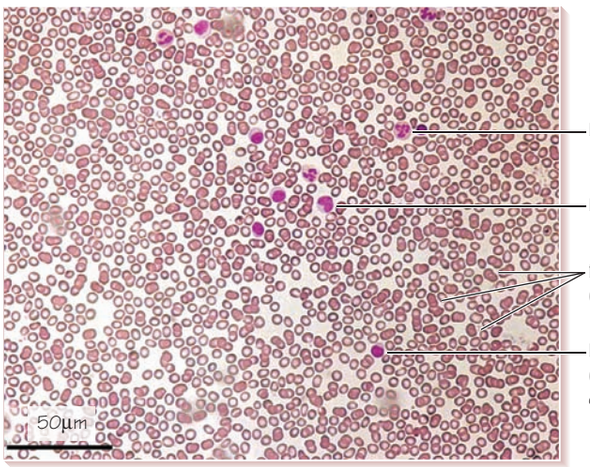
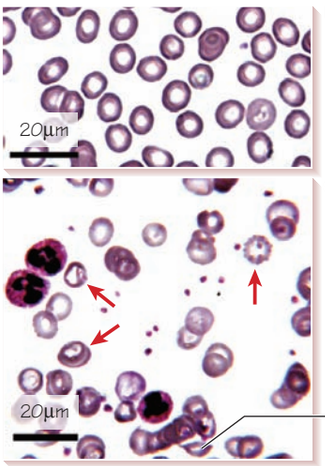
13 Blood

(a) Blood smear (normal)



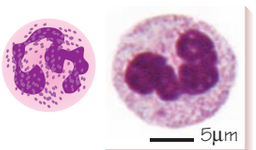
(b) Red blood cells in normal and sickle cell anemia blood smears



(c) Types of white blood cell

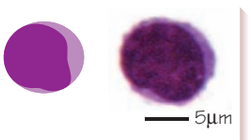
Most common

Neutrophil (granulocyte) 50-70%, 12-14 µm diameter. Multilobed nucleus and pale pink cytoplasm



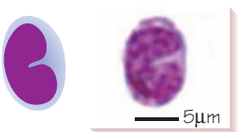
Enter tissues and destroy damaged tissue and bacteria

Lymphocyte (agranulocyte) 20-40%, 7-12 µm diameter. Densely stained nucleus occupies most of the cell, thin rim of cytoplasm



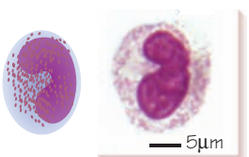
B- lymphocytes, develop into antibody producing cells.
T-lymphocytes recognize foreign antigens, and destroy foreign cells (killer-T cells) or help B cells mount an immune response(helper-T cells)

Monocyte (agranulocyte) 2-10%, up to 20 µm diameter. Bean shaped nucleus, with visible chromatin strands. Grey-blue cytoplasm



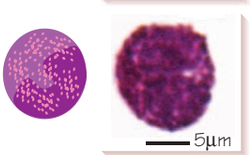
Enter tissues and differentiate into macrophages, which are highly phagocytic, and destroy bacteria and dead tissue

Eosinophil (granulocyte) 1-5%, 12-15 µm diameter Bilobed nucleus. Cytoplasm has lots of large granules



Defends against parasites, and role in triggering bronchial asthma

Basophil (granulocyte) 1%, 14-16 µm diameter. Bi-lobed dark blue/ purple nucleus, and large cytoplasmic granules



Release histamine as part of the allergic reaction

Least common

(d) Platelets

Platelets are 2-4 µm fragments of cytoplasm derived from megakaryocytes

Important for blood clotting, and repair of damaged blood vessels

Content and functions of blood

Blood transports gases, nutrients, waste, cells, and hormones throughout the body. It helps to regulate pH, temperature and water content of cells, protects against blood loss via clotting, and protects against disease through the actions of white blood cells and antibodies.

Blood consists of cells (~45%) and plasma (~55%). All the cells are made in the bone marrow.

The cells include red blood cells (erythrocytes: ~5×10^6 per mL), white blood cells (leucocytes: ~2×10^3 per mL), and platelets (thrombocytes: ~2×10^5 per mL).

Blood plasma contains water (92%), proteins (such as hormones, serum albumin, and serum globulin), lipids (such as cholesterol), salts (such as urea), and glucose.

Red blood cells

Red blood cells (erythrocytes) are 'born' in the bone marrow, lose their nuclei, and become packed full of hemoglobin, which binds oxygen and carbon dioxide. These biconcave cells move through narrow capillaries more easily without a nucleus. Red blood cells are 7 μm in diameter, and are eosinophilic due to their high protein content (Fig. 13a).

In **sickle cell anemia**, red blood cells have abnormal shapes, including the characteristic 'sickle' cell shape due to mutations in hemoglobin (Fig. 13b). Cells are less deformable, and can get stuck in the capillaries, reducing blood flow, causing pain and organ damage.

The cells circulate for about 120 days, before disposal in the liver. About 3×10^6 erythrocytes die and are scavenged by the liver every second.

White blood cells

White blood cells are less common than red blood cells, as shown by a blood smear (Fig. 13a). There are five main type of white blood cell (leucocytes; Fig. 13c), which are divided into:

- **granulocytes** (neutrophils, eosinophils and basophils), which have a granular cytoplasm; and
- **agranulocytes** (lymphocytes and monocytes), which do not.

Granulocytes

Neutrophils (most common) contain a multilobed (2–5 lobes) nucleus, and contain azure (primary) granules (colored purple, due to sulfated glycoproteins that react with the stain), which secrete elastase and myeloperoxidase (antimicrobial enzymes), and paler (secondary) granules, which contain lysozyme and other proteases. They circulate for about 6–10 hours in the blood, and then enter tissues. They are motile and phagocytic, destroying damaged tissue and bacteria. After this activity, they self-destruct. They are important in inflammatory reactions.

Eosinophils (fairly rare in blood smears) have a bilobed nucleus. They are rare because they leave the blood system quickly after being manufactured in the bone marrow, entering the loose connective tissue in the respiratory and gastrointestinal tracts. They phagocytose antigen–antibody complexes. They also release histaminase and arylsulfatase B, which inactivates inflammatory reagents released by mast cells.

Basophils (very rare in blood smears) contain IgE receptors and are involved in immune responses to parasites. Granules in these cells contain histamine, prostaglandins, heparin, and serotinin, and are released in areas of damaged tissue. The released components increase blood flow to the area (inflammatory response). Histamine release also plays a role in allergic reactions.

Agranulocytes

Monocytes are the third most common white blood cells. They circulate in the blood for 1–3 days after birth, before migrating into body tissues, where they differentiate into phagocytic macrophages, and phagocytose dead cells and bacteria. They are important in the inflammatory response. They can also differentiate into osteoclasts, which are found in bone (see Chapter 16).

Monocytes (and macrophages), neutrophils, eosinophils, basophils (and mast cells) are all derived from a common **myeloid** progenitor in the bone marrow.

Lymphocytes are the second most common white blood cell. There are two kinds, B-cells and T-cells, both of which are born in the bone marrow. They are both derived from a common lymphoid progenitor cell.

B-lymphocytes mature in the bone marrow. They are involved in the humoral antibody response: B-cells and their progeny develop into **plasma** cells, which manufacture and secrete antibodies. They are important in mounting an immune response to infectious bacteria.

Multiple myeloma (a type of blood cancer) develops when plasma cells become transformed and divide in an uncontrolled way.

T-lymphocytes mature in the thymus. They do not make antibodies, and the antigen receptors on their surfaces are different to those on B-cells.

The different types of T-cell and B-cell cannot be distinguished using histological stains, but can be distinguished using immunostaining for the different cell surface markers that these cells express.

Other immune cells

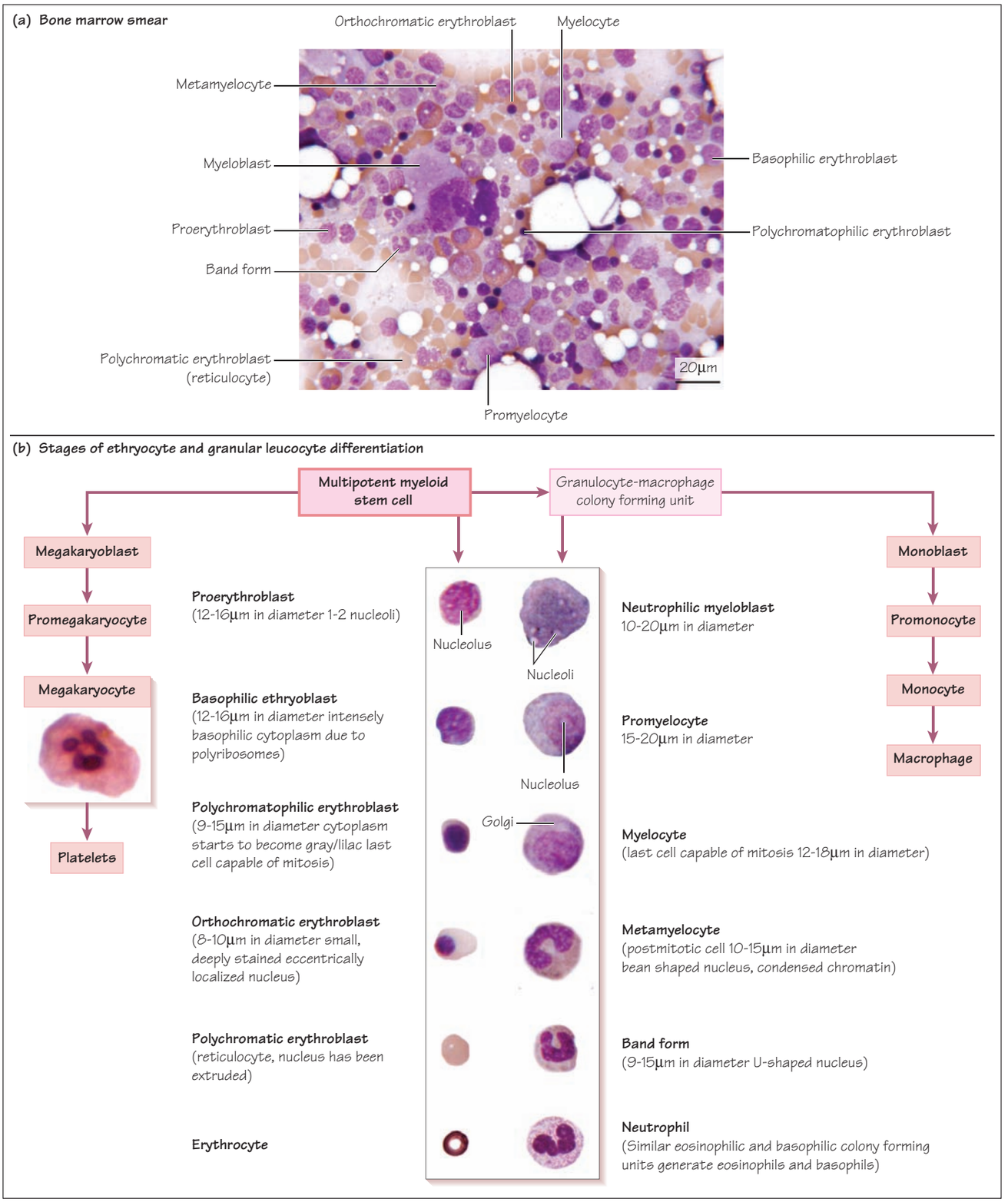
- **Dendritic and reticular cells:** present antigens to lymphocytes on their cell surface.
- **Mast cells:** bone marrow-derived cells involved in allergic reactions. They have receptors for IgE antibodies on its surface, and release histamine, heparin, etc.

Platelets

These are cytoplasmic fragments formed by multinucleated cells (**megakaryocytes**; see Chapter 14) in the bone marrow (Fig. 13d). They adhere to collagenous tissue at the edges of wounds to form plugs, promote the formation of clots, and secrete factors involved in vascular repair. They do not have a nucleus, but contain mitochondria, microtubules, actin filaments, glycogen granules, some Golgi, and ribosomes.

Red blood cells and platelets are derived from a common myeloid progenitor.

14 Hemopoiesis



Hemopoiesis is the process by which mature blood cells develop from precursor cells. It occurs continuously throughout embryonic and adult life, as new blood cells constantly replace old mature blood cells in the circulation.

Erythrocytes, granulocytes (neutrophils, eosinophils, and basophils), agranulocytes (lymphocytes and monocytes), and platelets are all formed in the bone marrow (Fig. 14a), which are found in the spaces between trabeculae in spongy bone.

The bone marrow contains **pluripotent stem cells** that differentiate into **multipotent lymphoid stem cells** and **multipotent myeloid stem cells**.

Multipotent lymphoid stem cells

These cells further differentiate into T- and B-**lymphocytes** (also known as T- and B-cells).

B-lymphocytes can develop into antibody-secreting **plasma** cells in lymphoid tissue.

B-cells mature in the bone marrow, start to express immunoglobulins on their surface (IgM and IgD), and are presented with 'self-antigens' to test their binding specificity. If they pass this test, and do not react with 'self-antigens', they leave the bone marrow and travel via the bloodstream to the lymph nodes and other lymphoid tissue.

T-cells mature in the thymus, by interacting with thymic epithelial cells (see Chapter 42). They then travel, via the bloodstream, to peripheral lymphoid tissue. Antigens are presented to T-cells via antigen-presenting cells in these tissues. T-cells can further differentiate into helper T-cells (CD4+) and cytotoxic T-cells (CD8+). CD4 and CD8 are types of 'cluster of differentiation' glycoproteins found on the cell surface.

Multipotent myeloid stem cells

These cells further differentiate (Fig. 14b), as follows.

Megakaryocyte colony-forming units

These develop into megakaryocytes, which form platelets. Megakaryocytes can be identified in the bone marrow as huge cells (up to 150 μm in diameter), which are multinucleated.

Erythroid colony-forming units

These cells differentiate into erythroblasts, and finally into erythrocytes (red blood cells). During differentiation, the cells gradually shrink from 12–16 μm in diameter, and finally, the nucleus is lost at the reticulocyte (polychromatic erythroblast) stage. Reticulocytes are released into the bloodstream, and mature into red blood cells within 24 hours.

Granulocyte/neutrophil colony-forming units

These differentiate into monocytes and neutrophils.

- **Monocytes** subsequently develop into macrophages.
- **Neutrophils** (Fig. 14b) develop via a number of immature stages. For example, myelocytes are an intermediate stage in neutrophil formation, and are the last stage at which this type of cell can undergo cell division.

Basophil colony-forming units

These generate basophils, via a number of stages, which appear similar to those of the neutrophil colony-forming units, except that the cells are basophilic. Basophils can develop further to form mast cells.

Eosinophil colony-forming units

These generate eosinophils, via a number of stages, which appear similar to those of the neutrophil colony-forming units, except that the cells are eosinophilic.

In general, precursor cells in the bone marrow are larger in diameter than mature red and white blood cells.

Blood disorders

Various leukemias can result from the abnormal proliferation of precursor white (or red) blood cells, as follows.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia (about 25% of all diagnosed cases) and mainly affects adults. The cells causing this disease are B-cells, which have not fully differentiated, but resemble fully mature B-lymphocytes. The increase in these immature B-lymphocytes can cause patients to become immunocompromised. This disease can be diagnosed from a blood smear. Normal blood smears do not normally contain more than 2.5×10^9 lymphocytes per liter. In CLL, this number can increase more than 4-fold to over 10×10^9 cells per liter (this is called lymphocytosis).

Acute lymphoblastic leukemia

This form of leukemia is most common in children (two-thirds of cases) and is a malignant disorder of lymphoblastic cells.

Acute myeloid leukemia

Acute myeloid leukemia (AML) results from proliferation of myeloid stem cells in the bone marrow, and is the most common malignant myeloid disorder in adults. It is a heterogeneous disorder, affecting any of the blast cell stages in hemopoiesis. It can be diagnosed from bone marrow smears, which are examined for abnormal levels of myeloblasts. (The numbers increase such that more than 30% of all the cells in the bone marrow will be immature white blood cell types.) AML commonly causes death as a result of bone marrow failure.

Aplastic anemia

This is a rare hemopoietic blood cell disorder, commonly caused by the destruction of bone marrow stem cells by reactive lymphocytes. It results in a reduction of all blood cells (white, red, and platelets). There is a range of other anemias including:

- **microcytic anemia** (red blood cells smaller than normal), commonly caused by lack of iron;
- **macrocytic anemia** (red blood cells larger than normal), commonly caused by a deficiency of vitamin B12 or folic acid;
- **hemolytic anemia**, results from an abnormal breakdown of red blood cells.