Imperial College London

White blood cells

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Session Plan

Part 1

Granulocytes and monocytes

- Origin
- Granulocyte maturation
- Cellular subsets
- Function

Part 2

Lymphocytes

- Origin
- Lymphocyte differentiation
- Function

Part 3

White blood cell abnormalities

- Leukocytosis
- Neutrophilia v neutropenia
- Introduction to leukaemia

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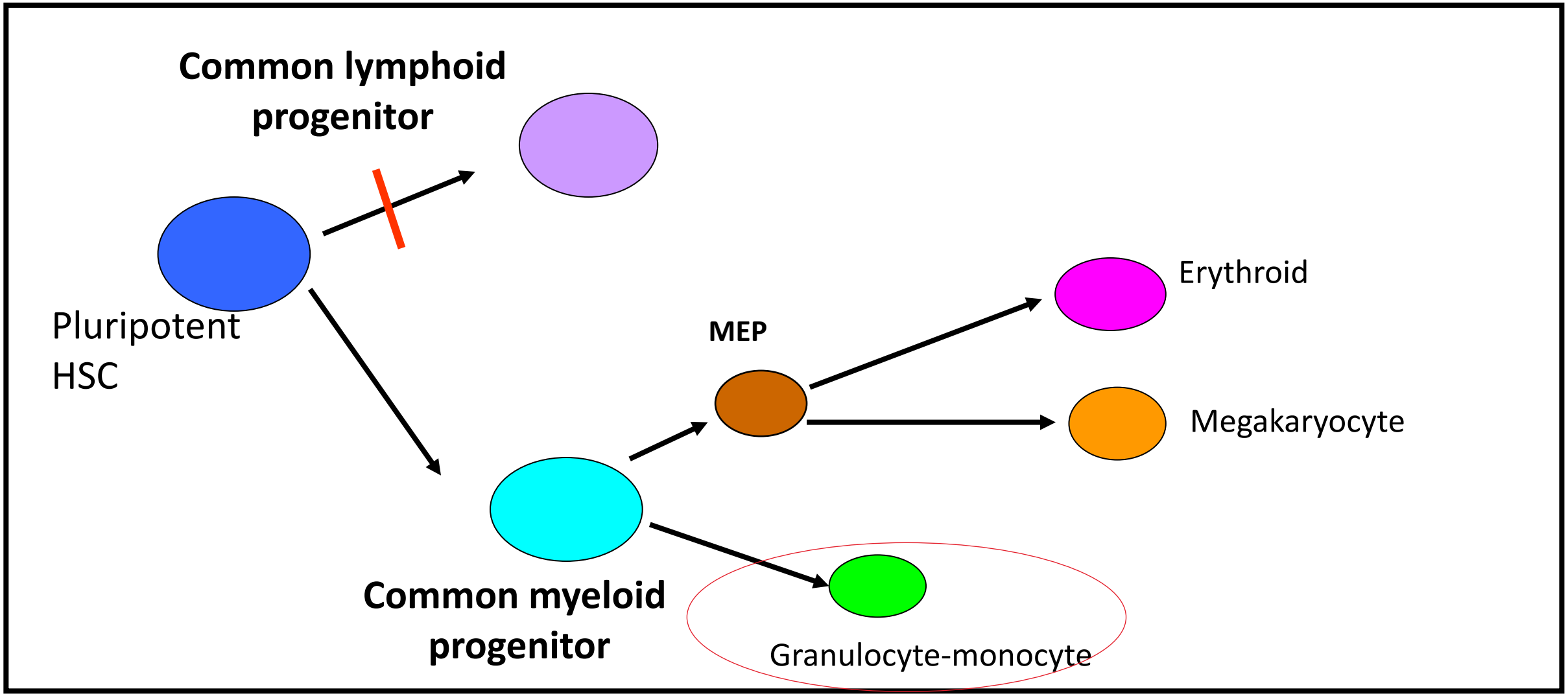
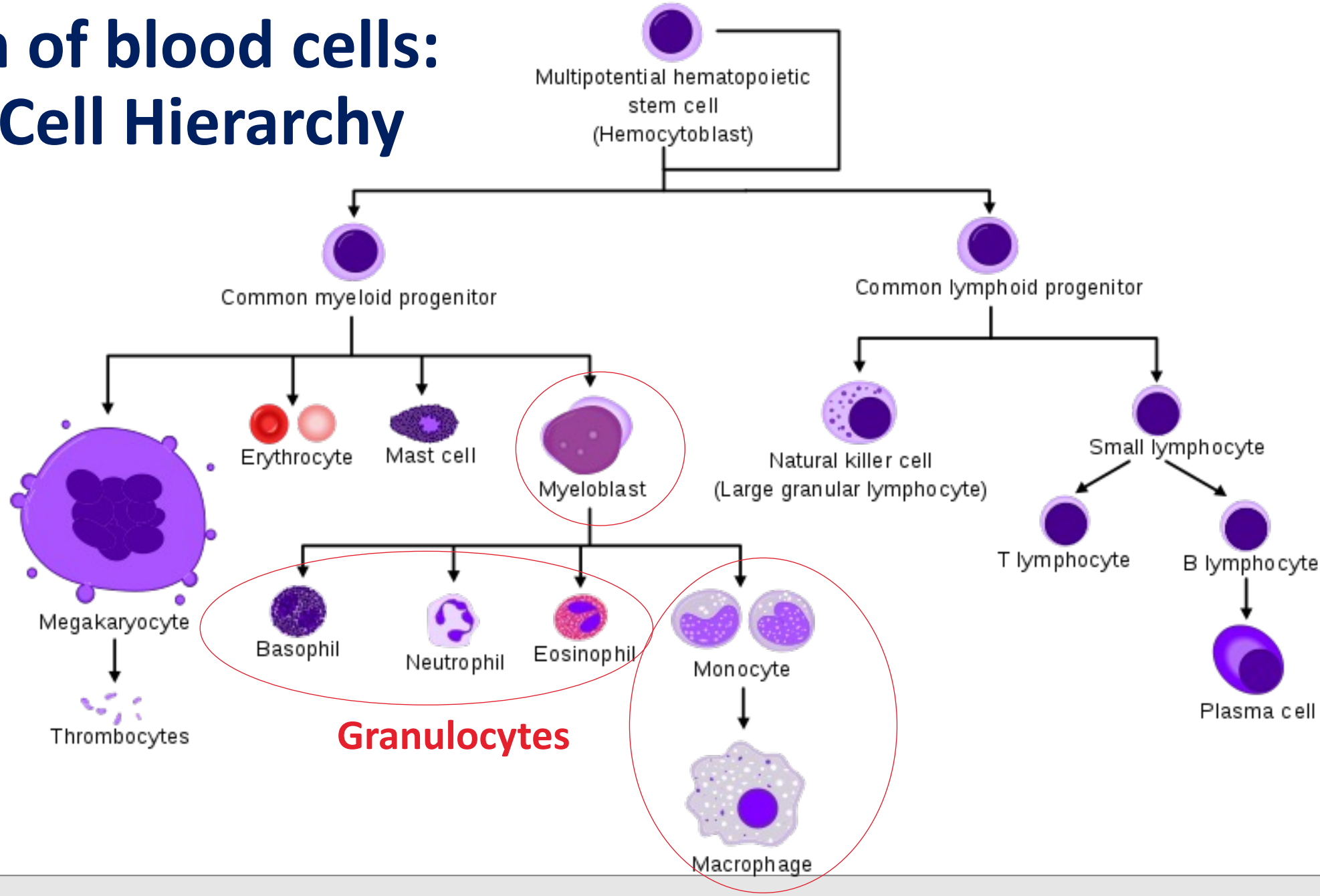
1-POM-2-2: White blood cells: Outline the origin and functions of white blood cells, and recall common causes of abnormalities, including cancer

Myeloid differentiation



Origin of blood cells: Stem Cell Hierarchy



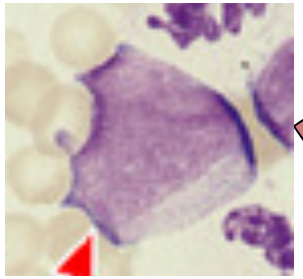
1-POM-2-2: White blood cells: Outline the origin and functions of white blood cells, and recall common causes of abnormalities, including cancer

Origin of white blood cells (leukocytes)

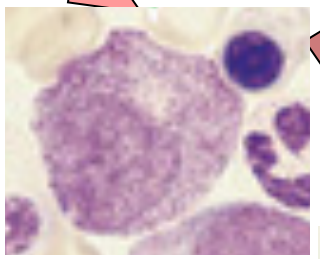
- The multipotent haemopoietic stem cell gives rise to a **myeloblast**, which in turn can give rise to **granulocytes** and **monocytes**
- **Granulocytes** refer to **neutrophils**, **basophils** and **eosinophils**, which have granules present in the cytoplasm that contain agents essential for their microbicidal function
- Signalling through myeloid growth factors such as as G-CSF, M-CSF, GM-CSF is essential for the proliferation and survival of myeloid cells

Abbreviations:
G-CSF granulocyte colony-stimulating factor;
M-CSF, macrophage colony-stimulating factor;
GM-CSF, granulocyte-macrophage colony stimulating factor

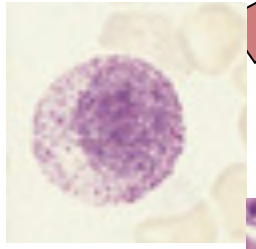
Normal granulocyte maturation



Myeloblast



Promyelocyte



Myelocyte

Band form

Neutrophil

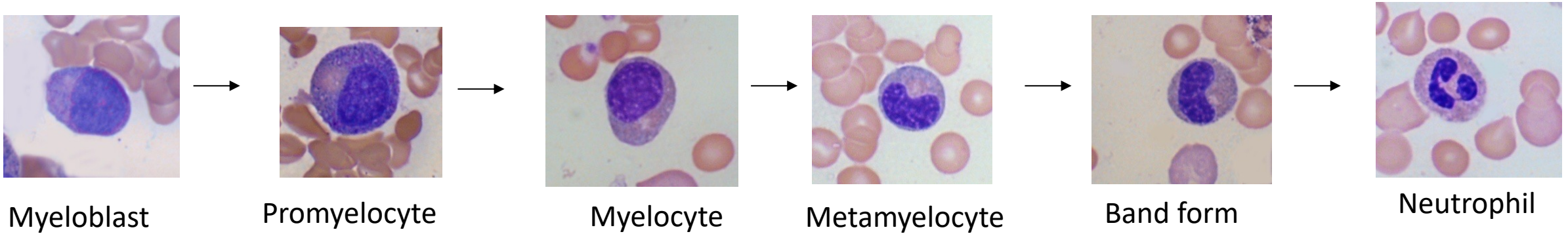
Bone Marrow

Cell division:

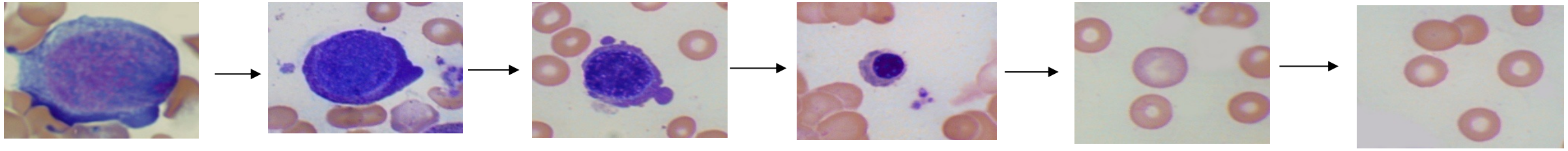
- occurs in myeloblasts, promyelocytes and myelocytes
- does not occur in metamyelocytes or band forms

You don't need to remember the names

Granulopoiesis and Erythropoiesis



Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → Band form → Neutrophil



Proerythroblast → Early erythroblast → Intermediate erythroblast → Late erythroblast → Polychromatic erythrocyte → Mature erythrocyte

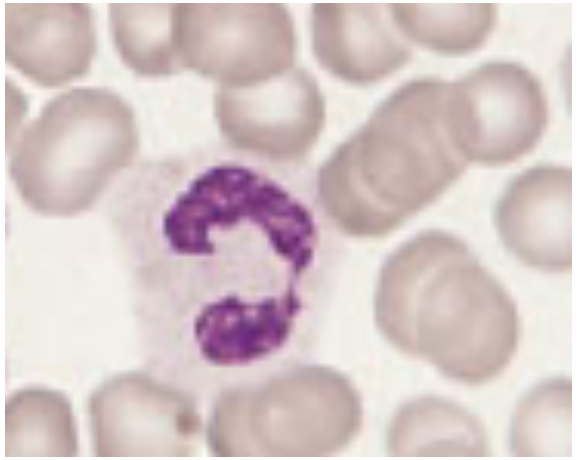
From Bain BJ, 2010, Haematology: A Core Curriculum, Imperial College Press. Recommended textbook.
All royalties go to the academic haematology department

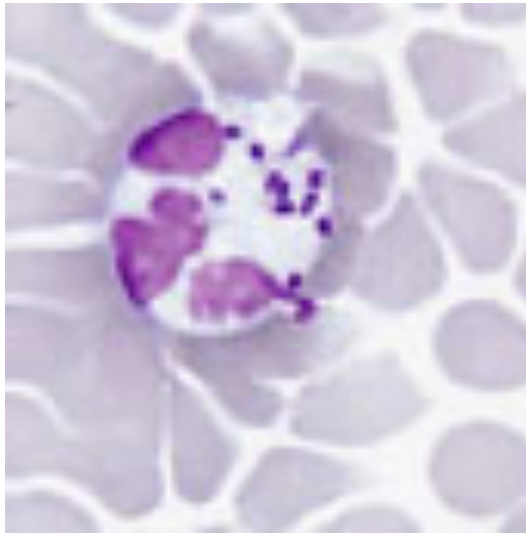
You don't need to remember the names

1-POM-2-2: White blood cells: Outline the origin and functions of white blood cells, and recall common causes of abnormalities, including cancer

White blood cells: the neutrophil

- The **neutrophil** granulocyte survives 7–10 hours in the circulation before migrating to tissues
- The nucleus of the mature neutrophil is **segmented** (sometimes referred to as lobulated)
- Its main function is defence against infection; it **phagocytoses** and then kills micro-organisms



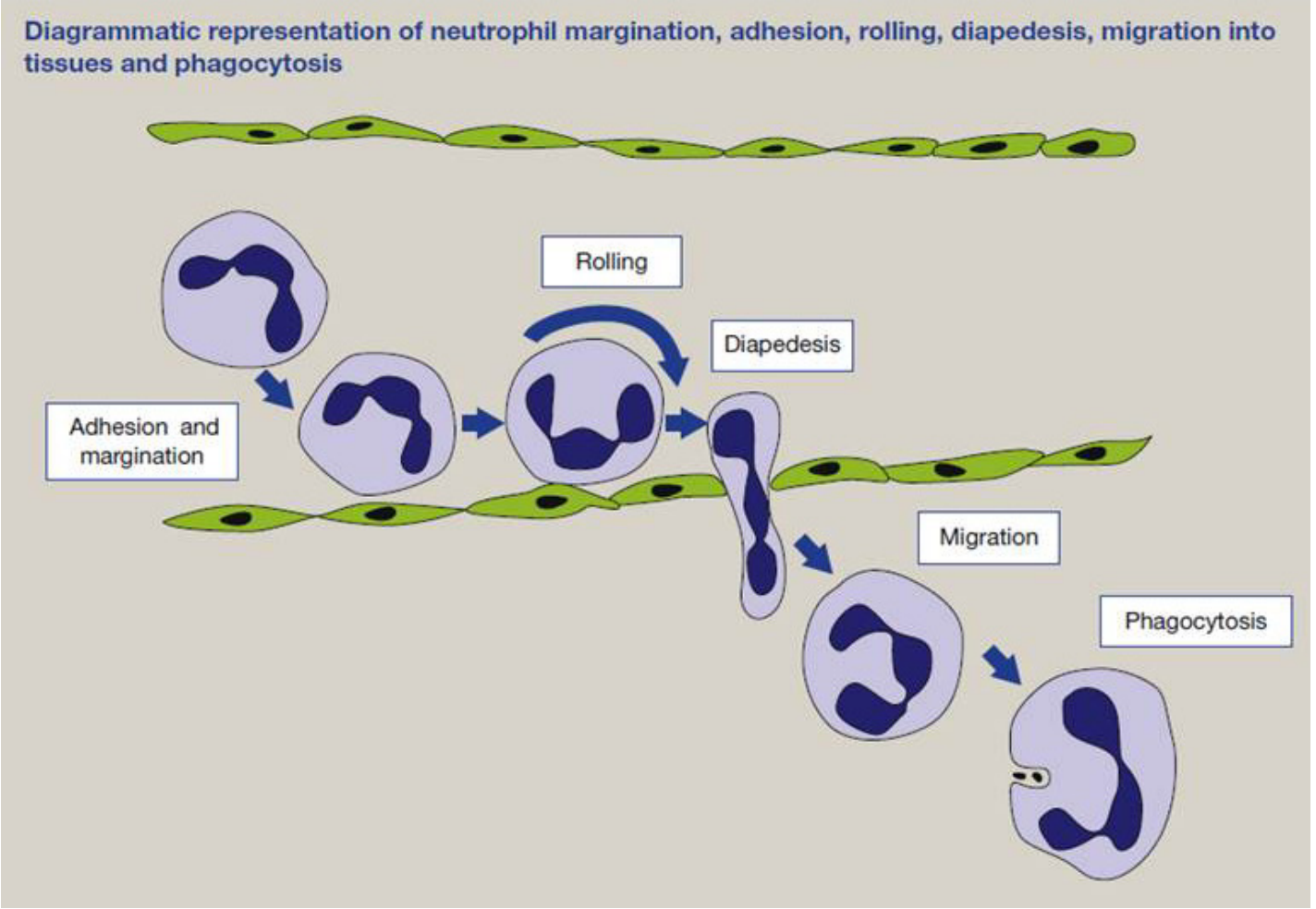


Q: What can you see within this neutrophil?

White blood cells: the neutrophil

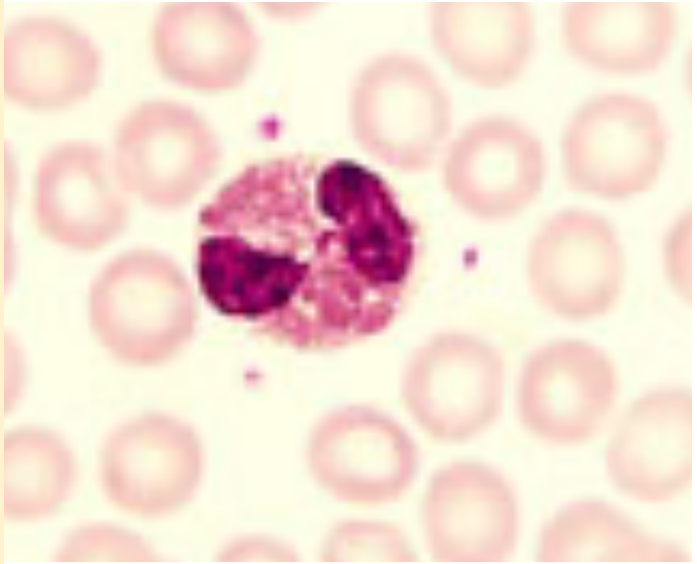
1-POM-1-9

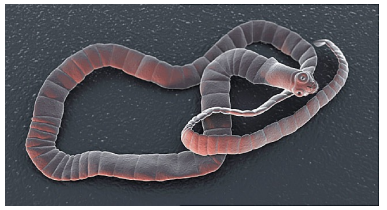
- The first step in neutrophil migration to tissues is **chemotaxis**
- Neutrophils become marginated in the vessel lumen, adhere to the endothelium and migrate into tissues
- **Phagocytosis** of micro-organisms occurs following cytokine priming



White blood cells: the eosinophil

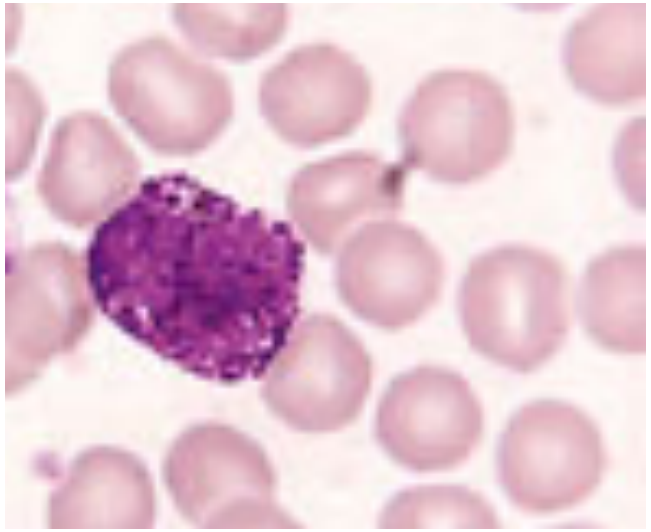
- A myeloblast can also give rise to **eosinophil** granulocytes
- The eosinophil spends less time in the circulation than the neutrophil
- Its main function is defence against parasitic infection
- Eosinophils are important in the regulation of Type I (immediate) hypersensitivity reactions: inactivate the histamine and leukotrienes released by basophils and mast cells (I&I hypersensitivity)



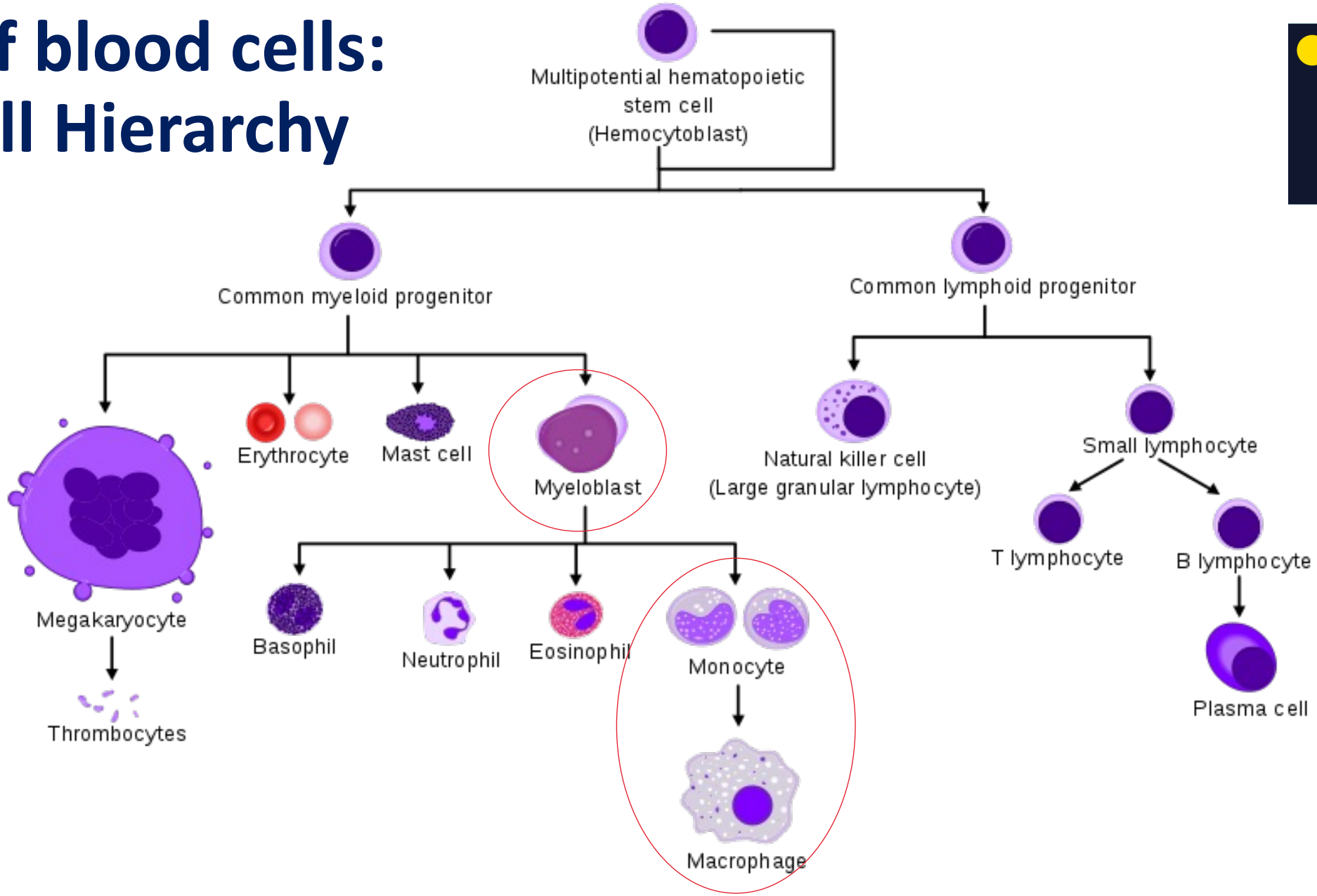


White blood cells: the basophil

- A myeloblast can also give rise to **basophil** granulocytes
- Its granules contains stores of histamine and heparin, as well as proteolytic enzymes
- Basophils are involved in a variety of immune and inflammatory responses
  - Mediation of the immediate-type hypersensitivity reaction in which IgE-coated basophils release histamine and leukotrienes
  - Modulation of inflammatory responses by releasing heparin and proteases
  - Mast cells are similar to basophils, but reside in tissues rather than the circulation (I&I hypersensitivity)



Origin of blood cells: Stem Cell Hierarchy

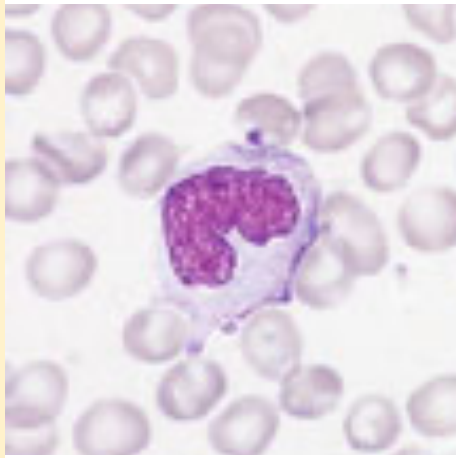


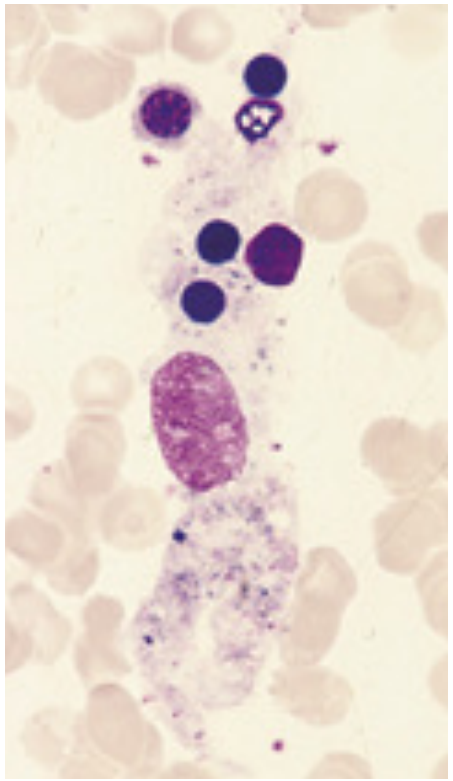
1-POM-2-2: White blood cells: Outline the origin and functions of white blood cells, and recall common causes of abnormalities, including cancer

White blood cells: the monocyte

1-POM-1-9

- The myeloid stem cell can also give rise to monocyte precursors and thence **monocytes**
- Monocytes spend several days in the circulation
- Monocytes play several key roles:
  - phagocytosis of micro-organisms covered with antibody and complement
  - phagocytosis of bacteria/fungi (cf antibody)
  - antigen presentation to lymphoid and other immune cells
- Monocytes migrate to tissues where they develop into **macrophages** (also known as histiocytes) and other specialised cells that have a phagocytic and scavenging function
- Macrophages also store and release iron





Summary: leukocyte function

Type of white cell	Main functions
Neutrophil granulocytes	Chemotaxis, phagocytosis, killing of phagocytosed bacteria
Monocytes and macrophages	Chemotaxis, phagocytosis, killing of some micro-organisms, antigen presentation
Eosinophil granulocytes	All neutrophil functions as above Main defence against parasitic infection Regulation of some (immediate-type) hypersensitivity reactions
Basophil granulocytes	Mediation of immediate-type hypersensitivity Modulation of inflammatory responses by releasing heparin and proteases

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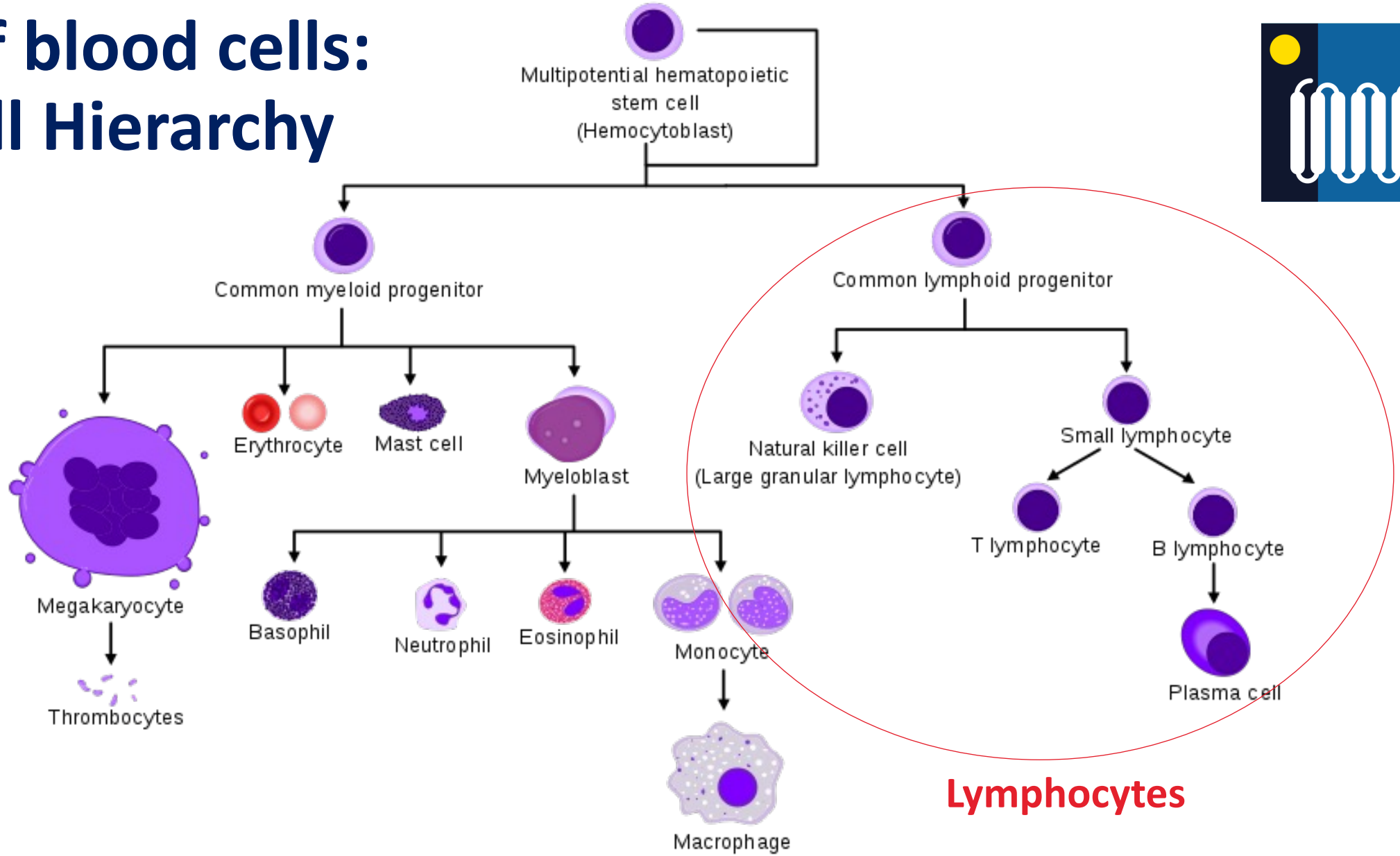
Origin of blood cells: Stem Cell Hierarchy



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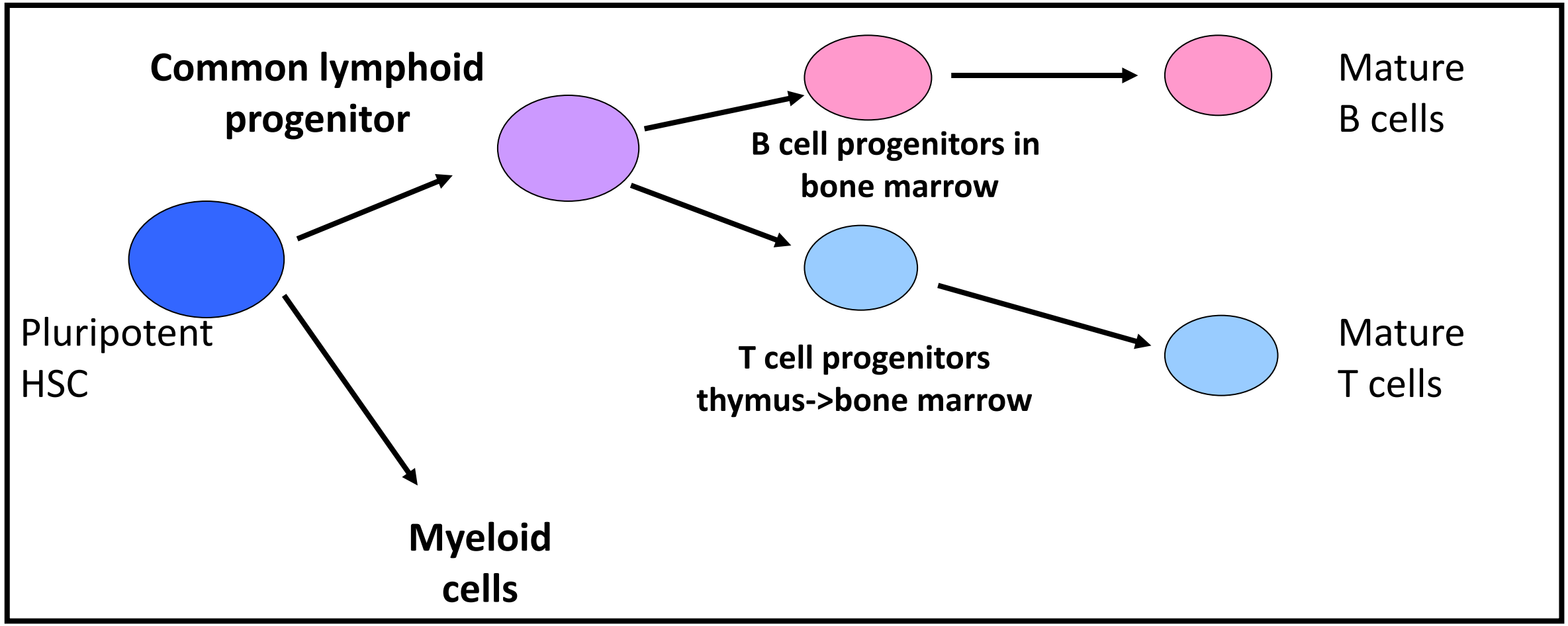
Lymphoid differentiation

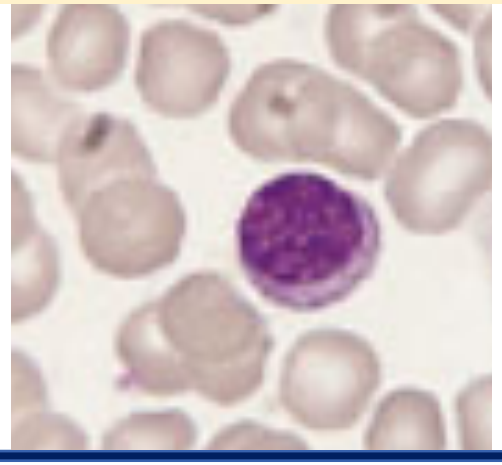
I&I Lymphocytes

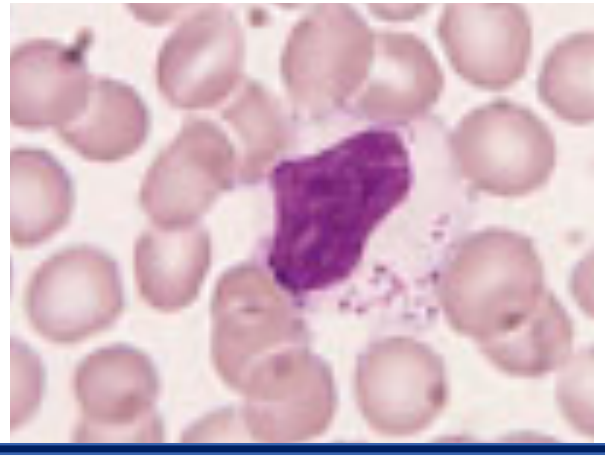


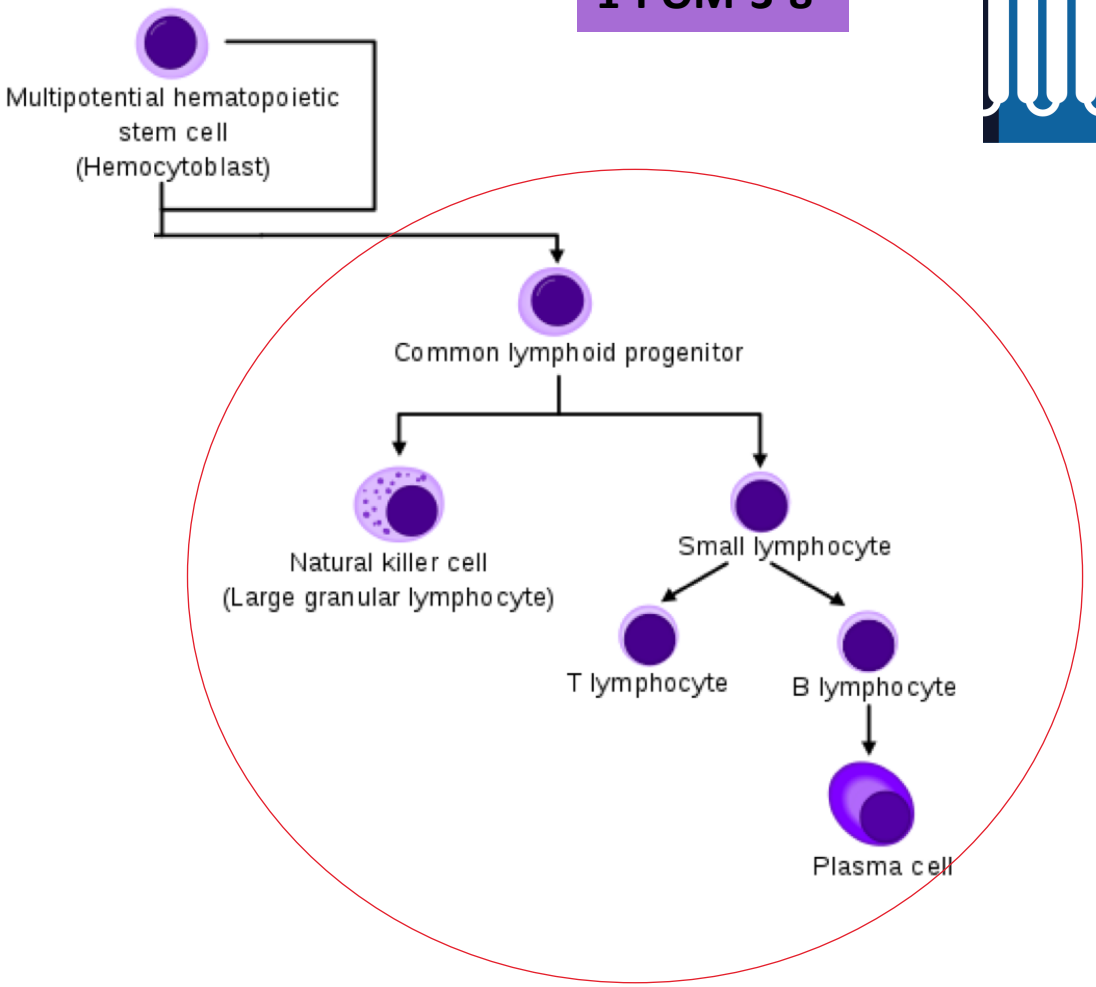
Origin of white cells: lymphocytes

1-POM-3-6
1-POM-3-8

- The multipotent haemopoietic stem cell also gives rise to a lymphoid stem cell
- The lymphoid stem cell gives rise to **T cells**, **B cells** and **natural killer** (**NK**) cells
- Lymphocytes recirculate to lymph nodes and other tissues and then back to the blood stream
- Intravascular life span is very variable



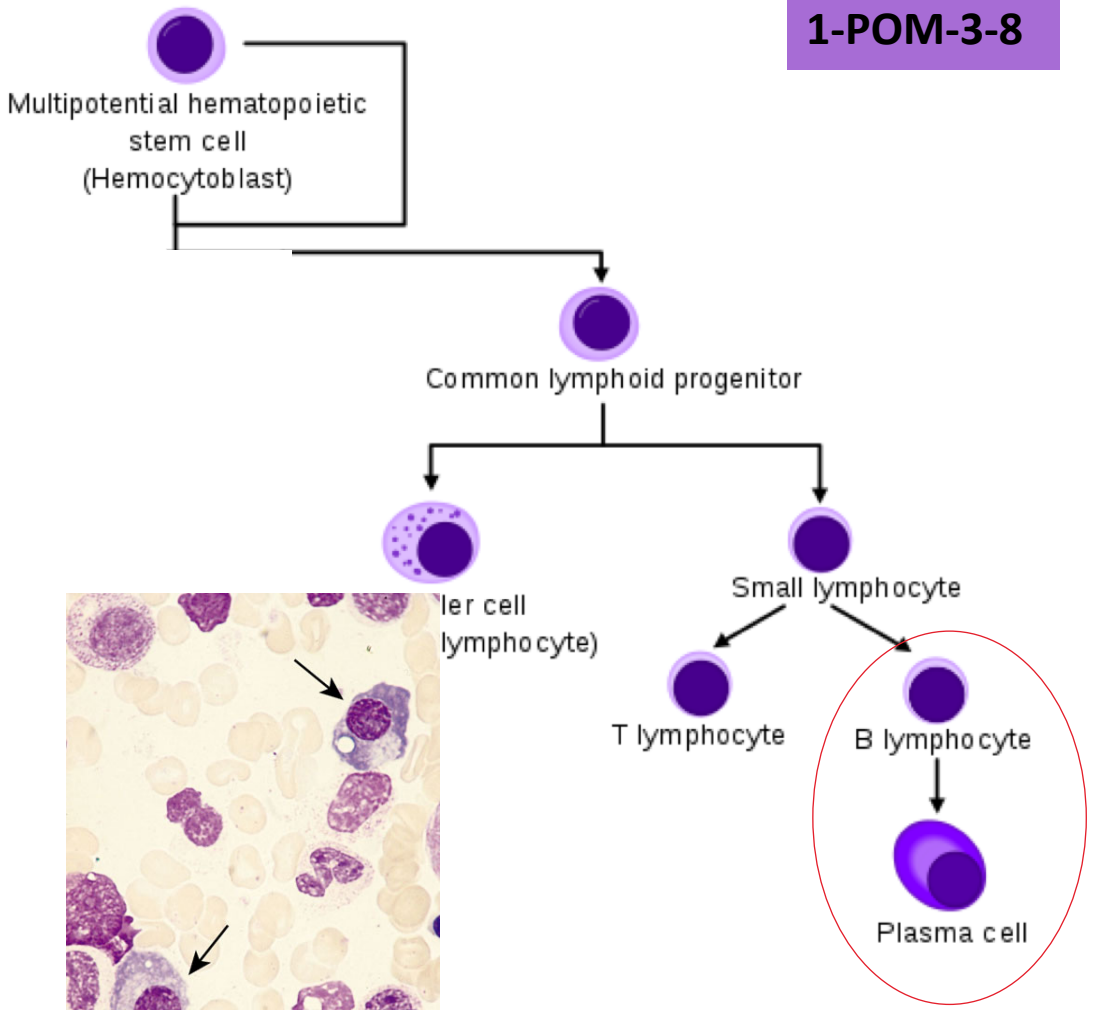




White blood cells: B lymphocytes

1-POM-3-6
1-POM-3-8

- **Originate** in fetal liver & bone marrow
- **Development** involves Ig heavy & light chain gene rearrangement
- This leads to production of surface Igs against many different antigens: **humoral immunity**
- Subsequent maturation requires exposure to antigens in lymphoid tissue e.g lymph nodes
- This results in recognition of non-self antigens by mature B cells and production of specific Igs & antibodies

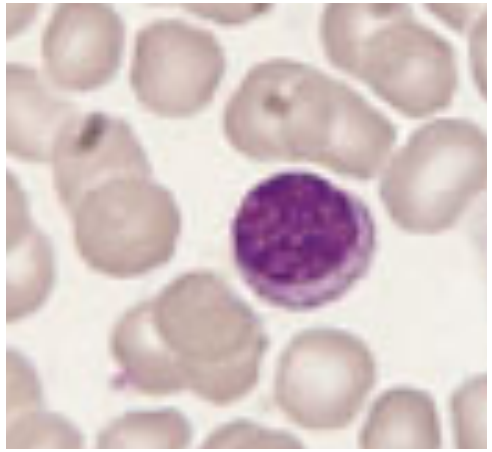


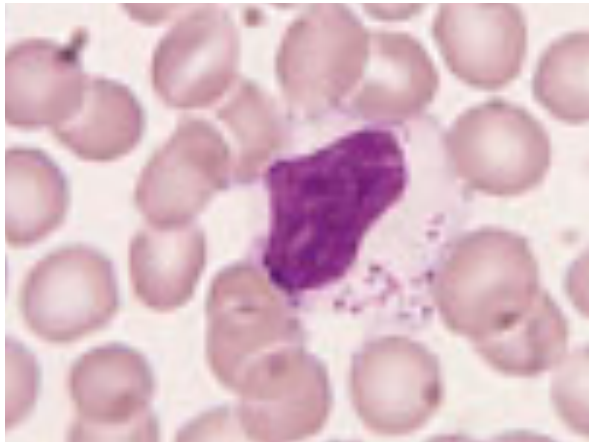
Maturation into **plasma cells,** which produce antibodies

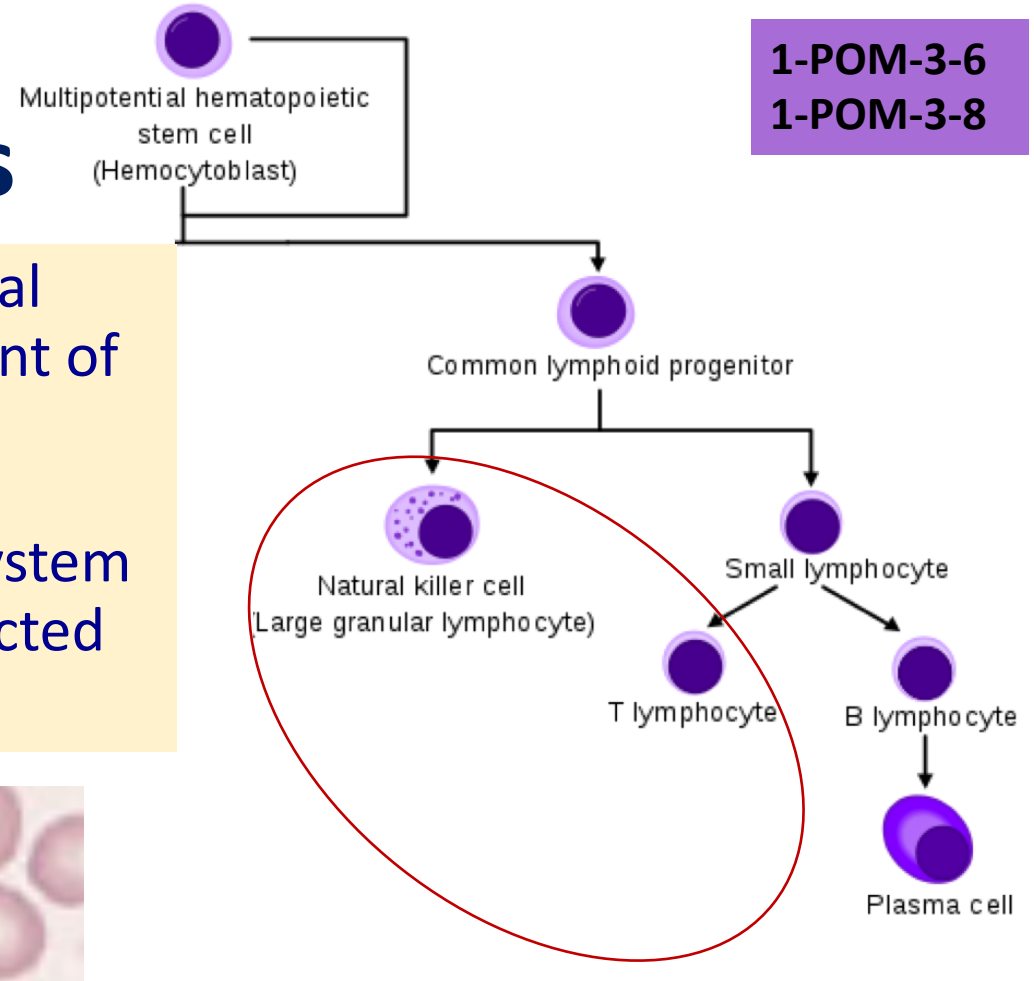
White blood cells: T lymphocytes & NK cells

1-POM-3-6
1-POM-3-8

- Lymphocyte progenitors migrate from fetal liver to the thymus leading to development of **T lymphocytes**
- Involved in **cell-mediated immunity**
- **NK cells** are part of the innate immune system – they can kill tumour cells and virus-infected cells

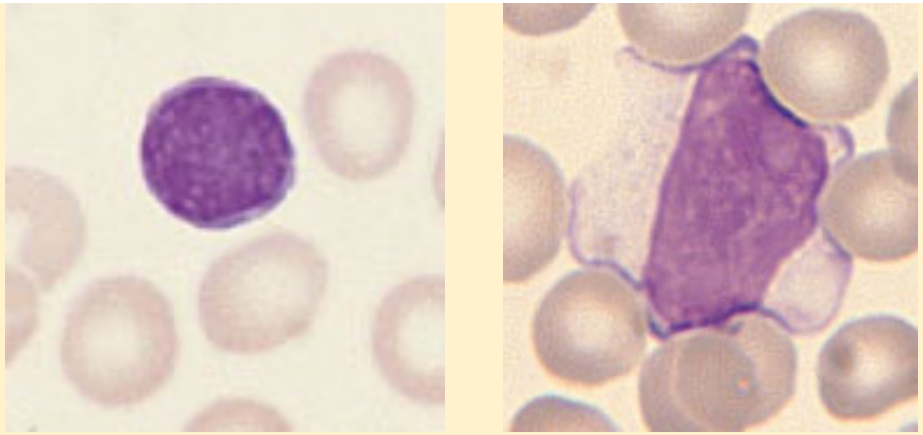




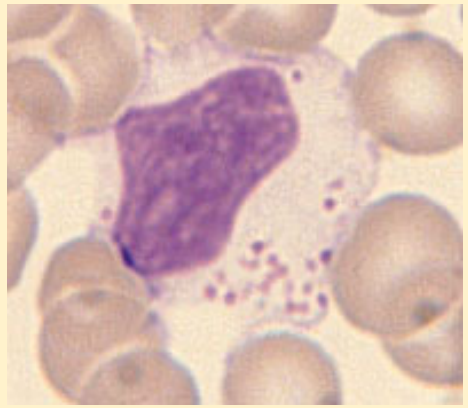


Not all lymphocytes look the same…

- These lymphocytes could be T cells or B cells

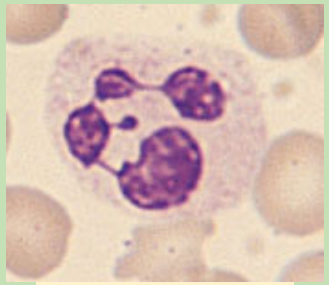


- This lymphocyte is either a cytotoxic T cell or a NK cell

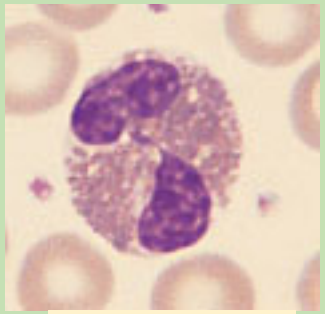


Question Time:

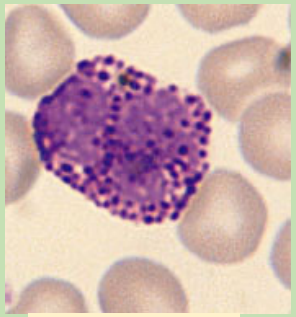
You should now be able to identify all these cells



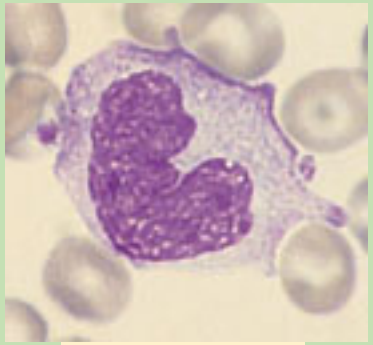
Neutrophil



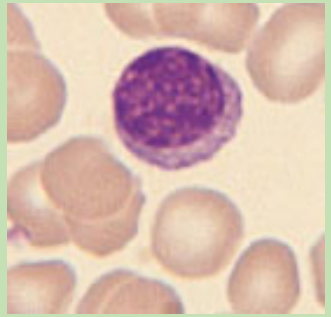
Eosinophil



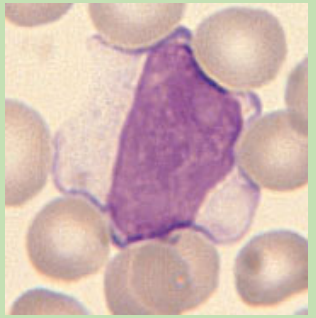
Basophil



Monocyte



Lymphocyte



Lymphocyte

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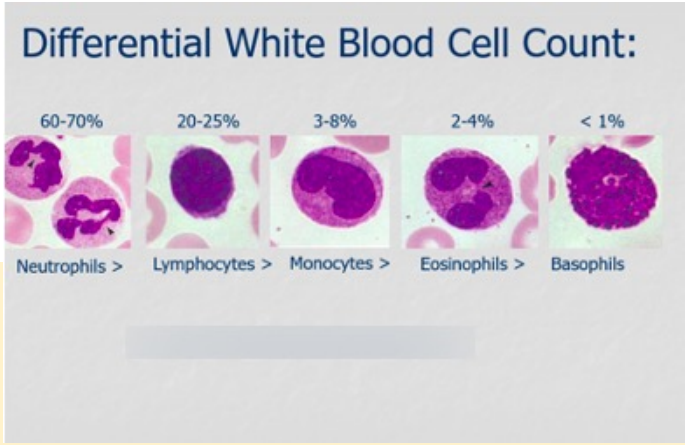
White cells (leukocytes) – what abnormalities can occur?



- Changes can be numerical, morphological or both

- **Transient leukocytosis suggest a Reactive (i.e.Secondary) cause** and occurs when a normal or healthy bone marrow responds to an external stimulus such as infection, inflammation or infarction:

bacterial infection:	neutrophilia / monocytosis
viral infection:	lymphocytosis
parasitic infection	eosinophilia

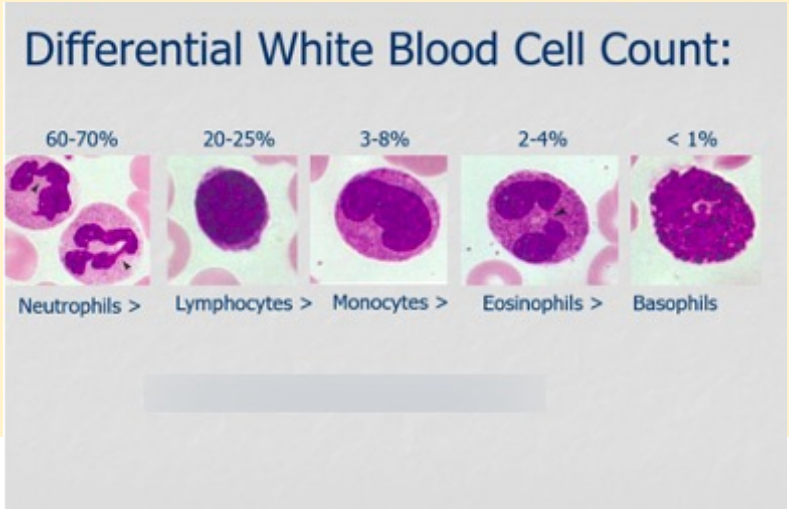
- **Persistent leukocytosis suggests a Primary blood cell disorder-** The leukocyte count is abnormal due to acquired somatic DNA damage affecting a haematopoietic precursor cell giving rise to blood cancers such as leukaemia, lymphoma* or myeloma*

* Taught in late phase curriculum (Y5 Pathology)

White cells (leukocytes) – why abnormalities occur?

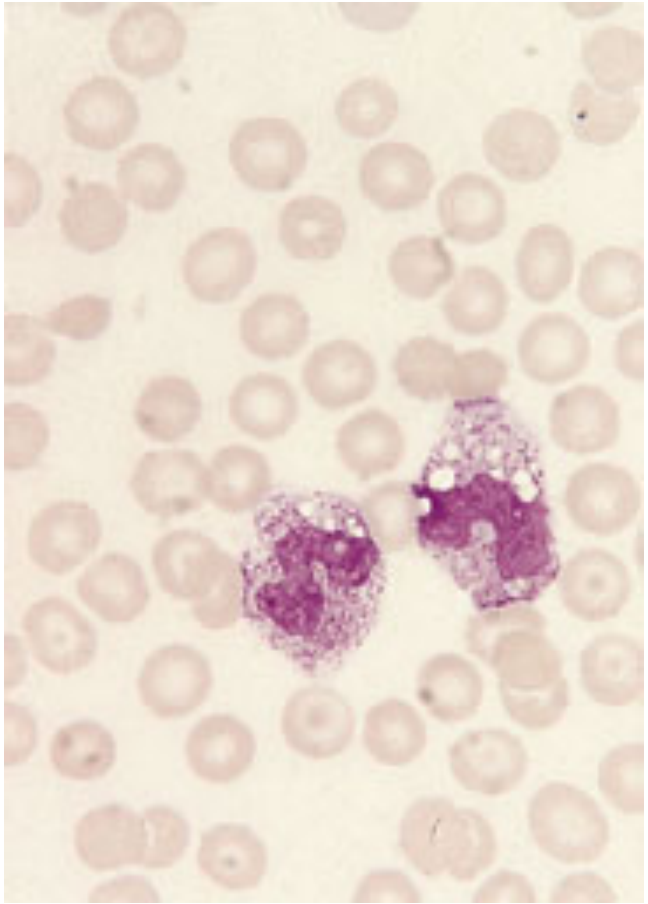
- Changes can be numerical, morphological or both can be divided into two groups
- **Leukocytosis** – too many white cells but which type of white cell is increased?
  - **neutrophilia**
  - **eosinophilia**
  - **basophilia**
  - **lymphocytosis**
  - **monocytosis**
- **Leukopenia** – reduction in total number of white cells
  - **neutropenia**: reduction in neutrophil count
  - **lymphopenia**: reduction in lymphocyte count

leukocytosis and **leukopenia** usually result from changes in the **neutrophil** count since this is usually the most abundant leukocyte in the circulation



Neutrophilia: too many neutrophils

- Causes: **infection** (particularly bacterial infection), **inflammation**, infarction or other **tissue damage**,
- Neutrophilia is also a normal feature in **pregnancy** and may be seen following **exercise** (caused by a rapid shift of neutrophils from the marginated pool to the circulating pool) and after administration of **corticosteroids**
- Neutrophilia may be accompanied by **toxic changes** and 'left shift' i.e. the presence of early myeloid cells such as metamyelocytes
- **Toxic granulation** is heavy coarse granulation of neutrophils
- **Chronic myeloid/granulocytic leukaemia (CML),** an example of a **myeloproliferative disorder** is a primary blood cancer associated with neutrophilia, basophilia and 'left shift' Genetics: Cancer and Genetics 5.9



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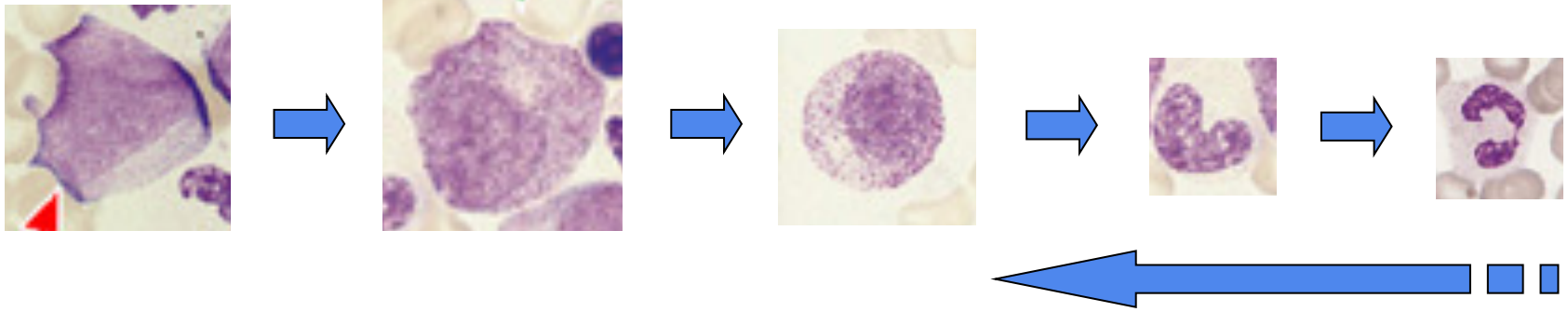
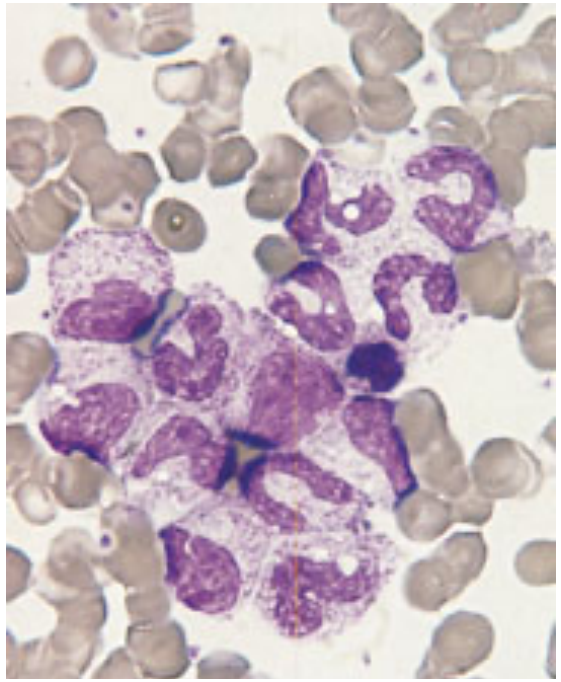
Q: Can you name any other myeloproliferative disorders?

Neutrophilia: too many neutrophils

- Neutrophilia may be accompanied by **left shift**
- **Left shift** means that there is an increase in **non-segmented neutrophils** or that there are **neutrophil precursors in the blood**





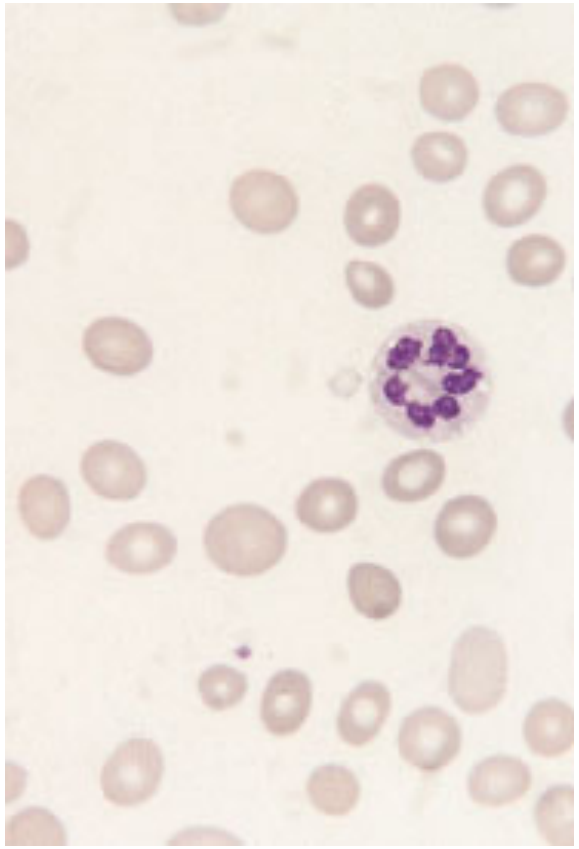
Increased non-segmented neutrophils, known as 'band forms'

Neutropenia: too few neutrophils

- Neutropenia can occur in a large number of conditions
- This includes in **acute leukaemia** and following **chemotherapy** and **radiotherapy**
- Neutropenia can also result from **autoimmune** disorders, **severe bacterial** infections, certain **viral** infections and **drugs**, e.g. some anticonvulsant and antipsychotic drugs and some antimalarials
- Sometimes, neutropenia has a physiological basis e.g. benign ethnic neutropenia in people of African or Afro-Caribbean ancestry
- Patients with very low neutrophil counts ($< 0.5 \times 10^9$/l) are at a high risk of serious infection and may need urgent treatment with intravenous antibiotics

Other abnormalities in neutrophils: the hypersegmented neutrophil

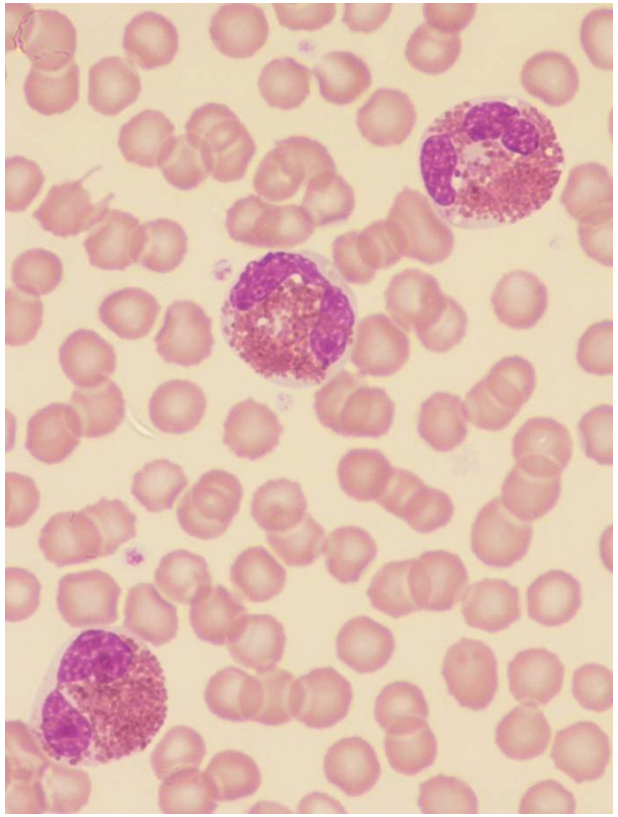
- A normal neutrophil should have between 3 and 5 segments or lobes
- **Neutrophil hypersegmentation** means that there is an increase in the average number of neutrophil lobes or segments ('right shift')
- It usually results from a lack of vitamin B_{12} or folic acid (megaloblastic anaemia)



Q: How many lobes can you see in this neutrophil?
A. 8 - 9

Eosinophilia – too many eosinophils

- Usually due to allergy or parasitic infection
  - asthma, eczema, drugs
- Can occur in some forms of leukaemia e.g. CML
- This blood film is from a patient with a parasitic infection called strongyloidiasis



Basophilia – too many basophils

- This is an uncommon finding is usually due to leukaemia or a related condition
- This blood film is from a patient with chronic myeloid leukaemia (CML)
- The arrows point to basophils

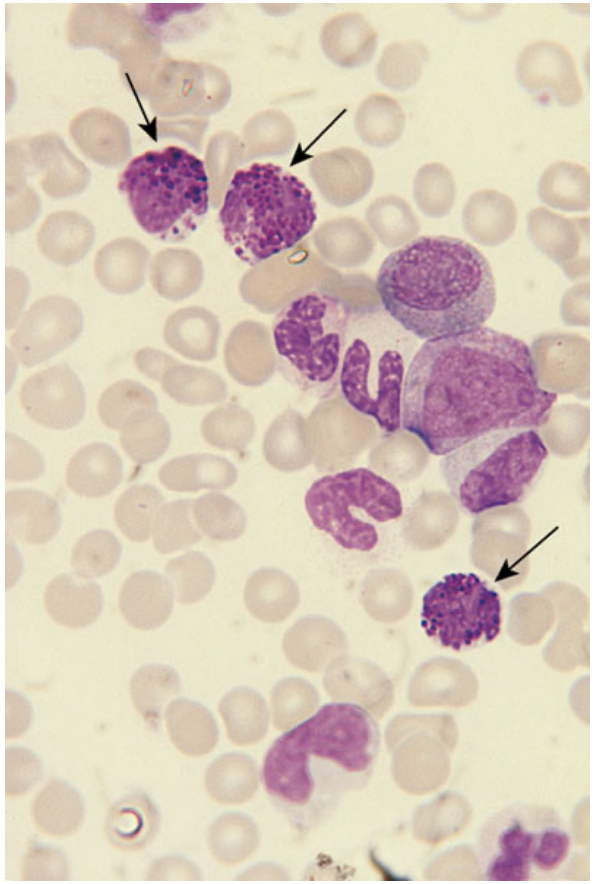
Q.What other cells are increased?

Myelocytes, Band forms

Q. What two other terms could you use to describe the abnormalities shown?

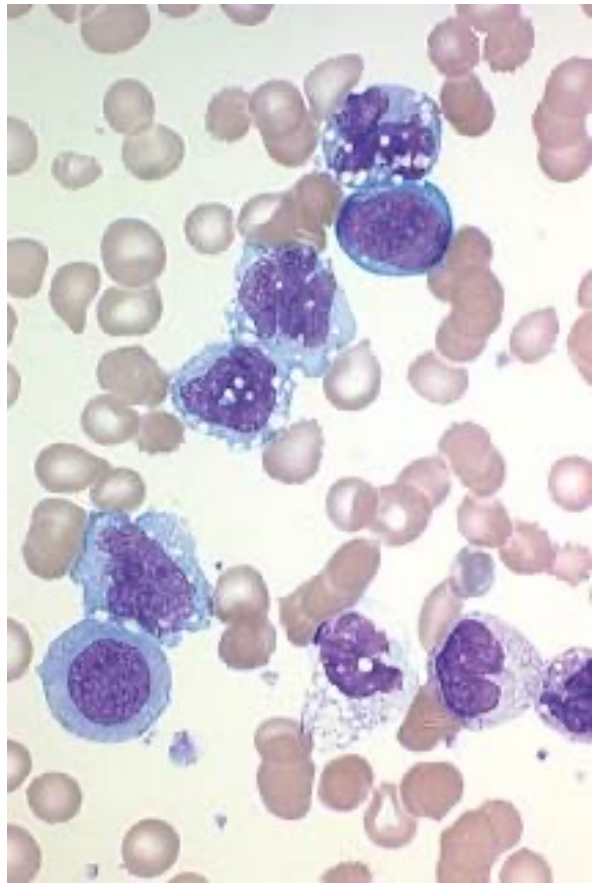
Neutrophilia

Left shift



Monocytosis: too many monocytes

- Causes: infection (particularly chronic i.e. long bacterial infection) or chronic inflammation
- Some types of leukaemia



Note: In medicine the terms ‘acute’ and ‘chronic’ refer to duration rather than severity
Acute – recent
Chronic – longstanding

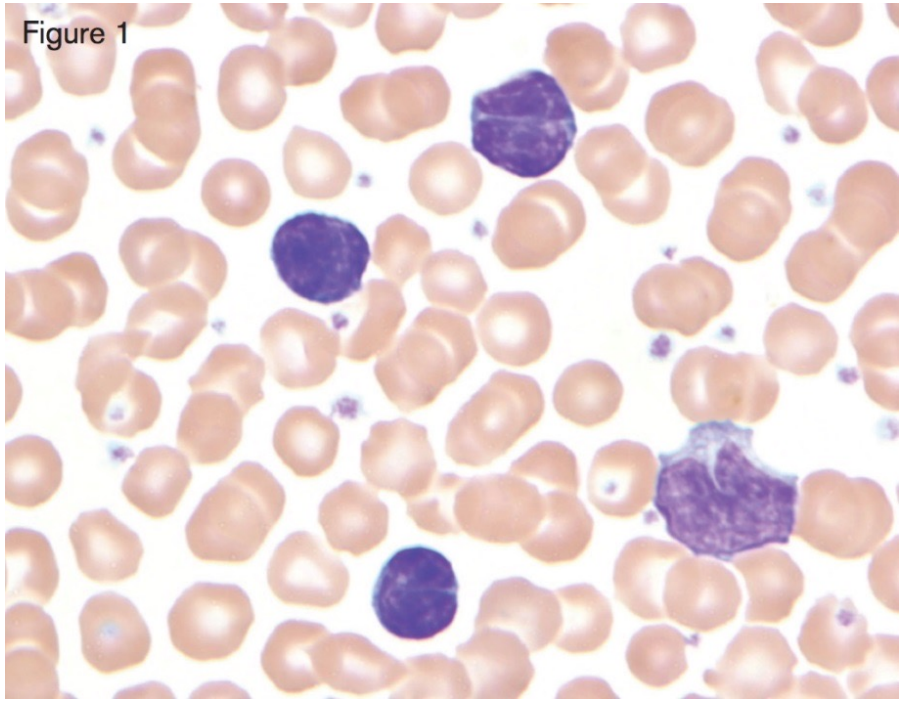
http://www.healthgala.info/2017/06/Monocytosis-icd-10-symptoms-causes-treatment.html

White cells (leukocytes) – what abnormalities can occur?

- Changes can be numerical, morphological or both
- **Leukocytosis** – too many white cells but which type of white cell is increased?
  - **neutrophilia**
  - **eosinophilia**
  - **basophilia**
  - **lymphocytosis**
  - **monocytosis**
  - **Leukopenia** – reduction in total number of white cells
- **neutropenia**: reduction in neutrophil count
- **lymphopenia**: reduction in lymphocyte count

Lymphocytosis: too many lymphocytes

- Often a response to viral infection **(transient)**
- Can result from a lymphoproliferative disorder e.g. chronic lymphocytic leukaemia **(persistent)**
- This blood film is from a child with whooping cough (*Bordatella pertussis*), an important cause of lymphocytosis in children

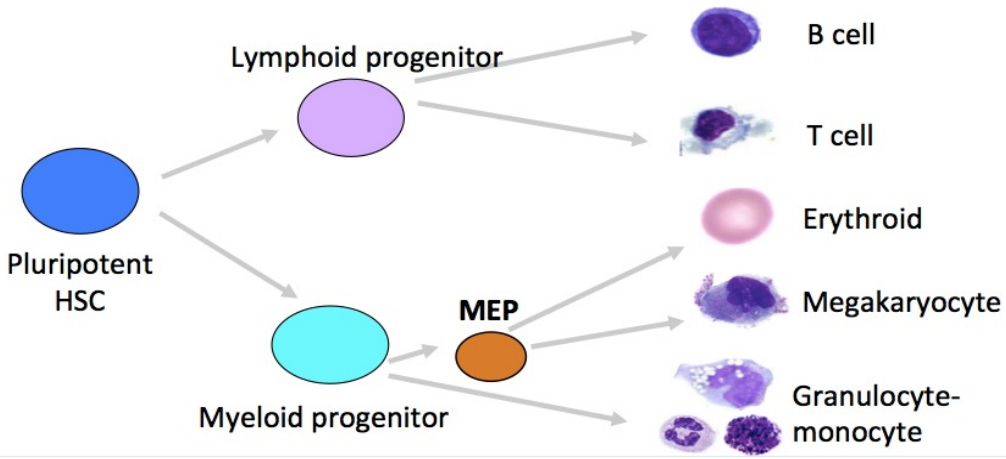


Lymphopenia: too few lymphocytes

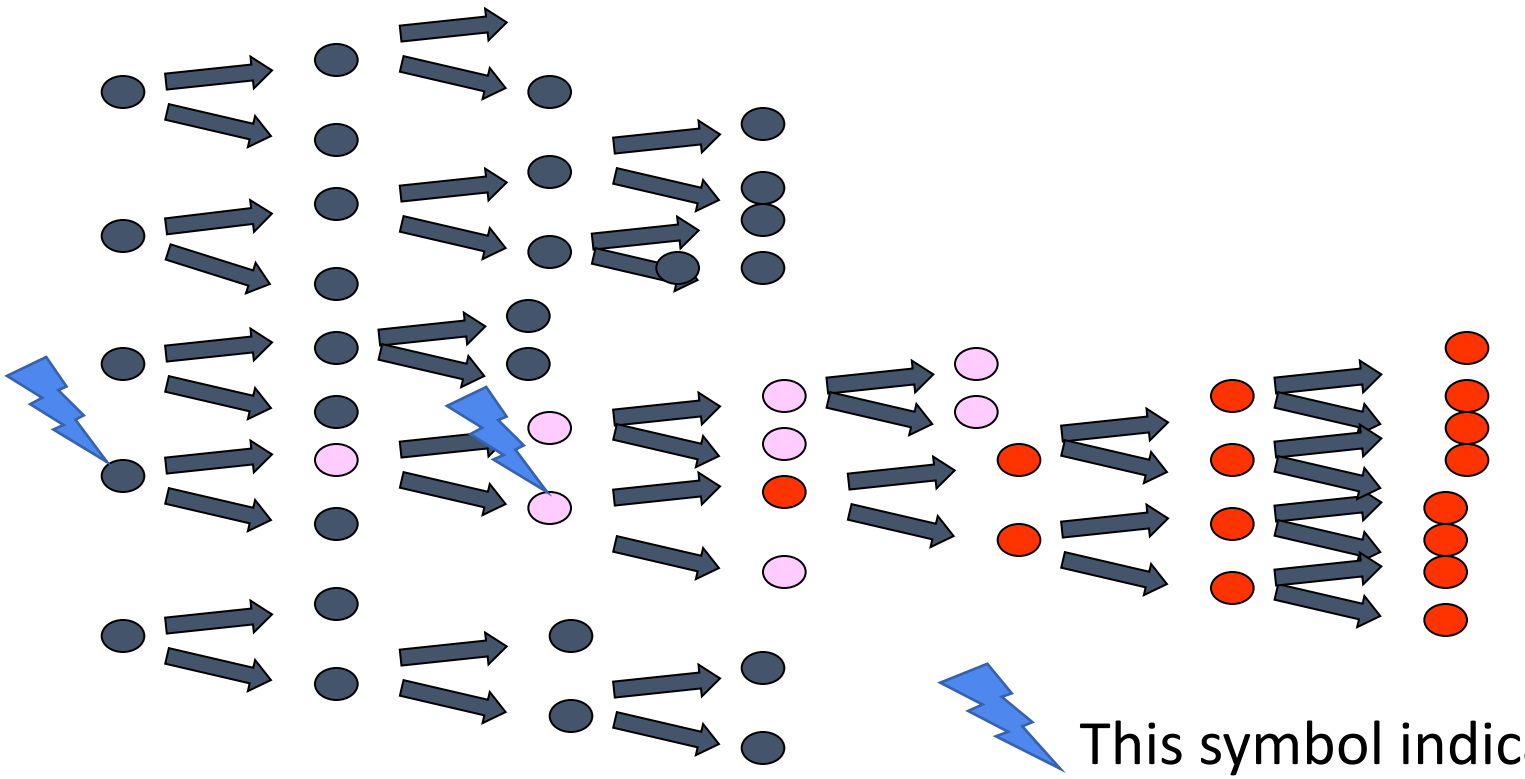
- Lymphopenia refers to a decrease in the number of circulating lymphocytes
- It is defined as a total lymphocyte count < 1×10^9/l
- In normal blood, most lymphocytes are CD4+ T cells
- Important causes of lymphopenia include:
  - HIV infection
  - Chemotherapy
  - Radiotherapy
  - Corticosteroids
- Patients with severe infection may develop a transient low lymphocyte count

What is leukaemia?

- "Leukaemia" is a cancer of the blood that is derived from the Greek words for **white** and **blood**
- Leukaemias are described as being **myeloid** or **lymphoid** according to whether the causative acquired mutation in the bone marrow is in a myeloid or lymphoid progenitor
- The leukaemic cells **replace** normal haemopoietic stem cells in the bone marrow and may overspill into the blood
- 5% of all cancers are cancers of the blood



What is leukaemia?



Emergence of a leukaemic clone

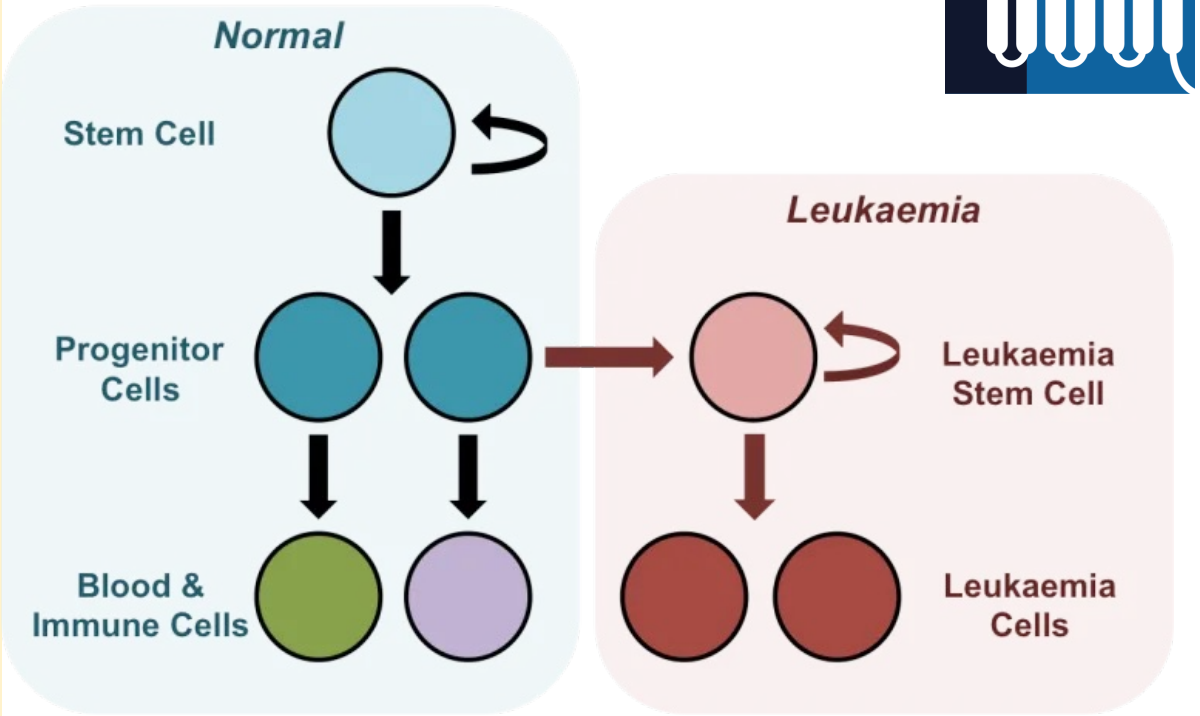
This symbol indicates a new mutation in a single cell giving it a growth or survival advantage

1-POM-2-1: Red blood cells: outline the origin and functions of red blood cells, their parameters used in clinical diagnosis and common abnormalities, including anaemia

1-POM-2-2: White blood cells: Outline the origin and functions of white blood cells, and recall common causes of abnormalities, including cancer

Why does leukaemia occur?

- Results from a number of **somatic mutations** occurring in a primitive cell that, as a result, has a **growth** or **survival advantage** over normal cells
- These mutations may be spontaneous, random or result from exposure to mutagens
- The single cell gives rise to a **clone** that steadily **replaces normal cells:**
  - May not require usual growth factors
  - Disturbance in proliferation +/- maturation
  - Failure of apoptosis (normal cell death)
- The mutations concerned are in **oncogenes** & sometimes in tumour suppressor genes



Genetics: Cancer genetics 5.9

How is leukaemia classified?

- Leukaemia differs from many other cancers in that the abnormal cells circulate in the blood stream and migrate into various tissues
  - Concepts of local invasion and metastasis do not apply
  - Terms **malignant** and **benign** used to describe **solid tumours** do not apply
- We therefore have to look at other characteristics of this disease to understand that leukaemia is a type of cancer
  - The terms used are **acute** and **chronic**
  - Describe the natural history of the leukaemia in the absence of effective treatment
  - **Acute conditions** are **severe** and **sudden** in onset
  - In **Chronic conditions** the disease and deterioration go on for a long period of time
- **Nature of the mutation** determines whether a leukaemia is acute or chronic

How is leukaemia classified?

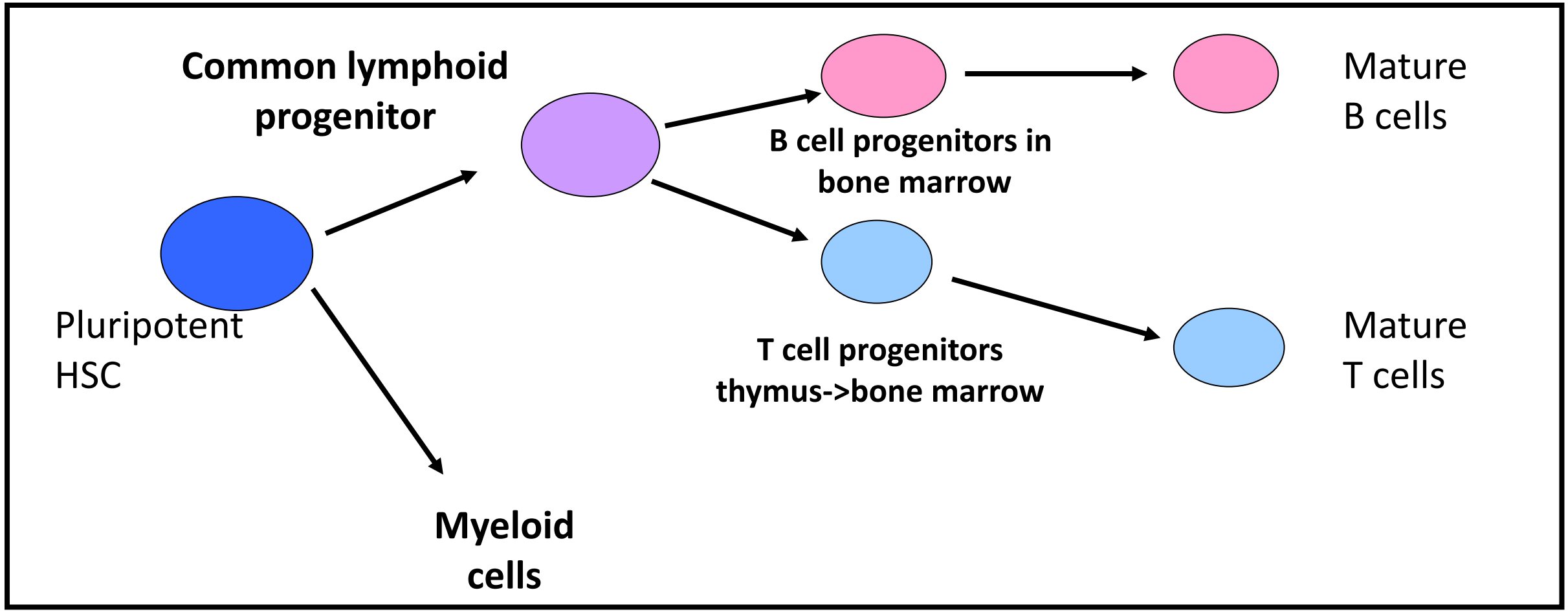
- The main types of leukaemia are:
  - Acute Lympho***blastic*** Leukaemia (**ALL**, ***blast*** because immature cells)
  - Acute Myeloid Leukaemia (**AML**) (blast cells)
  - Chronic Lympho***cytic*** Leukaemia (**CLL**, ***cytic*** because mature lymphoid cells)
  - Chronic Myeloid Leukaemia (**CML**) (mature myeloid cells)

- Different types of leukaemia differ in aetiology, nature of the mutational events, age of onset, clinical & haematological features and prognosis

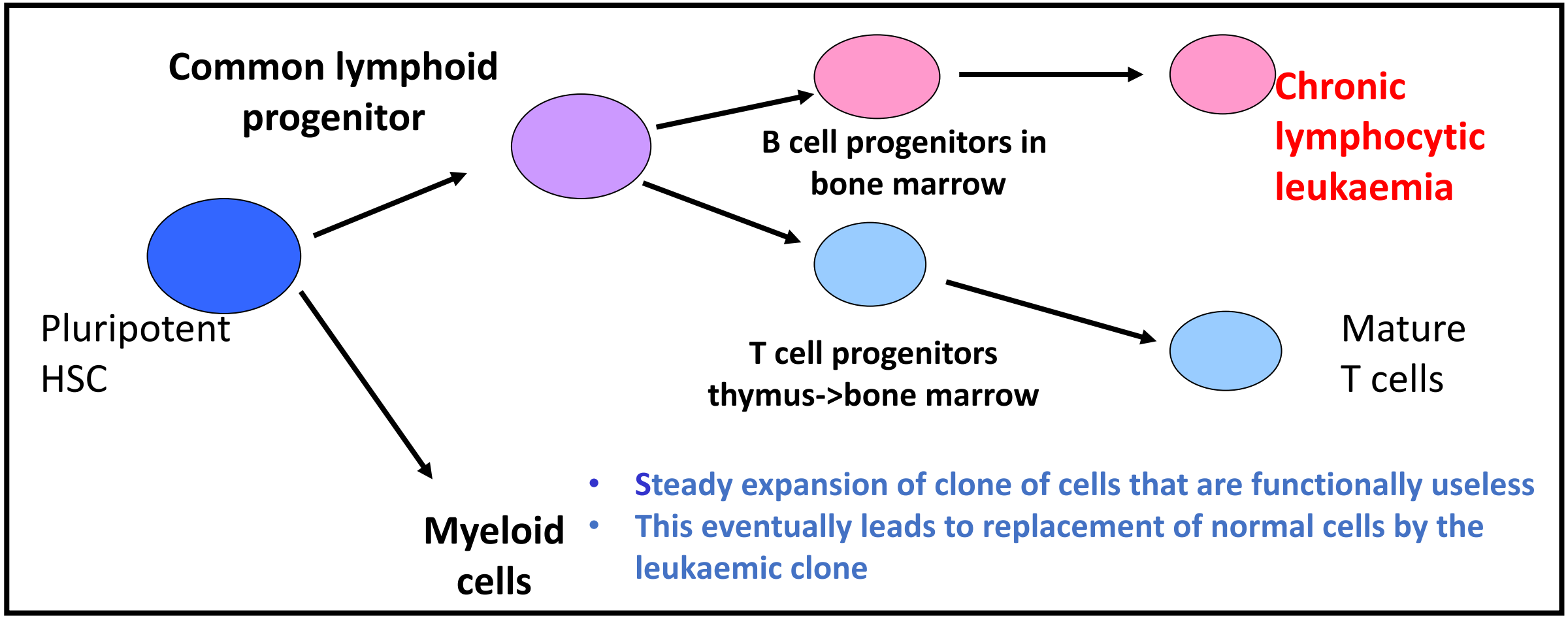
e.g.

- ALL is particularly a disease of childhood – results from somatic mutations *in utero*
- CLL predominantly affects the elderly
- CML results from the activation of signalling pathways by fusion protein BCR-ABL1

Lymphoid differentiation

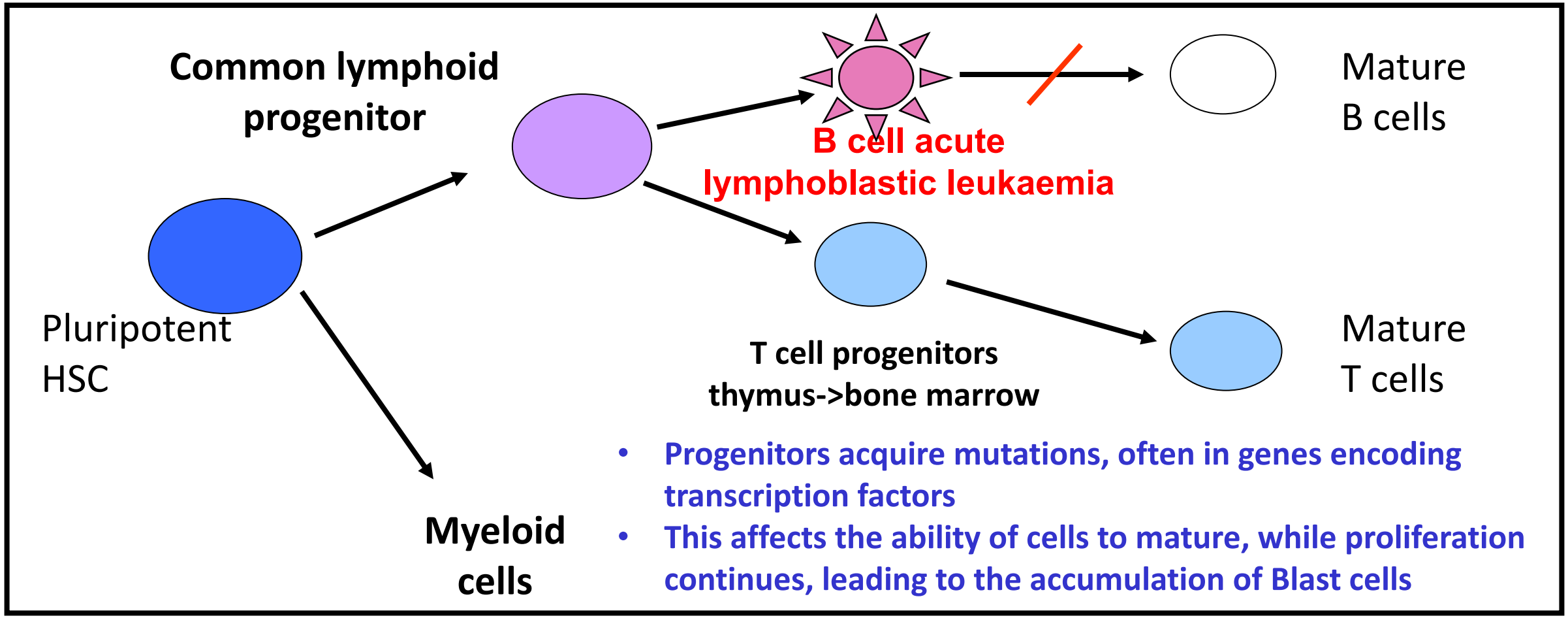


Lymphoid differentiation



- Steady expansion of clone of cells that are functionally useless
- This eventually leads to replacement of normal cells by the leukaemic clone

Lymphoid differentiation



- Progenitors acquire mutations, often in genes encoding transcription factors
- This affects the ability of cells to mature, while proliferation continues, leading to the accumulation of Blast cells

What clinical features may be found in leukaemia?

Accumulation of abnormal cells leading to:

- Leukocytosis
- Bone pain (if leukaemia is acute)
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy (if lymphoid)
- Thymic enlargement (if T lymphoid)
- Skin infiltration

Metabolic effects of leukaemic cell proliferation

- Hyperuricaemia and renal failure
- Weight loss
- Low grade fever
- Sweating

'Crowding out' of normal haemopoiesis:

- Fatigue, lethargy, pallor, breathlessness (caused by anaemia)
- Fever and other features of infection (caused by neutropenia)
- Bruising, petechiae, bleeding (caused by thrombocytopenia)

Loss of normal immune function*

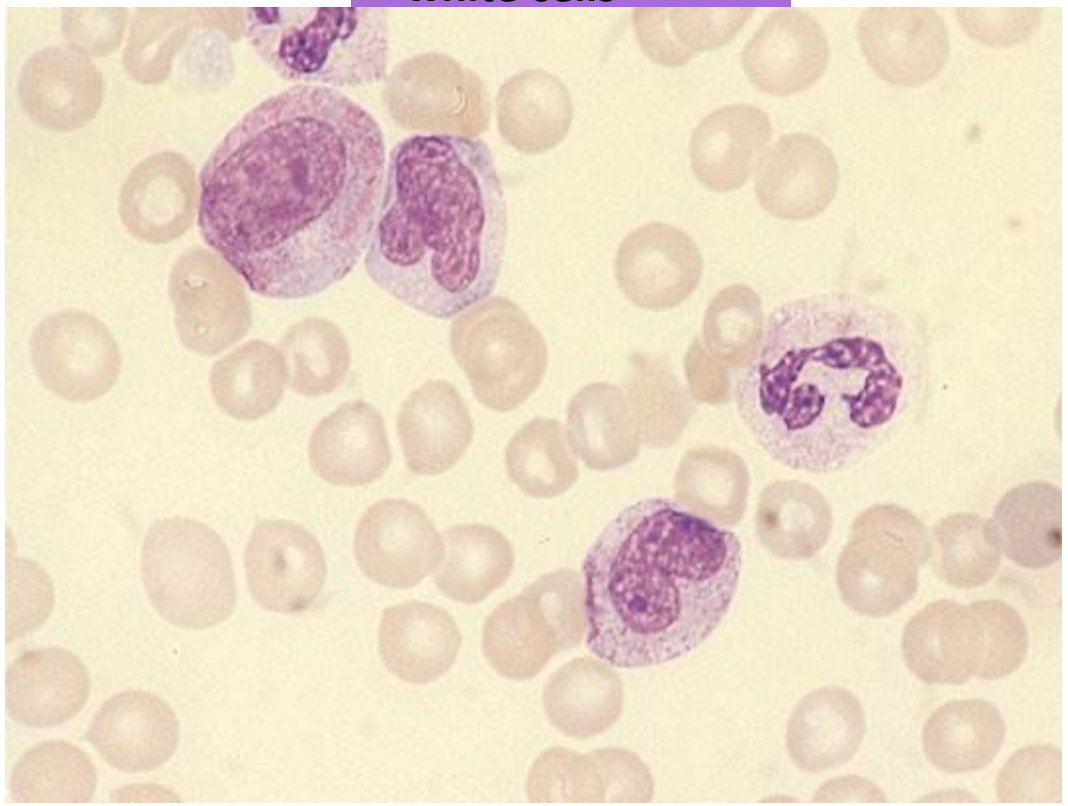
- loss of normal T cell and B cell function

*a feature of chronic lymphocytic leukaemia

Interpreting white cells on a blood count and film

Blood film Practical
1-POM-5-5
Tales from the Haematology Clinic – white cells

- Is there an abnormality?
- If so, which cell line is abnormal?
- Are there any clues in the clinical history?
- Are there any clues in the blood film?

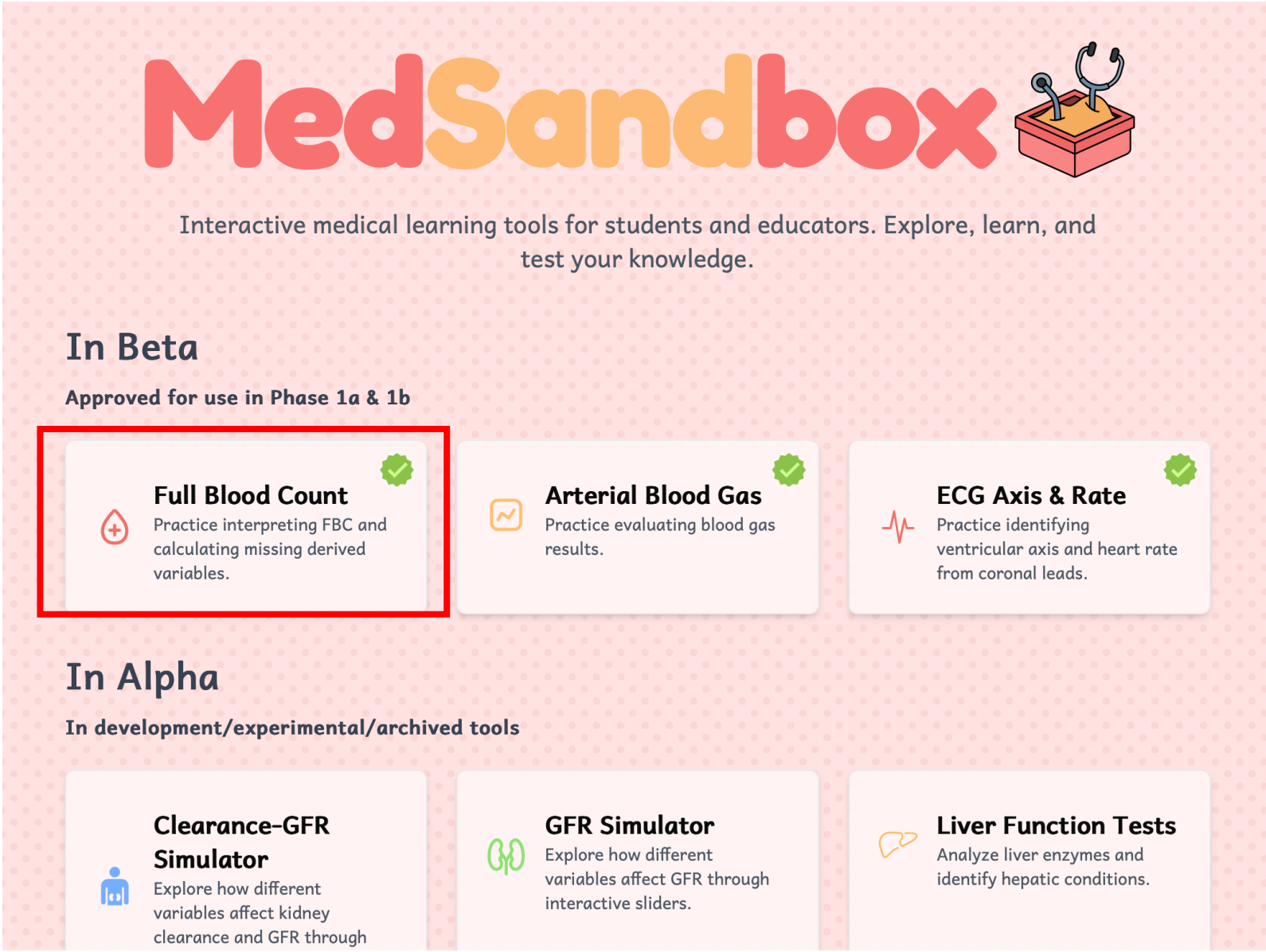


Session Review - update

- The division of haemopoiesis into myeloid and lymphoid components is fundamental to the understanding of haematological disease
- Production of granulocytes and macrophages is controlled by growth factors such as GM-CSF
- Maturation of granulocytes is characterised by a reduction in cell size together with the development of granules that contain agents essential for cell function

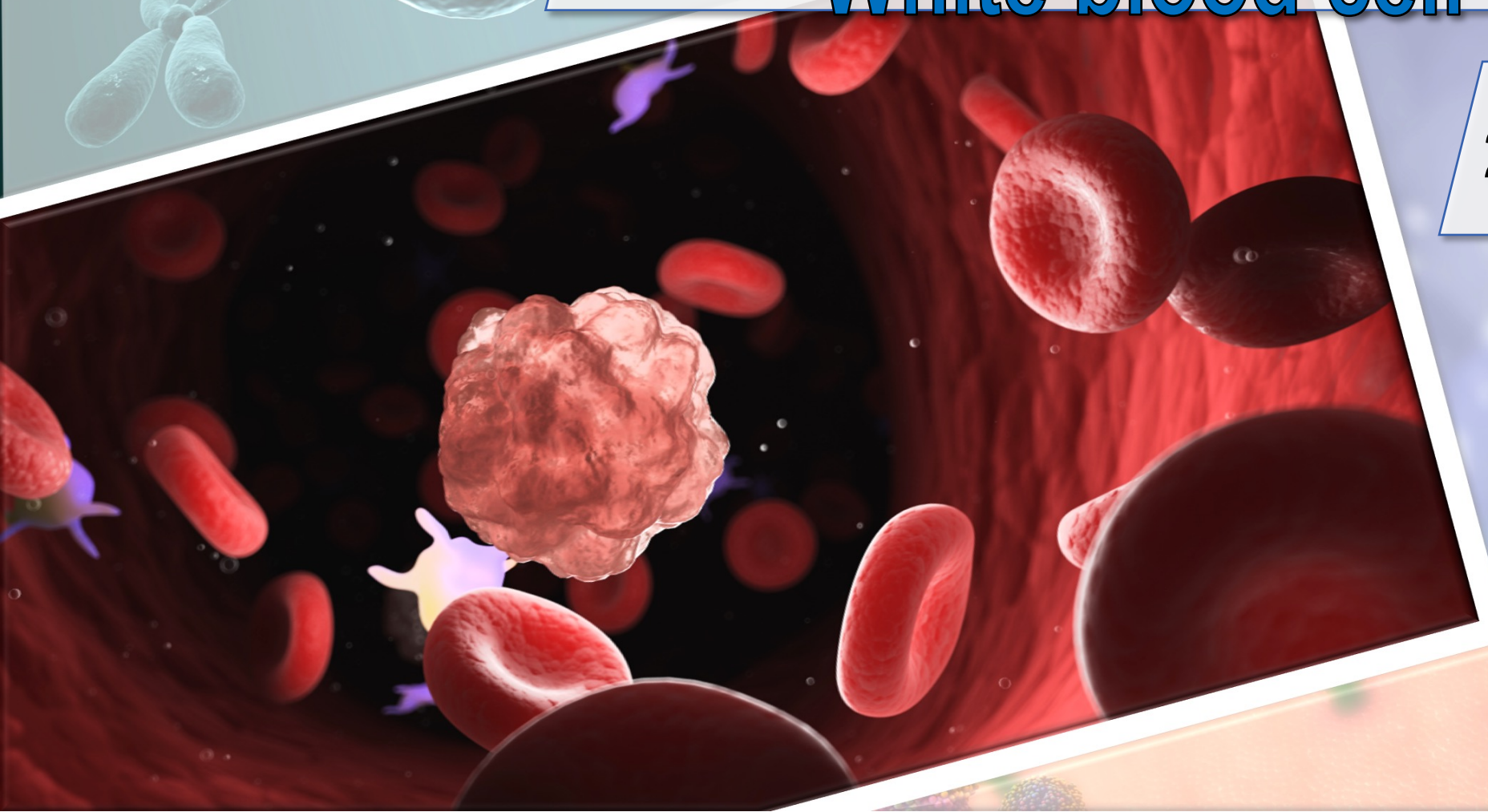
- Transient leukocytosis is frequently seen in association with infection:
  - bacterial: neutrophilia / monocytosis
  - viral: lymphocytosis
  - parasitic: eosinophilia
- Persistent leukocytosis may be caused by leukaemia
  - Chronic lymphocytic leukaemia, CLL
  - Chronic myeloid leukaemia, CML
- Leukopenia usually result from a low neutrophil count since this is usually the most abundant leukocyte in the circulation

https://medsandbox.vercel.app



Imperial College London

Tales from the Haematology clinic: White blood cell tutorials



27th October 2025