G. C. de Gruchy

Clinical Haematology in Medical Practice

EDITED BY

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BRYAN RUSH

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FOURTH EDITION

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WITH A FOREWORD BY

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Foreword

Professor Carl de Gruchy died from melanoma in October 1974 aged 52 and this prevented him from completing a Fourth Edition of this famous and much appreciated book. Three close friends and colleagues in Melbourne have, however, generously completed the typescript and have brought the work as far as they can up to date.

Carl de Gruchy was a remarkable man: a first rate clinician and teacher, and medical scientist, he had, too, a fine sense of judgement. It was these qualities which enabled him to write so effectively and they were responsible for the success of this book. It provided just what was wanted by general physicians faced with haematological problems and patients to diagnose and treat.

Carl de Gruchy will, however, be remembered for much more than his outstanding qualities as author and physician: he was a shrewd judge of character and was warm-hearted and generous and an excellent companion; he had a keen appreciation of art, particularly paintings, and he liked to travel, and his visits were always eagerly anticipated by his many friends throughout the world. His career and character were outstanding; his final illness and untimely death was, and still is, a cause of irremediable deep personal sorrow to his friends and admirers and to his family.

It was a privilege to write a Foreword to the First Edition of his book; I feel this now even more so.

Royal Postgraduate Medical School,
London, September 1977

JOHN DACIE

Preface to Fourth Edition

The Fourth Edition of *Clinical Haematology in Medical Practice* was in preparation at the time of Professor de Gruchy's death on 13 October 1974. The book has been highly successful, since it was first published in 1958, as an introduction to haematology for undergraduate students, for medical graduates studying for higher degrees and as a companion for those working both in the general field of haematology and in internal medicine. Perhaps its greatest strengths have lain in its fluent literary style and in the manner in which haematological disease is set firmly in a clinical context. Successive editions have grappled with the rapidly expanding field of haematology but yet retained this general character, a task which is by no means easy considering the great scientific and technological advances which have become part of the discipline in the twenty years which have followed the appearance of the first edition.

In this first revision of the work following Professor de Gruchy's death, we have sought to retain its general style and format, but at the same time to include major new developments in blood diseases. Professor de Gruchy had already revised the first three chapters of the book before his death and we have sought to keep further revision of these to a minimum. In every other chapter there have been many changes, particularly with the inclusion of a separate chapter dealing with disorders of haemoglobin synthesis, separating these from the haemolytic anaemias, and in chapters dealing with malignant diseases affecting the blood and lymphoid tissue where there have been many changes with respect to nomenclature and clinical practice including therapy. Many revisions appear in the chapters relating to bleeding disorders and an entirely new chapter has been added to cover the problems of thrombosis and its management, a field in which haematology firmly impinges on general internal medicine.

It was impossible, at this date, to ensure that all current new developments had been adequately handled without risking destroying the character of the book and alterations have, therefore, necessarily been selective. We have, however, endeavoured to include what we have judged to be the most important developments giving, where possible, indications in the bibliography as to sources for further reading suitable to those who wish to explore the advancing frontiers of the subject. S.I. units have been introduced in this edition in accordance with the

recommendations of the International Committee for Standardization in Haematology; however, not all biochemical values have been altered in this regard because of varying custom in different parts of the world. In respect of blood urea, most figures are expressed in both mg and mmol as those unfamiliar with the latter might have major difficulty in interpretation of the text. We offer our apologies if these changes cause inconvenience to the reader, but it appears to us that transition to the full S.I. system for most haematological values is inevitable. Difficulties arise with conversion from weight of a substance to mmol and a change to this form of expression has only been incorporated in the text where it appears certain that widespread usage of the latter has been adopted. An introduction to the S.I. system for haematology is provided on p. 37.

We wish to thank once more the many colleagues who contributed to previous editions of this book on which the present edition has drawn heavily. In particular, Professor Jack Hirsh and Dr Ron Sawers contributed to the chapters on haemorrhagic disorders in previous editions and their contributions are acknowledged. In the present edition, we wish to thank particularly Professor Selwyn Baker for his advice on the section relating to sprue, Dr Margaret Garson for advice on cytogenetics in leukaemia and for the provision of both illustrations relating to the Philadelphia chromosome. We wish to thank Dr Neil Merrillees for several new illustrations of cells and Mr Anthony Penington for making the models used to illustrate the globin chains of the different haemoglobin molecules (Fig. 8.2). This illustration is based on one used by Professor Lehman whose leadership in the field of haemoglobin over many years is also gratefully acknowledged. We wish also to express our gratitude to colleagues in St Vincent's Hospital who have given advice on many other areas of clinical practice impinging on haematology.

We wish to thank Dr Newton Lee for valuable assistance in the reading of proofs, Mrs B. Somerville for assistance in typing sections of the text and checking page references and bibliography and also Mrs Pam Woodward and Miss M. Donohoe for assistance in typing the manuscript. We are indebted to Mrs Irene Stanley for final checking of corrections. We wish also to thank Mr Per Saugman and Mr J.L.Robson of Blackwell Scientific Publications for their helpful collaboration in production of the new edition and also to thank our publisher for the preparation of the index.

D.G.PENINGTON
B.RUSH
P.A.CASTALDI

Preface to First Edition

The aim of this book is to present an account of clinical haematology which is helpful to the general physician. It is hoped that the book will also be of use to the senior and post-graduate student. Emphasis is laid throughout on diagnosis and management, with particular stress on clinical problems as they are met by the practitioner. Essential details of normal and pathological physiology are briefly discussed. In general, morbid anatomical findings are not given; however, a description of the bone marrow as seen at autopsy is given in some disorders in which the bone marrow findings have a direct relation to diagnosis. Haematological techniques are not discussed.

Chapters 2 to 7 give an account of the anaemias. In Chapter 2 the general principles of the diagnosis and management of a patient with anaemia are discussed. The succeeding chapters describe the various types of anaemia; at the end of each of these chapters, a method of investigation of a patient who presents with the type of anaemia described in the chapter is summarized. It should be realized that these summaries are only a guide, designed to include the clinical features and special investigations pointing to the more important causes of the type of anaemia under investigation, and that they are necessarily incomplete.

With a few exceptions, references have not been included in the text. However, a list of references suitable for further reading is given at the end of each chapter. Certain articles which are particularly helpful are listed in bold type; most are either general reviews or key papers.

I wish to express my thanks to the many colleagues and friends who, in various ways, have helped and advised me. I am particularly grateful to Dr T.A.F.Heale, Dr M.Verso, Dr G.Hale and Dr G.Crock who read the manuscript and proofs and who made many valuable suggestions and criticisms. Dr J.Niall, Dr P.Cosgriff, Dr J.Murphy, Dr E.Seal, Dr J.Madigan, Miss Hal Crawford and Mr I.Parsons have greatly assisted me by reading parts of the manuscript. I am most indebted to Dr R.Sawers who kindly consented to write the section on coagulation disorders; his authoritative account is based on an extensive personal experience in the investigation and management of these disorders. It is with pleasure that I express my indebtedness to Professor J.Hayden, Professor R.Wright, Dr A.Brenan, Dr R.M.Biggins, Dr W.Keane and Mr C.Osborn for the help they gave me in estab-

lishing the Haematology Clinical Research Unit. To my friend and teacher, Professor John Dacie, I cannot adequately express my thanks for the help, advice and encouragement he has always given me.

I wish to thank those authors who have given me permission to reproduce illustrations; detailed acknowledgments are given in the text. I also wish to thank the following publishers for permission to include illustrations; J. & A. Churchill Ltd, Blackwell Scientific Publications and the Australasian Medical Publishing Co., and the Editors of the following Journals: *Practitioner* and *Australasian Annals of Medicine*. Dr R.Walsh and Professor H.K.Ward have allowed me to quote extensively, in Chapter 15, from their book *A Guide to Blood Transfusion*. I am most grateful to Mr P.Sullivan who took most of the photographs, for his patient co-operation and skill. I am also indebted to Mr J.Smith who took a number of the photomicrographs, and who gave special help with those of the red cells. Mr T.O'Connor contributed the photographs of Figures 13.7 and 13.8 Figure 3.3 is reproduced by courtesy of Dr F.McCoy. The black and white figures were drawn by Miss P.Simms, Miss J.Nichols and Miss L.Hogg; I am very grateful to them for their careful and skilful work. Miss J.Chirnside kindly assisted in typing the manuscript. It is with pleasure that I acknowledge the efficient and willing co-operation of Mrs S.Luttrell in typing and retyping the manuscript and in proof-reading. I deeply appreciate the helpful and patient collaboration of Mr Per Saugman of Blackwell Scientific Publications. Finally, I wish to acknowledge my debt to my mother for her constant help, not only during the writing of this book, but throughout my medical studies.

Melbourne G. C. DE GRUCHY

Contents

Chapter 1

Blood formation
Bone marrow biopsy

Blood consists of three formed elements, namely the red cells (erythrocytes), white cells (leucocytes) and platelets (thrombocytes), suspended in a fluid medium, the plasma. These cells are continually being destroyed, either because of old age or as a result of their functional activities, and replaced by newly formed cells. In healthy subjects there is a finely adjusted balance between the rates of formation and destruction, and thus the number of each cell type remains remarkably constant, although there are minor daily physiological fluctuations.

In this chapter the site and control of blood formation will be discussed, together with the morphological appearances of the developing cells. The appearance of the cells as seen with the electron-microscope will not be described, but references to this are included at the end of the chapter. Bone marrow biopsy, a method of investigation which gives much information about disorders affecting blood formation, will also be described.

GENERAL ASPECTS OF BLOOD FORMATION

Site of blood formation

In the *fetus* all the blood cells develop from cells having their origin in the mesenchyme—the embryonic connective tissue. During the first 2 months of fetal life blood formation takes place in the yolk sac. The liver then becomes the main site of haemopoiesis until about the seventh month, and the spleen makes a small contribution. Haemopoiesis commences in the bone marrow in the third month, and from the fifth month until term the marrow progressively takes over from the liver, with the result that after the seventh month it is the major site of haemopoiesis, and that shortly after birth in the normal full-term infant it is the only site of formation of red cells, granulocytes and platelets. Although some lymphocytes and monocytes are formed in the liver and bone marrow, the main sites for their production are the spleen, lymph nodes and other lymphoid tissues. Occasional small erythropoietic foci are seen in the lymph nodes and thymus but their contribution to total erythropoiesis is not significant.

After birth, red cells, granular leucocytes and platelets are formed only in the bone marrow. Lymphocytes are formed mainly in the lymph nodes and other collections of lymphoid tissues, but a small proportion are formed in the marrow. Monocytes appear to be formed partly in the spleen and lymphoid tissue, but the bone marrow makes the major contribution.

The parent cell of all the blood cells, irrespective of their site of formation, is the undifferentiated stem cell or primitive reticulum cell of the reticulo-endothelial system.

Extramedullary haemopoiesis (*myeloid metaplasia*). After birth the spleen, liver and lymph nodes normally play no part in the formation of red cells, granulocytes or platelets. However, in certain circumstances these organs revert to their fetal role of haemopoiesis, as the reticulum cell retains its potential haemopoietic activity. The term extramedullary haemopoiesis is applied to blood formation in organs other than the marrow, and organs showing such haemopoiesis are said to be the site of 'myeloid metaplasia'.

The usual cause of extramedullary haemopoiesis is an increased demand for cells which cannot be met by marrow hyperplasia alone. It occurs most commonly in infants and young children, because the whole of their marrow cavity is occupied by red (haemopoietic) marrow and there is little or no room for expansion in response to increased demands, e.g. following haemorrhage or haemolysis. Extramedullary haemopoiesis may also occur in certain chronic severe anaemias in adults, e.g. pernicious anaemia and haemolytic anaemia, and in association with bone marrow replacement. It regularly occurs in myelosclerosis, and occasionally in secondary carcinoma of bone. Rarely extramedullary haemopoietic tissue occurs as nodules or masses in other sites, e.g. in the region of the spinal column (p. 308).

THE DEVELOPMENT OF THE BLOOD CELLS

Origin of the blood cells

All blood cells are derived from the undifferentiated primitive cell indistinguishable from a large lymphocyte with a loose nuclear chromatin structure and little cytoplasm; this cell is the embryonic stem cell which can give rise to both lymphoid and other blood cells. In the marrow, it differentiates to the multipotent haemopoietic stem cell which, in turn, differentiates to form the particular committed stem cells of each line and their progeny; it also provides a reserve of multipotent stem cells. These normally remain in a quiescent state in the bone marrow throughout life, but are available to be called into cell cycle and to differentiate, repopulating the bone marrow following any episode of cell damage, or under circumstances of increased demand for haemopoietic cell production. The morphological term, *haemocytoblast*, has ordinarily been used for cells with this function, as this describes the cell which is morphologically least differentiated in the bone marrow. However, the true morphological identity of these cells remains uncertain. Thus

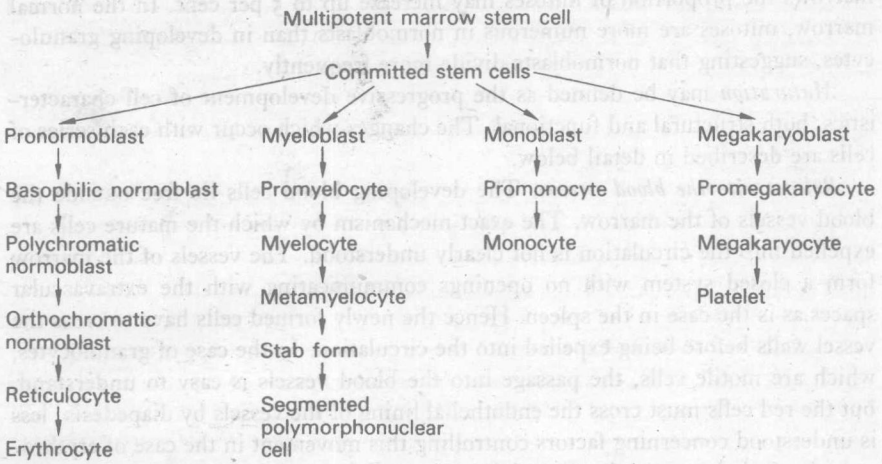

Figure 1.1. Diagrammatic representation of blood cell development

the stem cell may develop into a pronormoblast, myeloblast or a megakaryoblast according to the nature of the stimulus it receives (Fig. 1.1). The cells of the monocytic series also develop from the primitive stem cell but some are formed outside the marrow. The primitive cells of each family (the 'blast' cells) are similar in appearance and cannot always be differentiated from each other by their morphological appearance alone. It is likely that these early cells of each series are what are normally classified as haemocytoblasts. The development of cells of the lymphocytic series is discussed on page 8; it is known to be separate from other aspects of haemopoiesis from the embryonic stage onwards.

The morphology of the several stem cells of the bone marrow has not been resolved with any certainty. It is now known that the reticulum cell and classical haemocytoblast can no longer be regarded as serving these functions and attempts to concentrate stem cells from the bone marrow using buoyant density separation suggest that stem cells are indistinguishable from normal immature cells of a lymphoid appearance. They represent only a minute proportion of cells in the bone marrow and probably vary in morphological appearance, depending upon whether or not they are in cell cycle.

Steps in blood formation

Formation and delivery to the blood stream of mature blood cells of all three series from the primitive haemopoietic reticulum cell of the marrow involve three processes.

1 multiplication of the developing cells;
2 maturation;
3 release of mature cells from the marrow into the blood stream.

Multiplication of cells takes place by mitotic division. In a normal marrow film mitosis can be seen in about 1 per cent of the marrow cells, while in hyperplastic

marrows the proportion of mitoses may increase up to 5 per cent. In the normal marrow, mitoses are more numerous in normoblasts than in developing granulocytes, suggesting that normoblasts divide more frequently.

Maturation may be defined as the progressive development of cell characteristics, both structural and functional. The changes which occur with each series of cells are described in detail below.

Release into the blood stream. The developing blood cells lie free outside the blood vessels of the marrow. The exact mechanism by which the mature cells are expelled into the circulation is not clearly understood. The vessels of the marrow form a closed system with no openings communicating with the extravascular spaces as is the case in the spleen. Hence the newly formed cells have to cross the vessel walls before being expelled into the circulation. In the case of granulocytes, which are motile cells, the passage into the blood vessels is easy to understand, but the red cells must cross the endothelial lining of the vessels by diapedesis; less is understood concerning factors controlling this movement in the case of erythrocytes but it is known to be one of the points of regulation of erythropoiesis. The spleen was believed to play some role in release of cells from the bone marrow, but the effects ascribed to this function are now regarded as being due to its tendency to sequest, for a time, the newly released cells from the bone marrow.

ERYTHROPOIESIS

Two terms are used to describe the developing nucleated red cells, namely erythroblast and normoblast; however, authors vary in their definition of these terms. In this book the term erythroblast is used as a generic term to describe all nucleated red cells, and the term normoblast to describe erythroblasts showing the features of normoblastic (normal) erythropoiesis. In normal marrow the pronormoblast is the first cell recognizable as definitely belonging to the erythroid series; from it the red cell develops through a succession of maturing erythroblasts, namely, basophilic, polychromatic and orthochromatic normoblasts. Developing red cells are also sometimes described as early, intermediate and late normoblasts; these cells rougly correspond to basophilic, polychromatic and orthochromatic normoblasts respectively, but are classified on nuclear rather than cytoplasmic characteristics.

The process of normoblastic maturation is characterized by the following progressive changes.

1 Diminution in cell size.

2 Ripening of the cytoplasm. In Romanowsky-stained preparations, this is accompanied by a change in colour from deep blue to pink, due to the progressive formation of acidophil staining haemoglobin and the simultaneous lessening of the ribose nucleic acid, which is responsible for the basophilia of the cytoplasm.

3 Ripening of the nucleus. This is manifest by loss of nucleoli, decrease in total size and size relative to the cytoplasm, progressive clumping and condensation of the chromatin and deepening in colour. Thus the large reddish purple open net-

work nucleus of the pronormoblast is converted to the small deeply staining blue-black structureless nucleus of the orthochromatic normoblast.

The time for maturation from the pronormoblast to the mature red cell is estimated as about 7 days.

The characteristics of the developing normoblasts, as seen in Romanowsky stained films, are described below; however, it must be realized that the process of maturation is continuous and progressive and that transitional forms between the various types can be seen. In bone marrow films and sections, normoblasts are usually found in groups.

Mitotic division occurs up to the stage of the polychromatic normoblast, and mitosis is most active at this stage. The orthochromatic normoblast is not considered to be capable of mitotic division.

The *pronormoblast* is a round cell with a diameter ranging from 12 to 20 μm. It has a relatively large nucleus which occupies most of the cell, surrounded by a small amount of cytoplasm. The cytoplasm is of clear deep blue colour, often staining slightly unevenly, and showing a pale perinuclear halo; the blue colour is somewhat deeper than that of the blast cells of the white cell series, e.g. the myeloblast. Small rounded or pointed processes are commonly present at the periphery of the cell. The nucleus is round, and consists of a network of fairly uniformly distributed chromatin strands, giving a finely reticular appearance; it is reddish purple in colour and contains several nucleoli.

The *basophilic normoblast* varies in diameter from 10 to 16 μm, and still has a relatively large nucleus. The cytoplasm in general is similar to that of the pronormoblast but may be even more basophilic, and is usually regular in outline. The chromatin strands of the nucleus are thicker and more deeply staining, giving a coarser appearance; the nucleoli have disappeared.

The *polychromatic normoblast* varies in diameter from 8 to 14 μm, the nucleus occupying a relatively smaller part of the cell. The cytoplasm is beginning to acquire haemoglobin and thus is no longer a purely blue colour, but takes on an acidophilic tint, which becomes progressively more marked as the cell matures. The chromatin of the nucleus is arranged in coarse, deeply staining clumps.

The *orthochromatic normoblast* varies from 8 to 10 μm in diameter. Typically the cytoplasm is described as acidophilic. However, in well-stained films the cytoplasm still shows a faint polychromatic tint, and for this reason some authors prefer the term *pyknotic normoblast*. The nucleus is small and initially may still have a structure with very coarse clumped chromatin, but ultimately it becomes pyknotic, and appears as a deeply staining, blue-black, homogeneous structureless mass. The nucleus is often eccentric and is sometimes lobulated. The nucleus is then lost; the mechanism is not certain but it is probably extruded.

The *reticulocyte* is a flat, disc-shaped, non-nucleated cell, of slightly larger volume and diameter than the mature erythrocyte. In Romanowsky-stained films it shows a diffuse pale basophilia, while with a supravital stain such as brilliant cresyl blue the basophil material appears in the form of a reticulum. The haemoglobin content is approximately the same as that of the mature cell, but because of its larger size the haemoglobin concentration is slightly lower. The reticulocyte loses its basophil material and becomes a mature red cell; the maturation time of the reticulocyte is probably about 1 to 2 days. In

the experimental animal it has been shown that some reticulocytes produced in response to intense marrow stimulation may be significantly larger than normal and die prematurely (Stohlman 1962).

The *erythrocyte* is described in Chapter 2.

Ineffective erythropoiesis

The term *ineffective erythropoiesis* is used to describe erythropoiesis in which there is death of developing nucleated red cells in the marrow (intramedullary haemolysis) or other sites of production, and/or the production of non-viable red cells which survive only a few hours in the circulation. The discrepancy between haem synthesis in the marrow and the production of viable red cells results in an increased production of the products of haemoglobin breakdown, e.g. bilirubin and faecal urobilinogen (p. 337). Sometimes the increased bilirubin formation is sufficiently marked to cause clinical jaundice. Ineffective erythropoiesis is seen especially in association with extramedullary erythropoiesis, e.g. in myelosclerosis. Significant ineffective erythropoiesis also occurs in other disorders characterized by a hyperplastic but functionally abnormal marrow, e.g. megaloblastic anaemia, thalassaemia, erythroleukaemia and sideroblastic anaemia. Red cell iron turnover studies are helpful in its diagnosis (Haurani & Tocantins 1961).

LEUCOPOIESIS

The granulocytic (myeloid) series

The mature granular leucocyte (granulocyte) is a cell with a polymorphous nucleus, and a cytoplasm containing granules which with Romanowsky stains appear either neutrophilic, eosinophilic or basophilic. Because of their polymorphous nucleus these cells are often referred to as polymorphonuclear or polymorph leucocytes. The first recognizable cell of the granulocytic series is the myeloblast, from which the mature granulocytes develop through a series of cells, namely the promyelocyte, myelocyte, metamyelocyte and stab form. At the myelocyte stage the cell develops the specific granules which determine the nature of the mature cell, that is whether it is a neutrophil, eosinophil, or basophil.

THE POLYMORPHONUCLEAR NEUTROPHIL

Maturation of the neutrophilic granulocyte is characterized by:

1 the development of specific granules in the cytoplasm;
2 loss of basophilia of the cytoplasm;
3 progressive ripening of the nucleus which ultimately becomes segmented;
4 the development of motility and ability to act as a phagocyte.

Mitotic division occurs up to the stage of the myelocyte, in which it is most active. The metamyelocyte is not considered to be capable of mitotic division.