Hematology

Learning objectives

- After completing this lecture, the student will be able to:

Describe the significance of the field of hematology in relation to sickness and health.

✓ To understand the process of formation of blood cells

✓ To understand the concept of a stem cell

✓ To appreciate the process of lineage specifi cation of blood cells

✓ To recognize the diff erent types of mature blood cell

✓ To understand the normal role of each mature cell type in the blood

- In its most fundamental form, hematology is the study of blood in health and in pathological conditions. Blood is the window to the body; it is a predictor of vitality, of long life. In ancient times, blood was worshipped. Men were bled to obtain a cure, and blood was studied for its mystical powers. It was an elevated bodily fluid. The discipline of hematology was an outgrowth of this fascination with blood.

Blood has always been a fascinating subject for authors, poets, scholars, and scientists. References to blood appear in hieroglyphics, in the Bible, in ancient pottery, and in literature. Hippocrates laid the foundation for hematology with his theory of the body's four humors—blood, phlegm, black bile, and yellow bile— and his concept that all blood ailments resulted from a disorder in the balance of these humors. Unfortunately, these principles remained unchallenged for 1400 years! Gradually, men of science such as Galen, Harvey, van Leeuwenhoek, Virchow, and Ehrlich were able to elevate hematology into a discipline of medicine with basic morphological observations that can be traced to a distinct pathophysiology.It is to these men that we owe a huge debt of gratitude

Site of haemopoiesis In the first few weeks of gestation the yolk sac is a transient site of haemopoiesis. However, definitive haemopoiesis derives from a population of stem cells first observed on the AGM (aorta-gonads-mesonephros) region. These common precursors of endothelial and haemopoietic cells (haemangioblasts) are believed to seed the liver, spleen and bone marrow. From 6 weeks until 6–7 months of fetal life, the liver and spleen are the major haemopoietic organs and continue to produce blood cells until about 2 weeks after birth. The placenta also contributes to fetal haemopoiesis. The bone marrow is the most important site from 6–7 months of fetal life. During normal childhood and adult life the marrow is the only source of new blood cells. The developing cells are situated outside the bone marrow sinuses; mature cells are released into the sinus spaces, the marrow microcirculation and so into the general circulation

In infancy all the bone marrow is haemopoietic but during childhood there is progressive fatty replacement of marrow throughout the long bones so that in adult life haemopoietic marrow is confined to the central skeleton and proximal ends of the femurs and humeri. Even in these haemopoietic areas, approximately 50% of the marrow consists of fat. The remaining fatty marrow is capable of reversion to haemopoiesis and in many diseases there is also expansion of haemopoiesis down the long bones. Moreover, the liver and spleen can resume their fetal haemopoietic role (‘extramedullary haemopoiesis’).

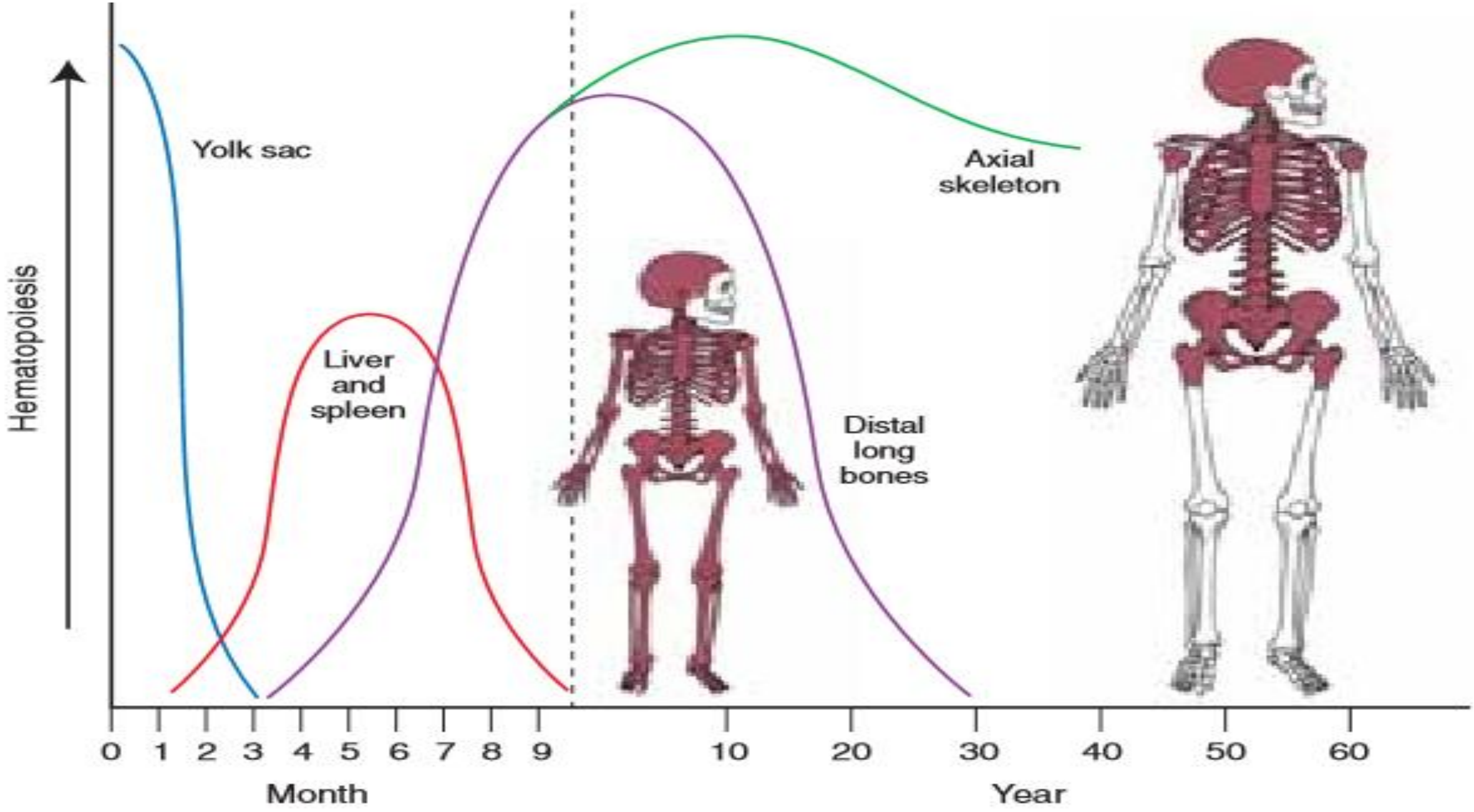


Figure 2.1 Marrow formation in fetus *(left)* versus the adult *(right)*

Table 1.1 Sites of haemopoiesis.

Fetus	0–2 months (yolk sac)
	2–7 months (liver, spleen)
	5–9 months (bone marrow)
Infants	Bone marrow (practically all bones)
Adults	Vertebrae, ribs, sternum, skull, sacrum and pelvis, proximal ends of femur

Haemopoietic stem cells

The process of haemopoiesis involves both the specification of individual blood cell lineages and cellular proliferation to maintain adequate circulating numbers of cells throughout life. This is accomplished using the unique properties of haemopoietic stem cells. Long-term haemopoietic stem cells (HSCs) in the bone marrow are capable of both self-renewal and differentiation into the progenitors of individual blood cell lineages.

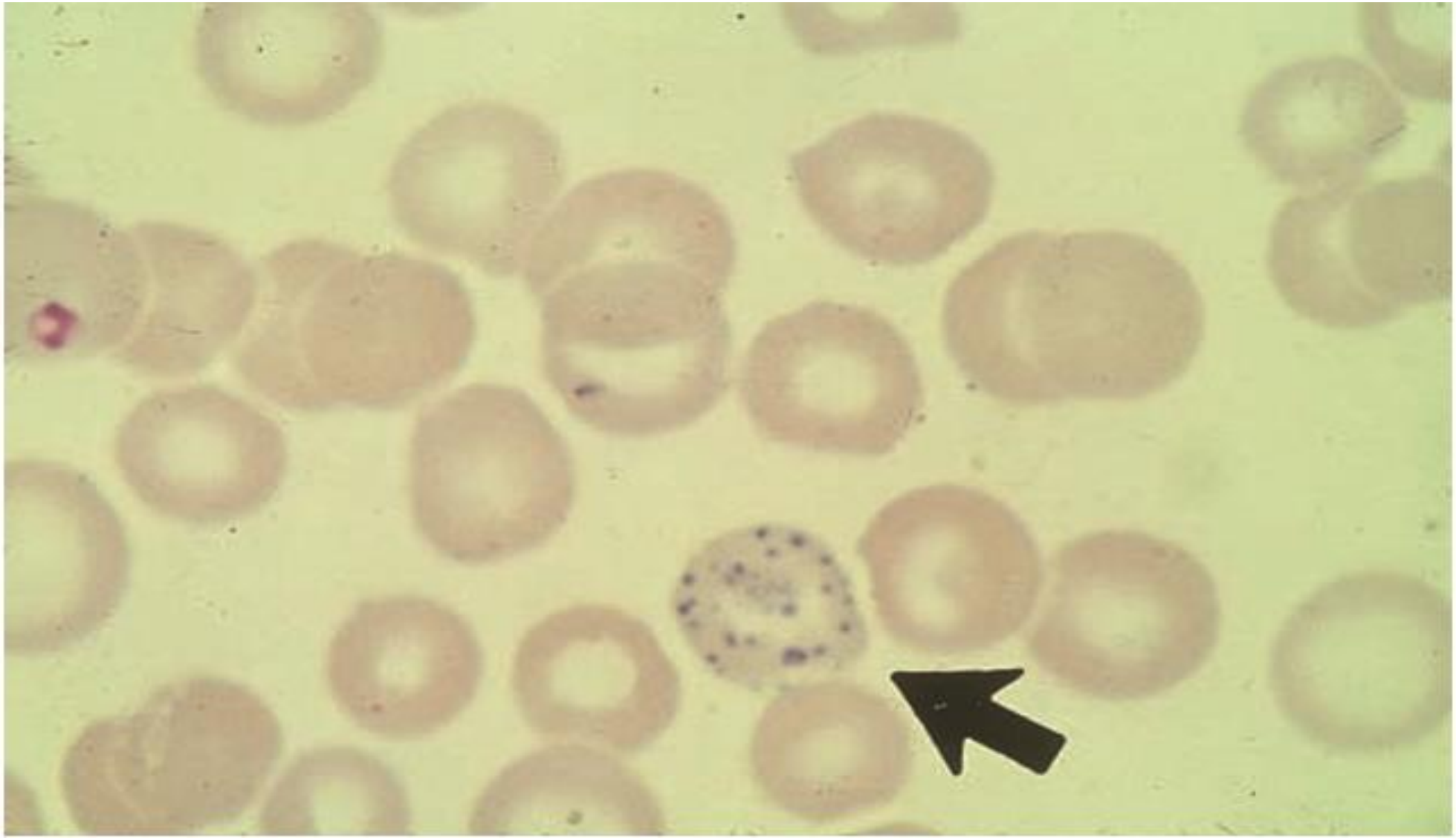
Long-term haemopoietic stem cells (HSCs) in the bone marrow are capable of both self-renewal and diff erentiation into the progenitors of individual blood cell lineages. The progenitor cells of individual lineages then undergo many rounds of division and further diff erentiation in order to yield populations of mature blood cells. This process can be represented as a hierarchy of cells, with HSCs giving rise to populations of precursor cells, which in turn give rise to cells increasingly committed to producing a single type of mature blood cell.

- Nuclei are always "baseball" round.
- Basophila of cytoplasm is an indicator of immaturity.
- Cell size reduces with maturity.
- As hemoglobin develops, the cytoplasm becomes more magenta.
- The N:C ratio decreases as the cell matures.
- The cytoplasm of the red cell does not contain specific granulation.
- Nuclear chromatin becomes more condensed with age.
- Nucleated red cells (orthochromic normoblasts) are not a physiological component of the normal peripheral smear.

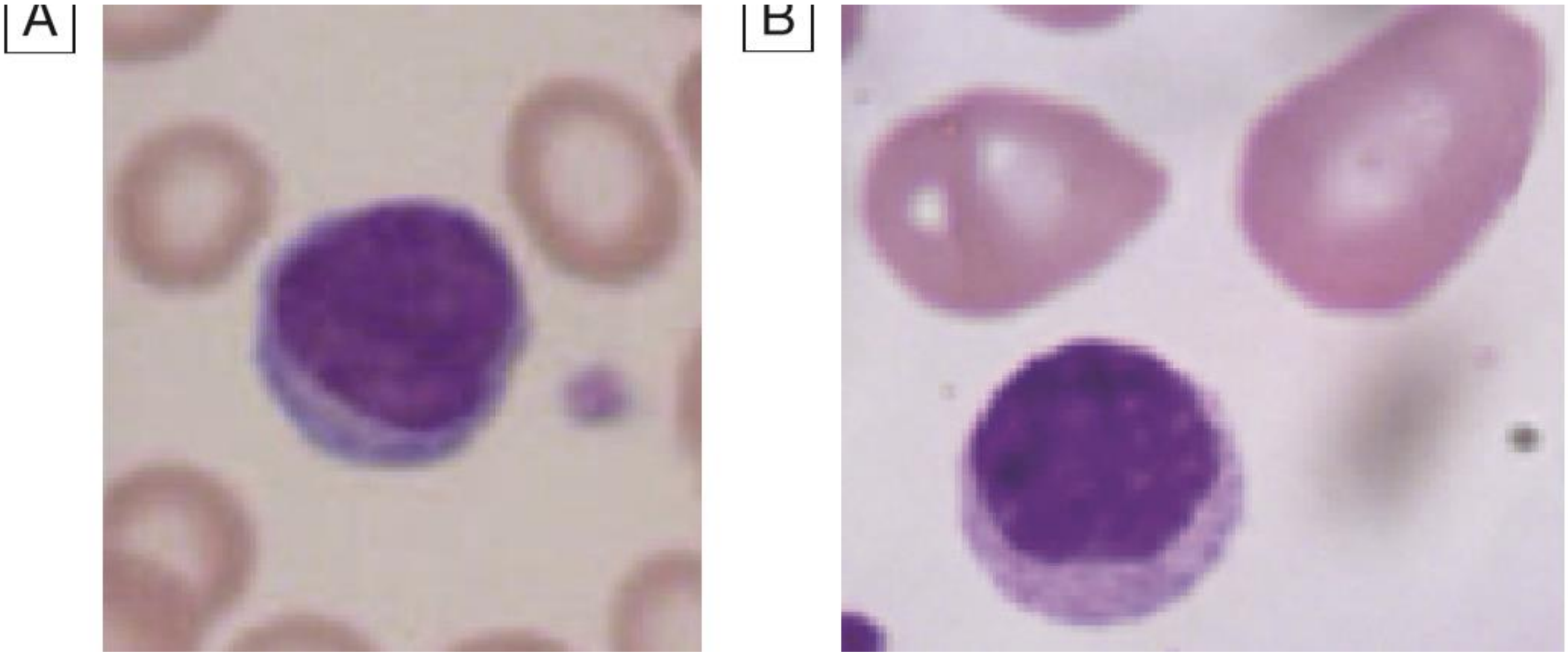
Summery of inclusions

Inclusion	Composition
Howell-Jolly body	DNA in origin
Basophilic stippling	RNA remnants
Siderotic granules/ Pappenheimer bodies	Iron
Heinz bodies	Denatured hemoglobin

Basophilic stippling



A. Microcytosis ------B. Macrocytosis



Different red blood cell morphology

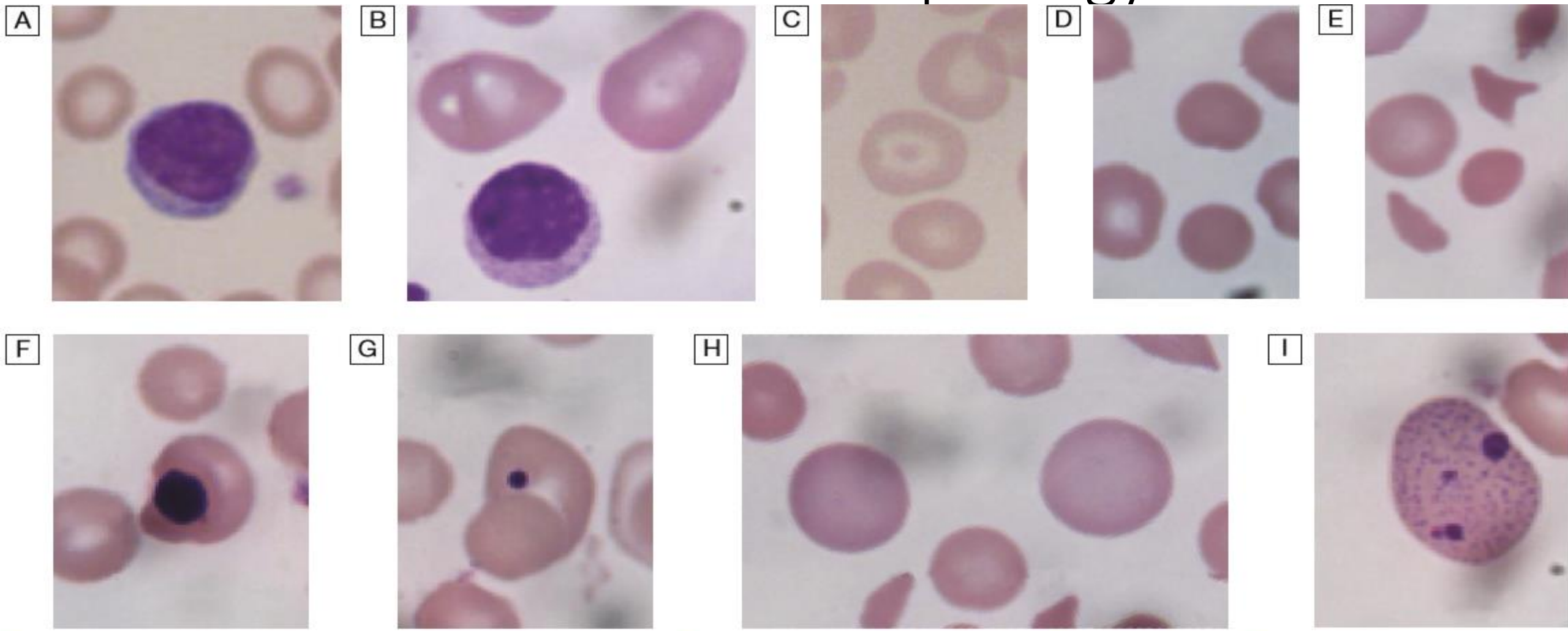
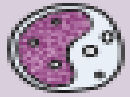
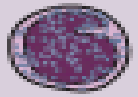


Fig. 24.8 Appearance of red blood cells. A Microcytosis. B Macrocytosis. C Target cells. D Spherocytes. E Red cell fragments. F Nucleated red blood cells. G Howell–Jolly bodies. H Polychromasia. I Basophilic stippling.

Table 1.3 The main functions of blood cells.

Type of cell	Main functions
Red blood cells (erythrocytes)	Transport O_2 from lungs to tissues (see Chapters 2 and 4)
Neutrophil granulocytes	Chemotaxis, phagocytosis, killing of phagocytosed bacteria
Eosinophil granulocytes	All neutrophil functions listed above, effector cells for antibody-dependent damage to metazoal parasites, regulate immediate-type hypersensitivity reactions (inactivate histamine and leukotrienes released by basophils and mast cells)
Basophil granulocytes	Mediate immediate-type hypersensitivity (IgE-coated basophils react with specific antigen and release histamine and leukotrienes), modulate inflammatory responses by releasing heparin and proteases
Monocytes and macrophages	Chemotaxis, phagocytosis, killing of some micro-organisms, antigen presentation, release of IL-1 and TNF that stimulate bone marrow stromal cells to produce GM-CSF, G-CSF, M-CSF and IL-6
Platelets	Adhere to subendothelial connective tissue, participate in primary haemostasis
Lymphocytes	Critical for immune responses and production of haemopoietic growth factors

Table 2.1 The blood cells.

Cell	Diameter (μm)	Lifespan in blood	Number	Function
Red cells 	6–8	120 days	Male: $4.5–6.5 \times 10^{12}$/L Female: $3.9–5.6 \times 10^{12}$/L	Oxygen and carbon dioxide transport
Platelets 	0.5–3.0	10 days	$140–400 \times 10^{9}$/L	Haemostasis
Phagocytes				
Neutrophils 	12–15	6–10 h	$1.8–7.5 \times 10^{9}$/L	Protection from bacteria, fungi
Monocytes 	12–20	20-40 h	$0.2–0.8 \times 10^{9}$/L	Protection from bacteria, fungi
Eosinophils 	12–15	Days	$0.04–0.44 \times 10^{9}$/L	Protection against parasites
Basophils 	12–15	Days	$0.01–0.1 \times 10^{9}$/L	
Lymphocytes  B T	7–9 (resting) 12–20 (active)	Weeks or years	$1.5–3.5 \times 10^{9}$/L	B-cells: immunoglobulin synthesis T-cells: protection against viruses; immune functions

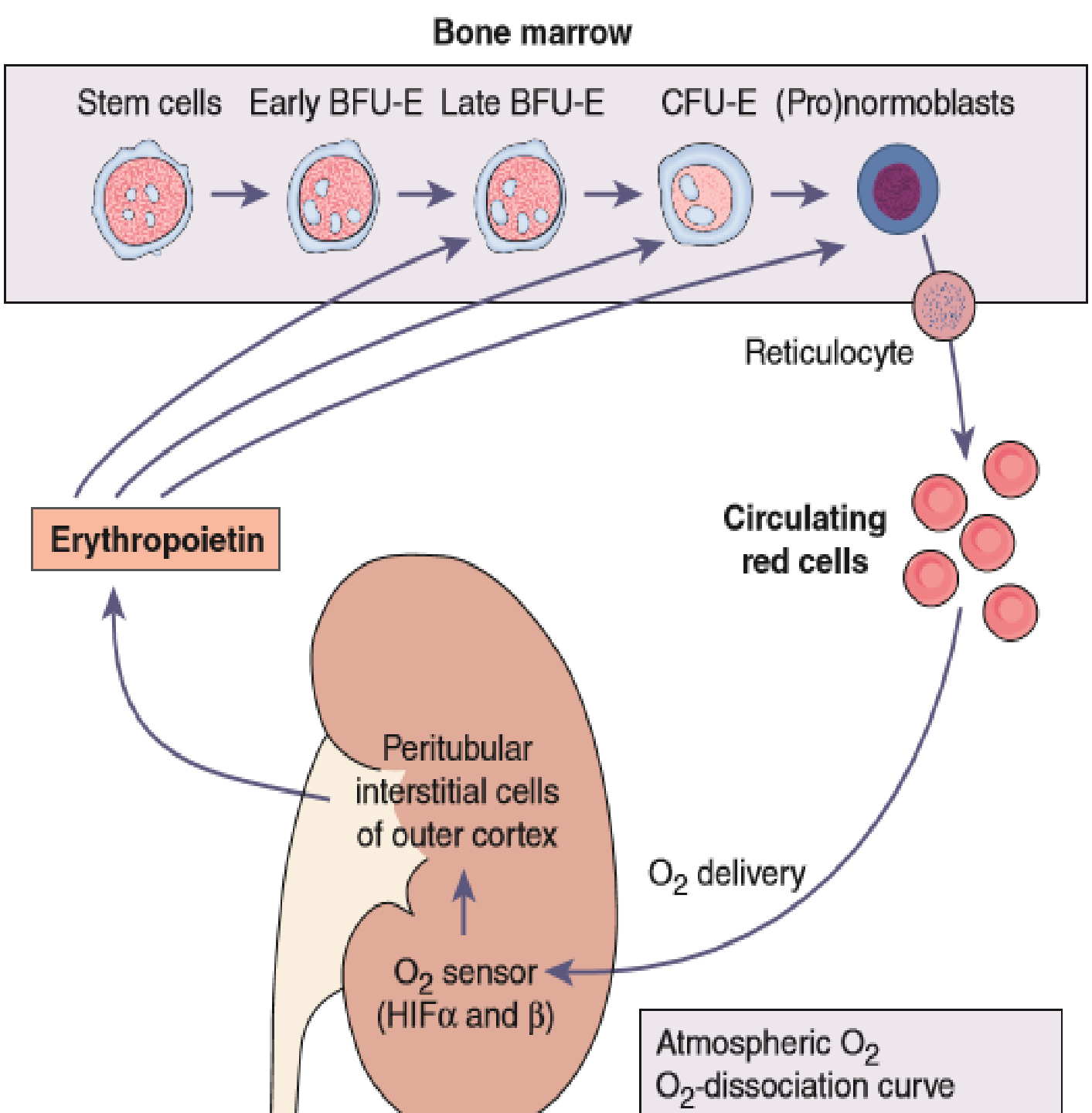


Figure 2.5 The production of erythropoietin by the kidney in response to its oxygen (O_2) supply. Erythropoietin stimulates erythropoiesis and so increases O_2 delivery. BFU_E, erythroid burst-forming unit; CFU_E, erythroid colony-forming unit. Hypoxia induces hypoxia inducible factors (HIFs) α and β, which stimulate erythropoietin production. Von-Hippel–Lindau (VHL) protein breaks down HIFs. PHD2 (prolyl hydroxylase) hydroxylates

Clinical uses of erythropoietin

Anaemia of chronic renal disease
Myelodysplastic syndrome
Anaemia associated with malignancy and chemotherapy
Anaemia of chronic diseases, e.g. rheumatoid arthritis
Anaemia of prematurity
Perioperative uses

Hemoglobin types in adult

	Hb A	Hb F	Hb A_2
Structure	$\alpha_2\beta_2$	$\alpha_2\gamma_2$	$\alpha_2\delta_2$
Normal (%)	96–98	0.5–0.8	1.5–3.2

Functions of the spleen

Hematopoietic function Can produce white cell, red cells, and platelets if necessary

Reservoir function One third of platelets and granulocytes are stored in the spleen

Filtration function Aging red cells are destroyed, spleen removes inclusion from red cells, if red cell membrane is less deformable or antibody-coated spleen presents a hostile environment leading to production of spherocytes

Immunologic function Opsonizing antibodies produced, trapping and processing antigens from encapsulated organs

Normal values using the standard international units

WBC	4.8 to 10.8 × 10^9/L
RBC	Males 4.7 to 6.1 × 10^{12}/L
	Females 4.2 to 5.4 × 10^{12}/L
Hgb	Males 14 to 18 g/dL
	Females 12 to 16 g/dL
Hct	Males 42% to 52%
	Females 37% to 47%
MCV	80 to 100 fL
MCH	27 to 31 pg
MCHC	32% to 36%
RDW	11.5% to 14.5%
Platelet count	150,000 to 350,000 × 10^9/L

Signs & symptoms of anemia linked to their pathophysiolgy

- Decreased oxygen transport leads to fatigue, **dyspnea, angina pectoris,** and syncope
- Decreased blood volume leads to pallor, **postural hypotension**, and shock
- Increased cardiac output leads to **palpitation**, strong pulse, and heart murmurs

CALCULATION OF RETICULOCYTE PRODUCTION INDEX

Correction #1 for Anemia:

This correction produces the corrected reticulocyte count
In a person whose reticulocyte count is 9%, hemoglobin 7.5 g/dL, hematocrit 23%, the absolute reticulocyte count = $9 \times (7.5/15)$ [or $\times (23/45)$]= 4.5%

Correction #2 for Longer Life of Prematurely Released Reticulocytes in the Blood:

This correction produces the reticulocyte production index
In a person whose reticulocyte count is 9%, hemoglobin 7.5 gm/dL, hematocrit 23%, the reticulocyte production index

$$= 9 \times \frac{(7.5/15)(\text{hemoglobin correction})}{2(\text{maturation timecorrection})} = 2.25$$

summary

■ Haemopoiesis (blood cell formation) arises from pluripotent stem cells in the bone marrow.

Stem cells give rise to progenitor cells which, after cell divisions and differentiation, form red cells, granulocytes (neutrophils, eosinophils and basophils), monocytes, platelets and B and T lymphocytes.

■ Haemopoetic tissue occupies about 50% of the marrow space in normal adult marrow. Haemopoiesis in adults is confined to the central skeleton but in infants and young children haemopoietic tissue extends down the long bones of the arms and legs.

■ Stem cells reside in the bone marrow in niches formed by stromal cells and circulate in the blood.

■ Growth factors attach to specific cell receptors and produce a cascade of phosphorylation events to the cell nucleus. Transcription factors carry the message to those genes that are to be ‘switched on,’ to stimulate cell division, differentiation, functional activity or suppress apoptosis.

■ The red cell membrane consists of a lipid bilayer with a membrane skeleton of penetrating and integral proteins and carbohydrate surface antigens.

■ Anaemia is defined as a haemoglobin level in blood below the normal level for age and sex. It is classified according to the size of the red cells into macrocytic, normocytic and microcytic. The reticulocyte count, morphology of the red cells and changes in the white cell and/or platelet count help in the diagnosis of the cause of anaemia.

■ The general clinical features of anaemia include shortness of breath on exertion, pallor of mucous membranes and tachycardia.

■ Other features relate to particular types of anaemia, e.g. jaundice, leg ulcers.

■ Bone marrow examination by aspiration or trephine biopsy may be important in the investigation of anaemia as well as of many other haematological diseases. Special tests, e.g. immunology, cytogenetics, can be performed on the cells obtained