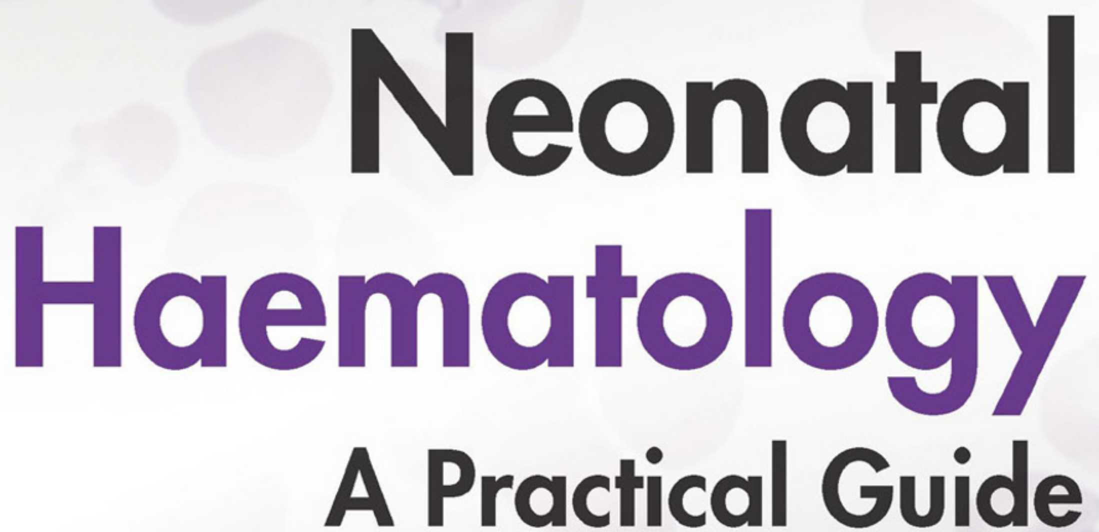
Neonatal Haematology

A Practical Guide



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This edition first published 2022
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Library of Congress Cataloging-in-Publication Data applied for

Hardback ISBN: 9781119371588

Cover Design: Wiley
Cover Image: Courtesy of Irene Roberts

Set in 9.5/12.5pt STIXTwoText by Straive, Pondicherry, India

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Preface

This neonatal haematology guide aims to fill a gap in an important, but often poorly understood, area of diagnostic haematology by focusing particularly on common blood problems in this unique group of patients, although not neglecting the rarities that can also be important. We specifically chose to use a text-atlas format because the starting point for so many haematological problems in neonates is the information to be found through careful evaluation of a blood film in conjunction with an automated blood count. Given that many neonates with haematological abnormalities weigh less than 1000 g at birth and have an estimated blood volume at birth of 40–80 ml with very precarious vascular access, there is huge practical value in being able to extract the maximum amount of diagnostic information from a single drop of blood.

The book has been organised into four chapters based on the most frequently occurring clinical problems: interpretation of normal results and blood film appearances (Chapter 1); anaemias and haematological causes of jaundice (Chapter 2); diagnosis of systemic disorders, such as infection, and less common leucocyte disorders, such as leukaemia and storage disorders (Chapter 3); and disorders of coagulation and thrombosis, including common causes of thrombocytopenia and their investigation (Chapter 4). We hope that this handbook will be a core resource for haematologists on call in any hospital with a maternity unit who may not be neonatal experts, and that it will act as a core text for neonatal and paediatric haematologists. It is very much aimed to be a practical resource, based on real-life experience of neonatal haematology in large teaching hospitals and contains algorithms, tables and illustrative cases with full colour images. While the focus is on common problems, we also describe when to look for, and how to spot, rare haematological disorders presenting in the neonatal period.

Almost all the images and cases described in this book derive from more than 25 years' experience as a 'neonatal haematologist', which involved daily examination of blood films from neonates in a number of neonatal intensive care units and special care baby units and daily conversations with the clinical teams responsible for their care. This was only possible with the support, open-mindedness and enthusiasm of the neonatalogists on the one hand and the dedication and rigour of the highly skilled biomedical scientists of the diagnostic haematology labs on the other. Particular thanks go to David Roper, Andrew Osei-Bimpong and the late Corinne Jury of the Hammersmith and Queen Charlotte's Hospitals Haematology Laboratories, who made possible the delivery of a daily 'baby films' service in the face of increasing NHS demands; to David Roper and the late Dr David Swirsky, former consultant

haematologist at Hammersmith Hospital, for their help with the photomicrographs in the earliest years of the neonatal haematology service; to countless biomedical scientists whose pride in delivering the highest quality 'baby films' on a daily basis was an inspiration to me; to paediatric haematology colleagues in London and Oxford who posed fascinating questions to keep me on my toes; and to the long-suffering haematology trainees who usually managed to look interested in this niche subject and helped to deliver the clinical advice.

This book would never have been written without the help and support of a number of other people. Above all, I am hugely indebted to my co-author, Professor Barbara Bain. She brought to the book her 50 years' experience of diagnostic haematology. Her expertise, experience, diligence and patience, as well as her friendly advice, were invaluable. I am similarly hugely grateful to Mandy Collison at Wiley who never gave up on the project despite repeated delays on my part. Finally, I have to thank my family (Allan, Duncan and Ewan), who accepted the neonatal haematology geek in their midst, and supported the whole project from the beginning.

Irene Roberts

Abbreviations

2,3-DPG	2,3-diphosphoglycerate
ADA	adenosine deaminase
ADP	adenosine diphosphate
AGM	aorto-gonado-mesonephros
aHUS	atypical haemolytic uraemic syndrome
AIHA	autoimmune haemolytic anaemia
ALL	acute lymphoblastic leukaemia
ALPS	autoimmune lymphoproliferative syndrome
AML	acute myeloid leukaemia
APTT	activated partial thromboplastin time
ATD	asphyxiating thoracic dystrophy
ATRUS	amegakaryocytic thrombocytopenia and radio-ulnar synostosis
BCG	bacille Calmette–Guérin
BCSH	British Committee for Standards in Haematology
BHFS	Bart's hydrops fetalis syndrome
BPI	bactericidal/permeability-increasing protein
BSS	Bernard–Soulier syndrome
CAMT	congenital amegakaryocytic thrombocytopenia
CDA	congenital dyserythropoietic anaemia
CHS	Chédiak–Higashi syndrome
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 19
DAT	direct antiglobulin test
DBA	Diamond–Blackfan anaemia
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
ECMO	extracorporeal membrane oxygenation
EDTA	ethylene diaminetetra-acetic acid
ELP	early lymphoid progenitor
EMA	eosin-5-maleimide
EOS	early-onset sepsis

EPO	erythropoietin
ERFE	erythroferrone
FFP	fresh frozen plasma
FNAIT	fetal/neonatal alloimmune thrombocytopenia
FPD/AML	familial platelet disorder with propensity to acute myeloid leukaemia
FRC	fragmented red cell
G6PD	glucose-6-phosphate dehydrogenase
G6PT1	glucose-6-phosphate transporter 1
G-CSF	granulocyte colony-stimulating factor
Gp	glycoprotein
GPI	glucose phosphate isomerase
Hb	haemoglobin concentration
HDFN	haemolytic disease of the fetus and newborn
HELLP	haemolysis, elevated liver enzymes and low platelets
HIE	hypoxic ischaemic encephalopathy
HIV	human immunodeficiency virus
HK	hexokinase
HLH	haemophagocytic lymphohistiocytosis
HNA	human neutrophil antigen
HPA	human platelet antigen
HPFH	hereditary persistence of fetal haemoglobin
HPLC	high performance liquid chromatography
HPP	hereditary pyropoikilocytosis
HS	hereditary spherocytosis
HSC	haemopoietic stem cell
HUS	haemolytic uraemic syndrome
IBMFS	inherited bone marrow failure syndromes
ICH	intracranial haemorrhage
IG%	immature granulocyte percentage
IGF	insulin-like growth factor
IgG	immunoglobulin G
IgH	immunoglobulin heavy chain
IgM	immunoglobulin M
IL-6	interleukin-6
IPF	immature platelet fraction
IRF	interferon regulatory factor
ITP	autoimmune thrombocytopenia
IUGR	intrauterine growth restriction
IUT	intrauterine transfusion
IVH	intraventricular haemorrhage
IVIg	intravenous immunoglobulin
JAK2	Janus kinase 2
JMML	juvenile myelomonocytic leukaemia
KHE	Kaposiform haemangioendothelioma
KMP	Kasabach–Merritt phenomenon

LAD	leucocyte adhesion deficiency
LDH	lactate dehydrogenase
LOS	late-onset sepsis
MAHA	microangiopathic haemolytic anaemia
MAIPA	monoclonal antibody-specific immobilisation of platelet antigens
MCA	middle cerebral artery
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
MDSC	myeloid-derived suppressor cell
ML-DS	myeloid leukaemia of Down syndrome
MPAL	mixed phenotype acute leukaemia
MPV	mean platelet volume
NA	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NEC	necrotising enterocolitis
NETs	neutrophil extracellular traps
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
NLR	neonatal leukaemoid reaction
NRBC	nucleated red blood cell
NS/MPD	Noonan syndrome-associated myeloproliferative disorder
PCC	prothrombin complex concentrate
PCR	polymerase chain reaction
PFK	phosphofructokinase
PGK	phosphoglycerate kinase
PK	pyruvate kinase
PMN	polymorphonuclear
PT	prothrombin time
RNA	ribonucleic acid
RP	ribosomal proteins
RSV	respiratory syncytial virus
RUSAT1	radio-ulnar synostosis with amegakaryocytic thrombocytopenia
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SCN	severe congenital neutropenia
SGA	small for gestational age
SIFD	sideroblastic anaemia, B-cell immunodeficiency, periodic fevers, and developmental delay
SLE	systemic lupus erythematosus
TACO	transfusion-associated circulatory overload
TA-GvHD	transfusion-associated graft-versus-host disease
TAM	transient abnormal myelopoiesis
TAPS	twin anaemia–polycythaemia sequence
TAR	thrombocytopenia with absent radii
TGFβ	transforming growth factor β

TOPs	Transfusion of Prematures trial
TPI	triosephosphate isomerase
TPO	thrombopoietin
TRALI	transfusion-related acute lung injury
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
TTTS	twin-to-twin transfusion syndrome
VKDB	vitamin K-dependent bleeding
VWD	von Willebrand disease
VWF	von Willebrand factor
WBC	white cell count
WHO	World Health Organization
XLSA	X-linked sideroblastic anaemia
XLT	X-linked thrombocytopenia

1

The full blood count and blood film in healthy term and preterm neonates

Introduction

Haemopoiesis is the process that ensures life-long production of haemopoietic cells. In newborn infants the process has many distinct features that differ from those in older children and adults. These differences reflect both the ontogeny of haemopoiesis during fetal development and the unique interaction between the fetus and mother, as well as the effects of birth itself. The sequential changes in the sites and regulation of haemopoiesis during development also help to explain the natural history of many neonatal haematological problems.

Brief outline of the ontogeny of haemopoiesis

Haemopoiesis in humans begins in the yolk sac between 2 and 3 weeks post-conception (Fig. 1.1).[1,2] This is known as primitive haemopoiesis. Studies in other species, particularly in mice, indicate that the predominant cell types produced in the yolk sac are erythroid cells and macrophages.[2,3] While megakaryocytes and lymphoid cells may also be yolk sac-derived, the current consensus of opinion is that true, long-lived haemopoietic stem cells (HSC) arise from a region of specialised endothelium ('haemogenic' endothelium), which is localised to the ventral wall of the dorsal aorta in a region known as the aorto-gonado-mesonephros (AGM).[4–6] In humans, haemopoiesis begins in the AGM at around 5 weeks post-conception and is known as definitive haemopoiesis.[6–8] Haemopoiesis in the aortic wall is only transient, presumably because this region lacks the necessary physical space and specialised microenvironment to support expansion and differentiation of the HSC and progenitor populations required to meet the needs of the growing fetus.

By 6 weeks post-conception, HSC and progenitor cells have migrated to the fetal liver,[8,9] which remains the main site of blood cell production throughout fetal life[10,11] and AGM haemopoiesis ceases. The first signs of haemopoiesis in the bone marrow are evident from around 11 weeks post-conception.[8,12] Although fetal bone marrow is able to give rise to cells of all lineages, it is becoming clear that the predominant cell types produced in the bone marrow are B lymphocytes and their progenitor cells together with granulocytes, monocytes and their progenitors. Although erythropoiesis and megakaryopoiesis take

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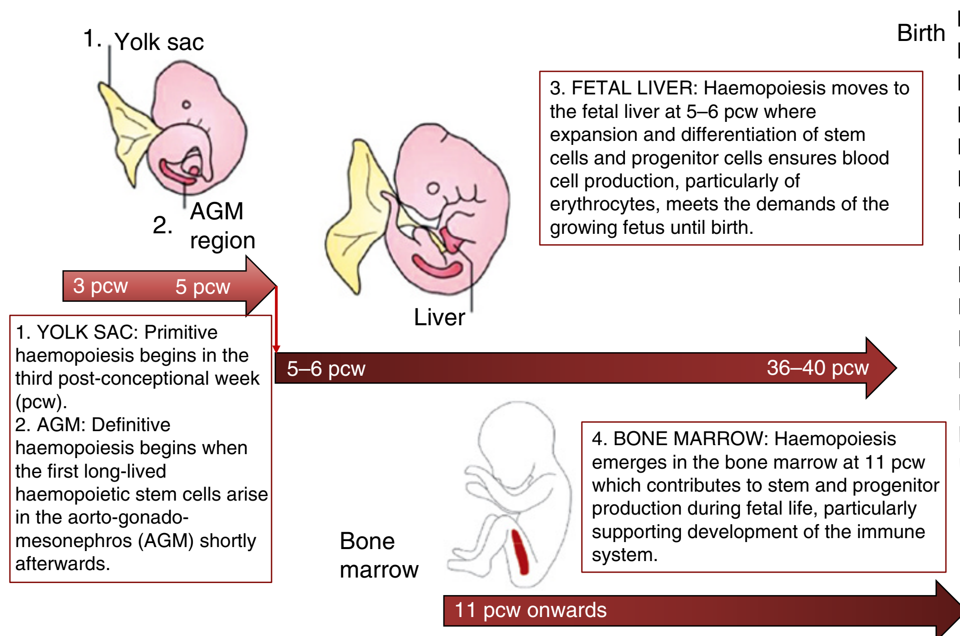

Fig. 1.1 Ontogeny of human haemopoiesis in embryonic and fetal life. AGM, aorto-gonado-mesonephros; pcw, post-conceptional week. Based on references 1 and 2.

place in the fetal bone marrow from the end of the first trimester, most red blood cell and megakaryocyte production takes place in the fetal liver until shortly before term.[8] Thus, for preterm infants, the liver is the main haemopoietic organ at and shortly after birth; this is likely to be a contributory factor in a number of disorders, including the haematological abnormalities seen in neonates with Down syndrome (see pages 154–160 and 206).

Properties of fetal haemopoietic stem and progenitor cells

Major advances in the immunological and molecular tools available to analyse haemopoietic stem and progenitor cells have allowed us to build up a much clearer picture of the process of haemopoiesis in fetal life and how this differs from adult life. Fetal HSC, like adult HSC, are the cells at the top of the haemopoietic hierarchy (Fig. 1.2). When HSC divide, they do so either through a process of 'self-renewal', where they generate more HSC (sometimes referred to 'symmetric cell division'), or through asymmetric division during which one of the two daughter cells differentiates into progenitor cells, which in turn generate the mature cells of all the haemopoietic lineages (Fig. 1.2).[9]

Fetal haemopoietic stem cells

Studies in mice, and more recently in humans, indicate that fetal HSC are markedly different from those in adult bone marrow.[9,13–16] Elucidating the nature of the differences between fetal and adult HSC, and the molecular mechanisms that underpin these differences, is likely to help our understanding of many of the haematological problems that

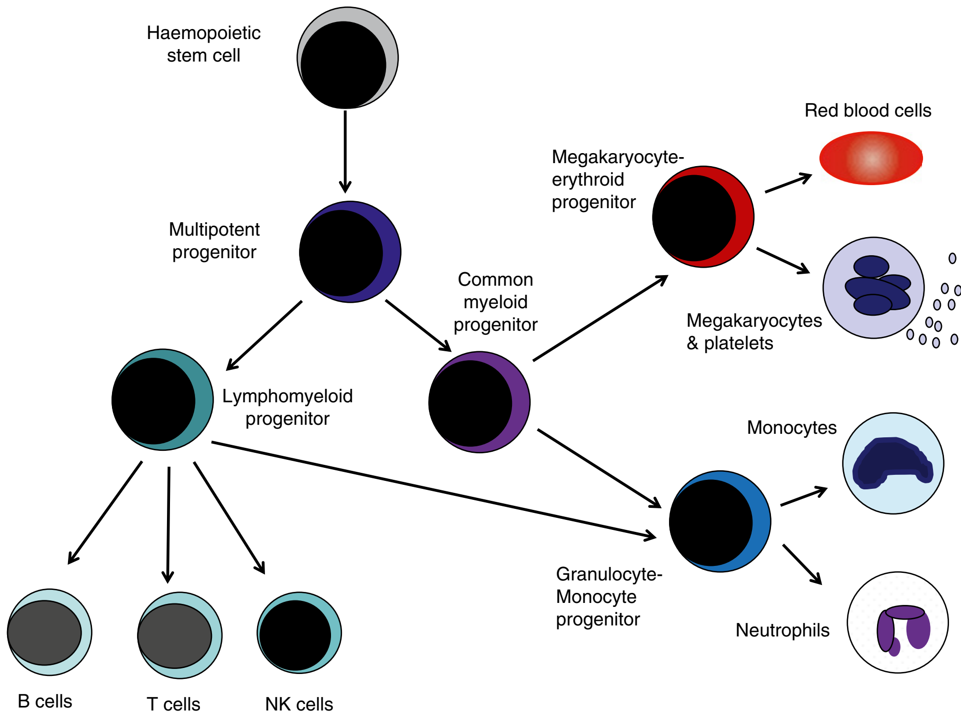

Fig. 1.2 A simplified scheme of the fetal haemopoietic stem and progenitor cell hierarchy showing the differentiation of multipotent and committed progenitor cells from haemopoietic stem cells. Details of the fetal-specific pathway of B lineage progenitor differentiation are shown in Fig. 1.3. Based on reference 9.

affect neonates and potentially open up new approaches to treatment. For example, the need for rapid expansion of haemopoietic cells to meet the needs of the growing fetus means that the numbers of fetal HSC have to increase more rapidly than at any other time of life. Furthermore, since HSC are responsible for life-long haemopoiesis, this process of HSC expansion needs to be precisely regulated to prevent either uncontrolled proliferation (and the risk of haematological malignancy) on the one hand or HSC 'exhaustion' (and the risk of bone marrow failure) on the other. These properties are thought to underlie the particular prevalence of certain haematological diseases in fetal and neonatal life, including Diamond–Blackfan anaemia and juvenile myelomonocytic leukaemia.[17]

There are differences both in the intrinsic properties of the HSC and in the regulatory signals produced by the haemopoietic microenvironment during fetal life.[16] One of the characteristic intrinsic differences in fetal HSC is the increased proportion of HSC that are actively cycling and undergoing a process of 'self-renewal' that results in expansion of the pool of long-lived HSC in fetal life.[18] This behaviour of fetal HSC contrasts dramatically with adult HSC which are largely quiescent cells that enter the cell cycle infrequently.[9,16,18] The amplification in fetal HSC numbers probably takes place mainly in fetal liver rather than in the bone marrow,[16,19] which may explain why so many haematological disorders in

neonates are accompanied by hepatomegaly. A second characteristic of fetal HSC is that they are primed to give rise to a higher proportion of erythroid and megakaryocytic progenitors compared with adult HSC, reflecting the requirement of the fetus for large numbers of red blood cells and the importance of adequate numbers of platelets to maintain vascular integrity.[9,17] Finally, fetal HSC exhibit different sensitivity to and dependence upon haemopoietic growth factors, such as insulin-like growth factors, compared with adult cells[20,21] and a different pattern of mature cell output.[9,16,18] Reflecting this, fetal HSC also have unique gene expression programmes,[13,15–17,22–26] which have recently been shown to be important in the leukaemic transformation events that lead to infant acute lymphoblastic leukaemia (ALL).[27]

Fetal haemopoietic progenitor cells

The different types of haemopoietic progenitor cell present in fetal life are shown in Figs 1.2 and 1.3. The overall scheme of differentiation of HSC is similar in fetal and adult life. However, recent studies have identified fetal-specific lymphoid progenitors, including early lymphoid progenitors (ELP) and PreProB progenitors that may be important not only to rapidly boost B cell production during the second trimester, but also to act as targets of leukaemic transformation in infant and childhood ALL.[9,27–29] ELP are found very early in fetal life (from around 6 weeks post-conception in the fetal liver and from around 11 weeks post-conception in bone marrow) but are very rare in adult haemopoietic tissues.[29] They are defined both by their immunophenotype ($CD34^+CD127^+CD19^-CD10^-$) and their ability to generate B, T and NK cells as well as a small number of myeloid cells.[8,29] PreProB progenitors are one of two types of committed B progenitor cell in fetal life; they lack expression of the CD10 molecule and, like ELP, are very rare in adult bone marrow. By contrast, the second type of B progenitor, the ProB progenitor, is $CD10^+$ and is the main, or sole, type of B progenitor found in adult bone marrow.[29] It is likely that ProB progenitors lie downstream of PreProB in B lymphoid differentiation and, consistent with this, they have been shown to have undergone complete V_H-D_H-J_H rearrangement of their immunoglobulin heavy chain (IgH) loci, in contrast to ELP and PreProB progenitors, which show only

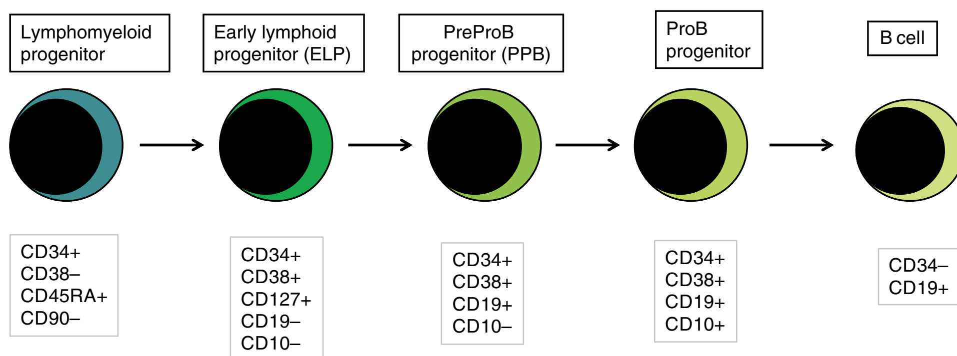

Fig. 1.3 Immunophenotypically defined progenitor populations along the B cell differentiation trajectory in the human fetus. The cell surface markers used to define these populations are shown below each cell type. Based on reference 9.

partial (D_H-J_H) IgH rearrangement.[8] The reasons for the existence of two types of B progenitor and a unique ELP cell in fetal life are unknown but it suggests that there are two pathways of fetal B cell production which may have different physiological roles.

Red blood cell production and development in the fetus and neonate

Normal erythropoiesis, the production of red blood cells, is crucial to early embryonic and fetal development. Most of our knowledge about the cells and genes involved in this process derives either from mouse models or from inherited anaemias, particularly in children. Almost all the characteristic features of red blood cells are different in the fetus and the newborn compared with their adult counterparts. These differences are even greater in preterm neonates and are directly relevant to our understanding of neonatal anaemias. The differences in erythropoiesis during fetal development are summarised in Table 1.1 and those that are important for our understanding of neonatal anaemias are discussed below.

Table 1.1 Features of fetal and neonatal red cells compared with adult red cells

Haemoglobin production	Embryonic haemoglobins (globin chains)
	Gower 1 ($\zeta_2\varepsilon_2$)
	Gower 2 ($\alpha_2\varepsilon_2$)
	Portland ($\zeta_2\gamma_2$)
	Fetal haemoglobin (globin chains)
	Fetal haemoglobin ($\alpha_2\gamma_2$)
	Adult haemoglobins (globin chains)
	Haemoglobin A ($\alpha_2\beta_2$) lower
	Haemoglobin A_2 ($\alpha_2\delta_2$) considerably lower
Red cell membrane	Gives resistance to osmotic lysis
	Altered expression of receptors (e.g. insulin)
	Increased lipid content and altered phospholipid profile
	More prone to oxidative damage
	Altered glucose transport
	Weak expression of A, B and I blood group antigens
	Increased variation in red cell shape (poikilocytosis)
	Red cell 'pocks' due to hyposplenism
Red cell metabolism	Glycolytic pathway
	Increased glucose consumption
	Altered enzyme levels, e.g. low 2,3-DPG and PFK
	Pentose phosphate pathway
	Increased susceptibility to oxidant-induced injury
	Lower level of glutathione peroxidase
	Reduced ability to generate NADPH

2,3-DPG, 2,3-diphosphoglycerate; NADPH, nicotinamide adenine dinucleotide phosphate; PFK, phosphofructokinase.

Erythropoietin production in the fetus and neonate

The principal cytokine responsible for regulating erythropoiesis in the fetus and newborn, as in adults, is erythropoietin (EPO).[30] Since EPO does not cross the placenta, EPO-mediated regulation of fetal erythropoiesis is predominantly under fetal control. The liver is the main site of EPO production in the fetus[31] and the only stimulus to production under physiological conditions is hypoxia with or without anaemia (reviewed in reference 32). Little or no EPO is produced under normoxic conditions, but hypoxia very rapidly triggers expression by up to 200-fold within 30 minutes, at least in hepatocyte cell lines.[33] This explains the high EPO levels in fetuses of mothers with diabetes mellitus or hypertension and in those with intrauterine growth restriction (IUGR) or cyanotic congenital heart disease;[34] EPO is also increased in fetal anaemia of any cause, including haemolytic disease of the fetus and newborn (HDFN). This, and the switch of EPO production from fetal liver to the neonatal kidney, may in part explain the physiological delay in triggering the production of new red blood cells, which is often not evident until the second month of life, even in healthy babies.

Haemoglobin synthesis and red blood cell production in the fetus and newborn

The rates of haemoglobin synthesis and red blood cell production fall dramatically immediately after birth and remain low for the first 2 weeks of life, probably in response to the sudden increase in tissue oxygenation at birth.[35] In healthy neonates the physiological rise in red cell production starts several weeks later, so that by 3 months of age a healthy infant, whatever the period of gestation at birth, should be able to produce up to 2 ml of packed red blood cells every day.[35] Studies in preterm neonates have estimated that over the first 2 months of life the maximal rate of red blood cell production may be closer to 1 ml/day. This is based on the observation that preterm babies receiving therapeutic EPO are unable to maintain their haemoglobin if more than 1 ml of blood per day is venesected for diagnostic purposes but can do so where sampling losses are less than this.[36]

The gestation-related changes in globin chain synthesis in the human embryo, fetus and neonate have been studied in detail and are summarised in Fig. 1.4.[37] The first haemoglobins, known as embryonic haemoglobins, are synthesised from approximately 2 or 3 weeks post-conception, predominantly in the blood islands of the yolk sac, by the erythroblasts and red blood cells generated there. There are three embryonic haemoglobins (see Table 1.1). ζ or α globin, encoded by adjacent genes in the α globin locus on chromosome 16, combine with ε or γ globin, encoded by genes in the β globin locus on chromosome 11, to produce haemoglobin Gower 1 ($\zeta_2\varepsilon_2$), haemoglobin Gower 2 ($\alpha_2\varepsilon_2$) and haemoglobin Portland ($\zeta_2\gamma_2$).

During normal human development, synthesis of embryonic haemoglobins is transient and largely restricted to yolk sac-derived erythroblasts which are larger than those generated once definitive haemopoiesis starts in the AGM and fetal liver (Figs 1.5 and 1.6) and express different transcription factor and epigenetic programmes. From 4 or 5 weeks post-conception, erythroblasts and red blood cells contain mainly haemoglobin F ($\alpha_2\gamma_2$), which remains the principal haemoglobin throughout fetal life. The factors that control the switch

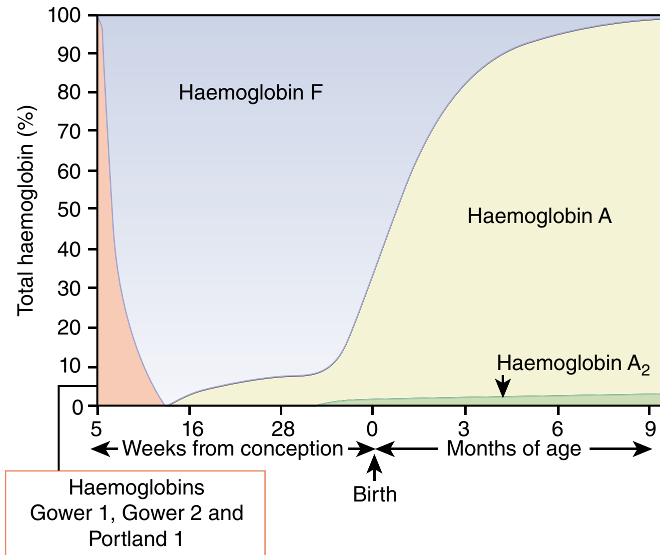

Fig. 1.4 Diagrammatic representation of the sites and rates of synthesis of different haemoglobins in the embryonic and fetal periods and during infancy. From Bain (2020)[37].

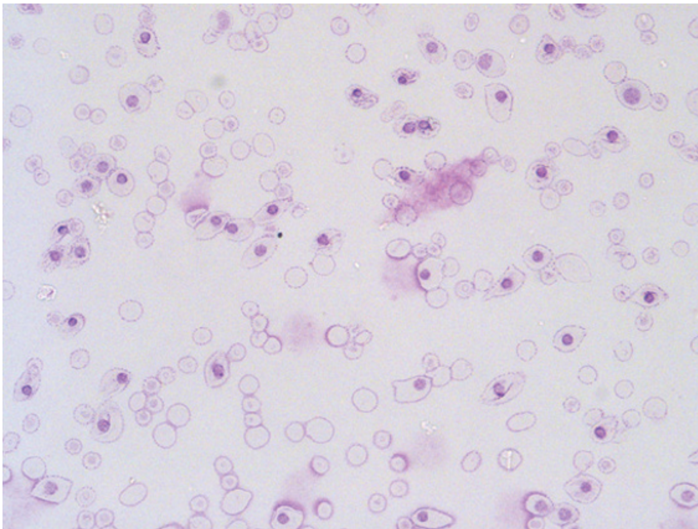

Fig. 1.5 First trimester (8 weeks) fetal blood film showing the large size of the erythroblasts (compare with Fig. 1.6) typical of those derived from the yolk sac. These erythroblasts contain mainly embryonic globins. Note the high proportion of red cells that are nucleated and the absence of white blood cells. May–Grünwald–Giemsa (MGG), ×40 objective.

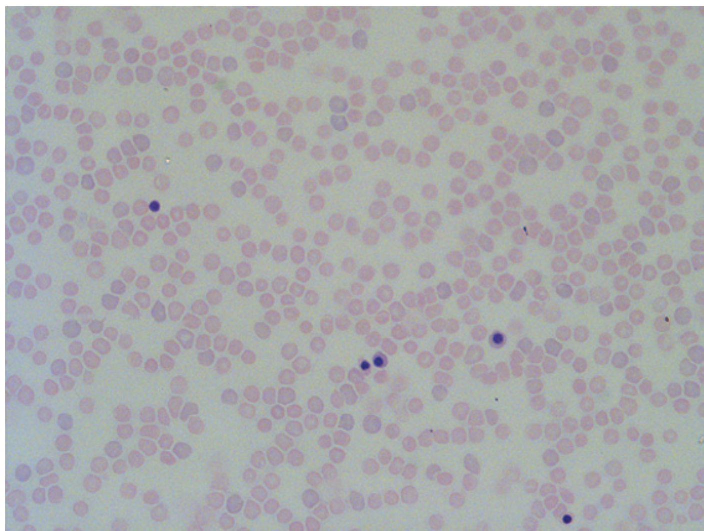

Fig. 1.6 Second trimester (14 weeks) fetal blood film showing typical erythroblasts derived from definitive haematopoiesis. These erythroblasts contain mainly fetal haemoglobin. Note the smaller size of the erythroblasts and the higher proportion of enucleated red cells compared with the first trimester (Fig. 1.5). MGG, ×40.

from primitive to definitive erythropoiesis are not yet clear due to the difficulties in studying this process at such an early stage of development. Understanding more about the mechanisms which normally silence expression of ζ globin would potentially open up new ways of treating α thalassaemia major,[38] an important cause of fetal and early neonatal death (see Chapter 2).

The production of adult haemoglobin (haemoglobin A; $\alpha_2\beta_2$) begins during the second trimester and remains at low levels until 30–32 weeks post-conception, when haemoglobin A production starts to increase concomitantly with a fall in haemoglobin F production. The net result is an average haemoglobin F in term babies of 70–80% and haemoglobin A of 25–30%.[39,40] After birth, haemoglobin F falls, to approximately 2% by the age of 12 months, with a corresponding increase in haemoglobin A. The molecular control of this change from haemoglobin F to haemoglobin A is termed globin switching. In recent years, there has been considerable research into the genes involved in globin switching (e.g. *BCL11A*) in order to identify strategies to delay or reverse this physiological switch after birth and so maintain haemoglobin F production for children affected by severe β globin disorders such as sickle cell disease or thalassaemia major.[41,42]

The timing of globin switching depends on post-conceptional age rather than postnatal age. In fact, in term babies there is little change in haemoglobin F in the first 15 days after birth, but in preterm babies who are not transfused, haemoglobin F may remain at the same level for the first 6 weeks of life before haemoglobin A production starts to increase. This delay in haemoglobin A production (i.e. the switch from γ globin production to β globin production) can make the diagnosis of β globin disorders in the neonatal period difficult, particularly in preterm infants. This is in contrast to α globin disorders,

which are almost invariably evident at birth since α globin chains are essential for the production of all but the very earliest embryonic haemoglobins (see Fig. 1.4 and Table 1.1).

Red blood cell lifespan and the red blood cell membrane in the fetus and neonate

Neonatal red blood cells, particularly in preterm babies, have a shorter lifespan than adult red blood cells. Red cell lifespan is inversely proportional to gestational age at birth. Studies over 50 years ago using isotopically labelled red blood cells estimated red blood cell lifespans for preterm infants at 35–50 days, compared with 60–70 days for term infants and 120 days for healthy adults.[35] More recent estimates, using mathematical modelling and transfusion of autologous cord blood cells, have also calculated the red cell lifespan in preterm neonates to be approximately 50 days.[43]

The reasons for a lower red cell lifespan in neonates, although not fully understood, are thought to include the many biochemical and functional differences in the membrane of neonatal versus adult red blood cells (see Table 1.1). Known differences between neonatal and adult red blood cells include increased resistance to osmotic lysis, increased mechanical fragility, increased total lipid content with an altered lipid profile, increased insulin-binding sites and reduced expression of blood group antigens such as A, B and I.[35] Together these differences translate into the characteristic morphological differences seen in neonatal blood films, particularly in preterm neonates (Figs 1.7–1.9), and are associated with accelerated red cell membrane loss[44] leading to reduced red cell lifespan. Indeed, the distinctive geometry of neonatal red blood cells and the membrane deformability of some of the irregularly shaped cells have been compared to the properties of red blood cells in the inherited red cell membrane disorders.[45]

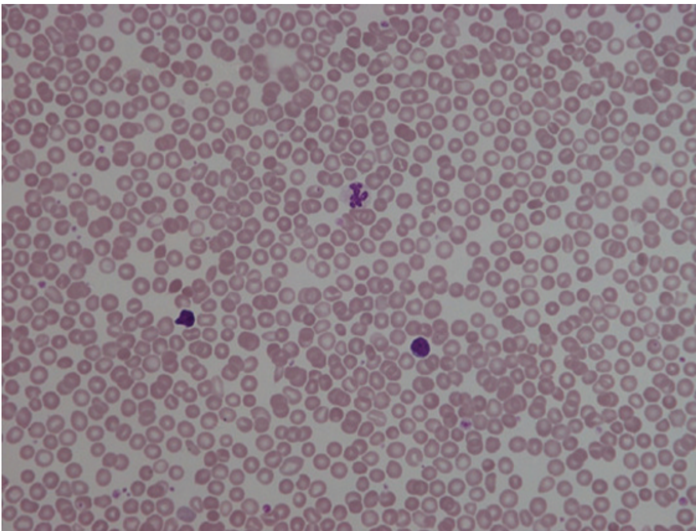

Fig. 1.7 Normal blood film at term. MGG, ×40.

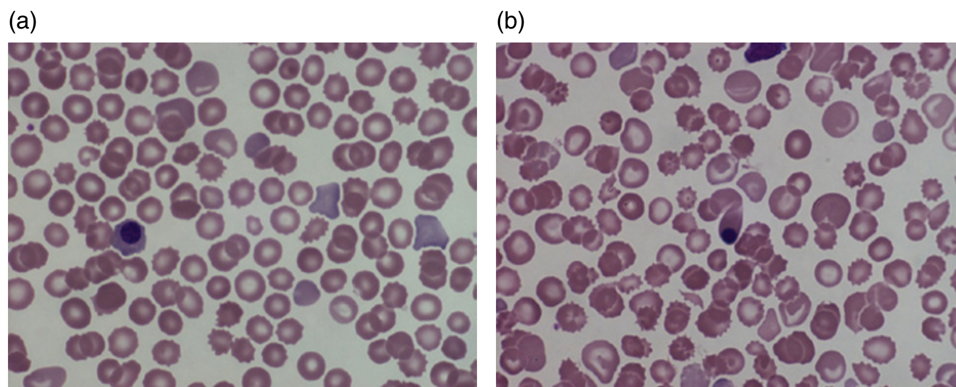

Fig. 1.8 Normal preterm red cells at different gestational ages: (a) baby born at 28 weeks' gestation showing echinocytes, polychromatic macrocytes and one nucleated red blood cell (NRBC); (b) baby born at 25 weeks' gestation showing numerous echinocytes, echinocytic fragments and one NRBC. Note that anisocytosis and poikilocytosis is greater at 25 weeks than at 28 weeks. MGG, ×100.

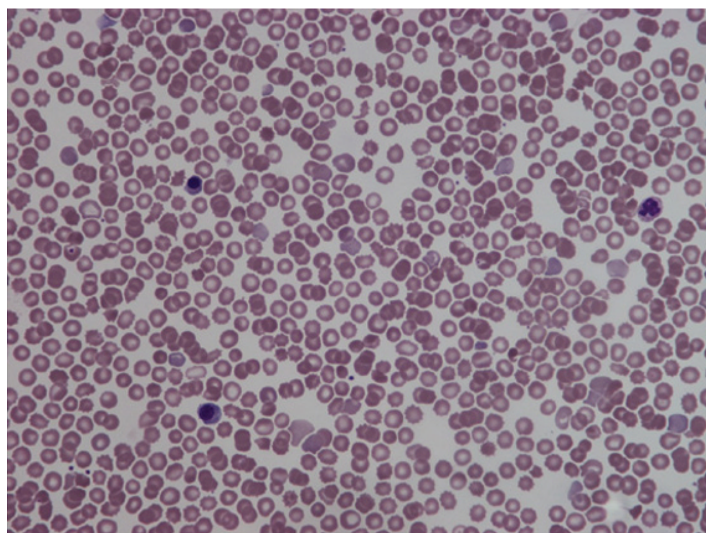

Fig. 1.9 Blood film of a normal preterm baby (born at 28 weeks' gestation) showing a degree of erythroblastosis. MGG, ×40.

Red blood cell metabolism in the fetus and neonate

There are major differences between the metabolism of fetal or neonatal red blood cells and that of adult red blood cells. These differences affect not only the functional properties of the red cells of healthy fetuses and neonates but also the clinical impact of inherited and acquired red cell disorders. Both the glycolytic pathway and the pentose phosphate pathway are affected (see Table 1.1). Overall, glycolysis and glucose consumption are lower in neonatal red blood cells than in adult red blood cells. This occurs despite the increased

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