

# Hematopoietic tumours in Rodents

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INHAND Classification of hemapoietic tumours

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# Hematopoietic tumours in Rodents

- Induction
- Incidence
- Classification

# Induction of Hematopoietic Tumours

- Chemicals
- Viruses
- Radiation
- Immunity
- Diet and others

# Incidence of hematopoietic tumours (%)

## Rats

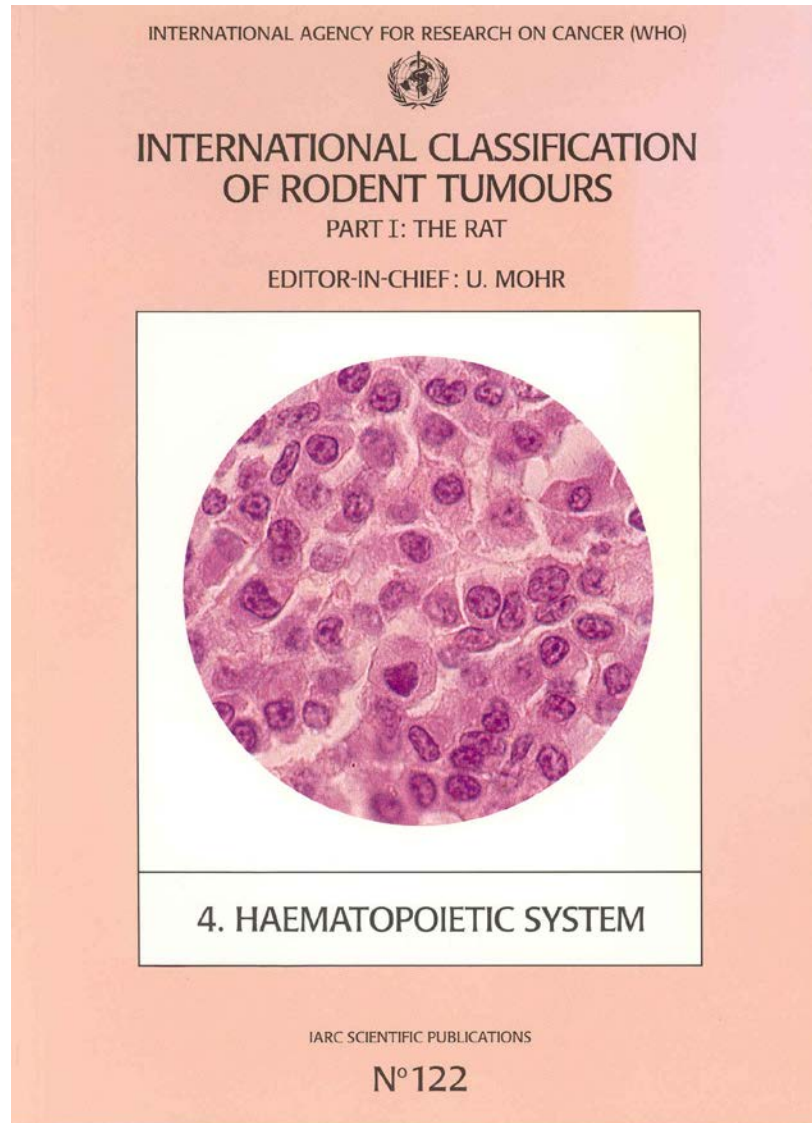
Tumour type	Males (n=5912)	Females (n=5714)
Leukaemia, granulocytic	0.3	< 0.1
- Eosinophilic		< 0.1
- Neutrophilic	0.2	< 0.1
- NOS	0.2	
Leukaemia, NOS	< 0.1	< 0.1
Lymphoma, malignant	<b>2.9</b>	<b>1.8</b>
- Lymphoblastic	0.6	0.1
- Lymphocytic	0.4	0.2
- NOS	0.2	0.4
- Plasmacytic		< 0.1
- Pleomorphic	0.6	0.4
- Large granular lymphocyte leukaemia	1.1	0.6
Tumour, mast cell, malignant	< 0.1	< 0.1
Thymoma, benign	<b>3.6</b>	<b>6.2</b>
Thymoma, malignant	0.4	0.4
Histiocytic sarcoma	<b>1.8</b>	<b>1.2</b>

# Incidence of hematopoietic tumours (%)

## Mouse

Tumour type	Males (n=2100)	Females (n=1992)
Leukaemia, granulocytic	0.4	0.6
- Neutrophilic	0.2	0.3
- NOS	0.2	0.3
Lymphoma, malignant	<b>10.3</b>	<b>25.5</b>
- Lymphoblastic	1.0	1.2
- Lymphocytic	1.0	2.0
- NOS	0.2	1.3
- Pleomorphic	<b>8.1</b>	<b>21.0</b>
Tumour, mast cell, malignant	0.1	<0.1
Thymoma benign	0.3	0.7
Histiocytic sarcoma	<b>4.5</b>	<b>11.5</b>

# Hematopoietic tumours in Rodents



Succeeded by the  
INHAND classification

Draft present on goRENI

## Haematopoietic Tissue

- Lymphoma
- Leukaemia, erythroid
- Leukaemia, myeloid (granulocytic)
- Leukemia megakaryocytic
- Leukaemia, nos
- Tumour, mast cell (benign, malignant, leukemia, sarcoma )

## Mononuclear Phagocyte System

Sarcoma, histiocytic

## Lymphoma (to differentiate or not?)

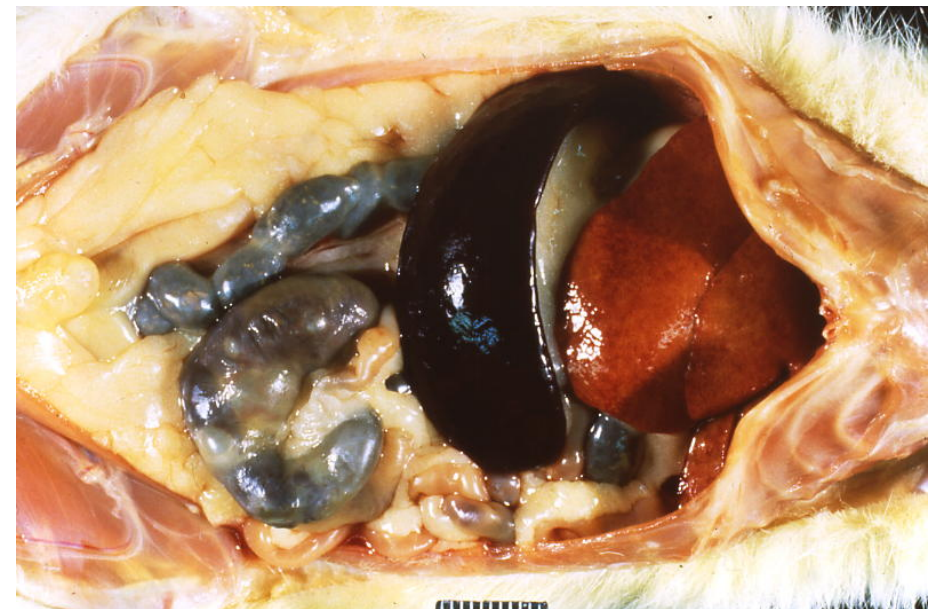
- Large granular lymphocyte leukaemia
- Lymphocytic
- Pleomorphic
- Epitheliotropic Cutaneous T-cell
- Lymphoblastic
- Immunoblastic
- Plasmacytic
- Marginal zone (spleen)
- NOS

## Large granular lymphocyte (LGL) leukaemia

- Synonyms: *Mononuclear cell leukaemia, monocytoid leukaemia, monocytoid malignant lymphoma, Fischer rat leukaemia.*
- Tumour is **composed of cell similar to the large granular lymphocyte.**
- Nuclei are round, oval, only slightly irregular or reniform, with varying degrees of differentiation. They have clumped nuclear chromatin including small nucleoli.
- The basophilic cytoplasm has several reddish granules in the peripheral blood smear stained with May Gruenwald Giemsa, but not in routine H&E-stained sections.
- Cells have a variable number and size of cytoplasmic granules.
- Cells **react positively with the OX-8 monoclonal antibodies.**
- Organs **most frequently involved** are **liver and spleen**, but other organs may also be infiltrated.
- Early and possibly primary lesions are frequently found in the spleen.
- Tumour is almost **by definition leukaemic.**
- Differentiation is made between LGL-leukaemia and malignant lymphoma, lymphocytic with the Giemsa stain of blood smears showing presence of reddish cytoplasmic granules in the tumour cells and/or positive labelling with OX-8 antibody. Most malignant lymphocytic lymphomas do not have a primary leukaemic growth pattern and have as a primary site lymph nodes.

# Hematopoietic tumours in Rodents

## Lymphoma large granular cell leukemia

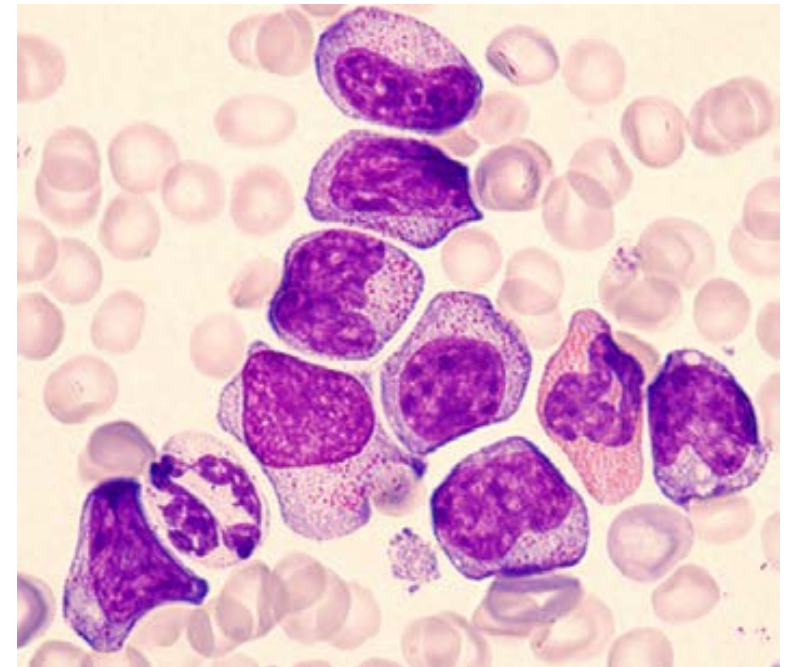
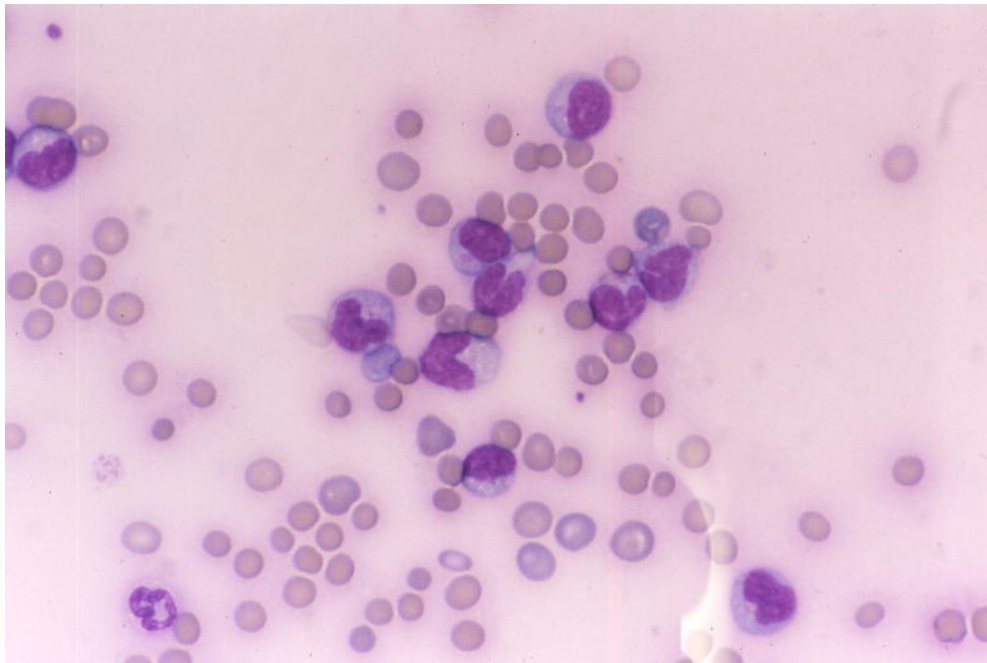


Malignant lymphoma, LGL-leukemia, Macro F344-rat anemia

Malignant lymphoma, LGL-leukemia, Macro F344-rat anemia, large spleen/liver

# Hematopoietic tumours in Rodents

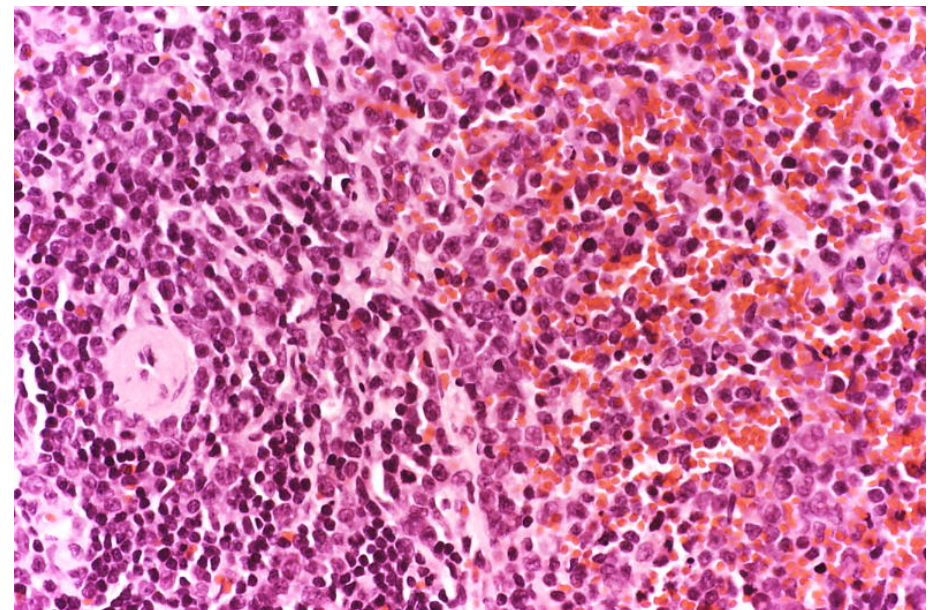
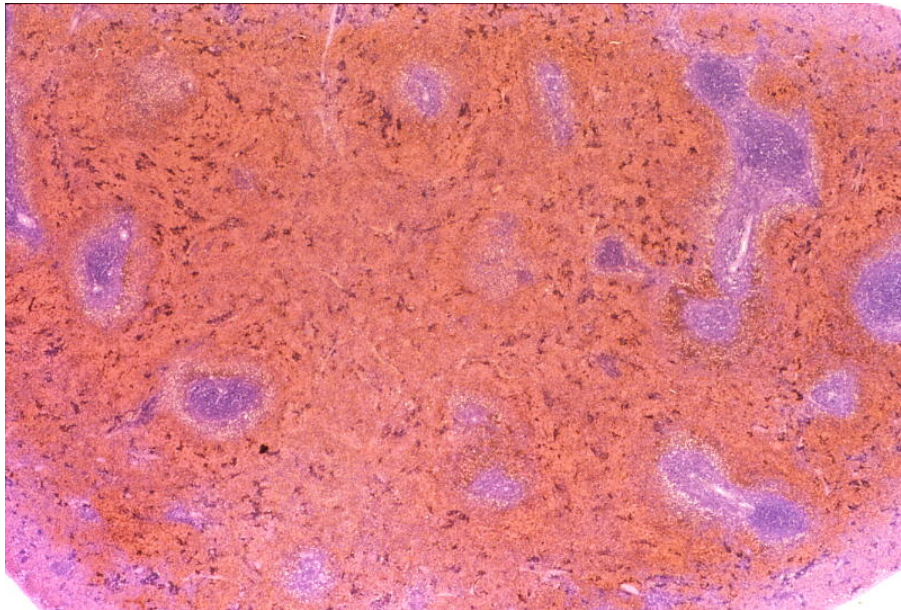
## Lymphoma large granular cell leukemia



(Stromberg), LGL-leukemia, blood smear, May Grunwald

# Hematopoietic tumours in Rodents

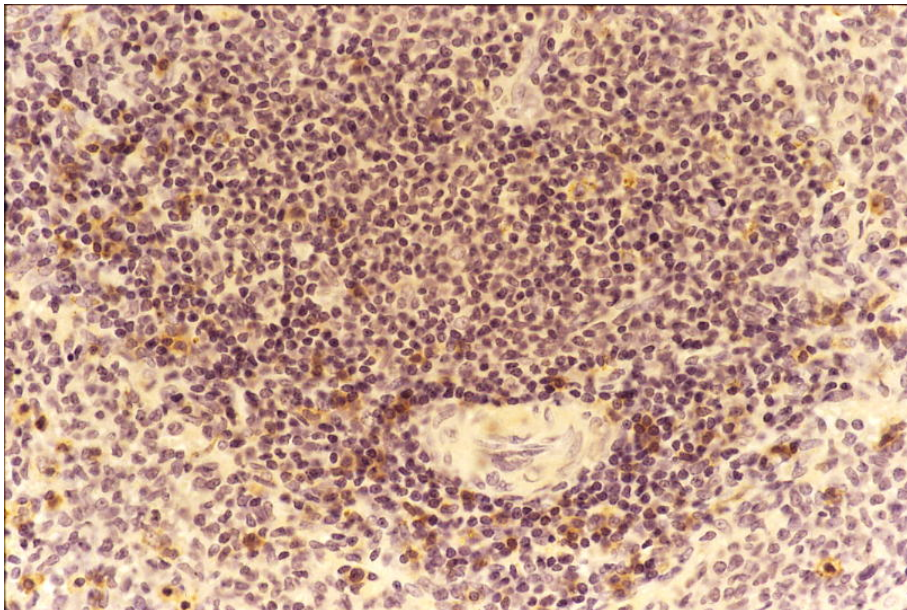
## Lymphoma large granular cell leukemia



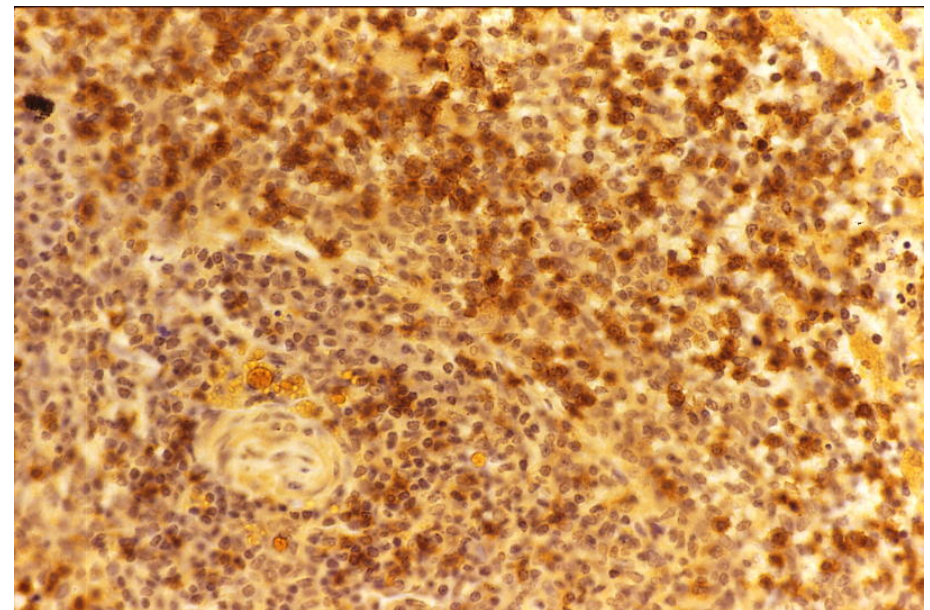
Malignant lymphoma, LGL-leukemia, spleen, H&E (Stage 2)

# Hematopoietic tumours in Rodents

## Lymphoma large granular cell leukemia



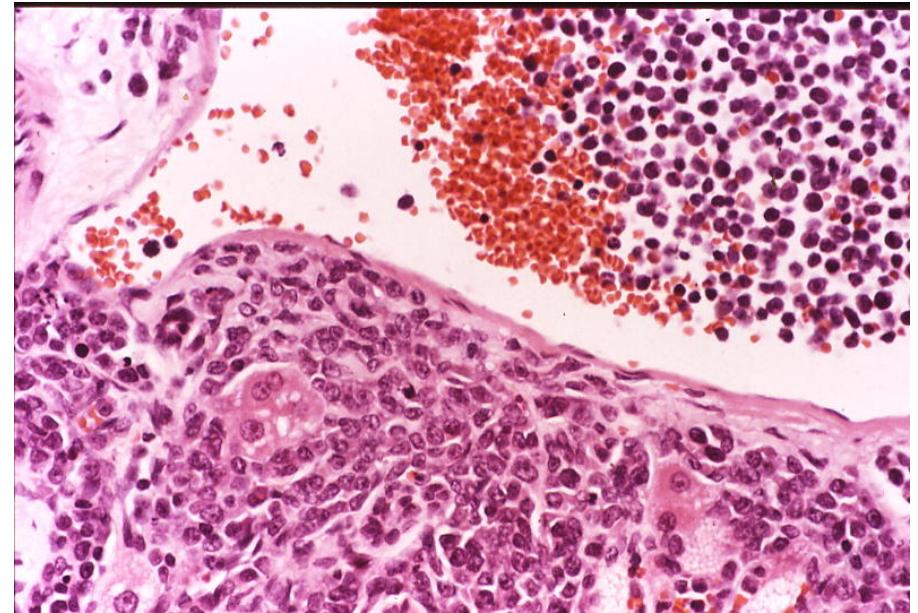
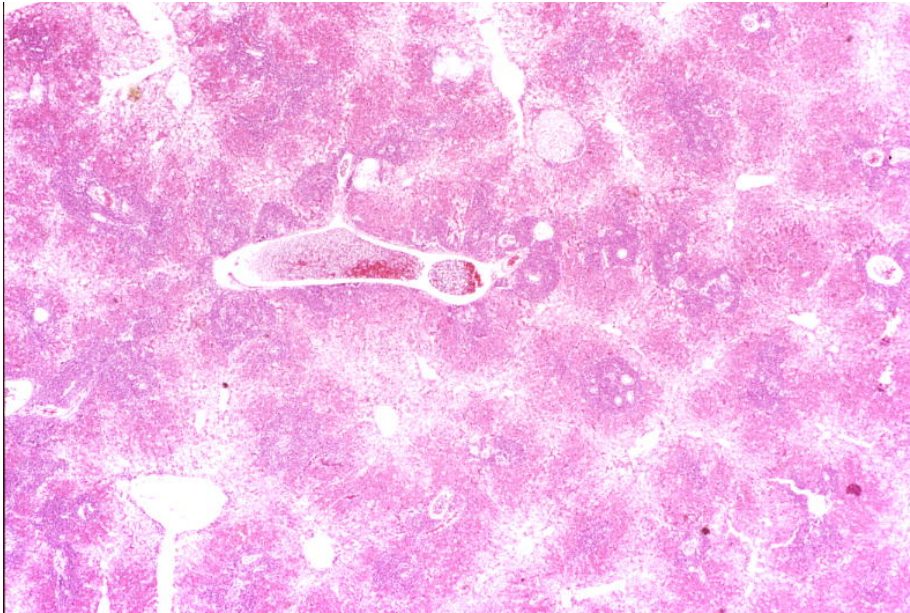
Malignant lymphoma, LGL-leukemia, spleen  
control OX-8 stain



Malignant lymphoma, LGL-leukemia, spleen  
control OX-8 stain (Stage 2)

# Hematopoietic tumours in Rodents

## Lymphoma large granular cell leukemia



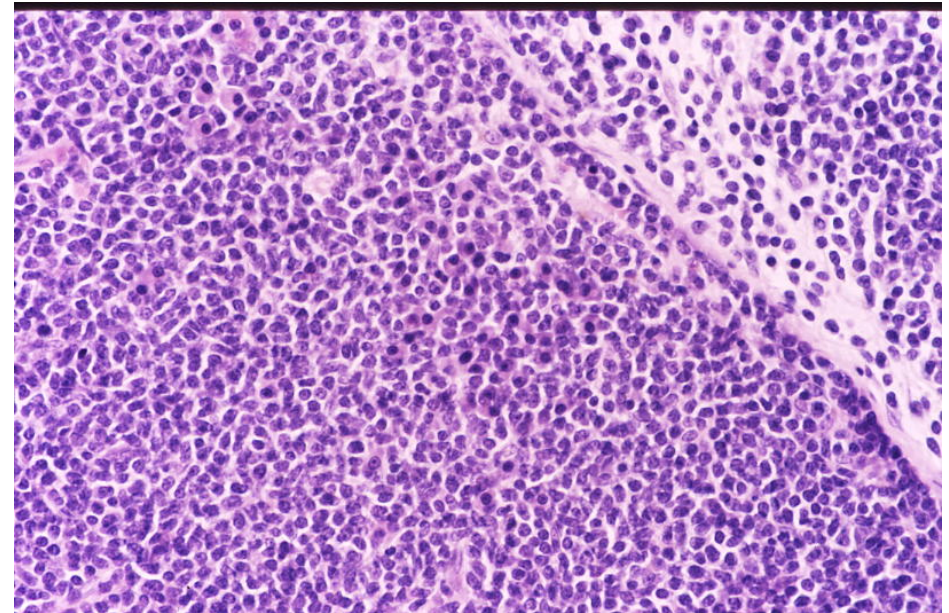
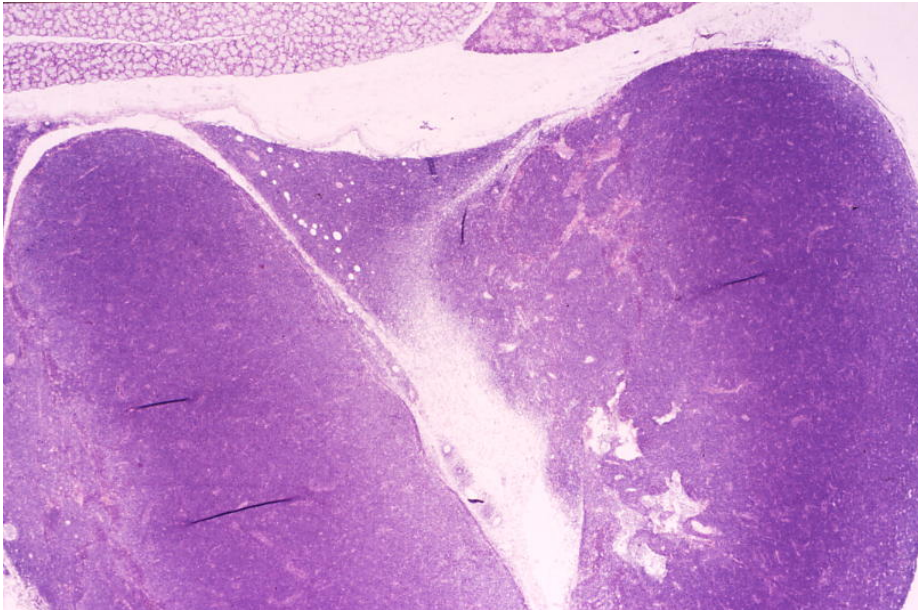
Malignant lymphoma LGL leukemia stage 2, liver, H&E

## Malignant lymphoma lymphocytic

- Tumour consists of **small to medium-sized well differentiated lymphocytes**.
- Tumour cells are **relatively uniform** and **generally non-cohesive**.
- The nuclear chromatin in the smaller cells is densely clumped and a narrow rim of cytoplasm is usually visible.
- Tumour cells differ little, if at all, from the normal circulating lymphocytes.
- Tumour may also contain some slightly larger cells with somewhat larger irregular nuclei, corresponding to the small cleaved follicular centre cells.

# Hematopoietic tumours in Rodents

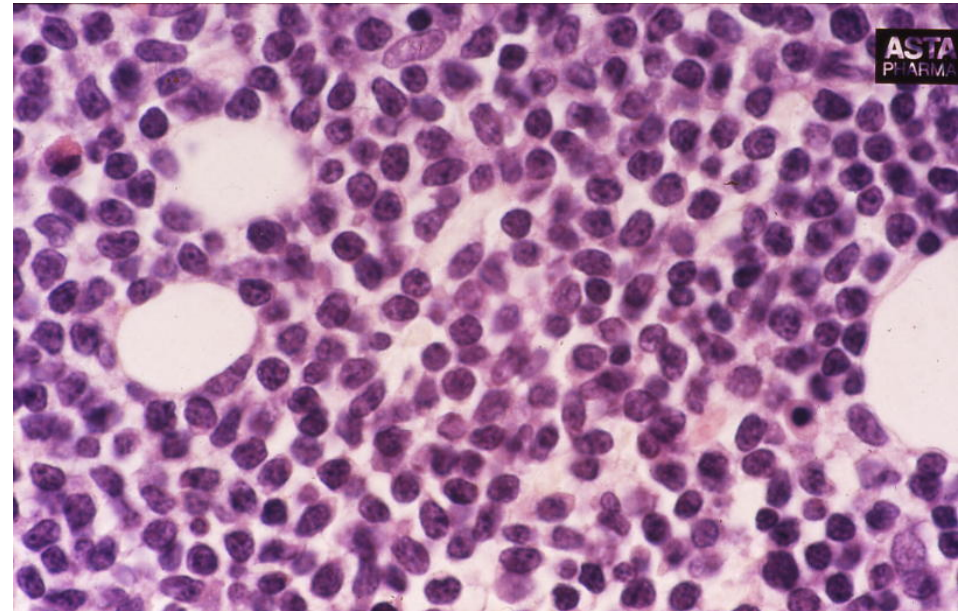
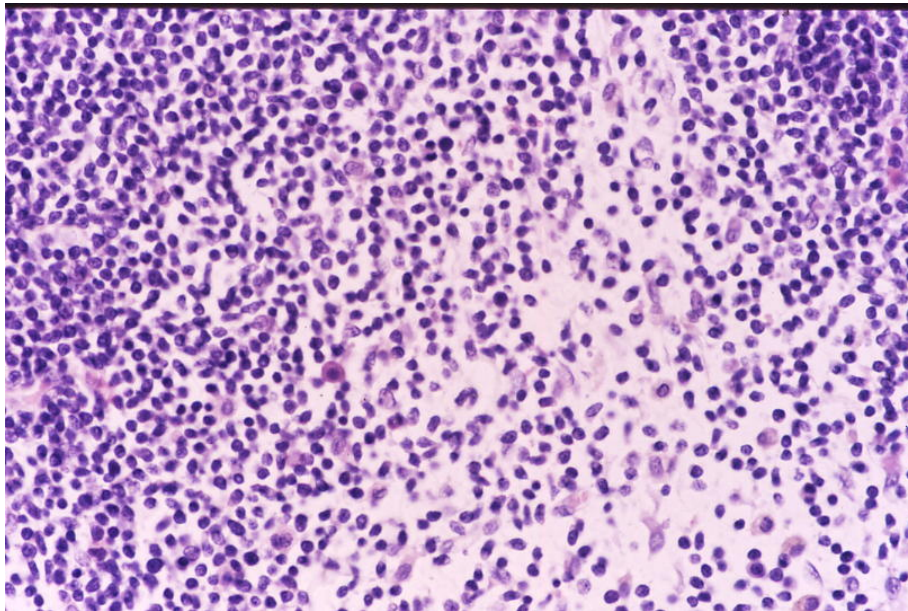
## Lymphoma lymphocytic



Malignant lymphoma lymphocytic, lymph node, H&E

# Hematopoietic tumours in Rodents

## Lymphoma lymphocytic



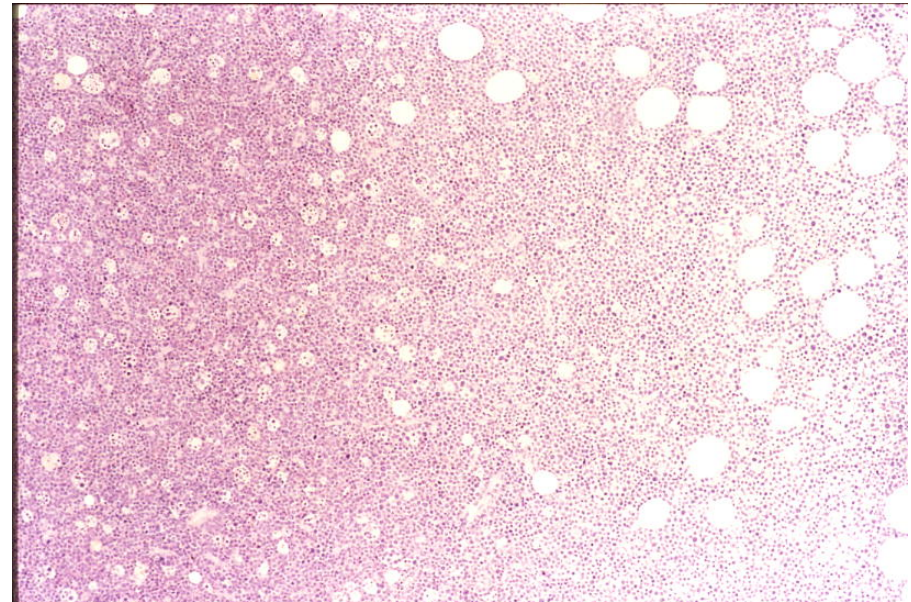
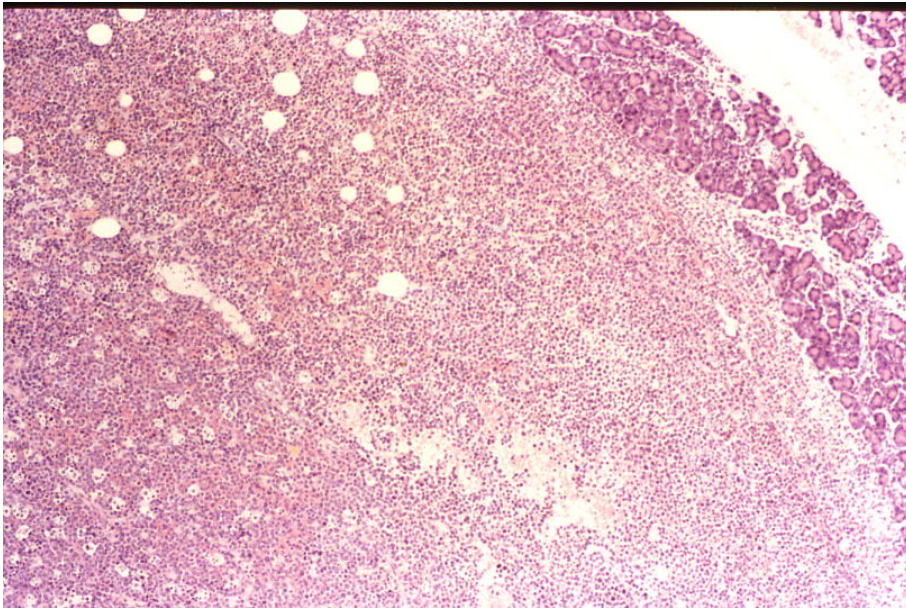
Malignant lymphoma lymphocytic, H&E

## Lymphoma pleomorphic (Follicular center cell)

- Tumour consists of **medium-sized to large cells**.
- Express a **varying degree of pleomorphism**, ranging from fairly uniform to considerable pleomorphism of cells and nuclei even within a tumour.
- The larger **cells are cohesive** and have a **more abundant cytoplasm**.
- Tumour contains cells resembling the large cells seen in germinal centres (follicular centre cells).
- Large irregular (cleaved or centroblastic) cells may be seen, as well as smaller cells with rounded nuclei and basophilic cytoplasm.
- Cells are usually mononuclear with marginated nuclear chromatin and may have prominent nucleoli, but occasionally multinucleated cells occur, which may resemble Reed-Sternberg cells.

# Hematopoietic tumours in Rodents

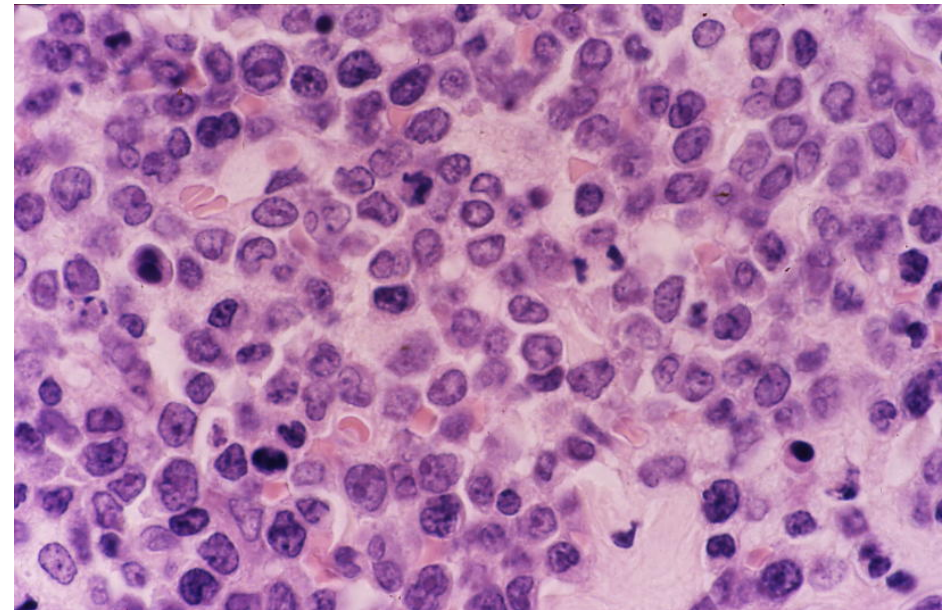
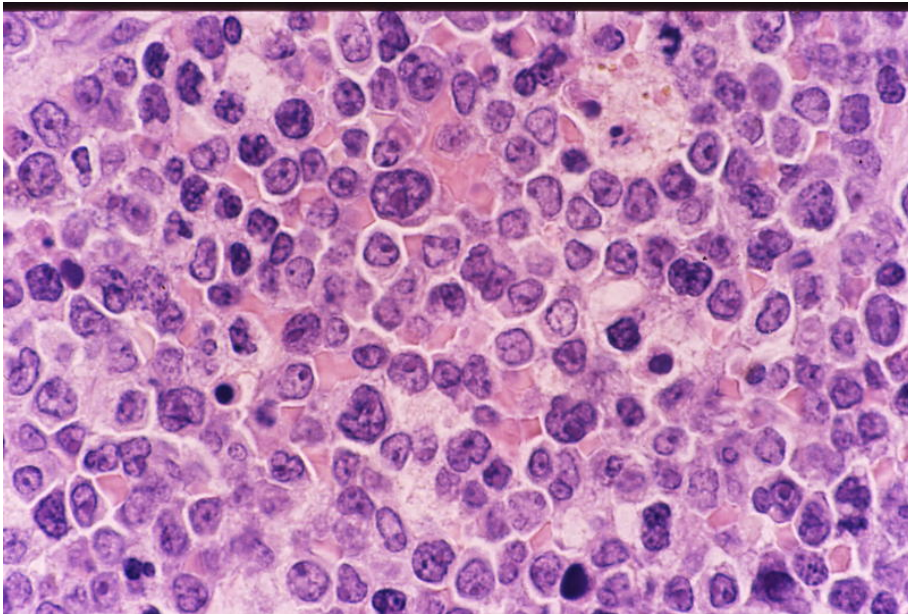
## Lymphoma pleomorphic



Malignant lymphoma pleomorphic, abdomen, H&E

# Hematopoietic tumours in Rodents

## Lymphoma pleomorphic



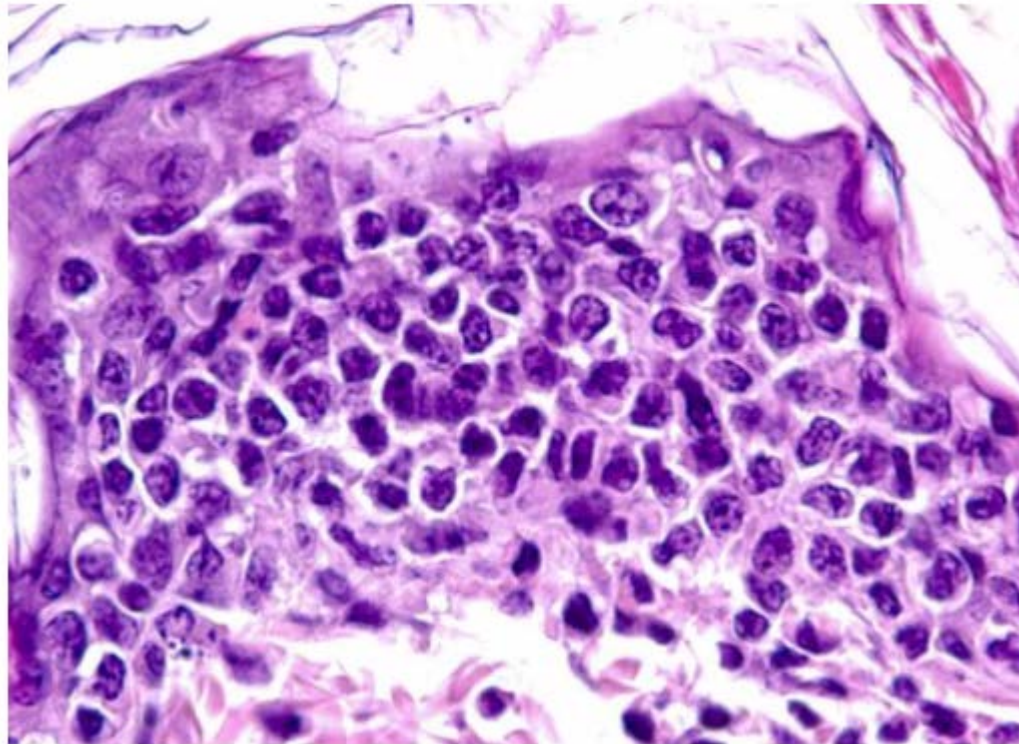
Malignant lymphoma, pleomorphic, H&E

## Lymphoma, epitheliotropic cutaneous T-cell

- Presents as a dermal gross lesion with hair loss and encrusted skin
- Tumour consists of **small to medium-sized cells with little cytoplasm and indented nuclei**
- Mitotic figures are rare
- **Infiltration of the dermis and squamous epithelium**
- **Pautriers microabcesses in epidermis and hairfollicles**
- Resembles “mycoides fungoides”
- Later stages may involve multiple sites
- Tumour expressing PAN- T cell markers (CD2,CD3 and CD 8)
- Rare lesion reported in rats

# Hematopoietic tumours in Rodents

## Epitheliotropic cutaneous lymphoma



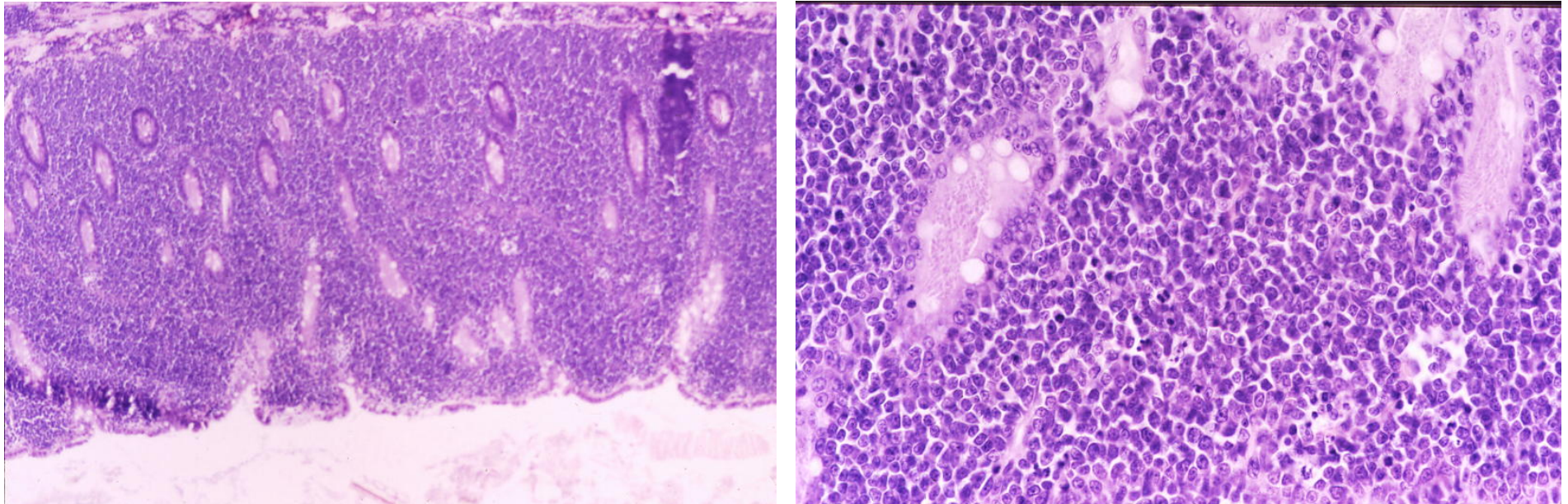
Malignant lymphoma epitheliotropic cutaneous , H&E (Jerry Regh)

## Lymphoma lymphoblastic

- Tumour principally composed of **large lymphoblast-like cells** with a high nucleus to cytoplasm ratio.
- The cells are **generally non-cohesive**.
- **Nucleus is round and not indented or twisted** and has prominent nucleoli.
- Nucleus is surrounded by a small rim of basophilic cytoplasm with few, if any, granules.
- Tumour has generally **a high mitotic index**.
- A rare form, the immunoblastic cell type, has more, generally basophilic cytoplasm and an excentric nucleus.

# Hematopoietic tumours in Rodents

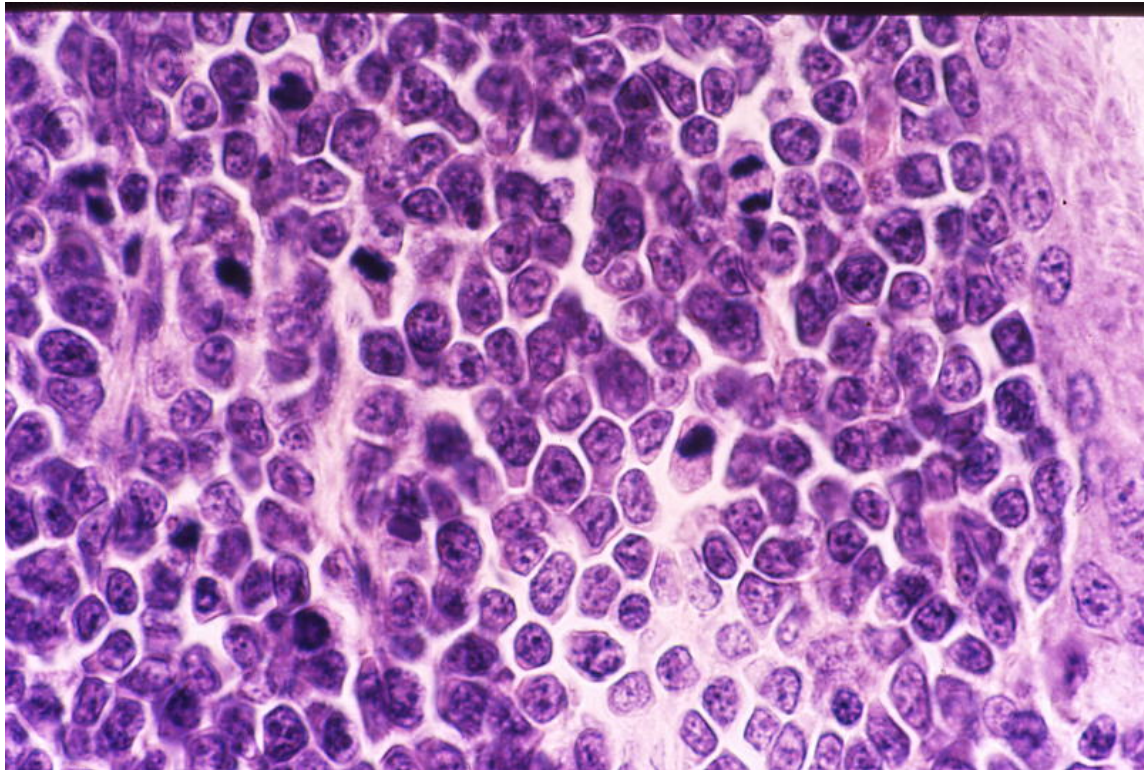
## Lymphoma lymphoblastic



Malignant lymphoma lymphoblastic, intestine, H&E

# Hematopoietic tumours in Rodents

## Lymphoma lymphoblastic



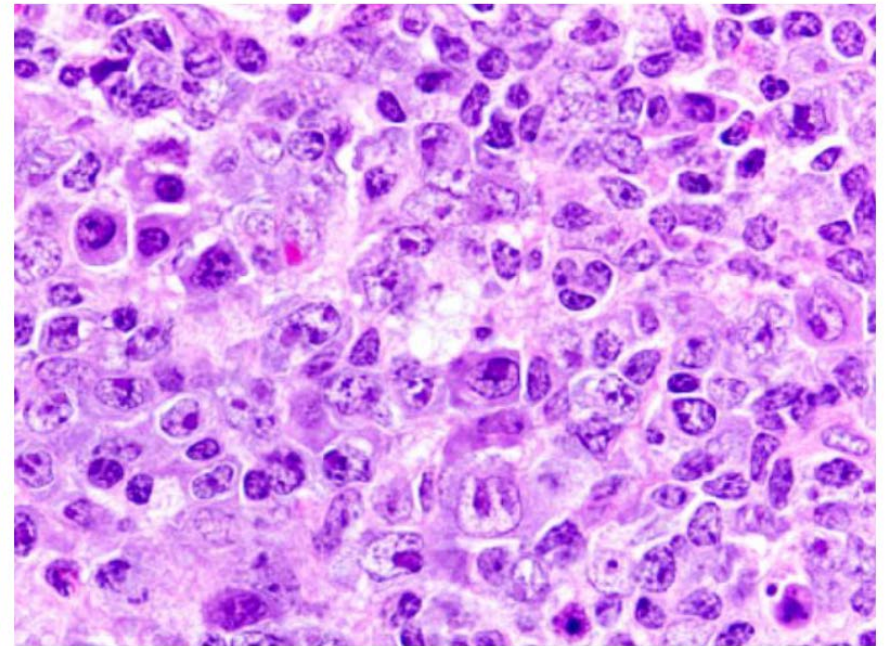
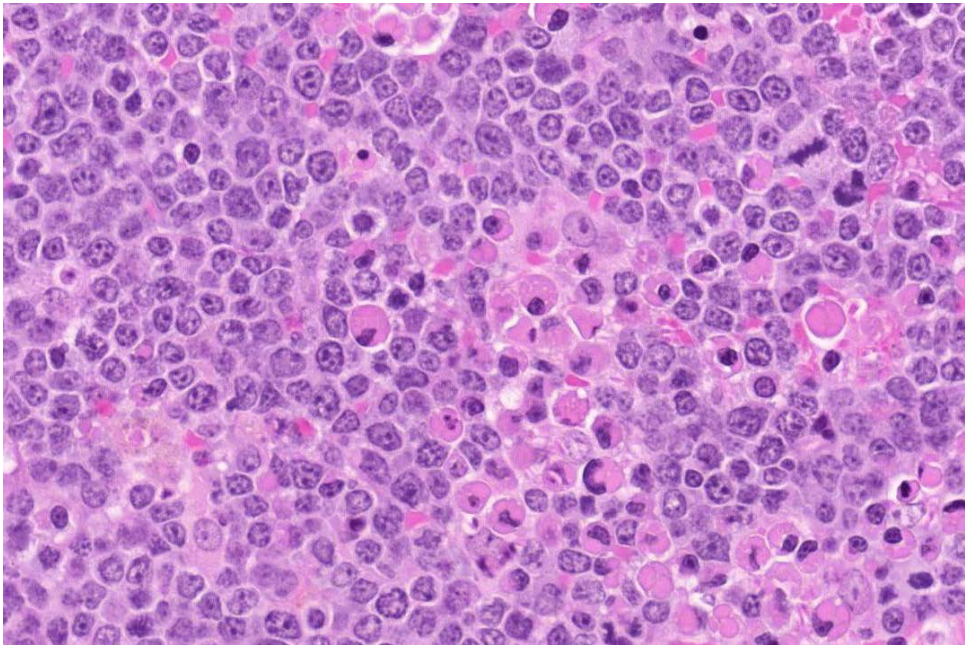
Malignant lymphoma lymphoblastic, intestine, H&E

## Lymphoma immunoblastic

- Tumour principally composed of **large lymphoblast-like cells** with a high nucleus to cytoplasm ratio.
- The cells are **generally non-cohesive**.
- **Nucleus is round and not indented or twisted** and has prominent nucleoli.
- Nucleus is surrounded by a conspicuously amphophilic to basophilic cytoplasm
- Tumour has generally **a high mitotic index**.
- Plasmacytoid and plasma cells may be present

# Hematopoietic tumours in Rodents

## Lymphoma immunoblastic



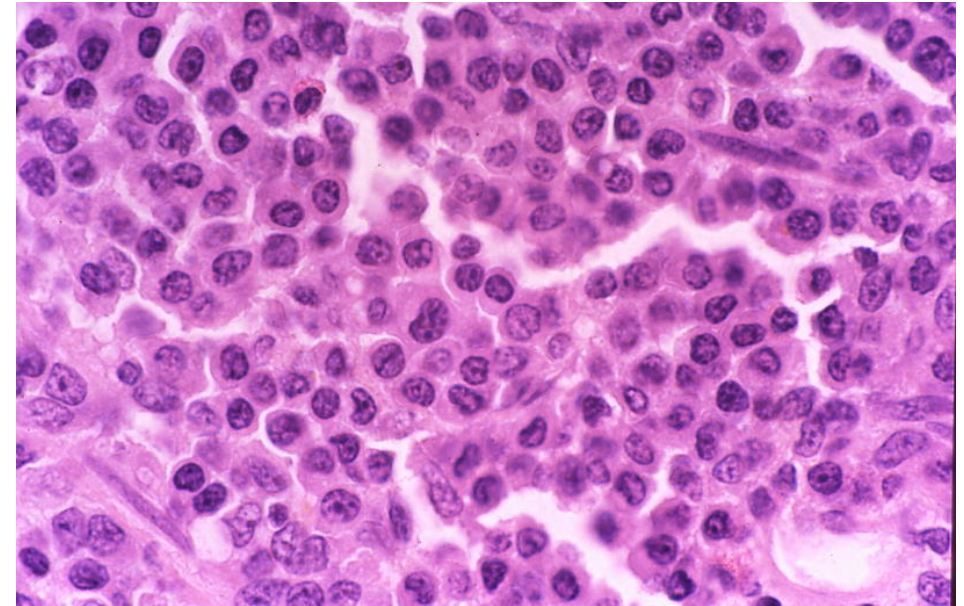
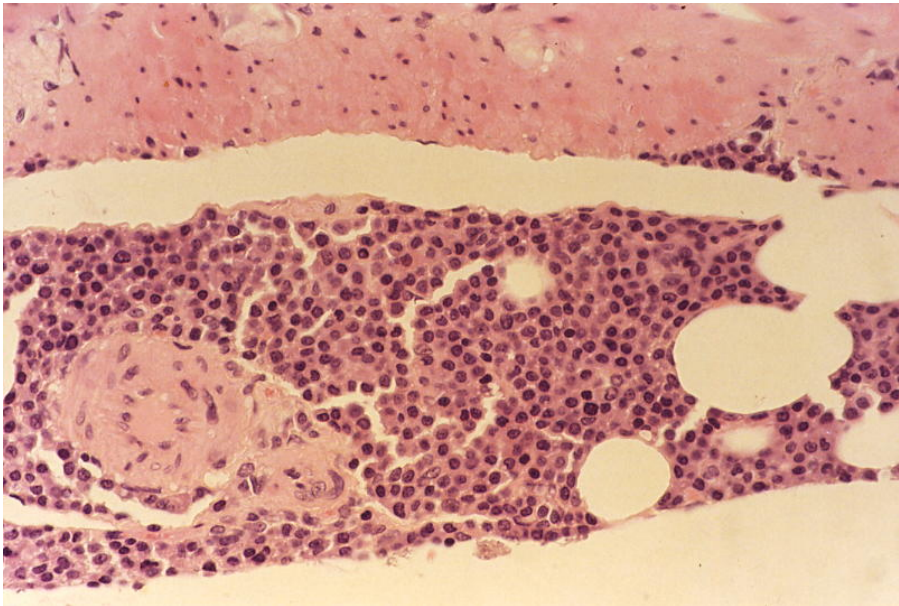
Lymphoma immunoblastic mouse (Rita-Jerry Ward) H&E

## Lymphoma plasmacytic

- Rare tumour, consisting primarily of plasma cells and/or **cells with an obvious plasmacytoid differentiation.**
- Nuclei are round and occasionally show a cartwheel appearance.
- **Cytoplasm is basophilic** and pyroninophilic and a small perinuclear halo maybe present.
- May arise in spleen or lymph nodes, rarely in bone marrow
- Rare in rats and most mouse strains (more common in NZB mice and inducible in BALB/c mice)
- Positive for heavy chain immunohistochemistry
- Most mouse cells express kappa light chain, hence light chain unsuitable for clonality determination (unlike humans where kappa to lamda ratio is 2:1)

# Hematopoietic tumours in Rodents

## Lymphoma plasmacytic



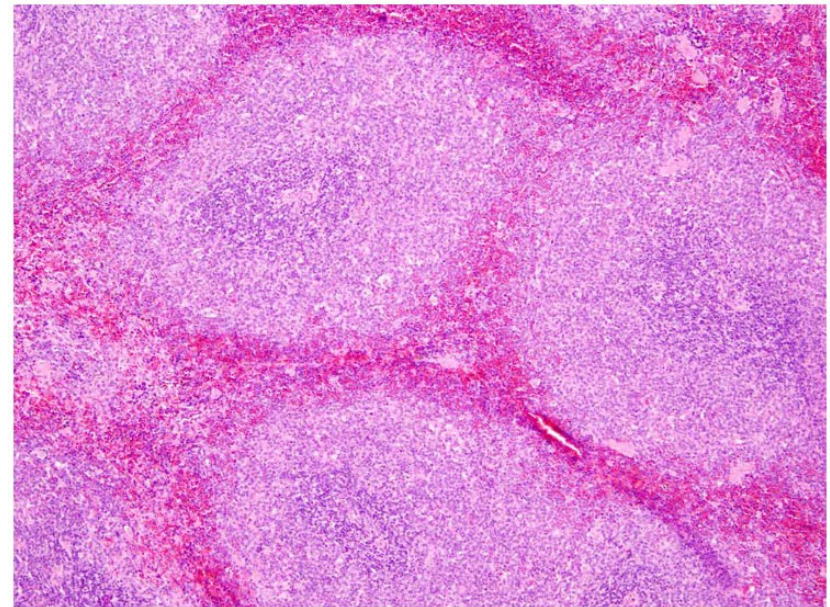
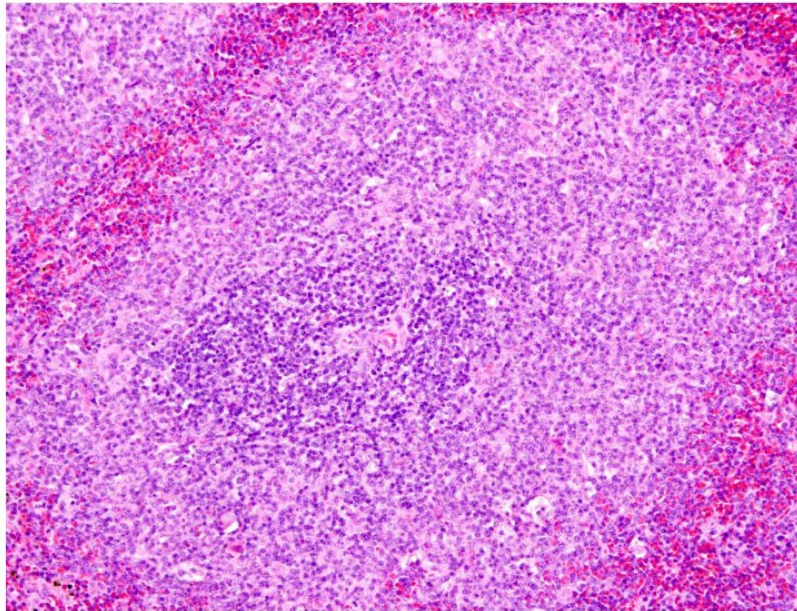
Malignant lymphoma plasmacytic, intestine NMRI mouse H&E

## Lymphoma marginal zone

- Progressive lesion, starts with widening of marginal zone
- **Very homogenous to pleomorphic population of medium sized cells.**
- Diffuse infiltration of red pulp
- In later stages there is invasion of the white pulp and compression of PALS and coalescence and bridging of follicles
- **Generally restricted to spleen** but may spread to other organs such as liver and lymph nodes
- Lesion not described in rats

# Hematopoietic tumours in Rodents

## Lymphoma marginal zone



Lymphoma marginal zone, mouse H&E (Jerry Ward)

## Classification of lymphomas in rats

.....

Morphology

Immunophenotype

.....

Lymphocytic

Small lymphocyte T or B

Pleomorphic

Follicular centre cell B

Cutaneous epitheliotropic

T-cell

Lymphoblastic

Lymphoblastic T or B

Immunoblastic

Immunoblastic B

Marginal zone

Marginal zone B

Plasmacytic

Plasmacytoma B

Large granular lymphocyte

Large granular lymphocyte T/NK

leukaemia

leukaemia non-T, non-B

## Leukaemia erythroid

### Histogenesis

Develops from the erythroid cell lineage in the haematopoietic tissues.

### Diagnostic Features

Characterized by **an excessive proliferation of erythroblastic cells.**

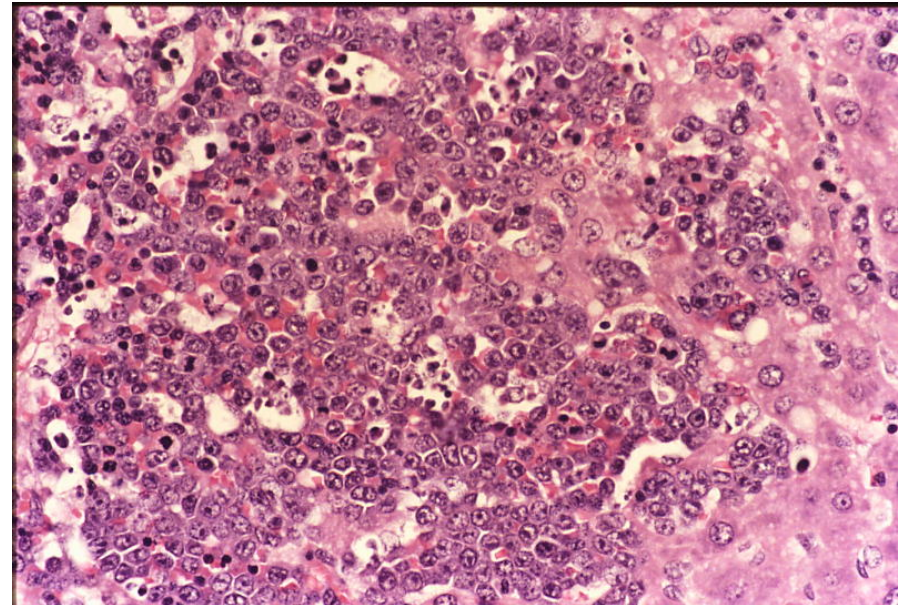
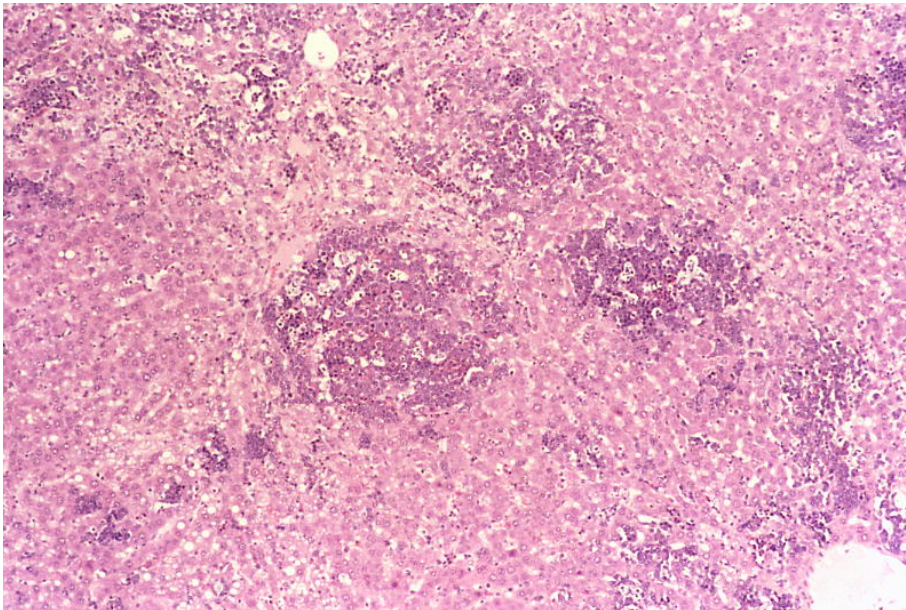
### Differential Diagnosis

Lymphoma, Malignant:

Differentiation from malignant lymphoma is made upon morphological criteria; erythroid leukaemia generally shows **signs of erythroid differentiation**. If differentiation of the erythroid leukaemia is arrested at a very primitive stage of erythroid differentiation, a diagnosis may be difficult. In such cases a definitive diagnosis is generally only possible with the use of specific antibodies recognizing antigens expressed during normal erythropoiesis, e.g. **carbonic anhydrase, haemoglobin.**

# Hematopoietic tumours in Rodents

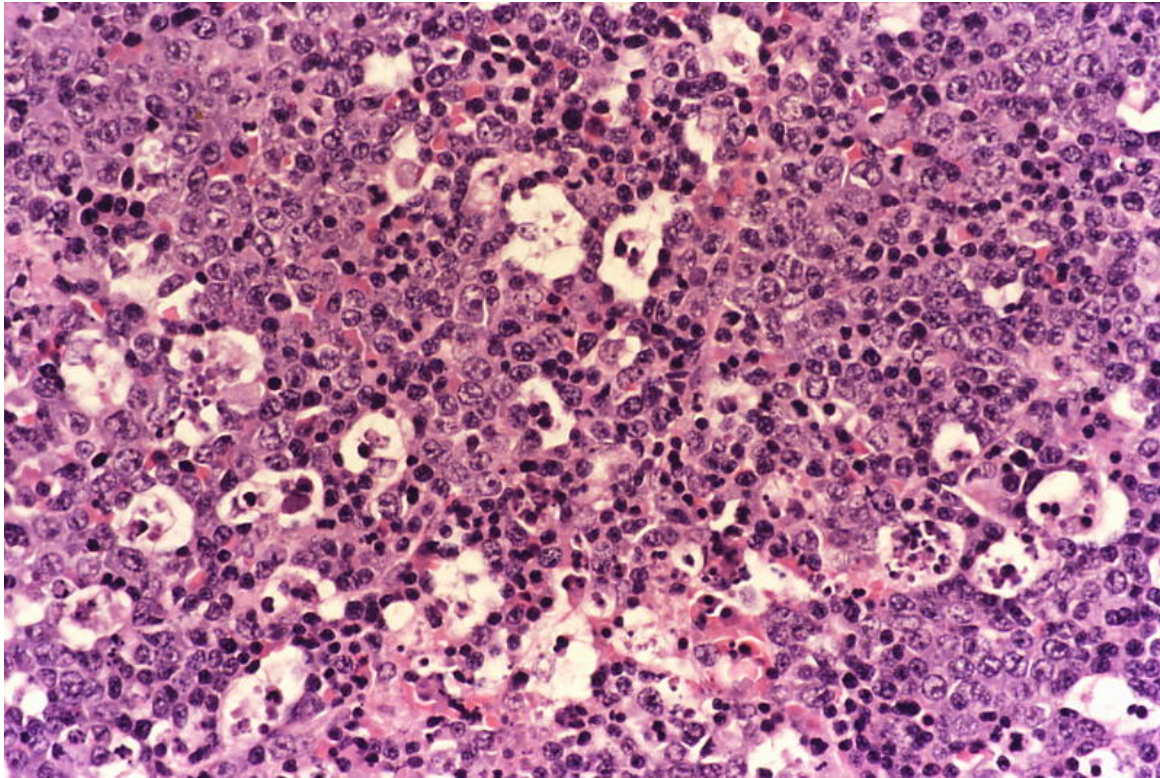
## Erythroid leukemia



Erythroid leukemia, spleen, H&E mouse (Jerry Ward)

# Hematopoietic tumours in Rodents

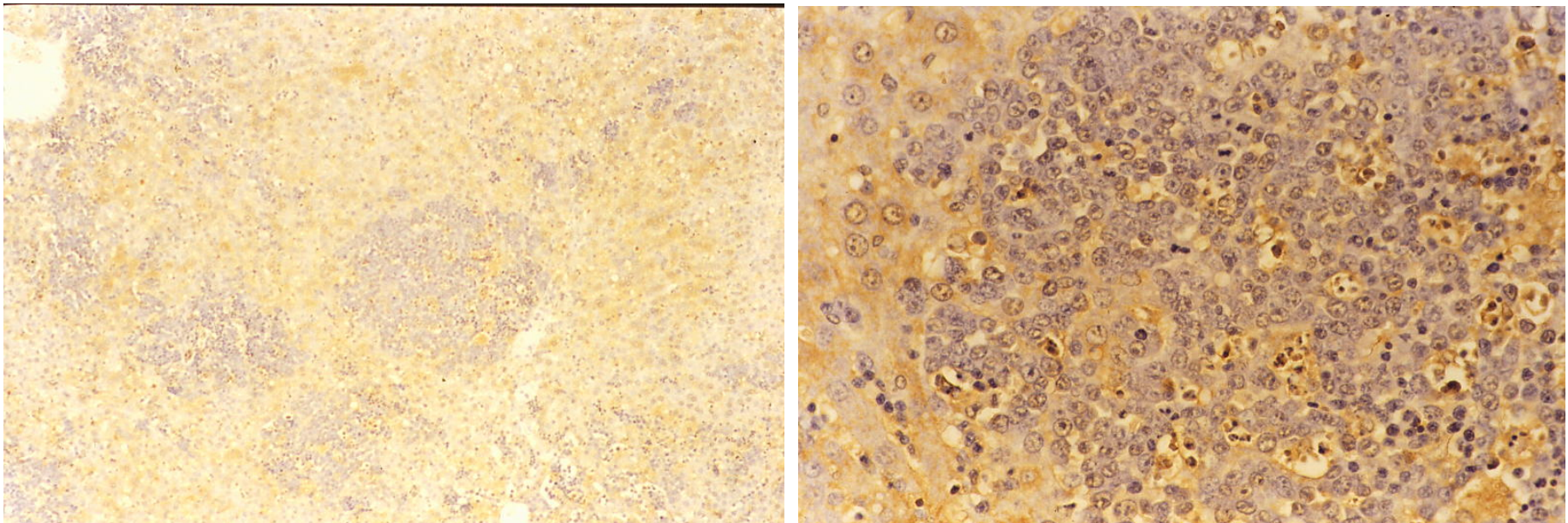
## Erythroid leukemia



Erythroid leukemia, spleen, H&E mouse (Jerry Ward)

# Hematopoietic tumours in Rodents

## Erythroid leukemia



Erythroid leukemia, spleen, H&E mouse (Jerry Ward)

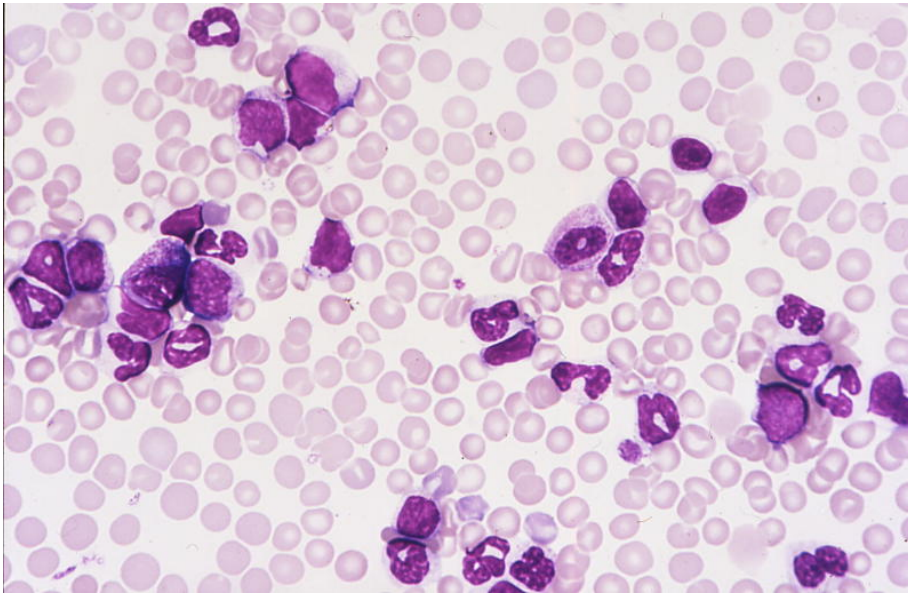
## Leukaemia myeloid (granulocytic)

### Diagnostic Features

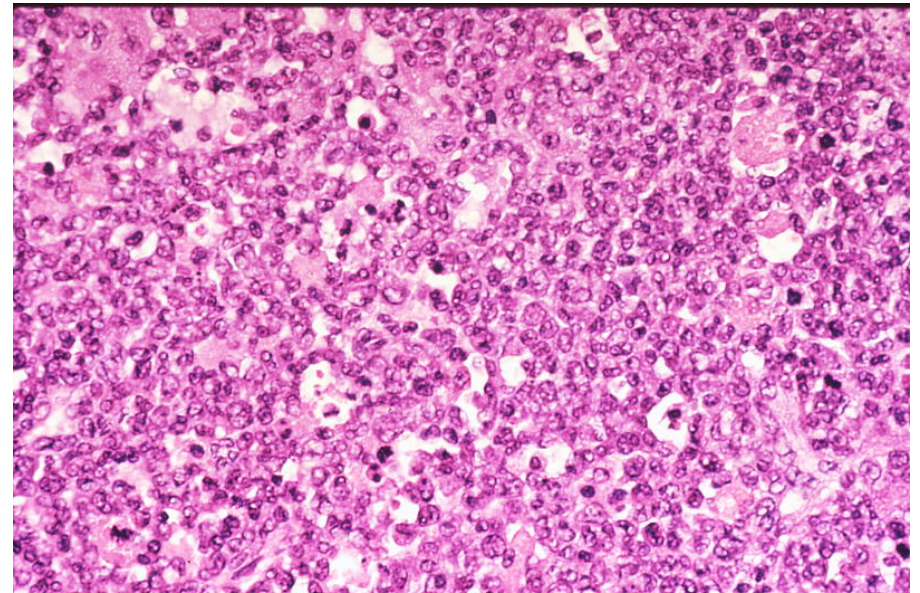
- Tumour cells may also show various degrees of maturation and differentiation.
- **One type** has variable, but often very high white cell counts up to 1 million cells/microliter. The cells are primarily **myelocytes and mature neutrophils**, blasts and promyelocytes are uncommon in the peripheral blood smear.
- The other form, also called myeloblastic leukaemia, has high WBC, but cells resemble more normal **myeloblasts and promyelocytes**. These cells are more regular and have abundant cytoplasm compared to the more mature cells.
- Nuclei have prominent nucleoli and azurophilic granules are frequently present.
- Cells are **positive for lysosome markers and granulocytic antigen** markers.
- This tumour is most frequently just leukaemic but may produce tissue masses. These tissue masses and infiltrated tissues may show **macroscopically a greenish discoloration**. With special techniques such as enzyme cytochemistry, these cells are chloroacetate esterase positive.
- Myeloid leukaemia is highly invasive with various organs involved.

# Hematopoietic tumours in Rodents

## Leukemia myeloid



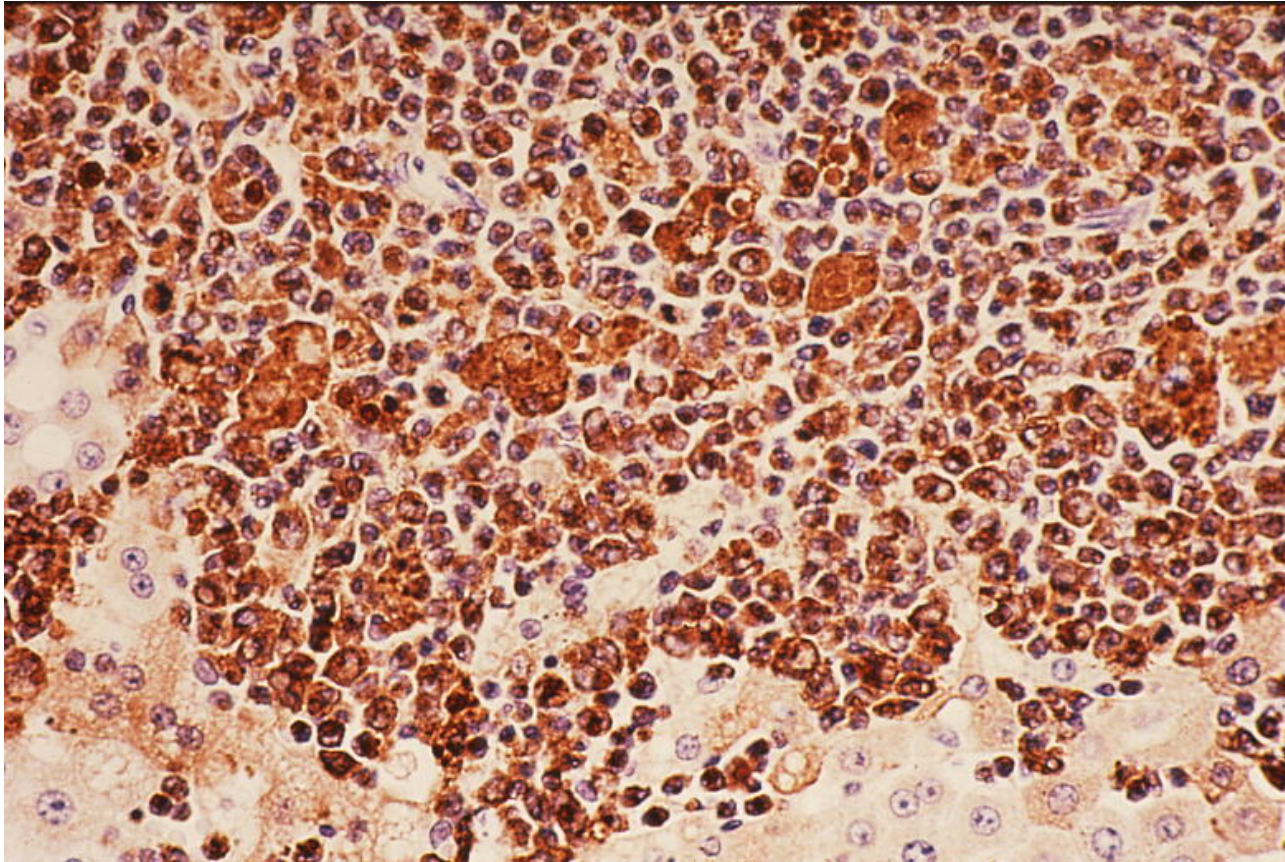
Granulocytic leukemia, blood smear, MGG



Granulocytic leukemia, spleen, H&E

# Hematopoietic tumours in Rodents

## Leukemia myeloid

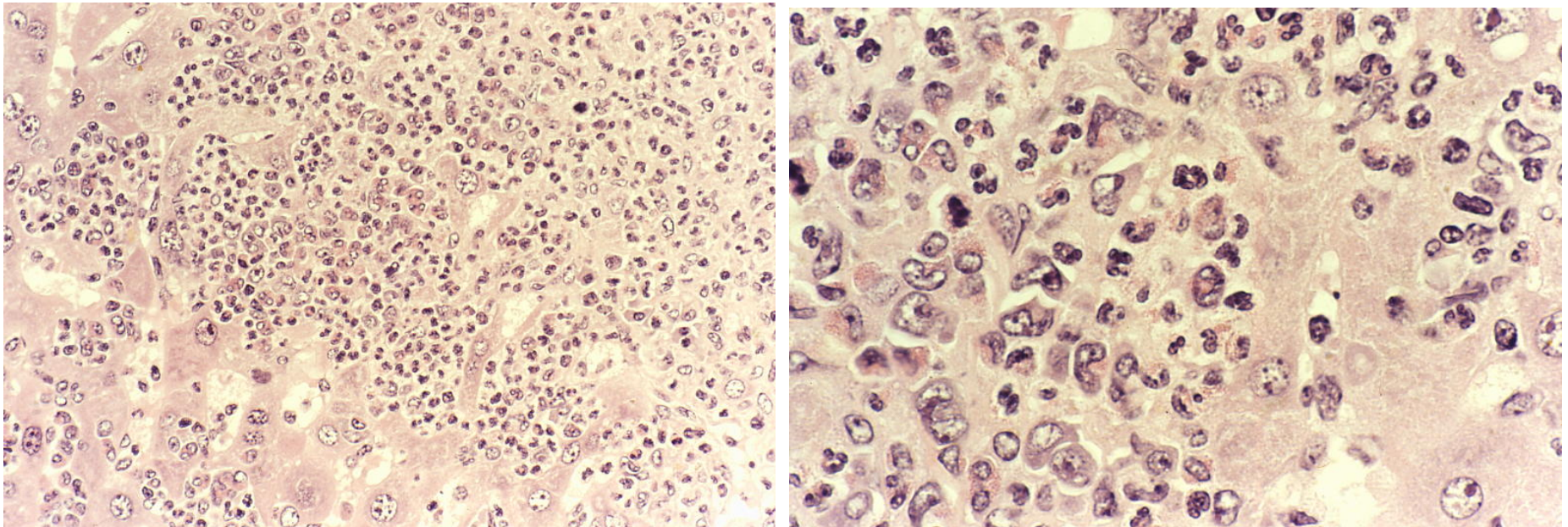


Myeloid leukemia, leukemia granulocytic, neutrophilic, Lysozyme (Jerry Ward)

Note the strong staining of the tumour cells

# Hematopoietic tumours in Rodents

## Leukemia myeloid



Myeloid leukemia mouse

# Leukaemoid Reaction / Extramedullary Hematopoiesis

## Versus Leukemia myeloid

	<b>Reactive extramedullary haematopoiesis</b>	<b>Myeloid leukemia</b>
Peripheral blood	Normal numbers of leukaemoid reaction with many mature cells	Increased numbers with many immature precursor cells
Tissues Foci of erythroid precursor cells	Present in fair amounts within the extramedullar haematopoietic tissue	Virtually absent
Megakaryocytes	Present in large numbers	Present in smaller numbers only in tissues where extramedullary haematopoiesis is seen
Liver	Normal size or minimally enlarged	Enlarged markedly
Lymph nodes	Normal size or minimally enlarged mostly in medulla. Cortex relatively spared.	Enlarged markedly with monotonous leukemic cell infiltration in cortex and medulla and outside the cortex
Stimulus	<ul style="list-style-type: none"> <li>- Abscess</li> <li>- Pneumonia</li> <li>- Acute pyelonephritis</li> </ul> Neoplastic growth. Necrotic tumours. Repeated blood loss. Increased red cell destruction	

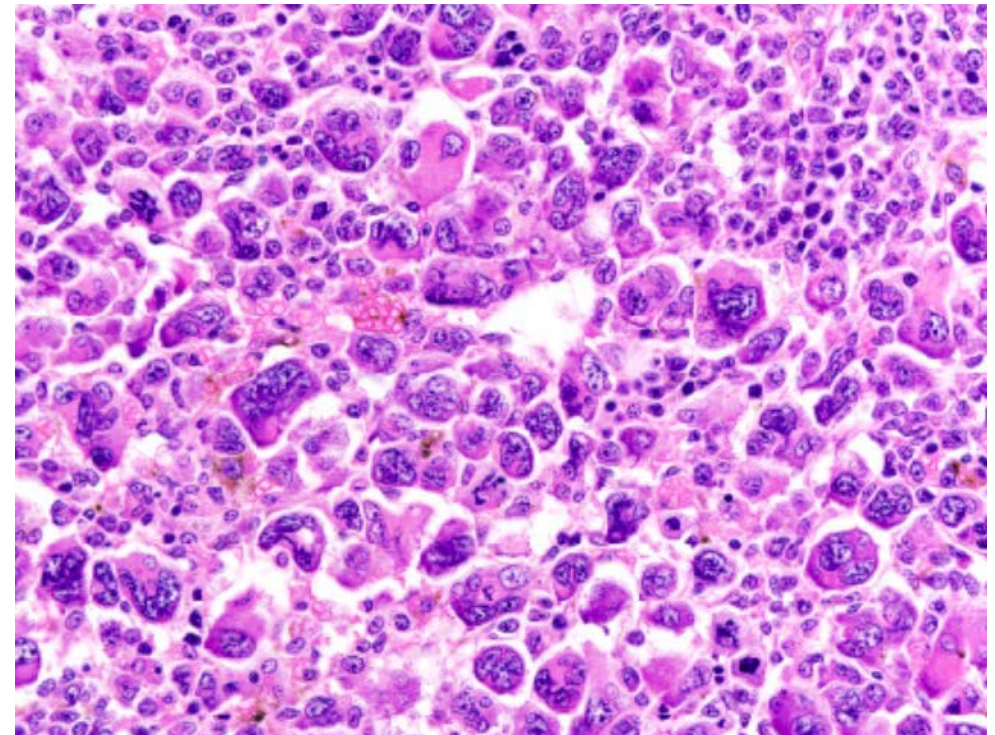
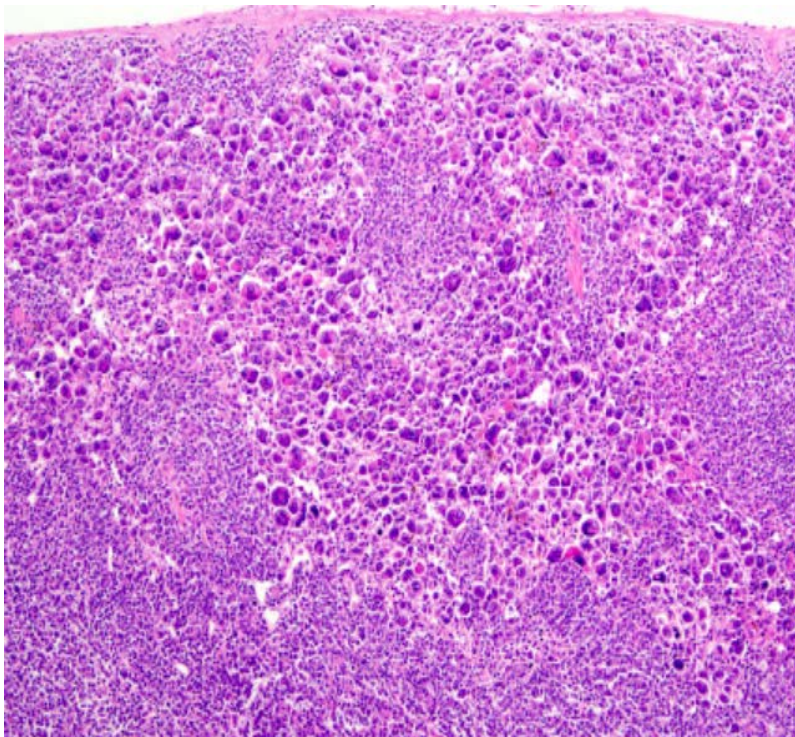
## Leukaemia Megakaryocytic

### Diagnostic Features

- Increase in megakaryocytes in various stages of differentiation
  - Marked increase of large megakaryoblasts and smaller immature cells
  - Nuclei often atypical and may or may not be multinucleated
  - Tumour cells may be present in bone marrow, lymph nodes, spleen liver and kidneys
  - Large aplastic platelets present in circulation
- 
- Rare tumour, described in mice.

# Hematopoietic tumours in Rodents

## Leukemia megakaryocytic



Leukemia megakaryocytic mouse H&E (Jerry Ward)

## Mast cell tumour (benign, malignant, leukemia, sarcoma)

### Histogenesis

Develops from the peripheral mast cells or mast cells and their precursors present in the haematopoietic and/or connective tissue.

### Diagnostic Features

- **Composed of well differentiated mast cells** showing the characteristic **metachromatic granules** with Giemsa or other metachromatic stains.
- Uniform large round nuclei with abundant granular slightly basophilic cytoplasm.
- Locally infiltrative growth pattern
- **Benign:** single nodule. Well differentiated
- **Malignant:** Single nodule, invasive growth pattern, atypia; or multiple nodules
- **Leukemia:** Atypical mast cells present in blood and bone marrow.
- **Sarcoma:** Sarcomatous growth of atypical mast cells, cytoplasm hypogranular, bizarre nuclei, bilobed/polyplobed nuclei, need special stain to differentiate from other sarcomas.

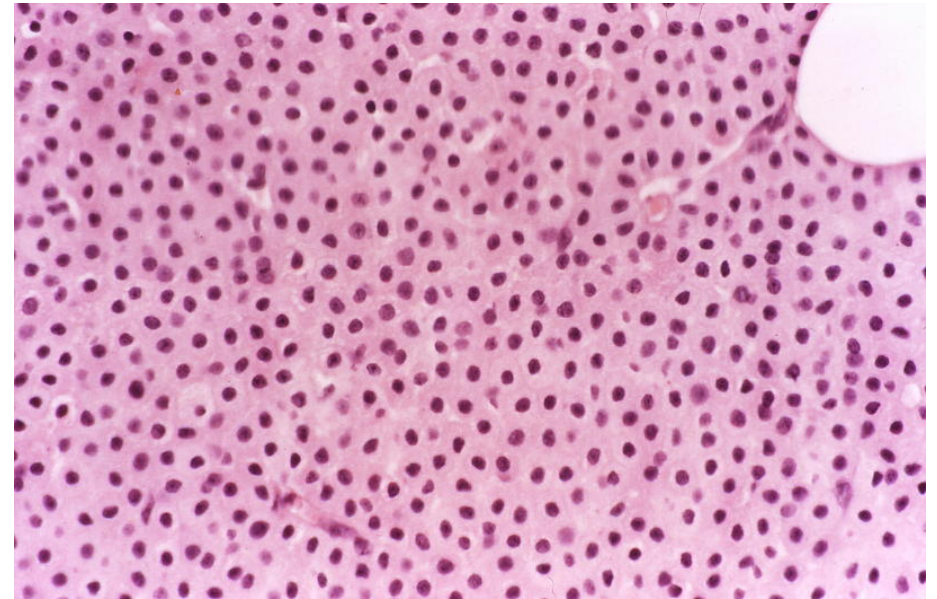
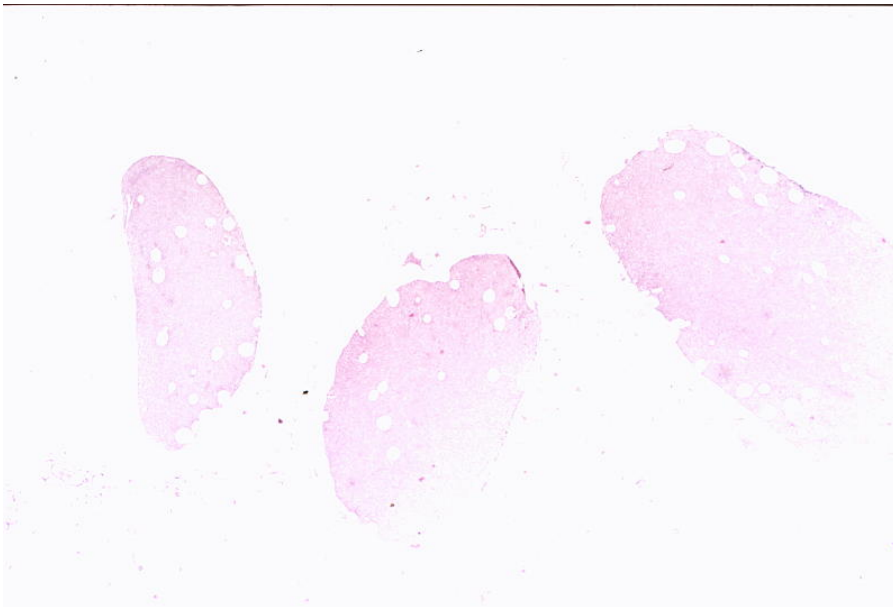
### Comment

This is a **rare tumour**.

Of the published cases, two were localized in the mesentery. Another case had a primary subcutaneous nodule which was generalized to other organs (lymph nodes, liver and kidneys).

# Hematopoietic tumours in Rodents

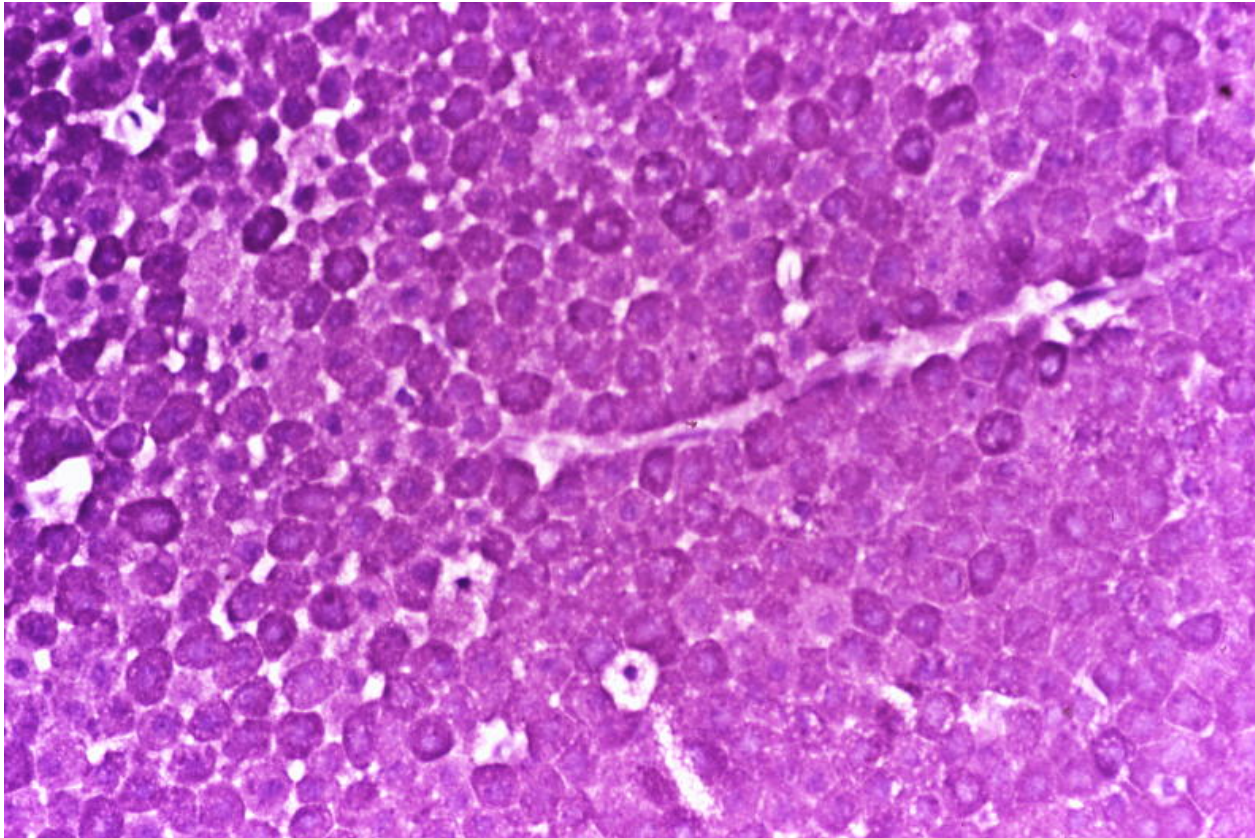
## Mast cell tumour



Mast cell tumour, H&E

# Hematopoietic tumours in Rodents

## Mast cell tumour



Mast cell tumour, Cresylviolet

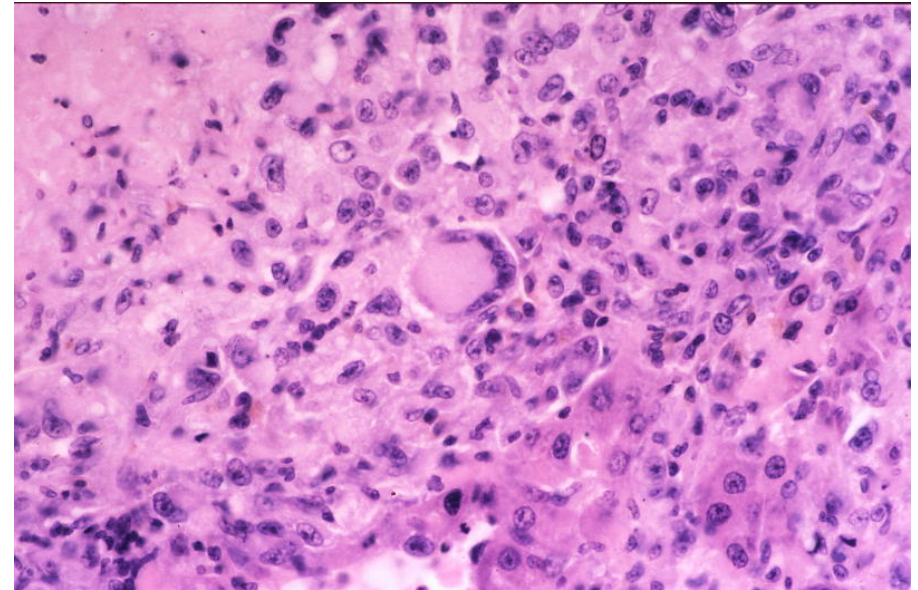
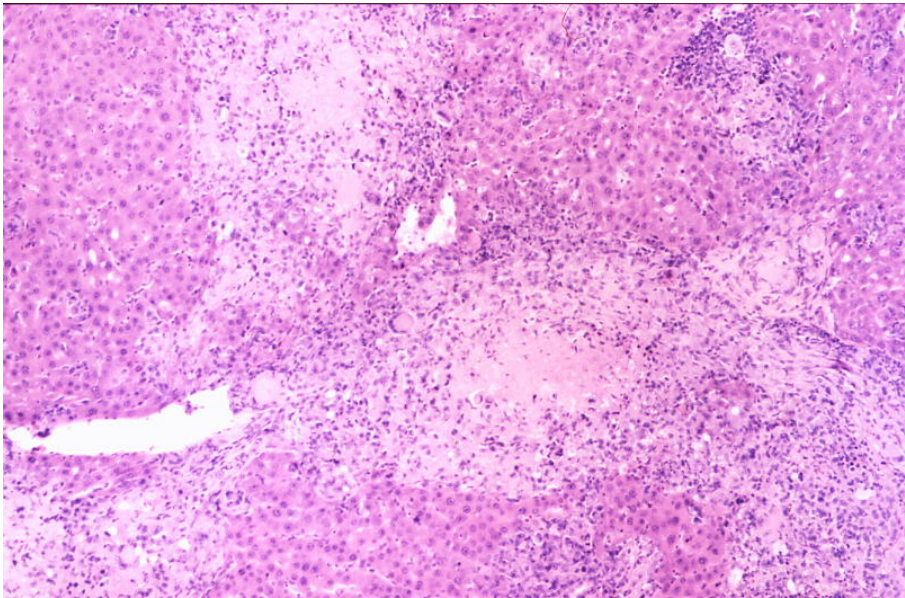
## Histiocytic Sarcoma

### Diagnostic Features

- Uniform population of rounded or oval cells with foamy, **eosinophilic cytoplasm** and **elongated or folded nuclei**.
- Areas of necrosis surrounded by palisaded tumour cells are common and characteristic.
- **Multinucleated giant cells** of foreign body or Langhans type are scattered throughout the tumour.
- Mitotic figures may be numerous.
- Atypical cells are sparse and pleomorphism is usually absent.
- **Minimal fibrosis** may be present.
- Metastases and spread on serosal surfaces and in the vascular spaces are common.

# Hematopoietic tumours in Rodents

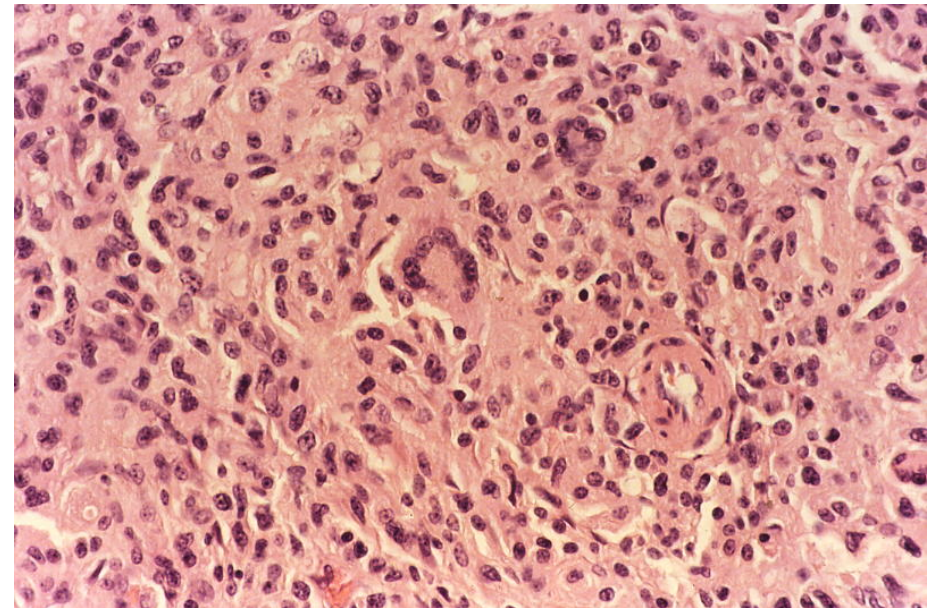
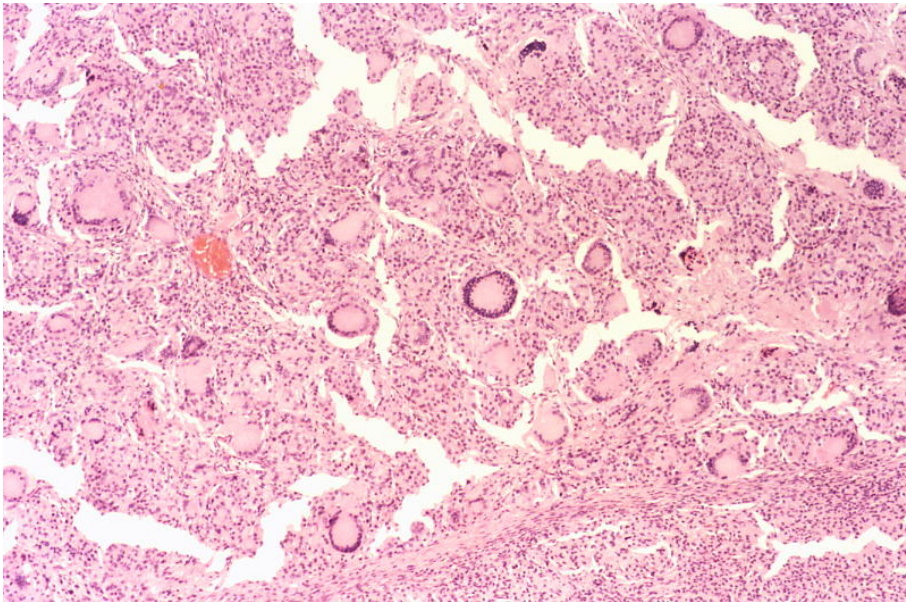
## Histiocytic sarcoma



Histiocytic sarcoma, liver, H&E

# Hematopoietic tumours in Rodents

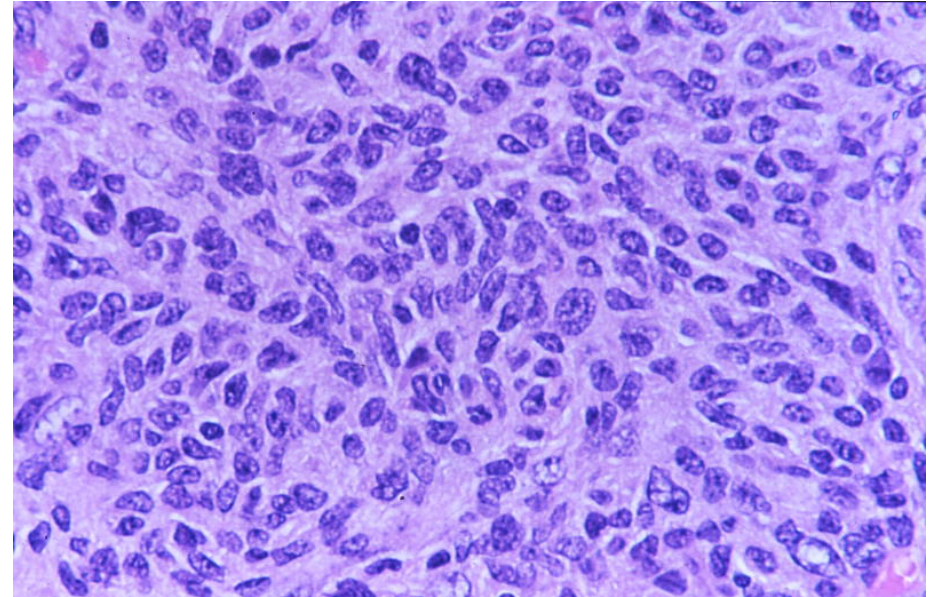
## Histiocytic sarcoma



Histiocytic sarcoma, subcutis, rat, H&E

# Hematopoietic tumours in Rodents

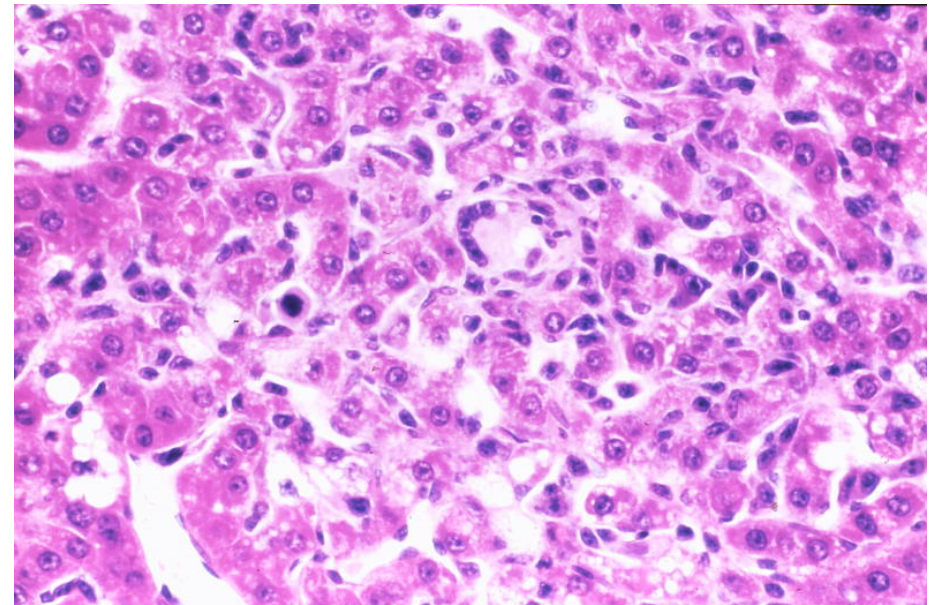
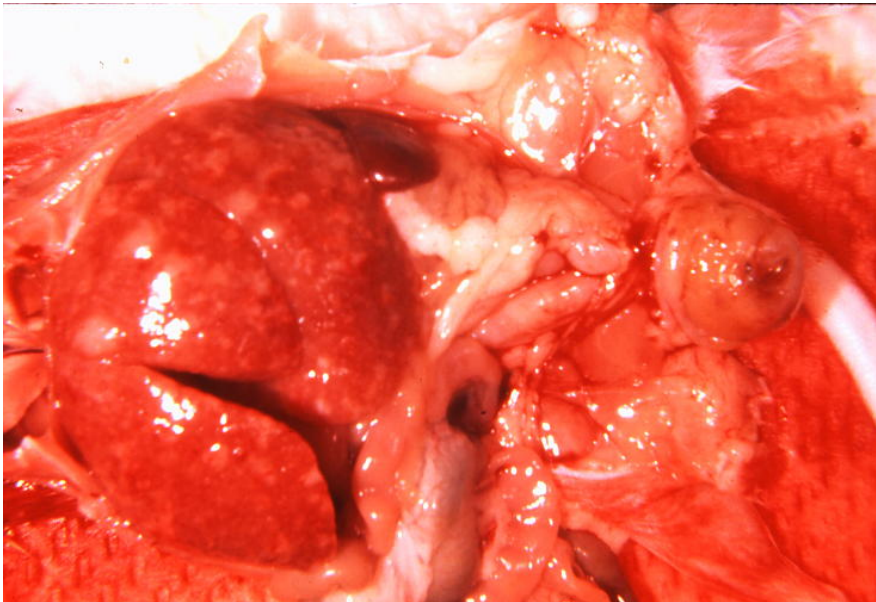
## Histiocytic sarcoma



Histiocytic sarcoma, uterus, mouse

# Hematopoietic tumours in Rodents

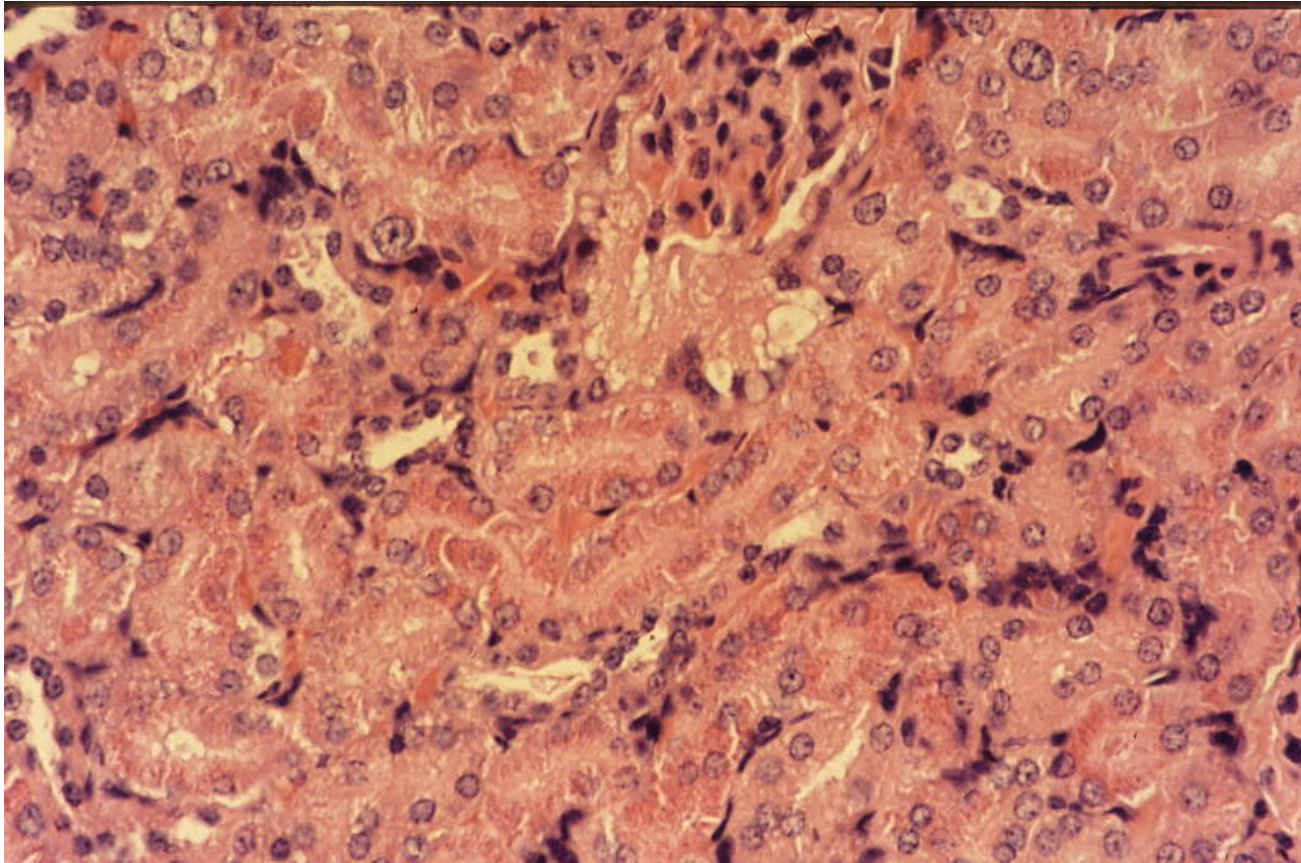
## Histiocytic sarcoma



Histiocytic sarcoma, liver, mouse

# Hematopoietic tumours in Rodents

## Histiocytic sarcoma

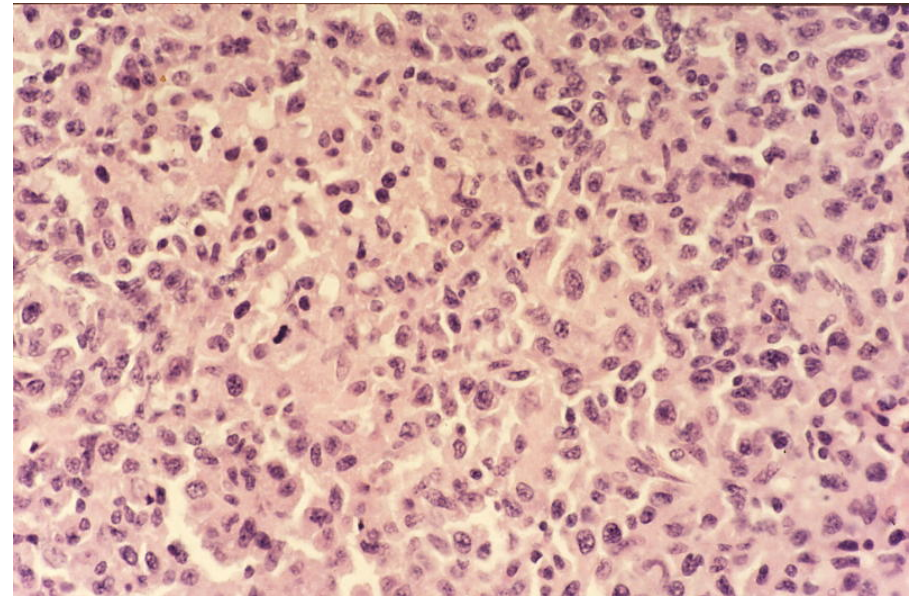
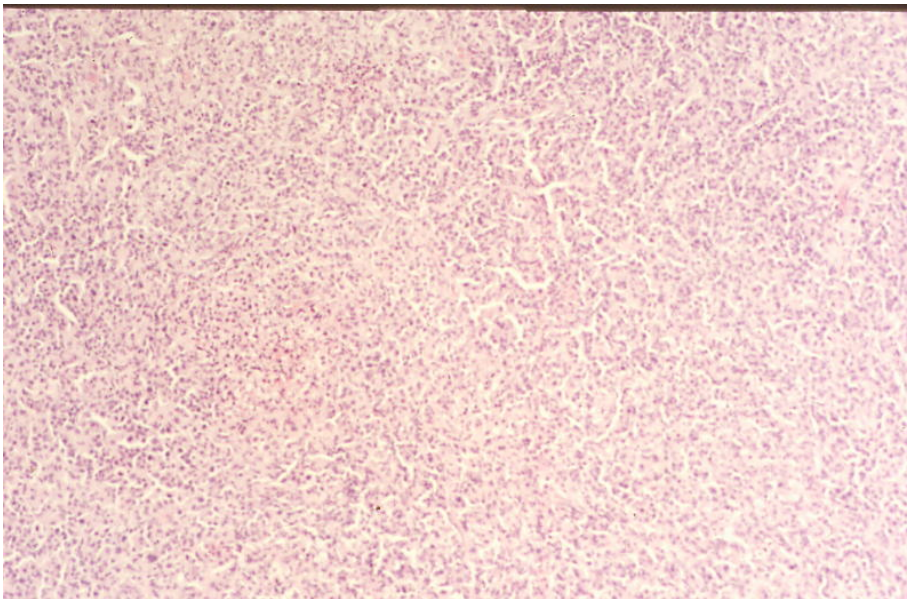


Increased hyaline droplets in proximal tubular epithelium

Note also can be seen in granulocytic tumours

# Hematopoietic tumours in Rodents

## Histiocytic sarcoma



Histiocytic sarcoma, mouse

# THANK YOU...

...For Your  
Attention



Any questions?