Block 5 Revision

Anatomy

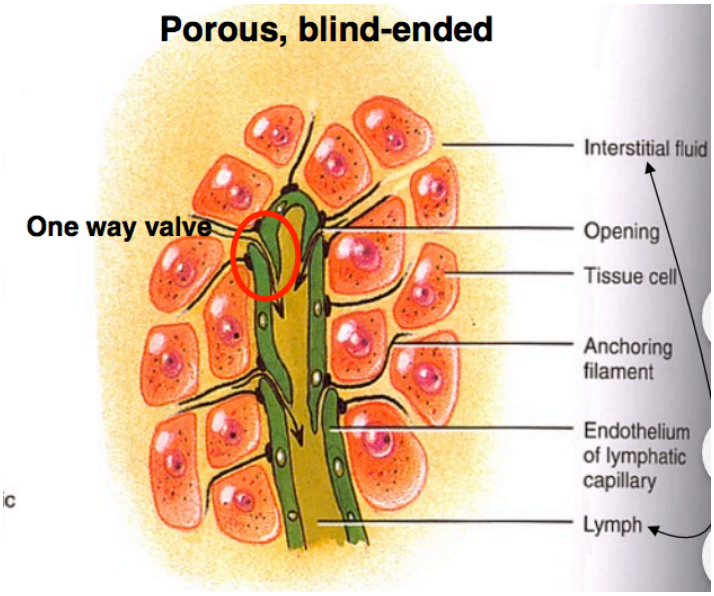
Anatomy of lymphatic drainage – 12/4/16

1. **Describe the components of the lymphatic system and the functions of these components**
   The lymphatic system is comprised of two semi-independent parts: the lymphatic vessels and lymph; and lymphatic organs and tissues. *Lymphatic vessels* play two key roles. Firstly, they drain excess interstitial fluid back into the blood, returning some lost plasma proteins in the process. Secondly, they transport dietary lipids from the intestine to the blood through specialised lymphatic capillaries called lacteals. *Lymphatic organs and tissues* play an important role in fighting infections through immune responses and are essential for both the adaptive and innate immune system. Lymphatic organs and tissues are classed into primary organs and tissues and secondary organs and tissues. *Primary lymphatic organs and tissues* are where stem cells divide and mature into B or T lymphocytes. It includes the red bone marrow (produces lymphocytes, B cell maturation) and the thymus (T cell maturation under the effects of thymosin). *Secondary lymphatic organs and tissues* are where most immune responses occur. They include lymph nodes (areas of concentrated lymphocytes in a special arrangement), spleen (similar to lymph node but large and filled with blood, plays a role in filtering and purifying the blood) and lymphatic nodules (which are congregations of lymphatic tissue, including the tonsils, Peyer's patches and mucosa associated lymphoid tissue [MALT]).

Primary lymphatic organs and tissues – B and T cell production and maturation	**Secondary lymphatic organs and tissues – sites of immune response**
Bone marrow • Lymphocyte production • B cell maturation	Lymph nodes • Concentrated lymphocytes in special configuration
Thymus • T cell maturation (thymosin)	Spleen • Similar to lymph nodes, but filled with blood • Blood filtering and purification
	Lymphatic nodules • NOT encapsulated • Congregations of lymphatic tissue • Tonsils • Peyer's patches • Mucosa associated lymphoid tissue (MALT)

2. **Explain the formation of lymph and the mechanism of lymph transport**
   In the systemic and pulmonary blood capillaries, the mean of interstitial and luminal oncotic and hydrostatic pressure can result in movement of blood (minus cells and large proteins) out of the capillaries and into the interstitium. The lymphatic

capillaries are closely associated with the interstitium and excess fluid flows into them to eventually enter the lymphatic vessels. The lymphatic vessels of the pulmonary circulation meet at the lymphatic duct where they empty into systemic blood circulation at the subclavian vein. The *lymphatic capillaries* play a key role in the formation of lymph. Found throughout the body except in avascular tissues (cartilage, epidermis, cornea), they are porous and blind-ended and the openings into them are between two tissue cells. These openings have a one-way valve that means that fluid entering them from the interstitium cannot re-enter the interstitium.



Once in the lymphatic system, there are no pumps so special mechanisms for flow are required. There are lots of *valves* in the lymphatic vessels to ensure that flow is only one-way. The exit of the lymph of the lymphatic duct is into a *low-pressure area* (the subclavian vein – 5mmHg) to give a pressure gradient. There are also special driving forces to keep lymph moving through the lymphatic circulation. The *smooth muscle* in the vessel wall assists in pumping the lymph through the vessels. The *skeletal muscle neighbour* assists in milking out lymph. *Respiration* causes the thoracic cavity pressure to decrease and the abdominal cavity pressure to increase, thus creating a pressure gradient to drive flow back into the thoracic cavity (that is, where the thoracic duct and the subclavian vein are located).

3. **Summarise the drainage routes of major lymphatic vessels and location of major clusters of lymph nodes**

   There are 10 principal groups of lymph nodes. The first two groups lie alongside key midline structures: the trachea (*tracheal nodes, x1*) and the aorta/celiac trunk/SMA/IMA (*deep nodes, x1*). The next three are where the upper limbs (*axillary nodes* in axilla, x2) and lower limbs (*inguinal nodes* along inguinal ligament, x2; *femoral nodes* along femoral vein, x2) attach to the trunk. The last two groups are where the head and neck attaches to the trunk (*cervical nodes* along course of internal jugular vein, x2; *pericranial ring* along base of head, x2).

4. **Compare and contrast the location, histological structure and functions of primary and secondary lymphatic organs**

See practical manual

5. **Relate the anatomy of the lymphatic system with clinical scenarios: cancer metastasis, lymphoedema**
   Having a good understanding of the lymphatic system is important as certain areas of the body drain through certain pathways. Therefore, the lymphatic spread of cancer can be predicted, or traced. Three examples are the *oesophagus*, testes and scrotum, and the upper limb and breast.

Part of oesophagus	Drains into	Sites of metastases
Upper 1/3	Deep cervical nodes	
Middle 1/3	Superior and posterior mediastinal nodes	
Lower 1/3	Left gastric nodes -> coeliac nodes	Stomach Duodenum Spleen Omenta

Testicular and scrotal cancers have different surgical treatments due to the differences in their lymphatic drainage. The testes drain into the para-artic/lumbar nodes, whereas the scrotum drains into the superficial inguinal nodes. As such, orchiectomy (removal of the testes) should be done through the inguinal route (NOT cutting through the scrotum but going through the inguinal canal) to avoid tumour spillage into the inguinal drainage route (i.e. it avoids the cancer possibly reaching the superficial inguinal).

Different areas of the *breast* drain into different nodes (e.g. the lateral breast drains into the pectoral lymph node). It is important to check for lymph node enlargement when doing a breast exam as this is one of the most common sites of metastasis. In fact, it is necessary for a breast cancer to spread to at least the sentinel lymph node in the axilla before spreading anywhere else through the lymphatic route.

Post-mastectomy lymphoedema occurs when there has been total excision of the axillary lymph nodes that occurs with a mastectomy. Because the lymphatic drainage is effectively cut off, there is no pressure gradient for the lymph to drain so the fluid remains in the interstitium. This will give a severe non-pitting oedema in the affected limb.

Physiology

Haematopoeisis and its regulation – 23/3/16

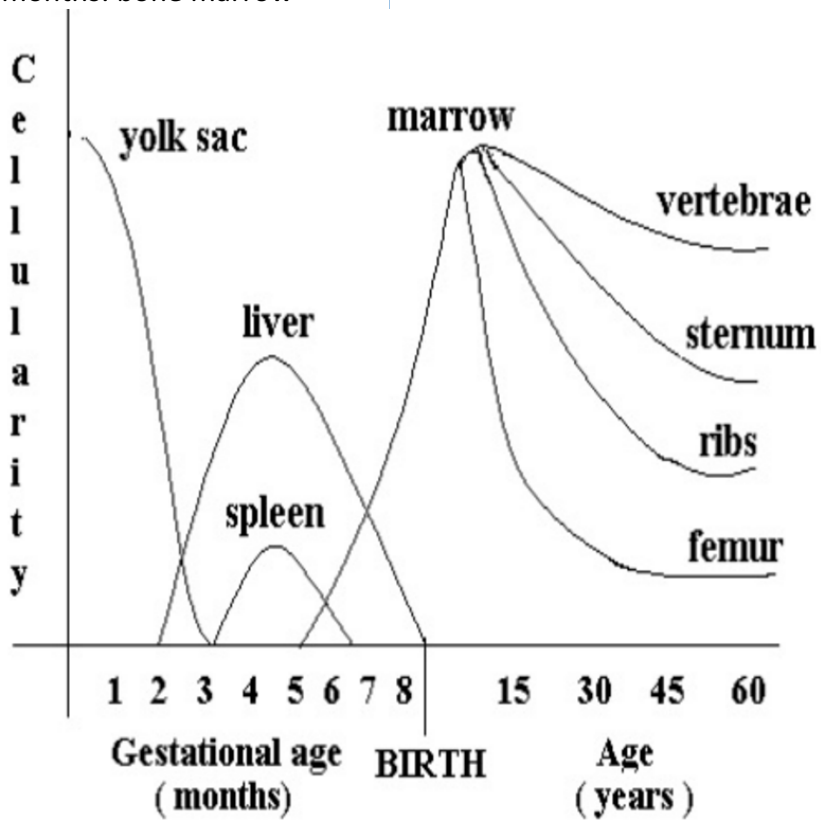
1. **Define haematopoeisis**
   Haematopoeisis is the process in which blood cells are formed in the body from stem cells.

2. **Contrast haematopoietic stem cells and progenitor cells**
   Haematopoietic stem cells (HSCs) have different properties to progenitor cells.

Feature	HSC	Progenitor cell
Haematopoeitic capacity (time)	Perpetual – can reconstitute and maintain haematopoeisis over a long period of time	Non-perpetual – cannot reconstitute and main haematopoesis over a long period of time
Proliferative capacity	Extensive proliferative capacity	Limited proliferative capacity
Self-renewal	Can self-renew	Limited or no self-renewal capacity
Pluripotency/unipotency	Pluripotency – can give rise to cells of many lineages (e.g. erythrocyte, granulocyte, B lymphocyte)	Multipotency or unipotency – commited to a lineage (e.g. lymphoid)
Activity	Quiescent	Actively cycling

3. **Describe the sites of haemopoeisis before and after birth**

Before birth	After birth
4-5 weeks: Aorta Gonad Mesonephros (AGM region)	Bone marrow (pelvic bones, ribs, spine, skull, proximal part of arm and leg bones)
4-6 weeks: yolk sac	
6-22 weeks: foetal liver	
16 weeks-9 months: bone marrow	

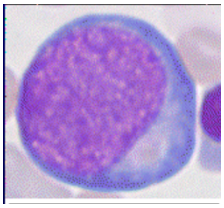


4. **Describe erythropoiesis, including its regulation, process, features and purpose of red blood cells**

Erythropoeisis is the process through which red cells are generated in the bone marrow. Red cells are essential for carrying oxygen to tissues on Hb. They are very simple cells. They do not have nuclei and therefore cannot do oxidative metabolism, relying instead on glycolysis and the pentose phosphate shunt. They are susceptible to free radicals as they do not have the pathways usually present to remove free radicals. They therefore rely on the PPP to generate antioxidants and if a person has G6PD deficiency the red cells are more likely to lyse under conditions of stress, resulting in hyperbilirubinaemia and jaundice.

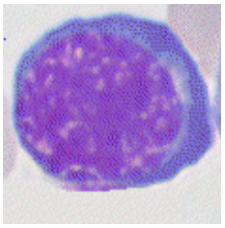
Erythropoeisis is regulated by erythropoietin, which is released from the kidney when low O2 tension is sensed by the proximal tubule. Epo is internalised by the Epo receptor (a JAK cytokine receptor) into the marrow progenitor cells and erythroid precursors where it has a number of effects, including the differentiation of HSCs into pronormoblasts. It does this by ALA synthetase formation, adenylyl cyclase activation and transferrin receptor synthesis. Epo is then broken down within the receptor so that the receptor can be recycled. Erythropoesis is also regulated by IL-3 which promotes the growth and reproduction of all the different types of committed stem cells. Other regulatory factors include IGF-1, IL-6, and glucocorticoids, allowing increase in production of red blood cells during times of acute or chronic stress. This can be done by increasing the activity of the committed progenitor cells or through production of more progenitor cells.

The process of erythropoiesis is shown in the diagram below. Basically, it goes from proerythroblast to normoblast to reticulocyte to erythrocyte (blast -> cyte) and takes about 7 days. RBCs then survive in the circulation for around 120 days. They are then broken down by macrophages in the spleen when they become senescent.



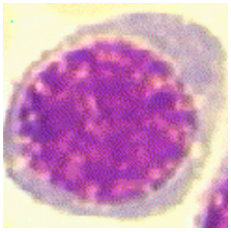
Proerythroblast

Day 1
15-20um
Basophilic cytoplasm (polyribosomes)
Mitosis
Nucleus within nucleoli
No Hb



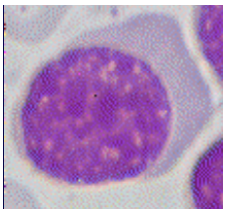
Basophilic normoblast

Day 2
14-17um
Mitosis
Basophilic cytoplasm
Nucleoli disappears



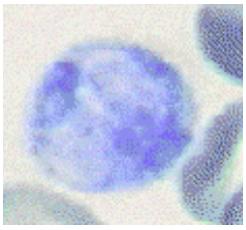
Polychromatic normoblast

Day 3
10-15um
Polychromasia (basophilic and eosinophilic)
Chromatin lumps
Hb appears
Nucleus condenses



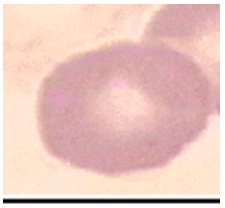
Orthochromatic normoblast

Day 4
7-10um
Pyknotic (shrunken) nucleus
Eosinophilic cytoplasm
Mitoses absent
Extrusion of nucleus
Hb is maximum



Reticulocyte

Day 5-7
7.3um
Enters circulation
Reticulum of basophilic material in the cytoplasm (clumped ribosomes, RER)

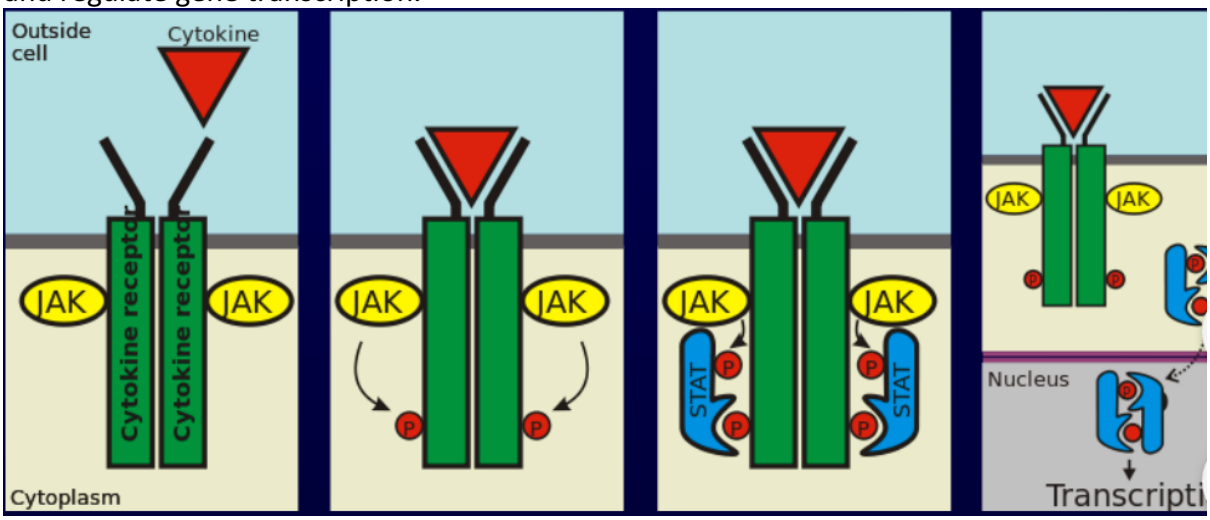


Erythrocyte

Day 7-120
7.2um
Hb

5. **Outline the role of JAK2 in haemopoeisis**
   JAK is an integral part of a cytokine receptor that sits on the membrane of many cells, including bone marrow progenitor cells. When the cytokine (e.g. Epo) binds to the outer membrane portion of the receptor, this causes a conformational change in the receptor that results in JAK phosphorylating the cytoplasmic domain of the receptor. When the receptor is phosphorylated, this allows the binding of STAT

protein to the cytoplasmic domain. Once STAT protein is bound, JAK phosphorylates the STAT protein, allowing the proteins to associate into a dimer to enter the nucleus and regulate gene transcription. ‘

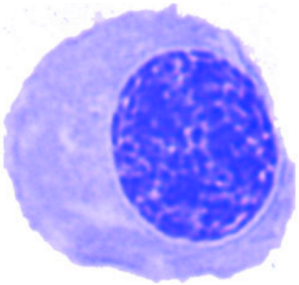


6. **Outline the structure of the haemoglobin molecule**
   Haemoglobin has 2 alpha globin chains and 2 beta globin chains, each of which carries 1 unit of heme. Each unit of heme carries an iron atom. The haemoglobin molecule can therefore carry 4 O2. It undergoes conformation change when O2 associates or disassociates, resulting in the O2 saturation curve.

7. **Describe granulopoeisis, including its regulation, process, features and purpose of the white blood cells**
   Granulopoiesis is the process by which granulocytes are formed from the myeloid stem cell. Granulocytes include neutrophils, monocytes, eosinophils and basophils. These cells have different features (stain differently, different nuclei) and roles within the immune system including phagocytosis release of granules and chromatins when neutrophils lyse to form an extracellular fibril matrix as a physical barrier to stop pathogen spread. Phagocytosis can be done by directly binding the bacterium, binding the bacterium+C3b on the C3b receptor, binding of the bacterium+antibody+C3b onto their C3b receptor and Fc receptor. They reach sites of inflammation, tissue damage and immune reactions by the process of chemotaxis, where they follow signals such as C5a to cross the endothelium and basement membrane of the capillary blood vessel to reach tissue.

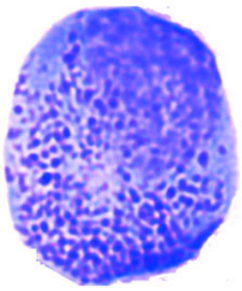
   Granulopoeisis is regulated by GCSF (granulocyte colony stimulating factor) which is produced by the endothelium, macrophages and other immune cells from a gene on chromosome 17. It binds to GCSF receptors on myeloid progenitors where it is then internalised. GCSF is used in the basal production of granulocytes. Another important regulator is IL6 which is secreted by monocytes and fibroblasts during acute stress (e.g. infection). IL6 is used in the emergency production of granulocytes.

   The following diagram describes the stages of granulopoeisis. The process takes over 14 days.



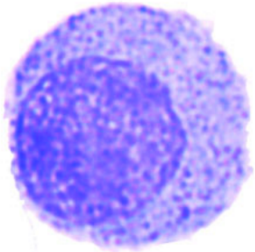
Myeloblast

Committed cell
Diameter 14-18nm
Oval nucleus with multiple nucleoli
No granules



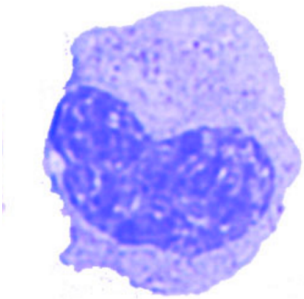
Promyelocyte

18-30um
Oval nucleus
Condensed chromatin
Purple-staining nonspecific azurophilic granules



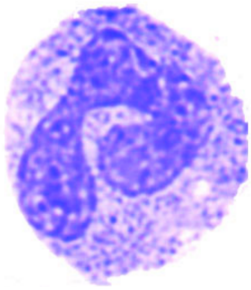
Myelocyte

12-15um
Presence of smaller specific or secondary granules
Cytoplasm becomes less basophilic



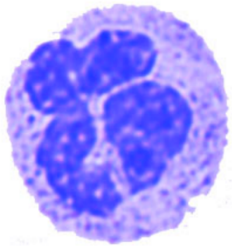
Metamyelocyte

12-15um
No more granule production
Reduced cell size
Nucleus becomes flattened
Chromatin condensation



Band cell

Nucleus horse-shoe shaped
Cell size decreases



Granulocyte

Nucleus segmented into lobes
Cell size decreases
Enters the bloodstream