding in dogs, likely represent residual effects of prior hemorrhage.
  • **Gross**: Granular, white to yellow-tan deposits within the splenic capsule.
  • **Histology**: Accumulations of hematoidin (yellow pigment), hemosiderin/iron (gold-brown pigment), mineral (blue deposits) and fibrosis within the affected capsule.

3) **Hemosiderosis / hemosiderin deposition**
  • 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 suggests increased erythrocyte destruction / decreased erythrocyte half-life; most commonly seen in hemolytic anemia (eg IMHA).
  • Only significant if excessive to the point of causing tissue injury.
  • **Gross**: The spleen may appear brown to black.
  • **Histology**: Macrophages within the red pulp contain abundant golden-brown, granular pigment.

4) **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 discoulouration, +/- firm prominent white pulp areas.
  • **Histology**: There is deposition of amyloid around follicular arteries (detect with Congo red).

5) **Splenic contraction**
  • Due to contraction of smooth muscle in the capsule/trabeculae. Induced by catecholamine release, circulatory shock, and acute splenic rupture.
• **Gross:** Small spleen, wrinkling of the capsular surface, dry on cut surface
• Can see **incomplete contraction** - due to failure of contraction of the smooth muscle in some areas.
  o **Gross:** Numerous dark red to black, raised soft blood filled areas of various size with intervening areas of depression. May be indistinguishable from acute splenic infarcts.

6) **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 neoplasia (eg, hemangiosarcoma, lymphoma) which cause thinning of the capsule.
• The result may be death by exsanguination or healing by scarring
• Occasionally following rupture there may be seeding of splenic explants on peritoneal / serosal surfaces forming **accessory spleens** (‘splenosis’).
• **Accessory spleens:**
  o **Gross:** One + small red nodules within the omentum (looks similar to hemangiosarcoma implants/metastases)
  o **Histology:** Identical to normal spleen

II) **Circulatory disturbances**
1) **Active hyperemia** *
• Seen with acute systemic infection and 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

• **Gross:** the spleen is enlarged/swollen and red-purple to black because of increased amounts of blood (unoxgenated) and oozes blood on cut surface.
• **Histology:** Vascular spaces are dilated and contain erythrocytes. The germinal centers are widely separated and the trabeculae are thinned.

3) **Splenic Infarction** * - due to thrombosis or embolism
• **Thrombosis and infarction**
  o Seen with diseases causing vascular damage: certain viruses (Classical swine fever), bacterial sepsis
  o Seen with hypercoagulable states: nephrotic syndrome, IMHA, steroid therapy/Cushing’s disease, neoplasia, pancreatitis
  o Splenomegaly for any reason makes the spleen prone to thrombosis and infarction
• **Embolism and infarction** is usually the result of septic emboli: eg. endocarditis of the left heart, vena caval thrombosis of cattle.
• **Gross:** Acutely, infarcts are discrete, slightly raised, dark red areas usually located at the margins of the organ. With time (chronicity) they become depressed, pale and firm (fibrosis)
4) Splenic hematoma*
• Splenic hematoma is one of the more common canine splenic “masses”.
• Usually the result of trauma. Can be associated with nodular hyperplasia or splenic vascular neoplasia.
• **Gross**: Red nodular mass(es), bloody consistency, often very large
• Histopathology necessary to rule-out underlying neoplasia*, especially hemangiosarcoma.

5) 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 the gastrosplenic 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, and often folded back on itself (C-shaped).

III) Inflammation
1) Acute Splenitis*:
A) Spleens of relatively normal size may contain multifocal small (1 to 2 mm diameter) foci of necrosis / suppurrative infiltration.
• Tularemia (*Francisella tularensis*) – esp. wild rodents, can affect most species, zoontic
  o Tularemia is found world-wide and is abundant in nature as an infection of rodents.
    In humans, it causes severe systemic disease. 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.

• **Gross**: Small white miliary foci scattered throughout the spleen. Similar lesions may be present in the lymph nodes and liver. Slightly larger older lesions may resemble granulomas.

B) In other septicemias there is marked splenomegaly = “septicemic splenitis”→ the spleen is soft, dark and engorged with viscous blood:
• Hog cholera (Classical swine fever) – may also see splenic infarction
• African swine fever
• Erysipelas
• Anthrax**

**Anthrax** is caused by *Bacillus anthracis*, a gram-positive bacillus. In horses, pigs, and dogs localization to the throat or intestine is more common and may be fatal before invasion of the blood occurs. In ruminants, Anthrax 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, characteristic findings are a carcass that bloats and autolyses 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) and either is 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. Dogs and pigs acquire infection by eating infected carcasses.

*You are not supposed to necropsy animals suspected to have died from anthrax!*

Diagnosis should be based on the identification of organisms in blood smears – usually from the ear or tail. These bacilli have a distinct capsule that stains pink with old methylene blue.

2) **Granulomatous splenitis***:
- Can lead to multiple pale nodules or a diffusely swollen and firm spleen (grossly it may be difficult to differentiate from neoplasia). Causes include: *Mycobacterium* spp. (eg. Tuberculosis), *Brucella* spp, systemic mycotic diseases (eg Histoplasmosis and Blastomycosis) and Leishmania.

3) **Splenic abscesses**:
- Relatively rare, but can follow sepsis with pyogenic bacteria: *Arcanobacterium pyogenes* in cattle, *Rhodococcus equi* in horses.

IV) **Disturbances of Growth**

*Splenomegaly* = enlarged spleen

1) **Aplasia, malformations**
- These tend to have little pathological significance.

2) **Atrophy**
- Causes include old age (dog, equine) or prolonged cachexia
- **Gross:** There is decreased size and weight with a thick wrinkled capsule (similar to contraction)
- **Histology:** see lymphoid depletion.

3) **Nodular hyperplasia***
- Common incidental finding in aged dogs and occasionally old bulls.
- The 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.
- **Histology:** Unencapsulated nodules are composed of aggregates of lymphoid tissue +/- extramedullary hematopoiesis, separated by congested red pulp
4) **Lymphoid hyperplasia***
- Hyperplasia of the lymphoid follicles and the PALS
- Response to blood-borne antigens/chronic antigenic stimulation.
- **Gross:** lymphoid follicles are visible as 1 – 3mm 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 (*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). Normal in fetuses and neonates.

V) **Splenic Neoplasia***
In dogs, nodular tumors must be differentiated from nodular hyperplasia and splenic hematomas; often requires histologic/cytologic examination.

1) **Primary Neoplasms**
   A) **Lymphoma / Lymphoid Leukemia***: *See primary neoplasia of the hematopoietic system*
   - May see nodular or diffuse splenomegaly; +/- coexisting lymphadenomegaly or lymphoid leukemia.

   B) **Myeloproliferative Diseases**
   - Most myeloproliferative diseases will involve the spleen and liver as the disease progresses.
   - See sections on histiocytic neoplasia and mast cell tumours in pathology of the bone marrow and blood.

   C) **Hemangioma***
   - Benign tumour of endothelial cell origin.
   - **Gross:** Single, soft, nodular, dark red mass.
   - **Histology:** Composed of cavernous blood-filled spaces lined by well-differentiated endothelium.

   D) **Hemangiosarcoma***
   - Malignant tumour 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).
• **Histology**: Composed of blood filled vascular spaces lined by anaplastic endothelial cells.
• **Sequelea**: Splenic hematomas, splenic rupture (leading to internal hemorrhage and death), neoplastic implants in the peritoneum (looks like splenosis), widespread metastasis.

E) **Others**
• Fibrosarcoma, leiomyosarcoma, fibrohistiocytic nodules/ malignant fibrous histiocytoma.

2) **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”</th>
<th>Diffuse splenomegaly with a meaty consistency “Meaty Spleen”</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Congestion</td>
<td>- Due to proliferation of cells</td>
</tr>
<tr>
<td>Septicemia (Anthrax, Salmonella)</td>
<td>Septicemia (Salmonella)</td>
</tr>
<tr>
<td>Hemolytic disease</td>
<td>Hemolytic disease</td>
</tr>
<tr>
<td>Splenic torsion</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Barbiturate euthanasia**</td>
<td>Mast cell neoplasia</td>
</tr>
<tr>
<td></td>
<td>Histiocytic sarcoma</td>
</tr>
<tr>
<td></td>
<td>Granulomatous disease (Histoplasmosis)</td>
</tr>
<tr>
<td></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</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>Metastatic 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.
• In the 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
1) Lymphocytolysis/Thymic atrophy
• Lymphocytolysis in the thymus (as in other organs) is caused by:
  o Malnutrition
  o Drugs/Toxins
  o 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)
  o see increased severity of infectious diseases and an increased susceptibility to opportunistic pathogens.
• 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:
  o 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.
    ▪ SCID (severe combined immunodeficiency) in foals, mice, dogs (Jack Russell terriers, Bassett hounds).
3) **Thymic hemorrhage/hematoma***
- Reported in dogs: sudden death due to hypovolemic shock resulting from massive thymic and mediastinal hemorrhage. Variety of causes have been implicated: trauma (HBC), ruptured aortic aneurysms, ingestion of anticoagulant rodenticide.

**II) Neoplasia**

1) **Thymic (mediastinal) lymphoma*** (also see primary hematopoietic neoplasia)
   - **T-cell neoplasm**, usually younger animals (calves, cats, dogs).
     - In cats: wide age distribution: 1 – 10 years, often associated with FeLV infection.
     - In cattle: yearlings, usually beef: no viral association.
   - **Gross**: Large space occupying mass in the cranioventral mediastinum (may see dyspnea).
     - Thoracic effusion is common and thoracic aspirates are often used for diagnosis.
   - **Histology**: Sheet-like infiltrates of neoplastic lymphocytes.

2) **Thymoma***
   - Less common than lymphoma; seen most commonly 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).
   - **Histology**: Neoplastic proliferation of thymic epithelial elements accompanied by varying amounts of non-neoplastic lymphoid tissue.
   - In dogs and humans can result in a paraneoplastic syndrome of **myasthenia gravis** (ie autoimmune attack of the acetylcholine receptors of the neuromuscular junction).

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**OTHER SECONDARY LYMPHOID ORGANS (for your information only)**

Including **tonsils, pharyngeal lymphoid follicles, Mucosal-associated lymphoid tissue (MALT)** (including BALT, GALT, and Peyer’s patches)

Pathology: Subjected to 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 (*Mycobacterium avium subsp. paratuberculosis, Listeria monocytogenes, Salmonella*).
- Please 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.

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**BURSA OF FABRICIUS (for your information only)**
- Located along the dorsal aspect of the cloaca; like the thymus it atrophies as the bird matures.
- 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.