Introduction to Anemia

Asst. Prof. Dr Ramiar Kamal Kheder

Clinical Hematology Theory

Spring Semester

Week 1

Date/31st January 2024

Objectives

1. Explore the various causes of anemia, including nutritional deficiencies, chronic diseases, and genetic factors.
2. Understand the classification of anemia based on morphological and etiological factors.
3. Recognize the signs and symptoms associated with anemia.
4. Discuss the impact of anemia on the overall health and well-being of individuals.

Anemia

This is defined as a reduction in the haemoglobin concentration of the blood below normal for age and sex (Table 2.4).

Typical values would be less than 135g/L in adult males and less than 115g/L in adult females (Fig. 2.13). From the age of 2 years to puberty, less than 110 g/L indicates anaemia. As newborn infants have a high haemoglobin level, 140g/L is taken as the lower limit at birth (Fig. 2.13).

Table 2.4 Normal values for blood cells and haematinics.

	Males	Females
Haemoglobin (g/L)	135.0–175.0	115.0–155.0
Red cells (erythrocytes) ($\times 10^{12}$/L)	4.5–6.5	3.9–5.6
PCV (haematocrit) (%)	40–52	36–48
Mean cell volume (MCV) (fL)	80–95	
Mean cell haemoglobin (MCH) (pg)	27–34	
Reticulocyte count ($\times 10^9$/L)	50–150	
White cells (leucocytes)		
Total ($\times 10^9$/L)	4.0–11.0	
Neutrophils ($\times 10^9$/L)	1.8–7.5	
Lymphocytes ($\times 10^9$/L)	1.5–3.5	
Monocytes ($\times 10^9$/L)	0.2–0.8	
Eosinophils ($\times 10^9$/L)	0.04–0.44	
Basophils ($\times 10^9$/L)	0.01–0.1	
Platelets ($\times 10^9$/L)	150–400	
Serum iron (µmol/L)	10–30	
Total iron-binding capacity (µmol/L)	40–75 (2.0–4.0 g/L as transferrin)	
Serum ferritin**(µg/L)	40–340	14–150
Serum vitamin B_{12}** (ng/L)	160—925 (20–680 pmol/L)	
Serum folate** (µg/L)	3.0–15.0 (4–30 nmol/L)	
Red cell folate** (µg/L)	160–640 (360–1460 nmol/L)	

PCV, packed cell volume.

* Lower limit 1.5×10^9/L in some ethnic groups, e.g. in Middle East and black-skinned people.

* *Normal ranges differ between different laboratories.

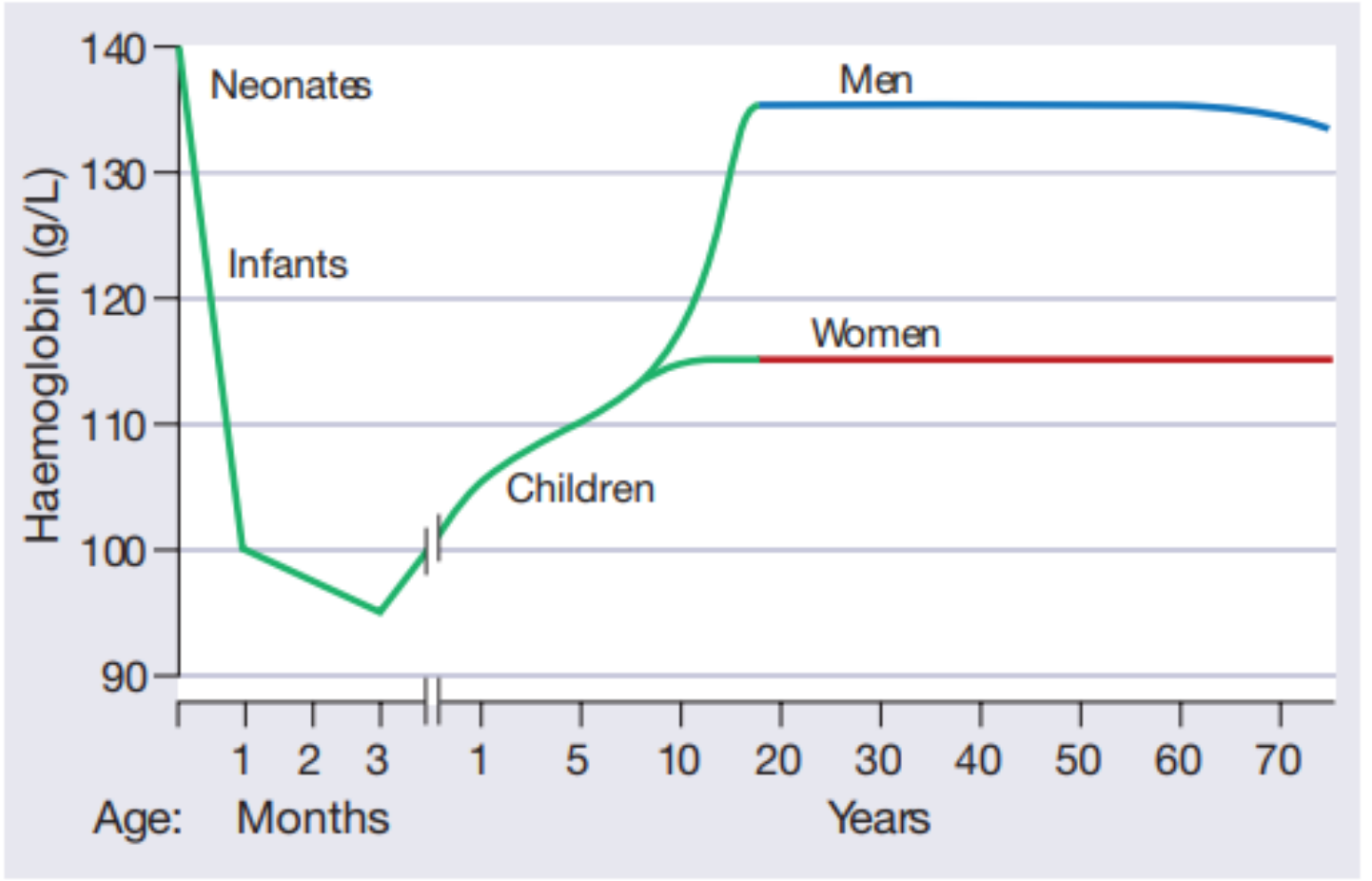


Figure 2.13 The lower limit of normal blood haemoglobin concentration in men, women and children of various ages.

Global incidence

- The WHO defines anaemia in adults as a haemoglobin less than 130g/L in males and less than 120 g/L in females. On this basis, anaemia was estimated in 2010 to occur in about 33% of the global population.
- Prevalence was greater in females than males at all ages and most frequent in children less than 5 years old. Anaemia was most frequent in South Asia, and Central, West and East Sub-Saharan Africa.
- The main causes are **iron deficiency (hookworm, schistosomiasis), sickle cell diseases, thalassaemia, malaria and the anaemia of chronic disorders**.

Clinical features of anaemia

The major adaptations to anaemia are in the cardiovascular system (with increased stroke volume and tachycardia) and in the haemoglobin O2 dissociation curve. In some patients with quite severe anaemia there may be no symptoms or signs, whereas others with mild anaemia may be severely incapacitated. The presence or absence of clinical features can be considered under four major headings.

1.Speed of onset

Rapidly progressive anaemia causes more symptoms than anaemia of slow onset because there is less time for adaptation in the cardiovascular system and in the O2 dissociation curve of haemoglobin.

2.Severity

Mild anaemia often produces no symptoms or signs but these are usually present when the haemoglobin is less than 90 g/L. Even severe anaemia (haemoglobin concentration as low as 60g/L) may produce remarkably few symptoms, when there is very gradual onset in a young subject who is otherwise healthy.

- **3.Age**
- The elderly tolerate anaemia less well than the young because normal cardiovascular compensation is impaired.
- **4. Haemoglobin O2 dissociation curve**
- Anaemia, in general, is associated with a rise in 2,3-DPG in the red cells and a shift in the O2 dissociation curve to the right so that oxygen is given up more readily to tissues. This adaptation is particularly marked in some anaemias that either raise 2,3-DPG directly (e.g. pyruvate kinase deficiency or that are associated with a low-affinity haemoglobin (e.g. Hb S) (see Fig. 2.10).

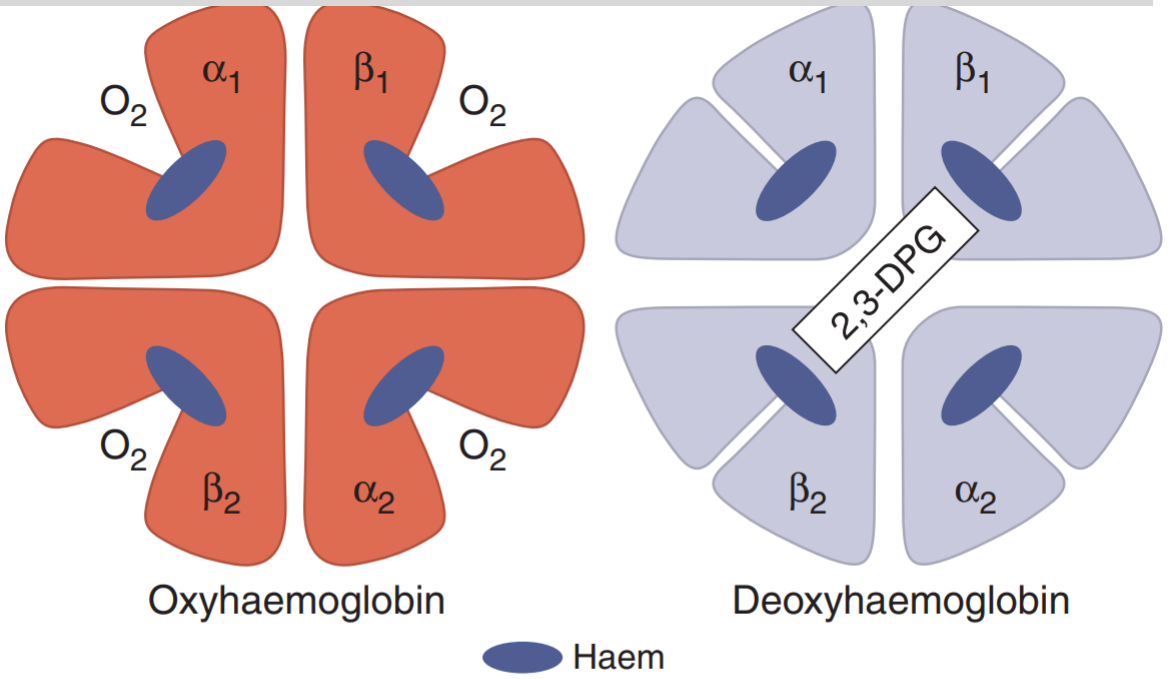


Figure 2.9 The oxygenated and deoxygenated haemoglobin molecule. α, β, globin chains of normal adult haemoglobin (Hb A). 2,3-DPG, 2,3-diphosphoglycerate.

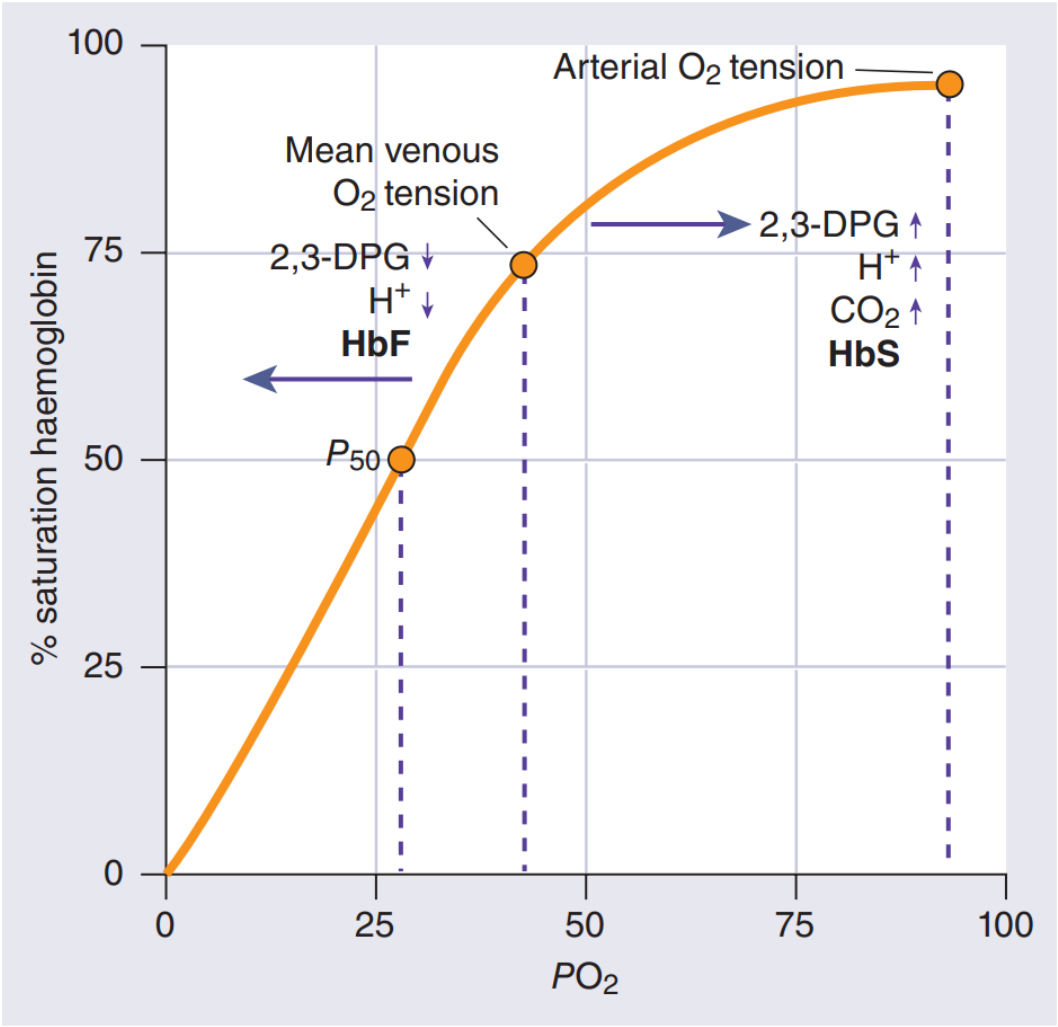


Figure 2.10 The haemoglobin oxygen (O_2) dissociation curve. 2,3-DPG, 2,3-diphosphoglycerate.

Symptoms

- If the patient does have symptoms these are usually shortness of breath, particularly on exertion, weakness, lethargy, palpitation and headaches. In older subjects, symptoms of cardiac failure, angina pectoris or intermittent claudication or confusion may be present. Visual disturbances because of retinal haemorrhages may complicate very severe anaemia, particularly of rapid onset (Fig. 2.14).

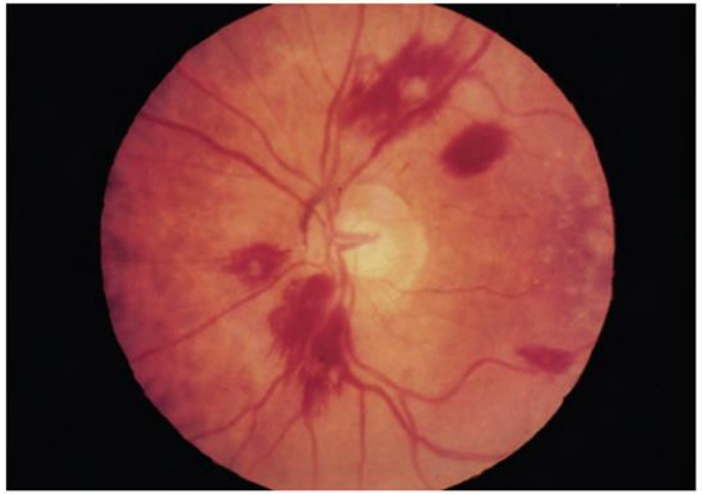
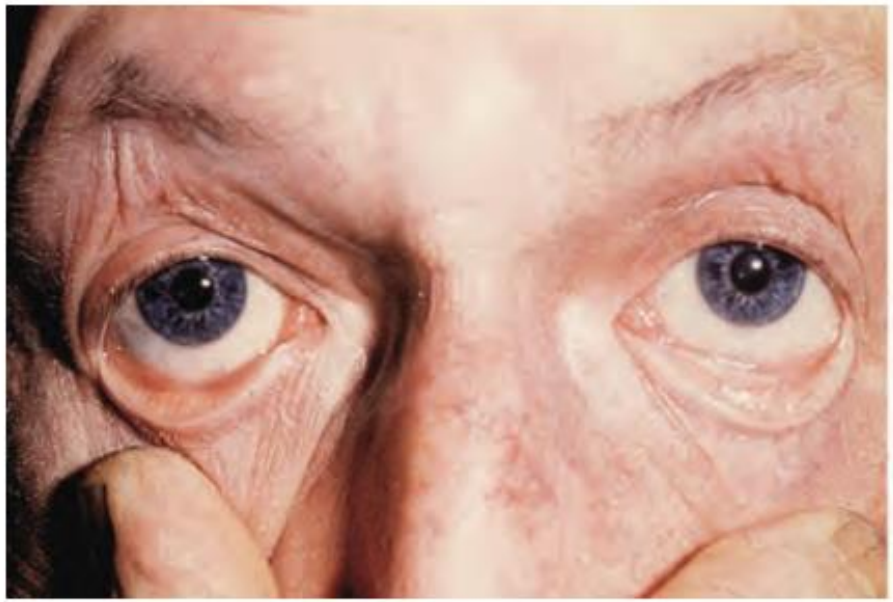


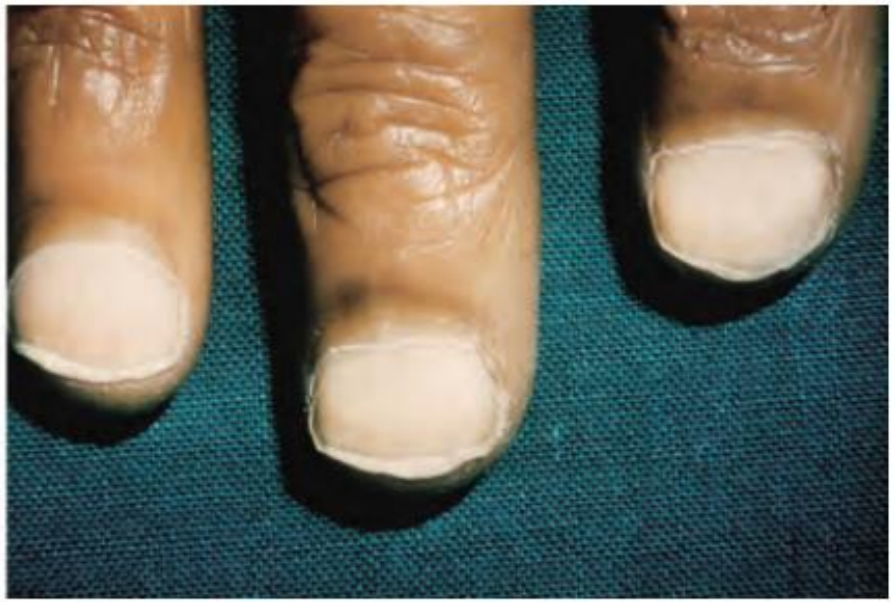
Figure 2.14 Retinal haemorrhages in a patient with severe anaemia (haemoglobin 25 g/L) caused by severe haemorrhage.

Signs

- These may be divided into general and specific. General signs include pallor of mucous membranes or nail beds, which occurs if the haemoglobin level is less than 90g/L (Fig. 2.15). Conversely, skin colour is not a reliable sign.
- A hyperdynamic circulation may be present with tachycardia, a bounding pulse, cardiomegaly and a systolic flow murmur especially at the apex. Particularly in the elderly, features of congestive heart failure may be present



(a)



(b)

Figure 2.15 Pallor of the conjunctival mucosa **(a)** and of the nail bed **(b)** in two patients with severe anaemia (haemoglobin 60 g/L).

- Specific signs are associated with particular types of anaemia, e.g. koilonychia (spoon nails) with iron deficiency, jaundice with haemolytic or megaloblastic anaemias, leg ulcers with sickle cell and other haemolytic anaemias, bone deformities with thalassaemia major.
- The association of features of anaemia with excess infections or spontaneous bruising suggest that neutropenia or thrombocytopenia may be present, possibly as a result of bone marrow failure.

Classification and laboratory findings in anaemia

- **Red cell indices**
- The most useful classification is that based on red cell indices (Table 2.4) and divides the anaemia into microcytic, normocytic and macrocytic (Table 2.5).
- As well as suggesting the nature of the primary defect, this approach may also indicate an underlying abnormality before overt anaemia has developed. In two common physiological situations, the mean corpuscular volume (MCV) may be outside the normal adult range.
- In the newborn for a few weeks the MCV is high but in infancy it is low (e.g. 70 fL at 1 year of age) and rises slowly throughout childhood to the normal adult range.
- In normal pregnancy there is a slight rise in MCV, even in the absence of other causes of macrocytosis (e.g. folate deficiency).

Table 2.5 Classification of anaemia.

Microcytic, hypochromic	Normocytic, normochromic	Macrocytic
MCV <80 fL	MCV 80–95 fL	MCV >95 fL
MCH <27 pg	MCH ≥27 pg	Megaloblastic: vitamin B_{12} or folate deficiency Non-megaloblastic: alcohol, liver disease, myelodysplasia, aplastic anaemia, etc. (see Table 5.10)
Iron deficiency	Many haemolytic anaemias	
Thalassaemia Anaemia of chronic disease (some cases) Lead poisoning Sideroblastic anaemia (some cases)	Anaemia of chronic disease (some cases)	
	After acute blood loss	
	Renal disease	
	Mixed deficiencies	
	Bone marrow failure (e.g. post-chemotherapy, infiltration by carcinoma, etc.)	

MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume.

Other laboratory findings

- Although the red cell indices will indicate the type of anaemia, further useful information can be obtained from the initial blood sample.
- **Leucocyte and platelet counts**
- Measurement of these helps to distinguish ‘pure’ anaemia from ‘pancytopenia’ (subnormal levels of red cells, neutrophils and platelets), which suggests a more general marrow defect or destruction of cells (e.g. hypersplenism).
- In anaemias caused by haemolysis or haemorrhage, the neutrophil and platelet counts are often raised; in infections and leukaemias, the leucocyte count is also often raised and there may be abnormal leucocytes or neutrophil precursors present.

Reticulocyte count

- The normal percentage is 0.5–2.5%, and the absolute count 50–150 × 109 /L (Table 2.4). This should rise in anaemia because of erythropoietin increase, and be higher the more severe the anaemia. This is particularly so when there has been time for erythroid hyperplasia to develop in the marrow as in chronic haemolysis.
- After an acute major haemorrhage there is an erythropoietin response in 6 hours, the reticulocyte count rises within 2–3 days, reaches a maximum in 6–10 days and remains raised until the haemoglobin returns to the normal level.
- If the reticulocyte count is not raised in an anaemic patient this suggests impaired marrow function or lack of erythropoietin stimulus (Table 2.6).

Table 2.6 Factors impairing the normal reticulocyte response to anaemia.
Marrow diseases, e.g. hypoplasia, infiltration by carcinoma, lymphoma, myeloma, acute leukaemia, tuberculosis
Deficiency of iron, vitamin B_{12} or folate
Lack of erythropoietin, e.g. renal disease
Reduced tissue O_2 consumption, e.g. myxoedema, protein deficiency
Ineffective erythropoiesis, e.g. thalassaemia major, megaloblastic anaemia, myelodysplasia, myelofibrosis
Chronic inflammatory or malignant disease

- **Blood film**
- It is essential to examine the blood film in all cases of anaemia. Abnormal red cell morphology (Fig. 2.16) or red cell inclusions
  - (Fig. 2.17) may suggest a particular diagnosis. During the blood film examination, white cell abnormalities are sought, platelet number and morphology are assessed and the presence or absence of abnormal cells (e.g. normoblasts, granulocyte precursors or blast cells) is noted.

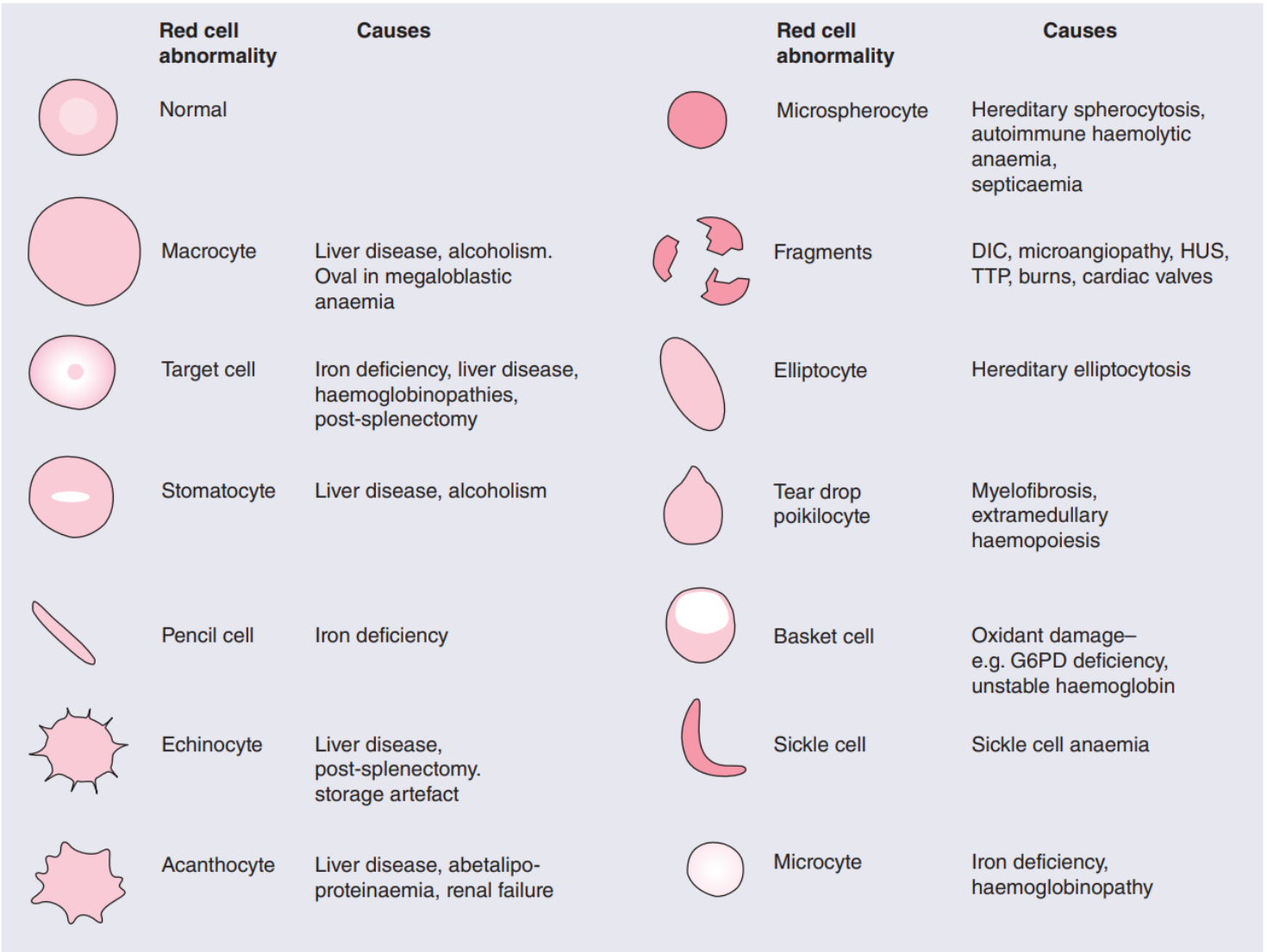


Figure 2.16 Some of the more frequent variations in size (anisocytosis) and shape (poikilocytosis) that may be found in different anaemias. DIC, disseminated intravascular coagulopathy; G6PD, glucose-6-phosphate dehydrogenase; HUS, haemolytic uraemic syndrome; TTP, thrombotic thrombocytopenic purpura.

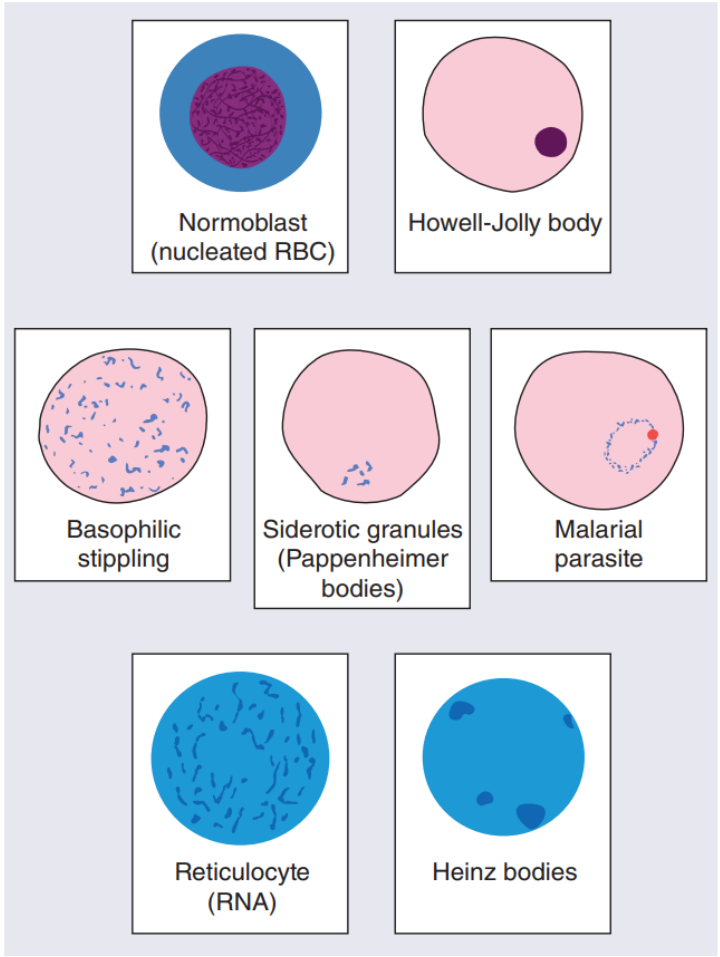


Figure 2.17 Red blood cell (RBC) inclusions which may be seen in the peripheral blood film in various conditions. The reticulocyte RNA and Heinz bodies are only demonstrated by supravital staining (e.g. with new methylene blue). Heinz bodies are oxidized denatured haemoglobin. Siderotic granules (Pappenheimer bodies) contain iron. They are purple on conventional staining but blue with Perls' stain. The Howell–Jolly body is a DNA remnant. Basophilic stippling is denatured RNA.

Common RBC Inclusions	Cartoon Image	Inclusion	May be associated with
Howell Jolly Bodies		DNA	Hyposplenism Asplenism Severe hemolytic anemia
Heinz Bodies	 Supravital stain	Hemoglobin	G6PD deficiency Oxidant drugs Unstable hemoglobin
Pappenheimer Bodies		Iron deposits	Thalassemia Sideroblastic anemia Hemolytic anemia Post-splenectomy
Hemoglobin H Inclusion	 Supravital stain	Hemoglobin	Hemoglobin H disease
Basophilic Stippling		Ribosomes	Lead poisoning Thalassemia Sickle cell anemia MDS

Cabot Ring		Heamoglobin	in patients with pernicious anemia, lead poisoning, certain other disorders of red blood cell production (erythropoiesis).

Conclusion

- 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.