Hematopoietic system

Myeloid Tissue
- Bone marrow
- Blood cells
- Mononuclear-phagocyte system

Lymphoid Tissue
- Lymph nodes
- Spleen
- Thymus
- Accessory lymphoid tissue
Clinical evaluation of the hematopoietic system

- Some components easily accessible:
  - CBC*
  - Blood smears*
  - Peripheral lymph node aspirates*

- Other components require more invasive techniques:
  - Bone marrow aspirates*
  - Biopsies: lymph nodes, spleen and bone marrow (core)
  - Necropsy: useful for lymphoid organs, less so for marrow

* These are done by clinical pathologists
Blood cells are made in the following sites:

- Embryo: yolk sac
- Fetus: liver, spleen, thymus, lymph node & bone marrow
- Neonates: mostly bone marrow (long & flat bones)
- Adults: bone marrow in all regions of flat bones & extremities of long bones
  - Elsewhere depending on need = Extramedullary hematopoiesis (EMH)
Development of hematopoietic system

Bone marrow of cattle of various ages
Basic concepts of hematopoiesis

(from Kierszenbaum AL: Histology and cell biology: an introduction to pathology, St Louis, 2002, Mosby.)
Basic concepts of hematopoiesis

- Hematopoietic tissue is highly prolific
- All blood cells are derived from a common stem cell
- Pluripotential stem cells are capable of self renewal and further differentiation
- Pluripotent stem cell committed cells maturing cells mature cells
- This system is controlled by soluble stimulatory factors:
  - Cytokines, hormones, and growth factors
- Production and turnover of blood cells are balanced in health
- Normally only mature cells are released into circulation
  - Release of immature cells indicates stress or disease
Bone marrow evaluation

• Located in multiple sites but responds as a single tissue
• Samples can be taken from any bone with red marrow:
  – proximal femur or the iliac crest of dogs
  – sternum of horses
  – proximal rib of cattle
• Aspirates and/or core biopsies
Bone marrow evaluation

• Indicated when abnormalities are identified on hematology
  • Unexplained cytopenias
  • Maturation or morphological defects (atypical cells in circulation)
  • Potential myeloproliferative diseases
• Potential malignancies metastatic to marrow
# Bone marrow evaluation

<table>
<thead>
<tr>
<th>Bone marrow aspirate/smears:</th>
<th>Important for:</th>
</tr>
</thead>
</table>
| Interpreted by clinical pathologists | • Cellular morphology  
• Erythroid to myeloid ratio  
• Primary or metastatic neoplasia |

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<tr>
<th>Bone marrow core biopsy:</th>
<th>Important for:</th>
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</table>
| Interpreted by morphologic pathologists | • Ratio of fat cells to hematopoietic cells  
• Myelofibrosis  
• Primary or metastatic neoplasia |

Should be interpreted in conjunction with a CBC!
Bone marrow and blood cells: Altered hematopoiesis

End result depends on the type of cell damaged

- Pluripotent stem cells = multiple cell lines affected
- Committed stem cells = one or more lines affected
- Differentiated cells = one cell type affected

Alterations are reflected in the peripheral blood

- Decreases in cell lines = cytopenias, anemia
- Increases in cell lines = ‘cytosis and ‘philias

In the bone marrow changes are reflected as increases or decreased cellularity

- Changes in the proportion of hematopoietic tissue (red marrow) to adipose tissue (yellow marrow)
Hematopoietic tissue is highly active → susceptible to insults

- Radiation
- Toxins/Drugs
  - Antineoplastic / immunosuppressive drugs
  - Idiosyncratic drug reactions
  - Toxic chemicals
- Infectious Agents
  - Feline and canine parvovirus
  - FeLV
  - FIV
  - EIA
- Immune-mediated
  - SLE
- Idiopathic
Bone marrow: Inflammation

- Inflammation of the bone (osteitis) and the medullary cavity (myelitis)

Vertebral osteomyelitis in a cow
Bone marrow and blood cells: Adaptations of growth

Bone marrow hypoplasia/aplasia

- Decreased proliferative activity
- One or multiple cell lines can be affected

• **Causes:**
  - Bone marrow suppression
    - Estrogen (exogenous and endogenous)
    - Chronic disease
    - Chronic renal disease
  - Lack of nutrients
    - Iron
    - Vitamin B12
    - Folate
  - Endocrine dysfunction
    - Hypothyroidism
  - Bone marrow degeneration
Bone Marrow Hypoplasia/Aplasia

- **Gross**
  - Increased yellow marrow

- **Histo**
  - Increased ratio of fat to hematopoietic cells

**Normal bone marrow**

**Hypoplastic bone marrow**
Response to increased peripheral demand or hypofunction of blood cells:

- Erythroid hyperplasia → response to decreased red cells
- Megakaryocytic hyperplasia → response to decreased platelets
- Myeloid hyperplasia → cell line depends on stimulus
  - Neutrophilia: bacterial infections, tissue necrosis
  - Eosinophilia: parasites, hypersensitivities
  - Monocytosis: chronic / specific infections

May affect one or more cell lines
Bone marrow and blood cells: Adaptations of growth

Bone Marrow Hyperplasia

Gross lesions:
- Red marrow replaces the yellow marrow
  - Metaphyses
  - Endosteal surface of diaphysis
  - Progress to occupy entire marrow cavity
**Histology**

- Increased cellularity (decreased ratio of fat to hematopoietic cells)
- One or more cell lines affected
- Shift toward immaturity (i.e., left shift in PMN’s)
- Extramedullary hematopoiesis (spleen & liver) if severe

**Bone Marrow Hyperplasia**

*Normal bone marrow*

*Hyperplastic bone marrow*
Serous atrophy of fat = gelatinous transformation of fat within the marrow. Due to cachexia
Primary Hematopoietic Neoplasia

- Clonal proliferative disorders of hematopoietic cell types
  - Affecting the bone marrow, the blood, and lymphoid tissue

- Common associated features:
  - Bone marrow hypercellularity
  - Anemia
  - Thrombocytopenia/neutropenia
  - +/- Leukemic cells in peripheral blood
  - Involvement of spleen and liver

- Divided into myeloproliferative and lymphoproliferative diseases:
  - Myeloid cells: granulocytes (neutrophils, eosinophils, basophils), monocytes/macrophages, erythrocytes, and megakaryocytes
  - Lymphoid cells: Lymphocytes (B and T Cells)
Primary Hematopoietic Neoplasia

Hematopoietic Neoplasia

Lymphoproliferative Disease

- Lymphoma
- Lymphoid leukemia
- Plasma cell tumours

Myeloproliferative Disease

- Histiocytic Neoplasia
- Myeloid leukemia
- Myelodysplastic Syndrome
- Mast cell tumour?
Lymphoproliferative disease

- Neoplastic disorders of lymphocytes
  - T cells and B cells (including plasma cells)
- Includes:
  - **Lymphoid leukemia** = Neoplastic lymphocytes in bone marrow/blood
  - **Lymphoma** = Neoplastic lymphocytes in tissues / organs
**Lymphoproliferative disease: Lymphoma**

***Lymphoma (lymphosarcoma) is one of the most common malignant tumor in domestic animals***

**Affects several species!**

**Causes include:**
- Viral infection
  - cats, cattle, mice, chickens
- Hereditary
  - porcine
- Unknown (sporadic)
Several methods of classification of lymphomas:

<table>
<thead>
<tr>
<th>Anatomical classification</th>
<th>Cellular morphology</th>
<th>Immuno-phenotype</th>
<th>Biologic behaviour</th>
</tr>
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<tbody>
<tr>
<td>• Multicentric</td>
<td>• Cell size</td>
<td>• B-cell</td>
<td>• Low grade</td>
</tr>
<tr>
<td>• Alimentary</td>
<td>• Nuclear features</td>
<td>• T-cell</td>
<td>(indolent)</td>
</tr>
<tr>
<td>• Thymic</td>
<td>• Mitotic rate</td>
<td>• Non-B/T</td>
<td>• Intermediate</td>
</tr>
<tr>
<td>• Cutaneous</td>
<td></td>
<td></td>
<td>grade</td>
</tr>
<tr>
<td>• Misc.</td>
<td></td>
<td></td>
<td>• High grade</td>
</tr>
<tr>
<td>• Leukemic</td>
<td></td>
<td></td>
<td>(aggressive)</td>
</tr>
</tbody>
</table>

Pathological classification is very significant and advanced in humans due to prognostic factors
- In animals: B-cell lymphomas may have better survival profiles and response to treatment when compared to T-cell lymphoma
- Small cell lymphoma with low mitotic rate – slow progression, poor response to chemotherapy
- Large cell lymphoma with high mitotic rate – rapid progression, respond to chemotherapy
Clinical signs vary:
- Non specific signs:
  - weight loss and loss of appetite
- Painless swelling of 1+ lymph nodes
  - Lymphadenopathy
- Other signs depend on anatomic location:
  - Retrobulbar lymph nodes $\rightarrow$ exophthalmos
  - Thymic $\rightarrow$ dyspnea, esophageal obstruction
  - Alimentary $\rightarrow$ diarrhea, obstruction or melena
Gross lesions of lymphoma

- Soft to firm, bulge on cut surface, homogenous, pale tan to white
- Foci of necrosis or hemorrhage are common
- Often firmly attached (fibrosis) to surrounding tissue
Gross lesions of lymphoma

Organomegaly: diffuse organ enlargement

Multiple tan-white to pink nodules within organs
Microscopic lesions of lymphoma

1. Homogenous populations of neoplastic round cells efface the normal architecture
2. Uniform population of small lymphocytes
3. Round cells with: Anisocytosis, Anisokaryosis, and Mitotic figures

Images: Dr SJ Newman, College of Veterinary Medicine, University of Tennessee
Canine lymphoma

- Most common canine hematopoietic neoplasia
- Middle aged to older animals
- 85% have multicentric lymphoma
  - Usually medium to high grade
- No known viral association
- Hypercalcemia of malignancy
Canine lymphoma

Cutaneous

Alimentary

Thymic
Feline lymphoma

- Most common malignant neoplasm of cats*
- Alimentary > multicentric > thymic > miscellaneous forms
- Leukemia and bone marrow involvement are common
Feline lymphoma

Association with Feline Leukemia Virus (FeLV):
- 10 - 20% of cats with lymphoma are FeLV +
- Mediastinal or multicentric form
- Young cats!
Bovine lymphoma

Enzootic Bovine lymphoma

- **Adult cattle**, especially dairy cattle
- Multicentric lymphoma of B cell origin

- **Bovine leukemia virus (retrovirus)**
  - 30% of infected cattle → persistent lymphocytosis
  - 3% of infected cattle → lymphosarcoma

**Transmission**: direct contact, natural breeding, contaminated needles, dehorning and ear-tagging equipment, arthropods
Enzootic Bovine lymphoma

Commonly affected sites:
- Lymph node
- Right Atrium
- Abomasum
- Spinal canal
- Uterus
- Kidney
Sporadic Bovine lymphoma

Affects young animals, 3 forms:

1. Calf Form
   - < 6 months of age
   - Symmetrical lymphadenopathy and leukemia
   - Terminally: Bone marrow involvement +/- organ infiltration

Looks similar to enzootic lymphoma in the late stages
2. Juvenile Form = Thymic Form

- Yearling beef cattle
- Mediastinal mass
# Bovine lymphoma

## Sporadic Bovine lymphoma

### 3. Cutaneous Form

- 2 – 3 year old cattle
- Plaque –like to nodular, round, raised skin lesions
- Waxing and waning
- Survive 12 – 18 months
- Eventual systemic involvement

![Image of a cow with cutaneous lesions](image-url)
Porcine lymphoma

- Most common neoplasm of pigs
- Multicentric
- Often < 1 year old
- Females > males
- Hereditary predisposition
  - Large White pigs
Equine lymphoma

• Separate forms based on topography
  1. Subcutaneous form – females
  2. Alimentary form
  3. Abdominal form
  4. Splenic form
  5. Multicentric
Plasma cell tumors - Plasmacytoma

1. Cutaneous plasmacytoma
   - Common benign skin masses in dogs
   - Surgical excision usually curative

2. Extramedullary plasmacytoma
   - Arising at sites other than BM
   - Often affect the GI tract
   - More aggressive, may metastasize to the lymph nodes

**Histologically:** Sheets of round cells (plasmacytoid). Can exhibit marked anisocytosis and anisokaryosis
3. Plasma cell myeloma / Multiple myeloma

- Malignant tumour of plasma cells arising in the bone marrow
- Uncommon (dogs > cats)
- Usually multiple masses within bone marrow:
  - Gross: Pale tan to pink-red, gelatinous masses replace bone
  - Histologically: Sheets of round cells! Again – with plasmacytoid morphology
Plasma cell tumors

3. Plasma cell myeloma / Multiple myeloma

- Any hematopoietically active bone
  - Especially vertebrae
Plasma cell tumors

3. Plasma cell myeloma / Multiple myeloma

• Any hematopoietically active bone
  • Especially vertebrae

courtesy Dr LeeAnn Pack, AVC
Affected bones have “punched” out appearance on radiographs

- Variety of clinical signs
  - Pain in affected bones
  - Paraplegia due to spinal cord compression
  - Hypercalcemia due to osteolysis of bone lesions

Plasma cell tumors

3. Plasma cell myeloma / Multiple myeloma

http://www.vetsurgerycentral.com/bonecancer.htm
3. Plasma cell myeloma / Multiple myeloma

- Neoplastic cells produce immunoglobulins/fragments
  - Monoclonal gammopathy on serum electrophoresis
  - Hyperviscosity syndrome
  - Bence-Jones proteinuria

![Normal Cat Serum](image1.jpg)

![Monoclonal gammopathy](image2.jpg)
Questions?