Haemopoiesis

By
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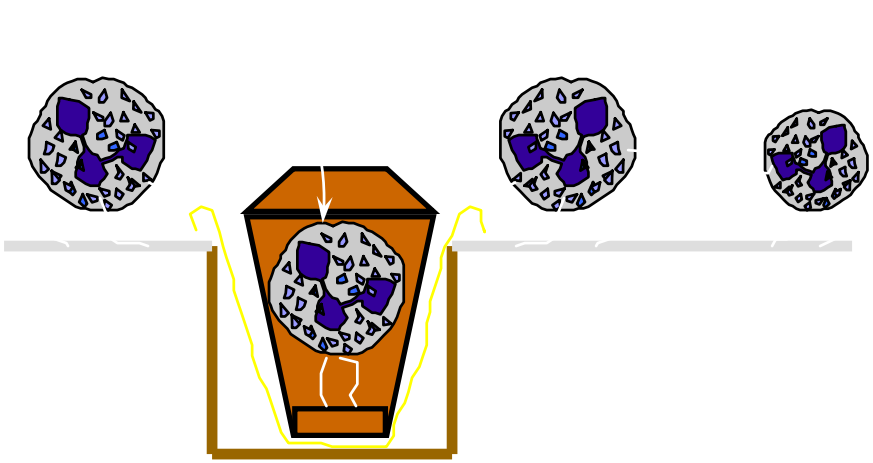
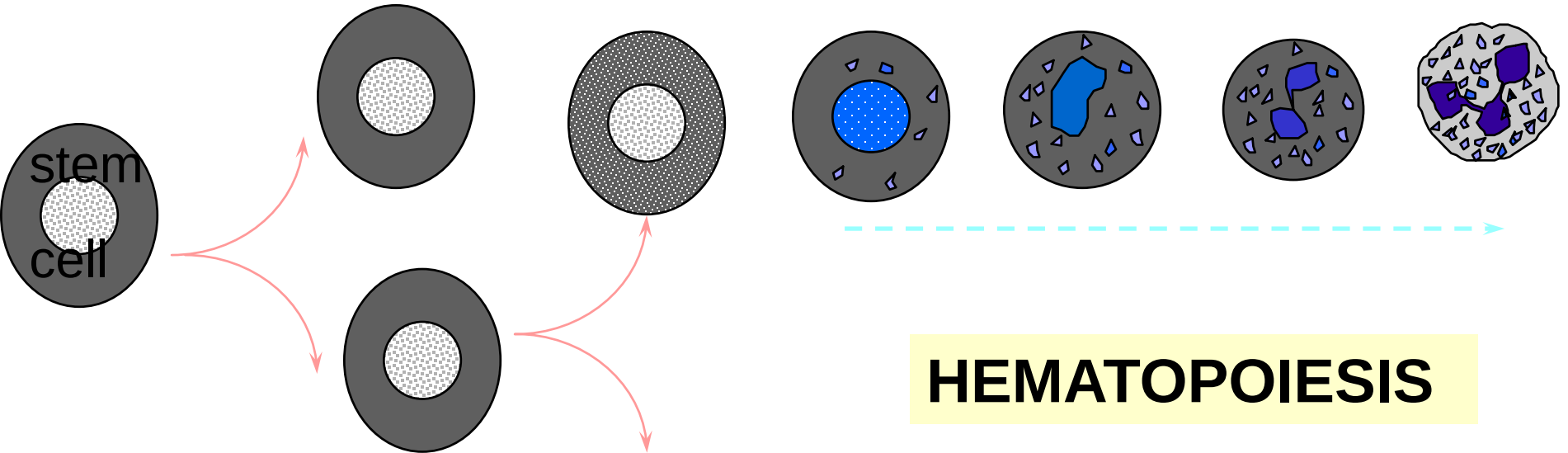
UON



Hematocytopoiesis

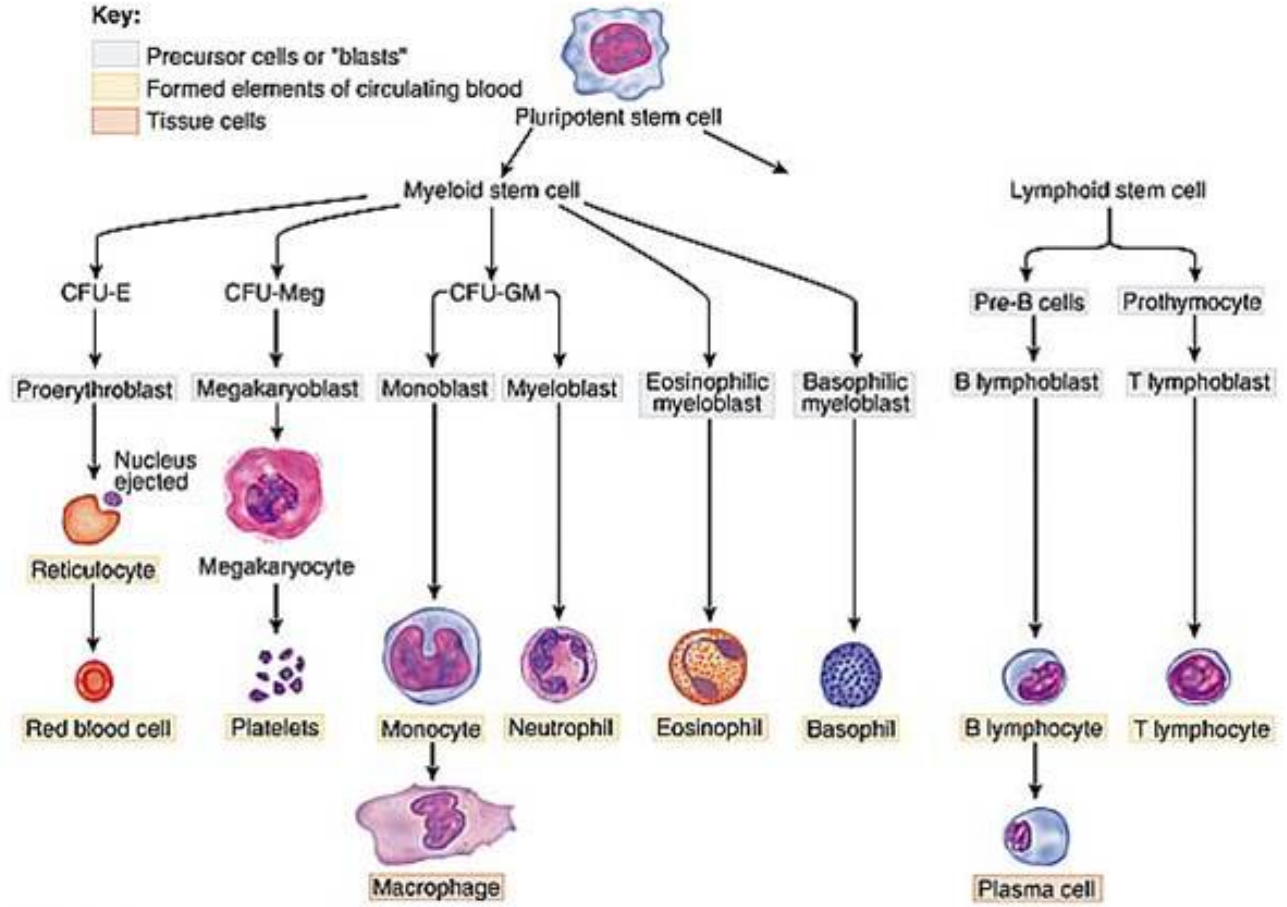
divisions **and**

steps of *differentiation*, from stem cells

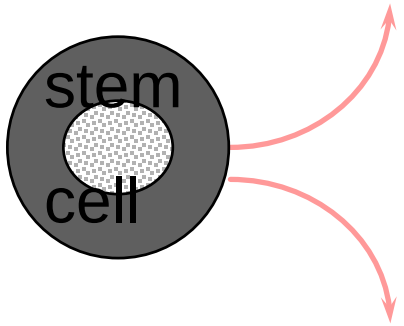


HEMATOPOIESIS

Cell hierarchy (Haemopoiesis schematic representation)



HEMATOPOIESIS Subdivisions



Lymphopoiesis

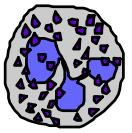
Lym

Myelopoiesis

Granulopoiesis

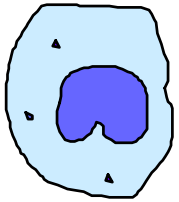
PMN

Eos



Bas

Monocytopoiesis



Mon

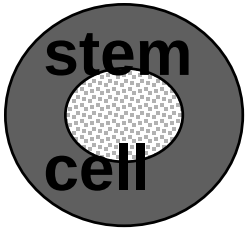
Erythropoiesis

RBC

Megakaryopoiesis
Thrombopoiesis

Pla

HEMATOPOIESIS Lineages for



Pluripotent stem cell (Hemocytoblast)

Lymphopoiesis

Monocytopoiesis

Granulopoiesis

Erythropoiesis

Thrombopoiesis

Lymphoblast

Monoblast

Myeloblast

Pro-Myelocyte

Myelocyte

Metamylelocyte

Band granulocyte

Pro-erythroblast

Basophilic erythroblast

Polychromatic erythroblast

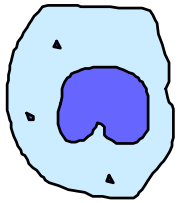
Orthocromatic erythroblast

Reticulocyte

Megakaryoblast

Megakaryocyte

Lymphocyte



Monocyte

Granulocyte

RBC

Platelets

FURTHER DIFFERENTIATIONS

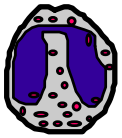
Lym

Similar precursor produces Natural killer cells

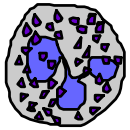
B lymphocytes become Plasma cells

PMN

Granulopoiesis



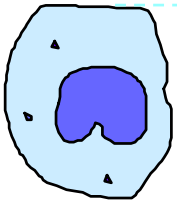
Eos



Bas

Similar precursor produces Mast cells

Monocytopoiesis



Mon

Monocyte or a related precursor gives rise to many specialized phagocytes & antigen-presenting cells

Macrophages Kupffer cells
Langerhans cells
Dendritic cells Microglia
Osteoclasts etc

Erythropoiesis

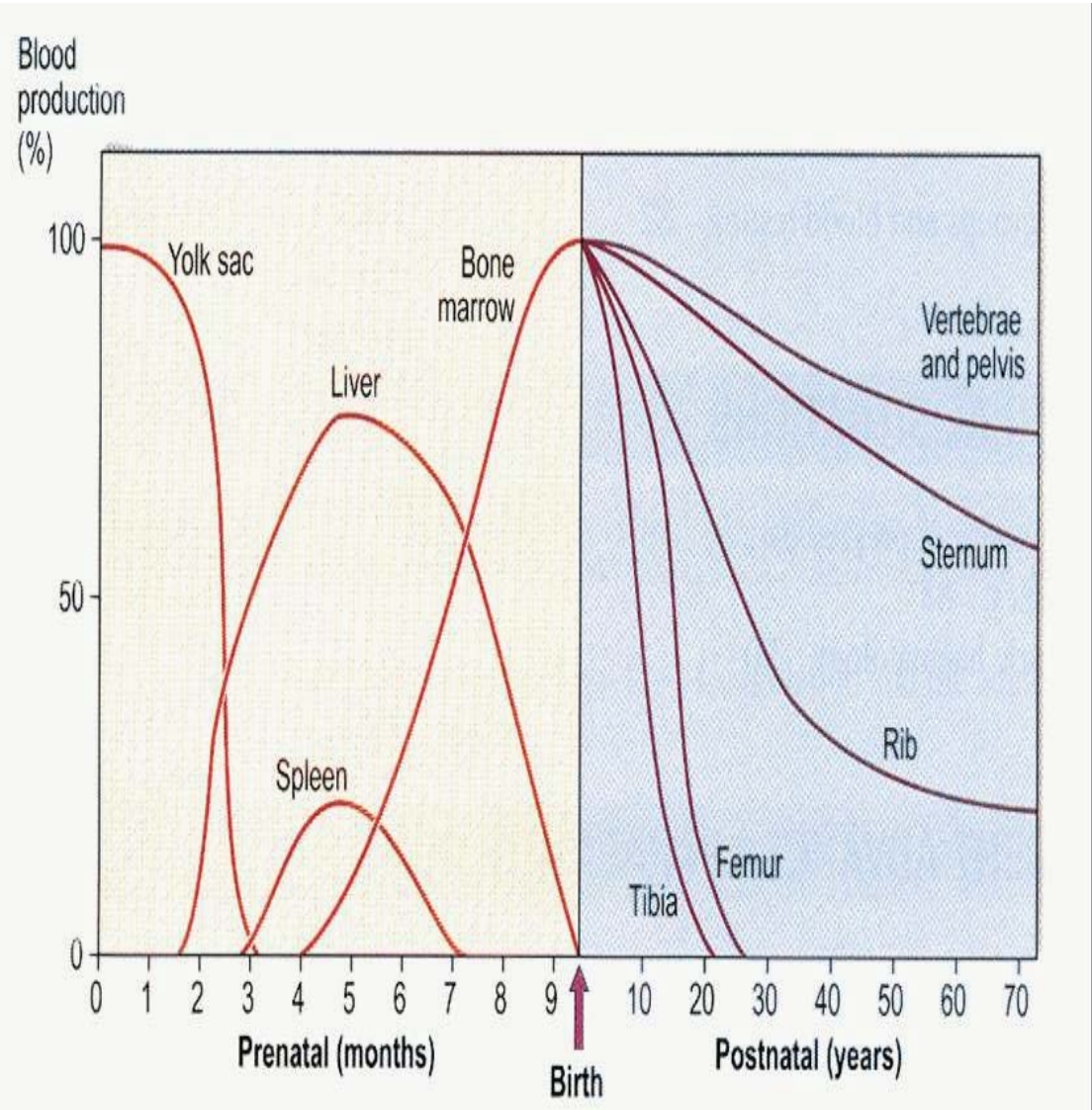
RBC

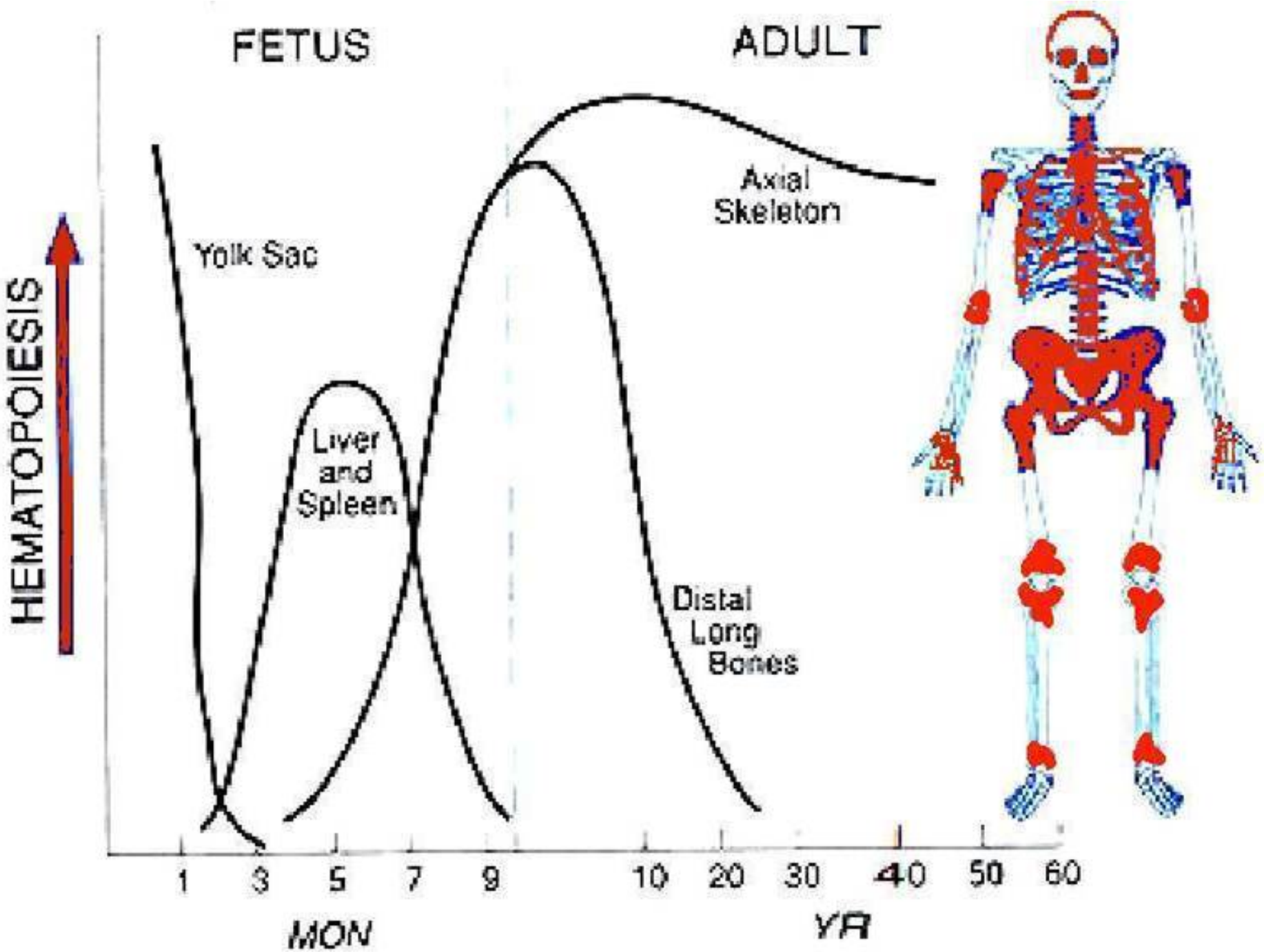
Megakaryopoiesis
Thrombopoiesis

Pla

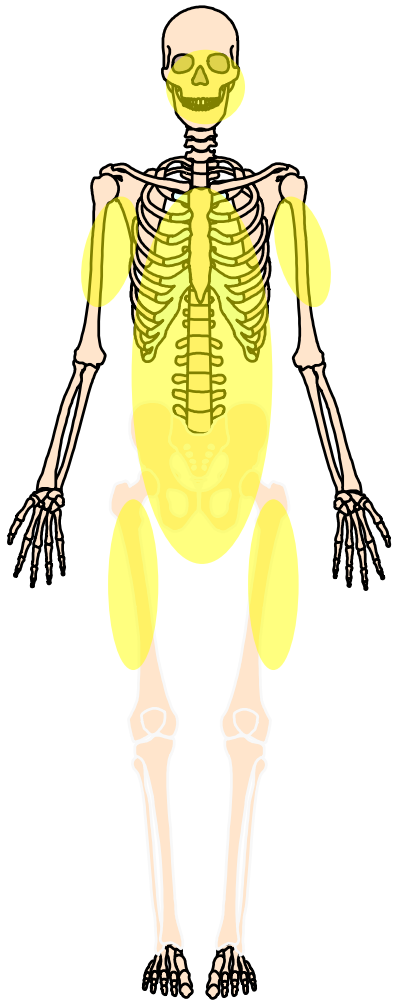
Sites of Haemopoiesis

- Yolk sac
- Liver and spleen
- Bone marrow
  - Gradual replacement of active (red) marrow by tissue inactive (fatty)
  - Expansion can occur during increased need for cell production



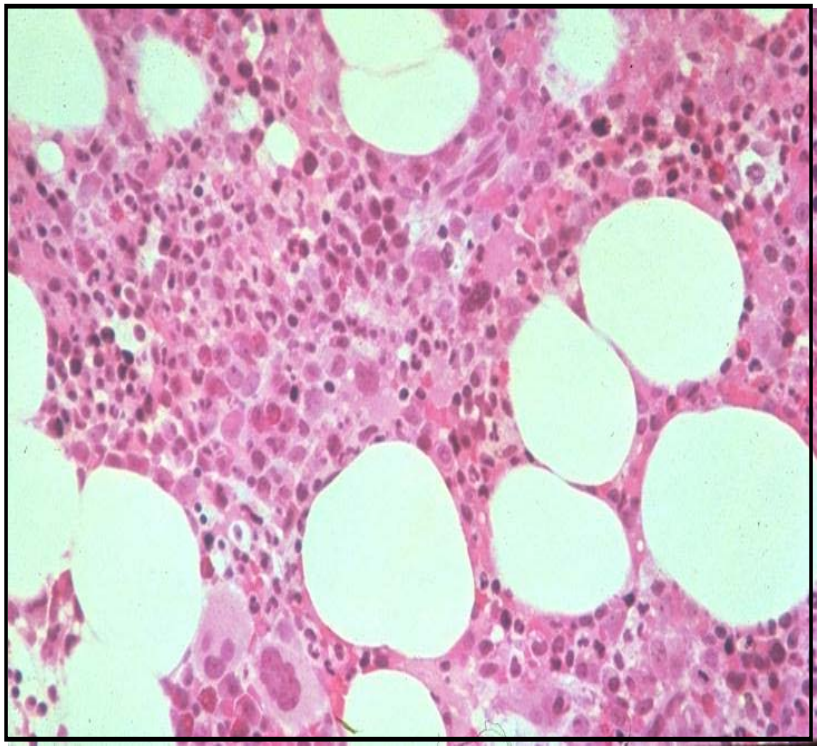

FETUS
ADULT
HEMATOPOIESIS
Yolk Sac
Liver and Spleen
Axial Skeleton
Distal Long Bones
1
3
5
7
9
10
20
30
40
50
60
MON
YR

BLOOD IS MADE IN THE BONE MARROW



- Axial skeleton
- Inner spongy bone
- Bone marrow is in the holes
- Bone marrow is a highly organized / regulated organ

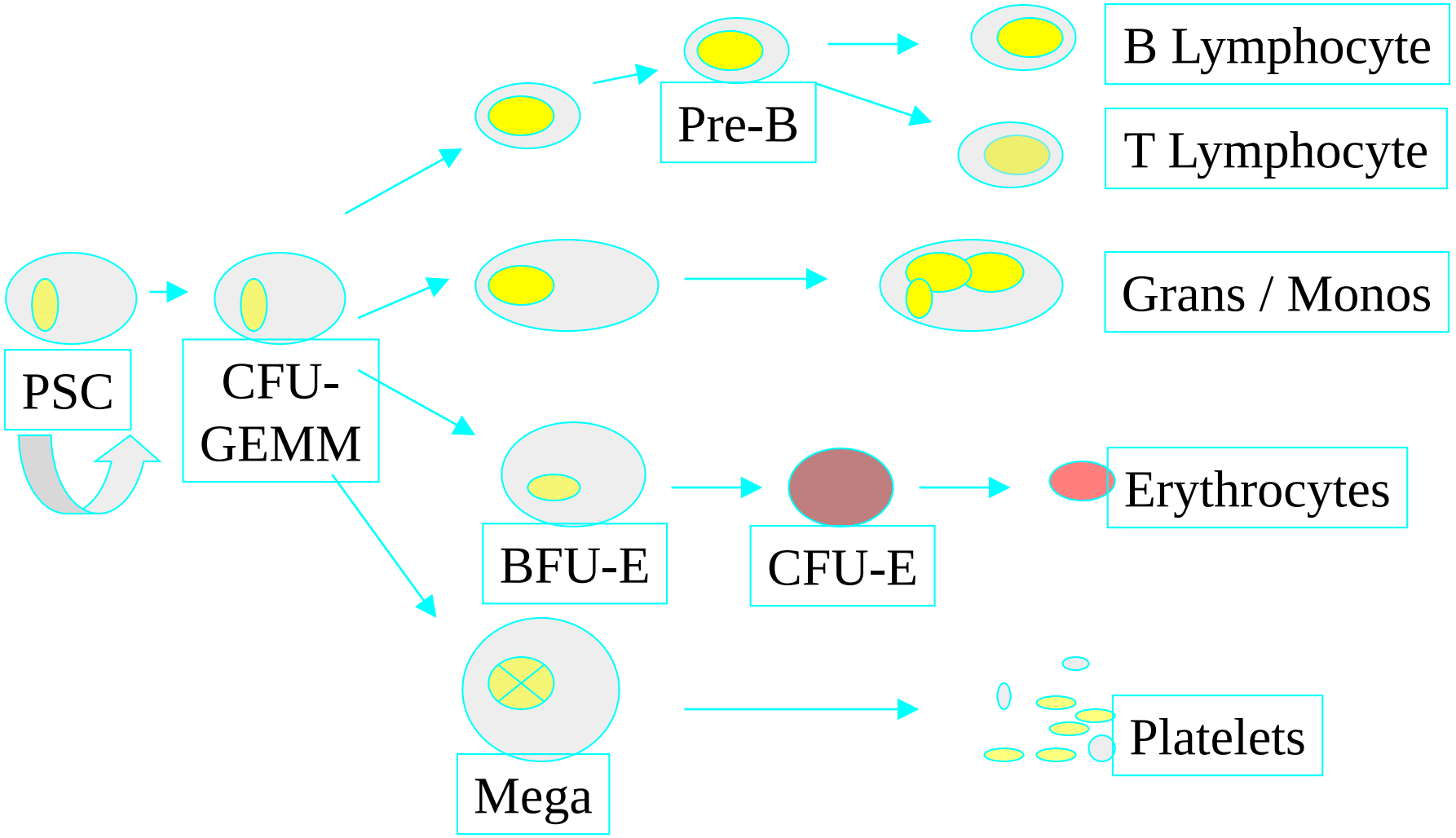
BONE MARROW: THE SOURCE OF BLOOD AND OUR IMMUNE SYSTEM



Normal bone marrow

- All blood cells arise from “mother” (stem) cells
  - Self renewing
  - Safe from harm
  - Pluripotent
- Blood production is highly regulated
  - Messages from the body (e.g. erythropoietin from kidney)
  - Microenvironments produce specific cells
    - Cytokines (SCF, IL3)
    - Growth factors (G-CSF)

SCHEMATIC OF HEMATOPOIESIS



Introduction

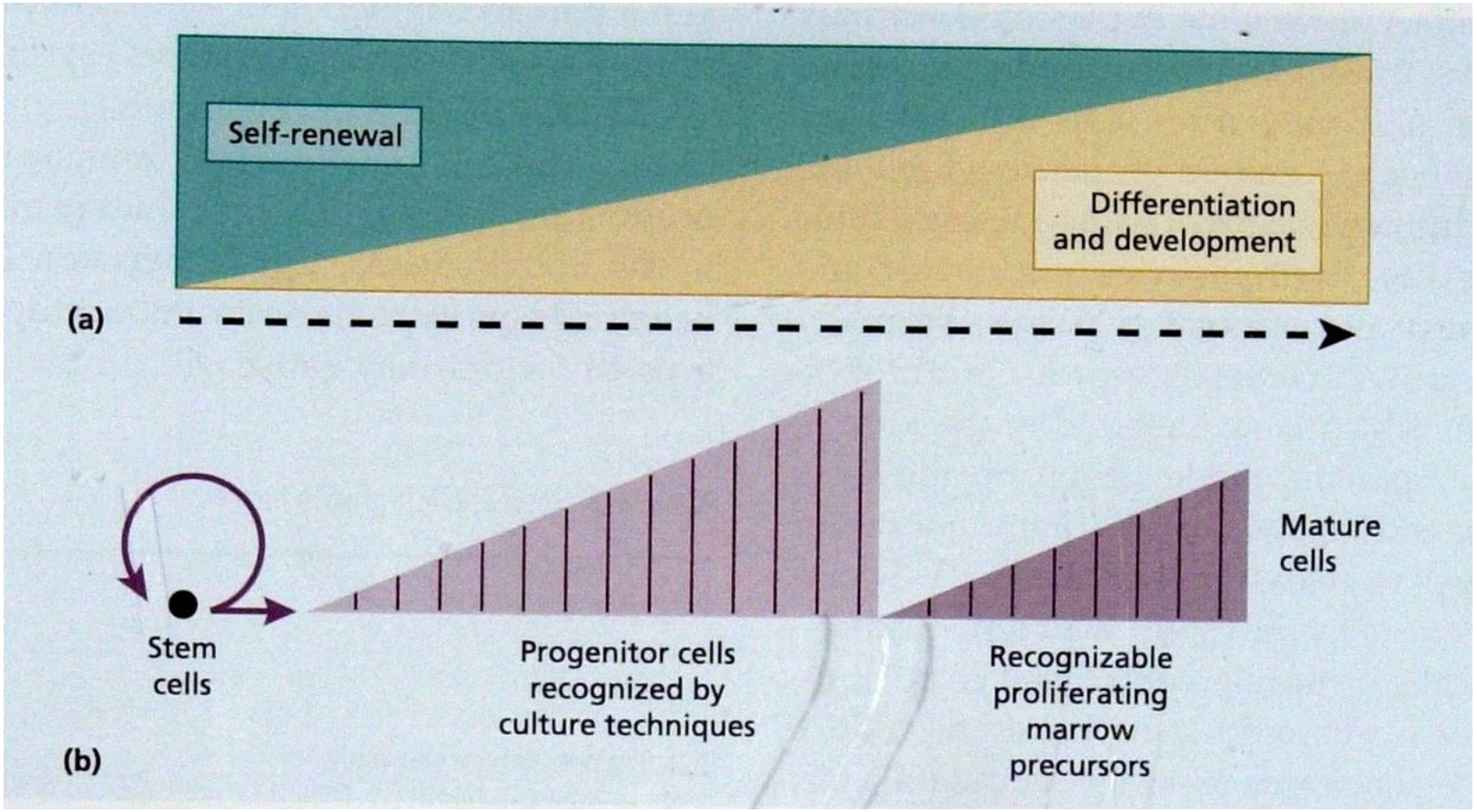
- Limited Life span of :
  - Granulocytes
  - Erythrocytes
  - Platelets
  - Lymphocytes

Introduction

- Stem cells
    - Self renewal
    - Plasticity
- Progenitor cells
    - Developmentally-restricted cells
- Mature cells
    - Mature cell production takes place from the more developmentally-restricted progenitors

Stem cells

- Self-renewal
    - Normally in G_0 phase of cell cycle
    - The capacity for self-reproduction is vastly in excess of that required to maintain cell production for normal lifetime
    - As cells increase in number they differentiate as well
- Multipotentiality
    - Capacity to generate cells of all the lymphohaemopoietic lineages

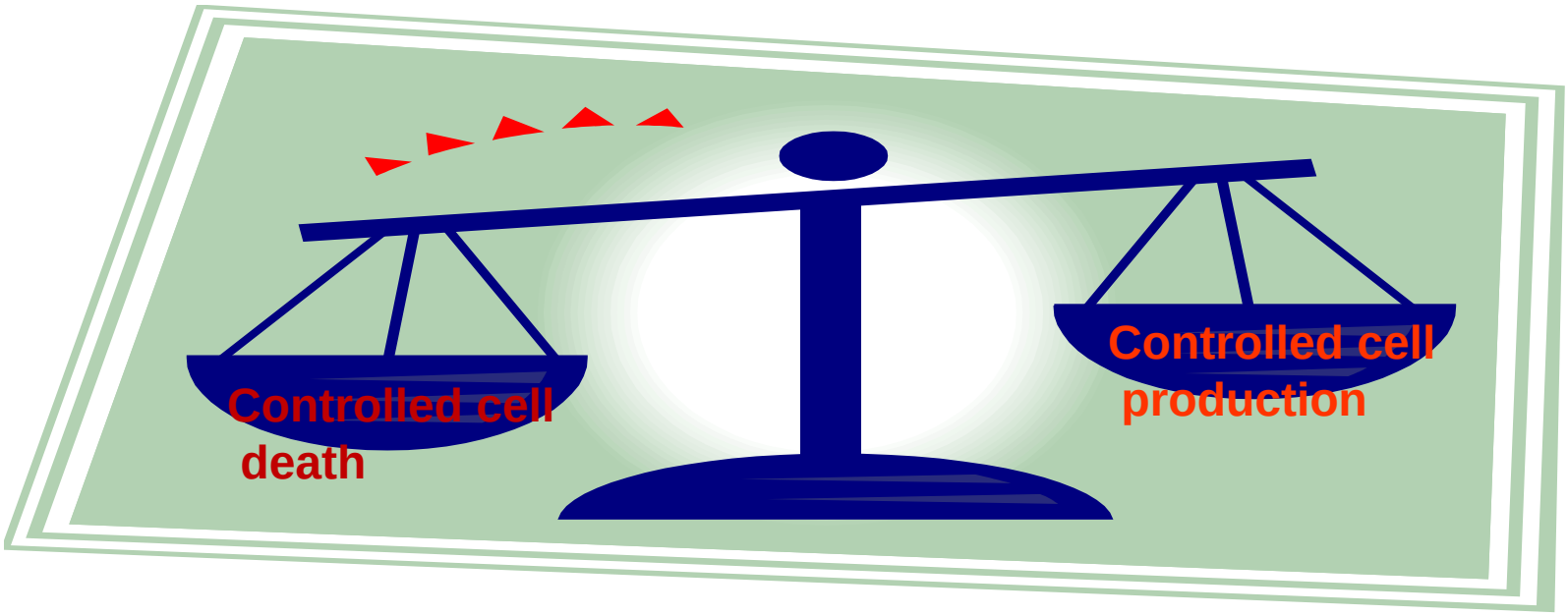

Self-renewal
Differentiation and development
(a)
Stem cells
Progenitor cells recognized by culture techniques
Recognizable proliferating marrow precursors
Mature cells
(b)

Progenitor cells

- Encompasses from immediate progeny of stem cells to differentiation cells committed to one lineage

- Progenitor cells become progressively more restricted in their differentiation and proliferation capacity
    - Late progenitor cells eventually restricted to one lineage

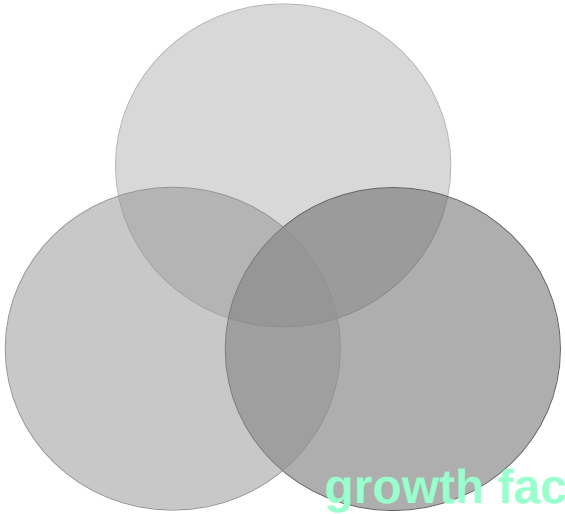
Regulation of Haemopoiesis



- There should be a balance between cell production and cell death except at the times of requirement

Regulation of Haemopoiesis

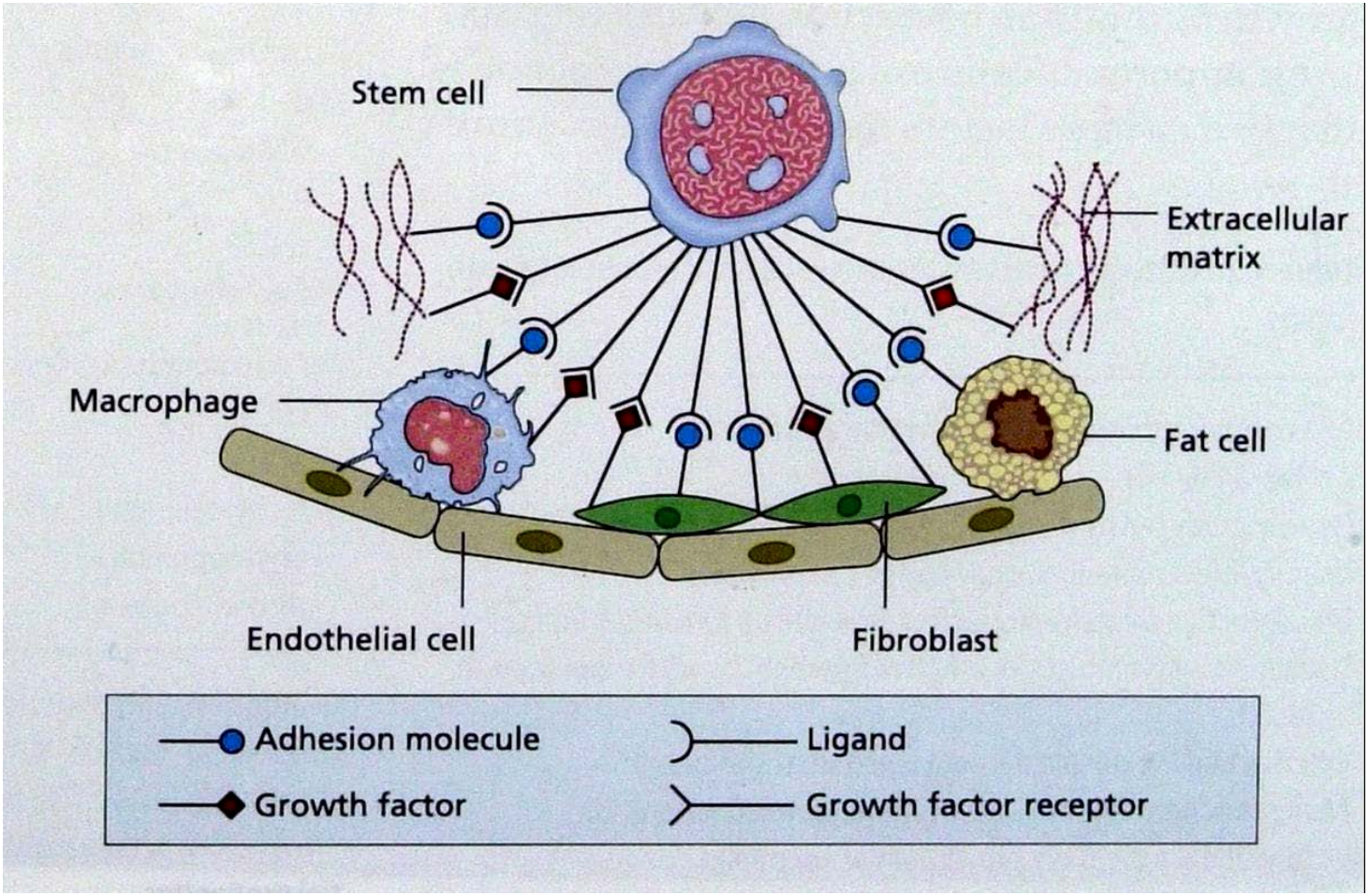
Local environmental control
Stromal cell mediated Haemopoiesis



Apoptosis

Haemopoietic
growth factors (Humoral regulation)

Interaction of stromal cells, growth factors and haemopoietic cells



Local and Humoral regulation of Haemopoiesis

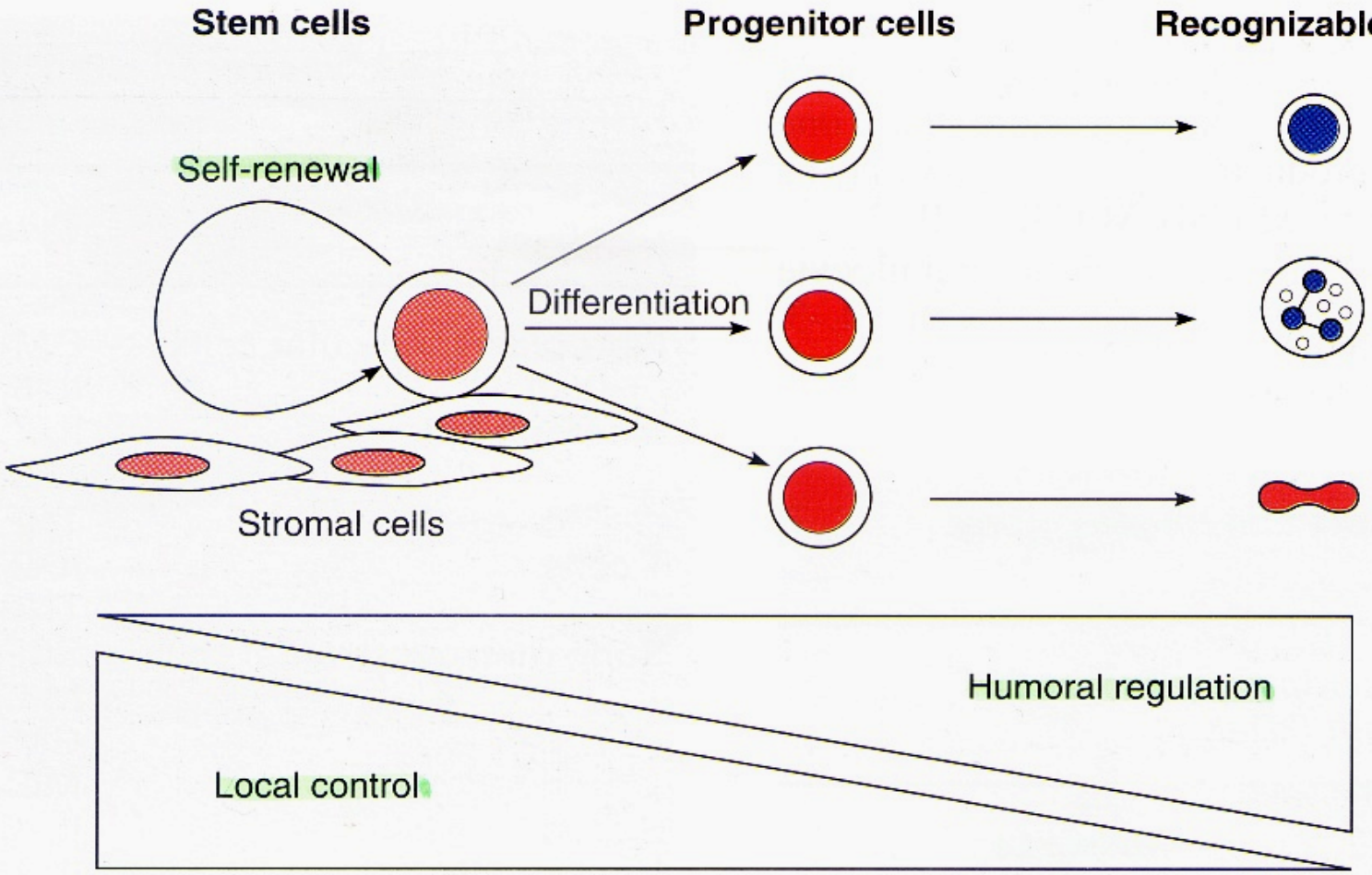


Figure 1.3 The relative influence of local control and humoral regulation at different stages of development.

Haemopoietic growth factors

- GM-CSF
    - Granulocyte-Macrophage colony stimulating factor
- M-CSF
    - Macrophage colony stimulating factor
- Erythropoietin
    - Erythropoiesis stimulating hormone

(These factors have the capacity to stimulate the proliferation of their target progenitor cells when used as a sole source of stimulation)

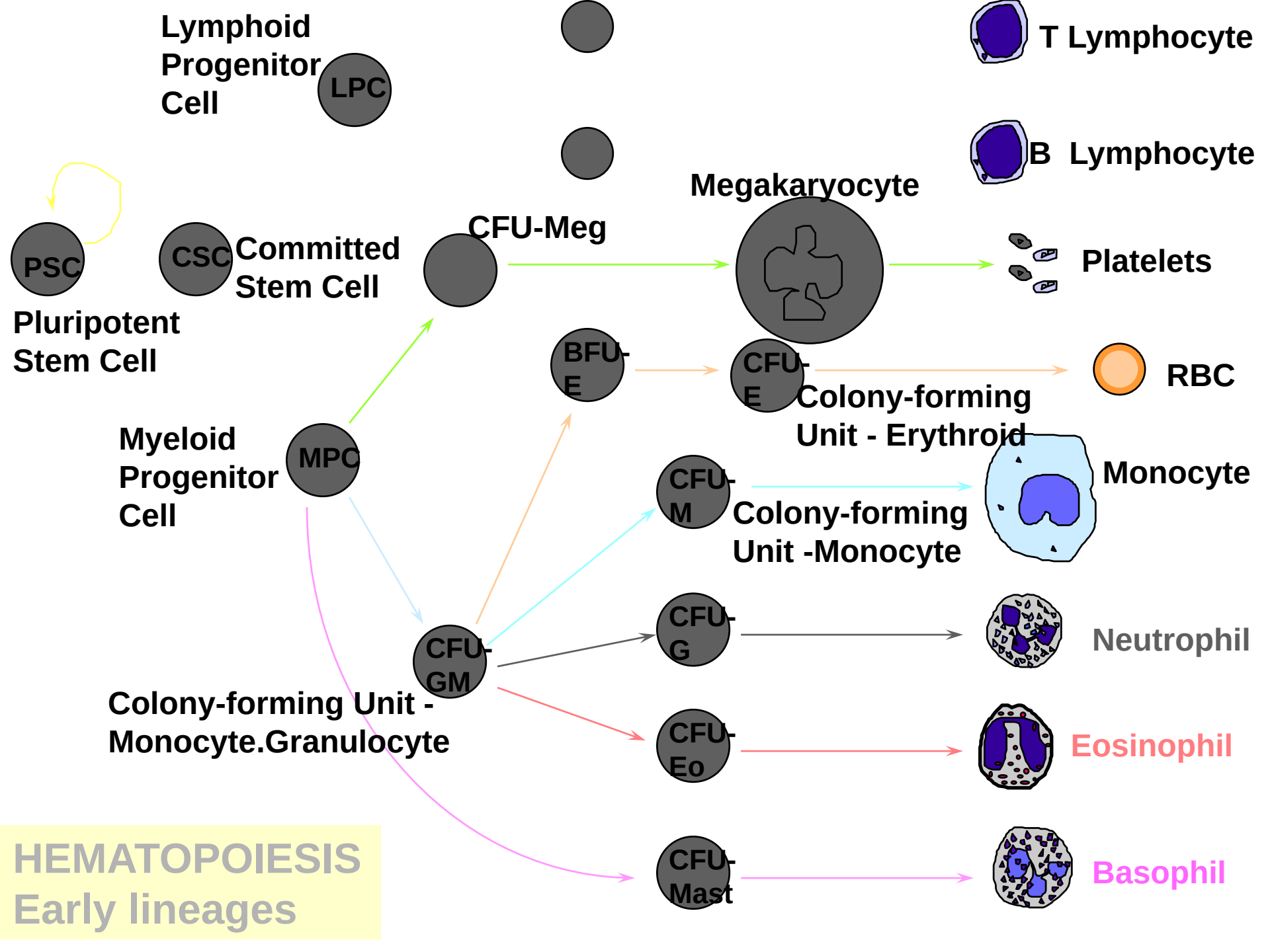
- Thrombopoietin
    - Stimulates megakaryopoiesis

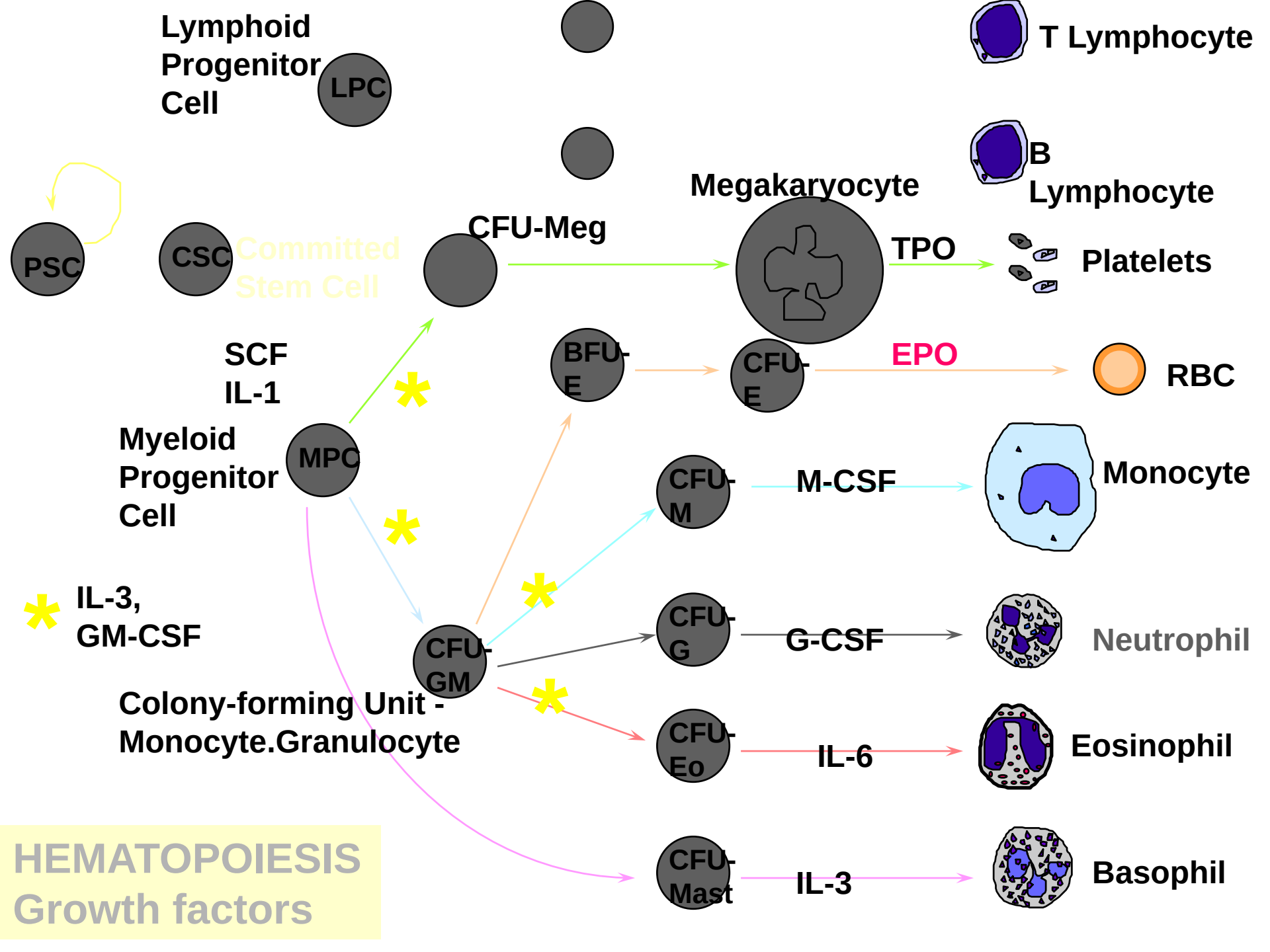
Haemopoietic growth factors

- Cytokines
    - IL 1 (Interleukin 1)
    - IL 3
    - IL 4
    - IL 5
    - IL 6
    - IL 9
    - IL 11
    - TGF-β

    - SCF (Stem cell factor, also known as kit-ligand)

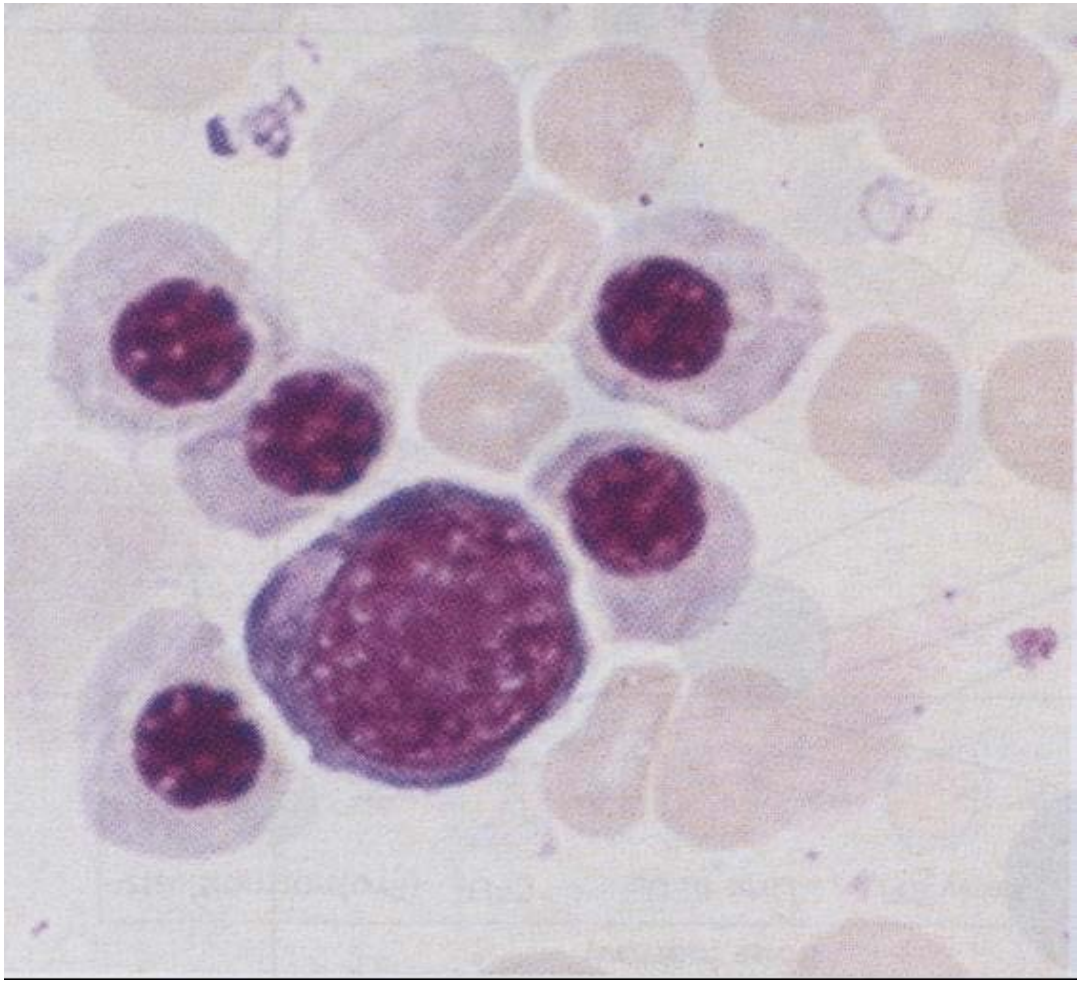
Cytokines have no (e.g IL-1) or little (SCF) capacity to stimulate cell proliferation on their own, but are able to synergise with other cytokines to recruit nine cells into proliferation


Lymphoid Progenitor Cell
LPC
T Lymphocyte
B Lymphocyte
Megakaryocyte
PSC
CSC
Committed Stem Cell
CFU-Meg
Platelets
Pluripotent Stem Cell
BFU-E
CFU-E
RBC
Colony-forming Unit - Erythroid
Myeloid Progenitor Cell
MPC
CFU-M
Monocyte
Colony-forming Unit -Monocyte
CFU-GM
CFU-G
Neutrophil
Colony-forming Unit - Monocyte.Granulocyte
CFU-Eo
Eosinophil
CFU-Mast
Basophil
HEMATOPOIESIS
Early lineages


Lymphoid Progenitor Cell
LPC
T Lymphocyte
B Lymphocyte
PSC
CSC
Committed Stem Cell
CFU-Meg
Megakaryocyte
TPO
Platelets
SCF
IL-1
BFU-E
CFU-E
EPO
RBC
Myeloid Progenitor Cell
MPC
CFU-M
M-CSF
Monocyte
IL-3, GM-CSF
CFU-GM
CFU-G
G-CSF
Neutrophil
Colony-forming Unit - Monocyte.Granulocyte
CFU-Eo
IL-6
Eosinophil
CFU-Mast
IL-3
Basophil
HEMATOPOIESIS
Growth factors

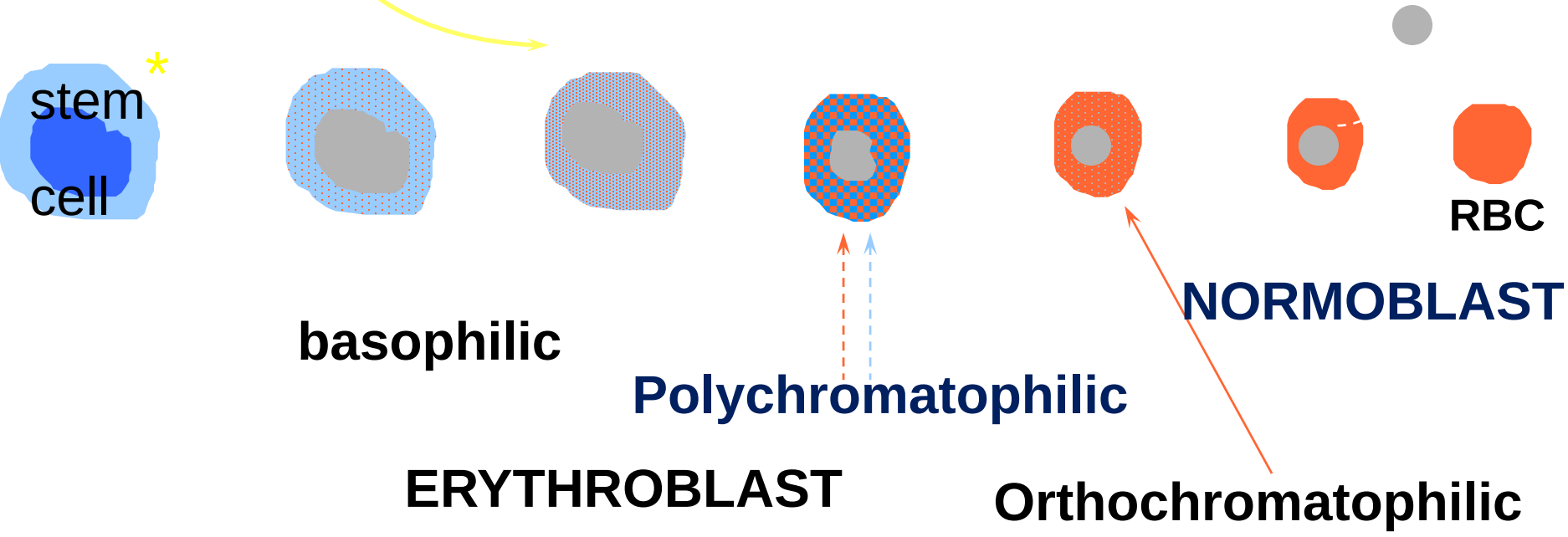
Erythropoiesis and erythrocytes

- Lifespan – 120 days
- Non nucleated
- Biconcave disc
- Production regulated by Epo
- Needs Fe, B12, folate & other elements for development



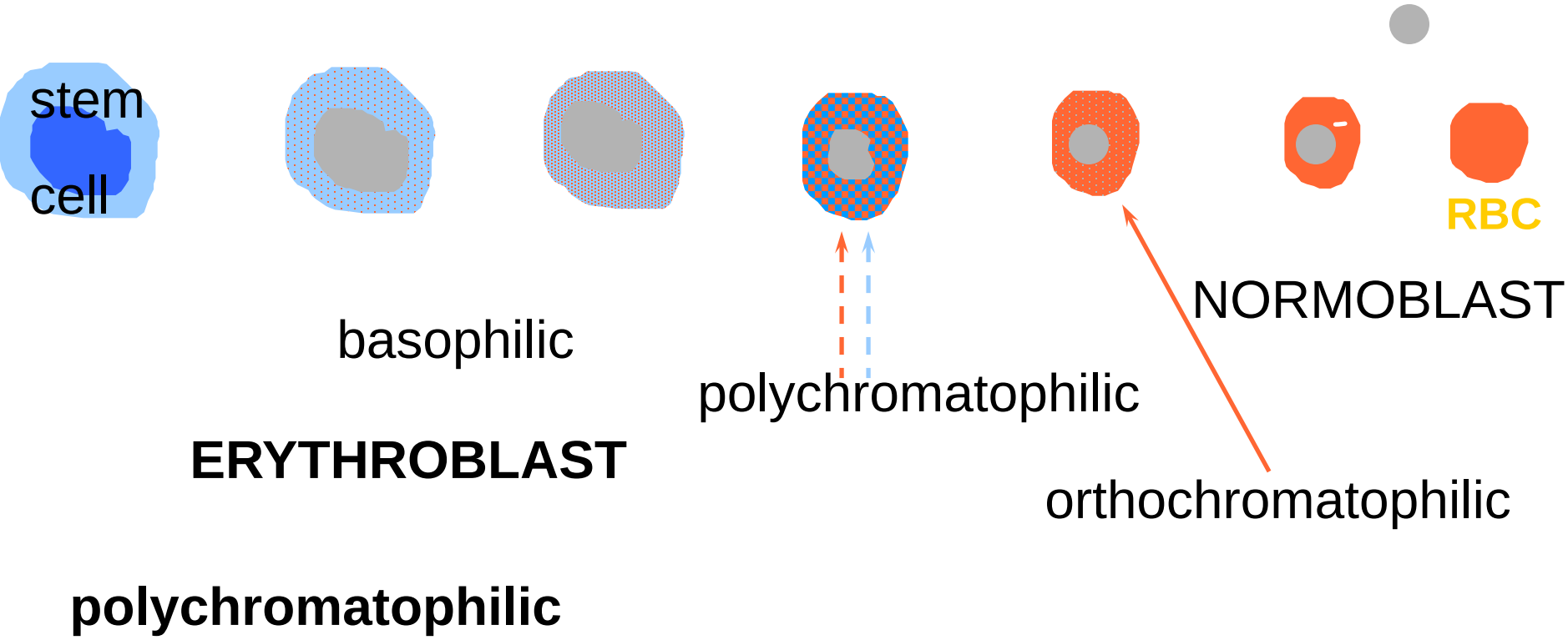
ERYTHROPOIESIS

In developing from the stem cell, the RBC has to undergo the most changes, which can be categorized into several morphological/stainable stages and into less easily detected early stages *



-blast is the common suffix for an immature form of a cell

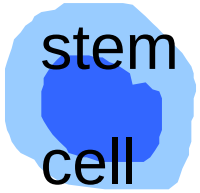
ERYTHROPOIESIS



This idea continues in the form of the *reticulocyte* which is an RBC released to the blood, but still with a network of blue ribosomal material persisting amongst the hemoglobin

ERYTHROPOIESIS 2

undergo the most changes, which can be categorized into several morphological/stainable stages and into less easily detected early stages



Pluripotent Stem Cell

PSC

Committed Stem Cell

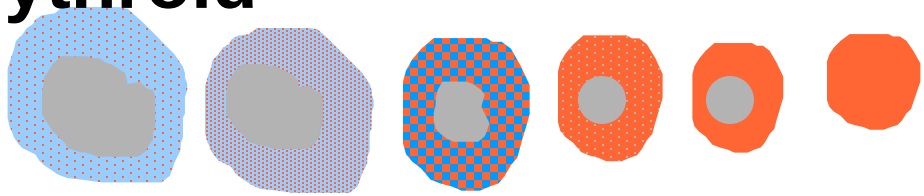
CSC

Myeloid Progenitor Cell

MPC

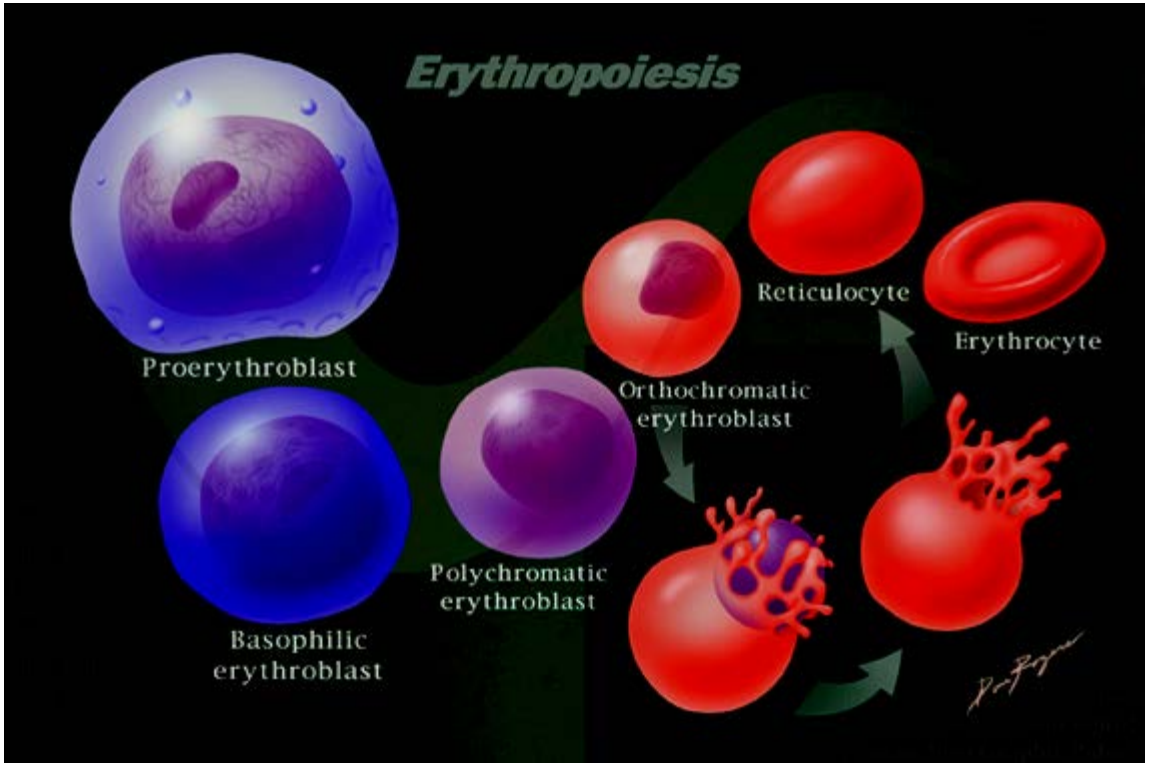
Burst-forming Unit - Erythroid

BFU-E



ERYTHROBLAST

Used for some specialization, but more for massive cell division, as conveyed by “burst”


Erythropoiesis
Proerythroblast
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast
Reticulocyte
Erythrocyte

Hemopoiesis

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Senior Lecturer
Haematology & Blood Transfusion

Lecture outline

- Definition
- History
- Anatomy
- Physiology

Definition

- Hemopoiesis is the formation, development, and specialization of cellular elements into mature functional cells. .

History

- Mid 17th century red cells observed in microscope
- 1868: Neumann demonstrated that red cells arise from precursors in the BM.
- Previously derived from leucocytes and platelets in the lymphoid system, adrenals and embryonal liver

- There are three basic stages of hemopoiesis;
  [1] Mesoblastic phase,
  [2] Hepatic phase, and
  [3] Medullary phase

Mesoblastic

- Begins at 2nd to 7th week of gestation:

  a. Embryonic;

  b. In **yolk sac**;

  c. Condensation of mesenchymal cells - form **blood islands**;

  d. **nucleated** blood cells form

Hepatic

- Begins 12^{th} – 16^{th} week of gestation
- In **liver, thymus, and spleen, lymph nodes** somewhat latter;
- Forms **anucleated** RBCs

Myeloid

- 20th week to adulthood
- **I**n bone marrow;
- Begins with establishment of ossification centers in bones;
- A**ll blood cell types** found in adults can be produced by the bone marrow;

Anatomy

- Active marrow space in a child about 15Kgs is 1000 – 1400 g: total marrow = 1600 cc
- Adult : active 1200 – 1500 g Total marrow 2600 – 4000 cc
- Large space in the neonate progressively decreases with age with the marrow becoming increasingly filled with fat

4. Hemopoietic differentiation requires an appropriate micro-environment
    1. Commences in the yolk sac of the embryo in the 2nd to 7th month apparent in the liver in the 12th – 16th week, in the bone: 20th – adult
    2. Newborns: Most bone cavities are active with increasing age upper shaft of femur, humerus and pelvis and vertebra
    3. Extra-medularly hemopoiesis in pathological states_ liver, spleen, lymph nodes, adrenals, adipose tissue, kidney

- Microenvironment of the marrow cavity is a vast network of vascular channels of sinusoids in which float fronds of hemopoietic cells plus fat cells
- Vascular and hemopoietic compartments are joined by reticular fibroblastoid cells that form the adventitial surfaces of the vascular sinuses and extend cytoplasmic processes to create a lattice supportive framework on which the blood cells are found

- Function of fibroblastoid cells
  - Supportive framework
  - Production of essential hemopoietic colony stimulating factors

Marrow micro-circulation

- Central and radial arteries ramify in the cortical capillaries which in turn join the marrow sinusoids and drain into the central sinus
- Cells leave the BM sinusoids and then join the venous circulation through the commit ant veins
- Luminal surfaces of the vascular sinusoids is lined with endothelial cells, the cytoplasmic extensions of which overlap, inter-digitate.
- Hemopoietic cells escape into the sinus for transport into the general circulation occurs through gaps that develop in this endothelial lining and thru' endothelial cells cytoplasmic pores
- N/B: destruction of the BM micro-environment inhibits long term marro cultures – aplastic anemia

Physiology

- Maintenance of a constant no. of red cells, white cells and platelets under regulatory mechanisms
  - $4 – 11 \times 10^{11}$ WBCs
  - $4.5 – 5.5 \times 10^{12}$
  - $150 – 450 \times 10^{9}$ per microliter of blood \

1. A single pleuropotent stem cell is capable of:
    1. Giving rise to many committed progenitor cells
    2. Pleuropotent stem cells capable of self renewal
2. Committed progenitor cells:
    1. Form differentiated recognizable precursors of the specific types of blood cells
    2. Are limited in proliferative potential and are not capable of indefinite self renewal ’die by differentiation’ and are repopulated on influx from pluripotent stem cell pool
    3. Proliferative potential and differentiation of stem cells and committed progenitor influenced by
        1. Adventitial cells
        2. Alpha HGF – produced in the reaction to the circulating levels of a particular differentiated cell type

- Large reserve
  - 2 x 10^{11} Rbc/day and increased by x 4 when required
  - WBC capacity can be increased to x 12 in normal demand
- Maintenance by regulatory substances – HGF
  - Properties
  - Lineage MAP
  - Cytokine sources and actions
  - Various maturation pathway

Leucopoiesis

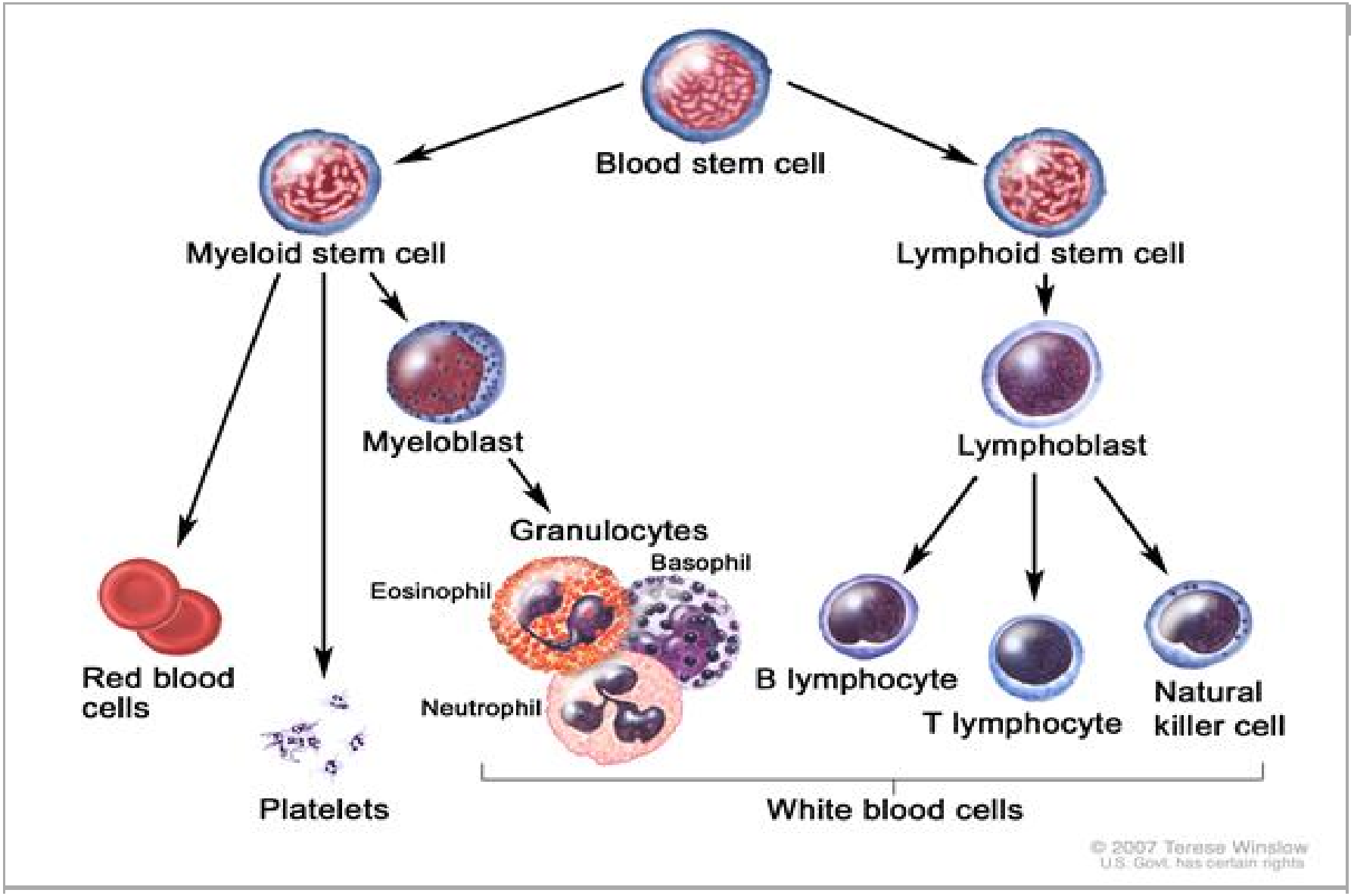
- Myeloblast
- Promyelocyte
- Myelocyte
- Metamyelocyte
- Band or stab
- Polymorphonuclear granulocyte
  - Eosinophil
  - Basophil
  - Monocyte

Erythropoiesis

- Proerythroblast
  - Loss of nucleolus, sideroblastic granules
- Basophilic Erythroblast
- Polychromatic normoblast
- Intermediate (Orthochromatic)
  - Loss of nucleus
- Reticulocyte
  - Matures in 2-3/7
- Mature Erythrocyte
  - No synthetic activity
  - Hemoglobinisation in 2-4/7

Thrombopoiesis

- Pluripotent stem cell
  - CFU – M
  - Erythropoietin
  - Thrombopoietin
- Megakarycyte precursor
  - 4 – 8 – 16 – 32 Nucleus
- Megakarycyte



Blood cell development. A blood stem cell goes through several steps to become
a red blood cell, platelet or white blood cell.

Hemopoietic growth factors

- Colony stimulating factors (CSFs)
- Cytokines
  - Interferons
  - Interleukins
- HGFs
  - FIK2 ligand
  - GM CSF
  - G CSF
  - M GSF
  - Erythropoietin
  - Thrombopoietin

Sources

- Sources:
  - Fibroblasts
  - Endothelial cells, epithelial cells
  - Activated T cells
  - Monocytes, macrophages

Clinical Use

- Clinical use:
  - EPO, GCSF, GMCSF