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Hoffbrand’s Essential Haematology

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Cover image: P242/0207. Blood cells, SEM. NATIONAL CANCER INSTITUTE/SCIENCE PHOTO LIBRARY. Blood cells and platelets. Coloured Scanning Electron micrograph (SEM) of human blood showing red and white cells and platelets. Red blood cells (erythrocytes) have a characteristic biconcave-disc shape and are numerous. These large cells contain haemoglobin, a red pigment by which oxygen is transported around the body. They are more numerous than white blood cells (yellow). White blood cells (leucocytes) are rounded cells with microvilli projections from the cell surface. Leucocytes play an important role in the immune response of the body. Platelets are smaller cells (pink) that play a major role in blood clotting.

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Preface to the Seventh Edition

There have been remarkable advances in the understanding of the pathogenesis of diseases of the blood and lymphatic system and in the treatment of these diseases, since the 6th Edition of *Essential Haematology* was published in 2011. This new knowledge is due largely to the application of next generation sequencing of DNA which has enabled the detection of the genetic mutations, inherited or acquired, that underlie these diseases. As examples, sequencing has revealed the *CALR* mutation underlying a substantial proportion of patients with myeloproliferative diseases and the *MYD88* mutation present in almost all cases of Waldenström’s macroglobulinaemia. Multiple ‘driver’ gene mutations affecting signalling pathways and epigenetic reactions involved in cell proliferation and survival have been discovered which underlie myelodysplasia, acute myeloid and lymphoblastic leukaemias, chronic lymphocytic leukaemia and the lymphomas. The complexity of the molecular changes underlying the malignant diseases and the relevance of this to their sensitivity or resistance to therapy is becoming apparent.

This new knowledge has been accompanied by spectacular improvements in therapy. Inhibition of the B cell receptor signalling pathway has transformed the life expectancy in many patients with resistant chronic lymphocytic leukaemia and some of the B cell lymphomas resistant to other therapy. *JAK2* inhibitors are improving the quality of life and survival in primary myelofibrosis. Survival in myeloma is improving remarkably with new proteasome inhibitory and immunomodulatory drugs. Life expectancy has also improved for patients with diseases such as thalassaemia major receiving multiple transfusions with the worldwide introduction of orally active iron chelating agents. New anticoagulants which directly inhibit at a single point in the coagulation cascade and rarely need monitoring are now used commonly in preference to warfarin for the treatment and prevention of arterial and venous thrombosis.

These advances in knowledge have been incorporated as new text, diagrams and tables for this seventh edition. New multiple choice questions have been added to the website and short summary boxes are included at the end of each chapter.

We thank Dr Trevor Baglin for his helpful suggestions for the coagulation section of the book. We wish to thank our publishers Wiley-Blackwell and the staff who have helped us with the production of this 7th Edition. We also thank Jane Fallows for once more producing clear, expertly drawn scientific diagrams. We hope it will be widely used both by undergraduates and by postgraduates in medicine and related sciences wishing to gain a grounding in one of the most exciting and advanced fields of medicine.

Victor Hoffbrand
Paul Moss
Preface to the First Edition

The major changes that have occurred in all fields of medicine over the last decade have been accompanied by an increased understanding of the biochemical, physiological and immunological processes involved in normal blood cell formation and function and the disturbances that may occur in different diseases. At the same time, the range of treatment available for patients with diseases of the blood and blood-forming organs has widened and improved substantially as understanding of the disease processes has increased and new drugs and means of support care have been introduced.

We hope the present book will enable the medical student of the 1980s to grasp the essential features of modern clinical and laboratory haematology and to achieve an understanding of how many of the manifestations of blood diseases can be explained with this new knowledge of the disease processes.

We would like to thank many colleagues and assistants who have helped with the preparation of the book. In particular, Dr H.G. Prentice cared for the patients whose haematological responses are illustrated in Figs 5.3 and 7.8 and Dr J. McLaughlin supplied Fig. 8.6. Dr S. Knowles reviewed critically the final manuscript and made many helpful suggestions. Any remaining errors are, however, our own. We also thank Mr J.B. Irwin and R.W. McPhee who drew many excellent diagrams, Mr Cedric Gilson for expert photomicrography, Mrs T. Charalambos, Mrs B. Elliot, Mrs M. Evans and Miss J. Allaway for typing the manuscript, and Mr Tony Russell of Blackwell Scientific Publications for his invaluable help and patience.

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Features contained within your textbook

CHAPTER 1
Haemopoiesis

Key topics

- Site of haemopoiesis
- Haemopoietic stem and progenitor cells
- Bone marrow stroma
- The regulation of haemopoiesis
- Haemopoietic growth factors
- Growth factor receptors and signal transduction
- Adhesion molecules
- The cell cycle
- Transcription factors
- Epigenetics
- Apoptosis

Every chapter begins with a list of Key topics of the chapter.

Every chapter ends with a Summary that can be used for study and revision purposes.

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.
- Haemopoietic 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 leading 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.

- Adhesion molecules are a large family of glycoproteins that mediate attachment of marrow precursors and mature leukocytes and platelets to extracellular matrix, endothelium and each other.
- Epigenetics refers to changes in DNA and chromatin that affect gene expression other than those that affect DNA sequence. Histone modification and DNA methylation are two important examples relevant to haemopoiesis and haematological malignancies.
- Transcription factors are molecules that bind to DNA and control the transcription of specific genes or gene families.
- Apoptosis is a physiological process of cell death resulting from activation of caspases. The intracellular ratio of pro-apoptotic proteins (e.g. BAX) to anti-apoptotic proteins (e.g. BCL-2) determines the cell susceptibility to apoptosis.

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Differential diagnosis of macrocytic anaemias

Macrocytic anaemias show an increased size of circulating red cells (MCV >105fl). Causes include vitamin B₁₂ (B₁₂, cobalamine) or folate deficiency, alcohol, liver disease, hypothyroidism, myelodysplasia, panhypopituitarism, cyclical drug, aplastic anaemia, pregnancy and the neonatal period.

- B₁₂ or folate deficiency causes megaloblastic anaemia, in which the bone marrow erythroblasts have a typical abnormal appearance.
- Thalassaemia trait in haemoglobin variants in DNA synthesis B₁₂ has an indirect role by its involvement in DNA methylation.
- B₁₂ deficiency may also cause a neuropathy due to damage to the spinal cord and peripheral nerves.
- B₁₂ deficiency is usually caused by B₁₂ malabsorption brought about by pernicious anaemia in which there is autoimmune gastritis, resulting in severe deficiency of intrinsic factor, a glycoprotein made in the stomach which facilitates B₁₂ absorption by the ileum.
- Other gastrointestinal diseases as well as a vegan diet may cause B₁₂ deficiency.
- Thalassaemia trait can be caused by a poor diet, malabsorption (e.g. celiac-induced enteropathy) or excessive cell turnover (e.g. pregnancy, haemolysis, malignancy).
- Haemolytic anaemias are usually caused by lymphocytic or bile duct deficiency with oral iron deficiency.
- Rare causes of megaloblastic anaemia include intermural B₁₂ or folate transport or metabolism, and defects of DNA synthesis not related to B₁₂ or folic acid.

The laboratory features of particular importance are the shape of megaloblasts typical of megaloblastic anaemia, the presence of hyposegmented neutrophils, of lymphocytes and plasmacytosis in megaloblastic anaemia, and the bone marrow appearance. Access of serum B₁₂ and folate is essential. Echocardiography (particularly if the patient is not anaemic), liver and thyroid function tests, and bone marrow examinations for myelodysplasia, aplasia or disarray are important in the investigation of megaloblastic anaemia not caused by B₁₂ or folic acid deficiency.
About the companion website

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- Interactive multiple choice questions
- Figures and tables from the book

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CHAPTER 1

Haemopoiesis

Key topics

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This first chapter is concerned with the general aspects of blood cell formation (haemopoiesis). The processes that regulate haemopoiesis and the early stages of formation of red cells (erythropoiesis), granulocytes and monocytes (myelopoiesis) and platelets (thrombopoiesis) are also discussed.

### 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 (Table 1.1; see Fig. 7.1b). 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 (Table 1.1). Even in these haemopoietic areas, approximately 50% of the marrow consists of fat (Fig. 1.1). 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’).

### Haemopoietic stem and progenitor cells

Haemopoiesis starts with a pluripotent stem cell that can by asymmetric cell division self-renew but also give rise to the separate cell lineages. These cells are able to repopulate a bone marrow from which all stem cells have been eliminated by lethal irradiation or chemotherapy. This haemopoietic stem cell (HSC) is rare, perhaps 1 in every 20 million nucleated cells in bone marrow. Many of the cells are dormant and in mice it has been estimated that they enter cell cycle approximately every 20 weeks. Although its exact phenotype is unknown, on immunological testing the HSC is CD34+ CD38− and negative for lineage markers (Lin−) and has the appearance of a small or medium-sized lymphocyte (see Fig. 23.3). The cells reside in specialized osteoblastic or vascular ‘niches’.

Cell differentiation occurs from the stem cell via committed haemopoietic progenitors which are restricted in their developmental potential (Fig. 1.2). The existence of the separate progenitor cells can be demonstrated by in vitro culture techniques. Very early progenitors are assayed by culture on bone marrow stroma as long-term culture initiating cells, whereas late progenitors are generally assayed in semi-solid media. An example is the earliest detectable mixed myeloid precursor which gives rise to granulocytes, erythrocytes, monocytes and megakaryocytes and is termed CFU (colony-forming unit)-GEMM (Fig. 1.2). The bone marrow is also the primary site of origin of lymphocytes, which differentiate from a common lymphoid precursor. The spleen, lymph nodes and thymus are secondary sites of lymphocyte production (see Chapter 9).

The stem cell has the capability for self-renewal (Fig. 1.3) so that marrow cellularity remains constant in a normal healthy steady state. There is considerable amplification in the system: one stem cell is capable of producing about 10⁶ mature blood cells after 20 cell divisions (Fig. 1.3). In humans HSCs are capable of about 50 cell divisions, telomere shortening affecting viability. Under normal conditions most are dormant. With aging, the number of stem cells falls and the relative proportion giving rise to lymphoid rather than myeloid progenitors also falls. Stem cells also accumulate genetic mutations with age, an average of 8 at age 60, and these, either passenger or driver, may be present in tumours arising from these stem cells (see Chapter 11). The precursor cells are capable of responding to haemopoietic growth factors with increased production of one

### Table 1.1 Sites of haemopoiesis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetus</td>
<td>0–2 months (yolk sac)</td>
</tr>
<tr>
<td></td>
<td>2–7 months (liver, spleen)</td>
</tr>
<tr>
<td></td>
<td>5–9 months (bone marrow)</td>
</tr>
<tr>
<td>Infants</td>
<td>Bone marrow (practically all bones)</td>
</tr>
<tr>
<td>Adults</td>
<td>Vertebrae, ribs, sternum, skull, sacrum and pelvis, proximal ends of femur</td>
</tr>
</tbody>
</table>
Chapter 1: Haemopoiesis

Figure 1.2 Diagrammatic representation of the bone marrow pluripotent stem cell and the cell lines that arise from it. Various progenitor cells can be identified by culture in semi-solid medium by the type of colony they form. It is possible that an erythroid/megakaryocytic progenitor may be formed before the common lymphoid progenitor diverges from the mixed granulocytic/monocyte/eosinophil myeloid progenitor. Baso, basophil; BFU, burst-forming unit; CFU, colony-forming unit; E, erythroid; Eo, eosinophil; GEMM, granulocyte, erythroid, monocyte and megakaryocyte; GM, granulocyte, monocyte; Meg, megakaryocyte; NK, natural killer.

Figure 1.3 (a) Bone marrow cells are increasingly differentiated and lose the capacity for self-renewal as they mature. (b) A single stem cell gives rise, after multiple cell divisions (shown by vertical lines), to >10^6 mature cells.