HEMATOLOGY

Principles and Practice

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Preface

THE AVAILABILITY and transfer of medical information for educational and patient-care needs in the 1970s undoubtedly will involve utilization of new and traditional audio and/or visual techniques. The usual devices for these purposes have been textbooks and the various medical journals. Although the need for new and established texts has been questioned, they do continue to provide both a ready access to, and a certain perspective of, a selected information base. Fortunately, the style and content of textbooks have varied considerably, even within similar specialty areas. This heterogeneity provides the reader with multiple *approaches* to a given topic.

With the rapid expansion of medical knowledge, one of the increasingly employed variations in textbook development has been the use of multiple contributors. This practice provides each author the opportunity to formulate and express a subject in which he is particularly interested in a fashion which he feels will be most useful. Such has been the intent of this book: a presentation of topics in the broad field of hematology by experts in the various areas of this specialty. The authors were given substantial freedom regarding the style and content of their individual efforts. The development of reference lists, either for documentation purposes or further entry into a given data base, was also left, to a large extent, to the discretion of the contributor.

All portions of the book are not necessarily intended to be of equal interest and benefit to every prospective reader whether he is a medical student, house staff officer, practicing physician, hematologist, or academician, but we hope that each will find portions of it valuable. Certain areas have received special emphasis, particularly where there is little textbook coverage elsewhere as, for example, in the malignant diseases of the blood and chemotherapy.

As the growth of this volume proceeded, the editors and contributors developed a greater admiration for participants in all other textbooks.

We gratefully acknowledge the many persons who have contributed their assistance and encouragement throughout the preparation of the manuscript for this book. In particular, I wish to thank Miss Diane Tammeus for outstanding help in typing, editing, and attending to numerous time-consuming tasks necessary for completion of this work. I would be particularly remiss not to acknowledge, additionally, the superb efforts and cooperation of all contributors, especially Doctors Frei and Nachman.

C. E. M.

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Table of Contents

PART 1. The Erythron

PART 2. Myeloproliferative and Lymphoproliferative Disease

PART 3. Disorders of Hemostasis

PART I

The Erythron

1

Erythropoiesis, Red Cell Maturation, and Stem Cell Kinetics

CLIFFORD GURNEY, M.D.

Red Cell Production

ERYTHROPOIESIS is the dynamic process by which mature erythrocytes are formed. Until recently, this process was appreciated almost exclusively in histologic terms, but in the last decade, the physiologic and biochemical aspects of erythropoiesis have come under investigation. Kinetic analyses of red cell production have, in turn, led to extensive consideration of the nature and behavior of the most primitive bone marrow precursors from which erythroblasts develop. It is important, therefore, to have some understanding of the implications of recent studies of so-called "stem cells."

Embryonic Red Cell Production

Embryonic erythropoiesis is distinct from formation of red cells in the adult. Initially, mesenchymal cells of the yolk sac, and later the liver, spleen, and bone marrow, give rise to groups of basophilic cells ("blood islands"). The peripheral cells of these blood islands and basophilic cells which form angioblastic cords connecting the blood islands develop into a continuous system of blood vessels.

These peripheral cells flatten and their nuclei elongate as they become the first endothelium. From within the lumen of the blood islands develop two distinct cell types in the chick embryo.[1] Large, immature cells, seen at 30 hours, serve as stem cells for further blood production. Other angioblastic cells form hemoglobin, and these red cells of the first generation have diffuse distribution of chromatin within their nuclei. These first red cells are prominent by the fifth day. Red cells of the second generation arise from the stem cells and predominate by the seventh day. They differ from mature erythrocytes of the primitive

generation by the aggregation of chromatin into clumps of electron-dense material which is separated by light areas of the same electron-scattering power as cytoplasm.

In the human fetus, red cell formation occurs in the yolk sac during the first 2 months. The liver, and to a lesser extent the spleen, are the major sites of red cell production between the third and seventh month. Some erythropoiesis occurs in the marrow as early as the third month; after the seventh month, the marrow is the primary site of red cell production. Erythropoiesis in the rat fetus is confined primarily to the liver until birth, but moves to myeloid sites in the neonatal period.[2]

Until birth, the hemoglobin produced is mainly hemoglobin F, different from adult hemoglobin in that two gamma chains rather than beta chains are present in each globin molecule. Some hemoglobin A has, however, been found in the youngest embryos studied. At least two early embryonic hemoglobins are formed before hemoglobin F. One of these, known as hemoglobin Gower I, may consist of four epsilon chains. The slower-moving fraction, hemoglobin Gower II, may consist of two alpha and two epsilon chains.[3]

Adult Red Cell Production

In adult man, red cells normally form in portions of the bone marrow. Approximately 40% of the marrow of the sternum, vertebrae, ribs, skull, and proximal ends of the femur and humerus consists of cellular elements engaged in the production of blood. The remaining fraction of this marrow is occupied by fat cells. Although hematopoiesis, together with circulating blood in marrow sinusoids, imparts a red color to hematopoietic marrow, red cell precursors usually constitute the minor fraction of the total cellular elements, while the white cell precursors and juvenile leukocytes are present in larger numbers. The total cellularity of hematopoietic marrow can be evaluated properly only from microscopic sections of aspirated particles of bone marrow.[4] Most of the 2.5 kg of marrow in normal adults, exclusive of the regions mentioned, consists primarily of fat. In times of increased demand for blood production, the proportion of hematopoietic marrow occupied by fat decreases. With more excessive stress on normal blood production, and especially in a number of hematologic diseases, hematopoiesis is seen in marrow not normally engaged in hematopoiesis, as well as in sites outside the marrow. Among the latter, the splenic red pulp and the liver are most common.

Profound species differences exist in distribution of hematopoietic tissue. For example, in the young adult mouse, which has been studied in great detail, the marrow in the femur is strikingly more cellular than the normal marrow of man, the tibia is a hematopoietic site, and blood production also occurs in the spleen.

Blood production occurs in medullary tissues outside the blood stream. Erythrocytes, when ready for liberation into the circulation, are said to slip through the wall of the venous sinusoidal membrane and into the blood stream.[5]

Red Cell Maturation

Mature erythrocytes are end cells which can be traced back to primitive red cell precursors. The latter, in turn, are presumed to arise from undifferentiated cells, generally referred to as stem cells. Current opinion holds that these stem cells are multipotential, capable of giving rise to the various differentiated cells in the bone marrow. The erythro-differentiated progeny of stem cells arrive at an end stage as non-nucleated erythrocytes by the process of maturation which entails a limited capacity for replication. They are then liberated from the marrow into the peripheral circulation. Several color atlases contain excellent reproductions of photographs showing erythrocytes in various stages of maturation.[6,7]

The earliest recognizable cell in the erythroid series is the *pronormoblast*, a round or oval cell, normally less than 20 microns in diameter. When Romanowsky stains are applied to appropriately prepared films of bone marrow, this cell is characterized by thick strands of nuclear chromatin, prominent nucleoli, and a large ratio of nuclear diameter to cell diameter. A thin rim of basophilic cytoplasm, rich in ribonucleic acid, surrounds the nucleus. Although hemoglobin is not normally apparent, traces of this pigment can be seen when special stains are used; these cells, obtained from rodent spleens and bone marrow, have an affinity for radioactive iron, as demonstrated by autoradiography. It has been inferred that these cells arise from undifferentiated precursors, in response to the action of the humoral regulator, erythropoietin. The biochemical and cellular genetic events characterizing differentiation remain to be established, but ribonucleic acid production is the earliest recognizable event after addition of erythropoietin to marrow cultures, preceding iron uptake and hemoglobin production.[8] Although proerythroblasts, the earliest recognizable cells in the erythroid line, are replicating cells, studies with radioactive iron in bled dogs indicate that these cells are probably not self-sustaining, but rather, that they are replenished continually from a pool of primitive precursors.[9] Approximately 4% of the cells of normal adult bone marrow samples are proerythroblasts. A wide normal range of 1–8% is reported.[10]

As proerythroblasts mature, they become smaller. A smooth transition appears to exist between pronormoblasts and *basophilic normoblasts*, cells which have lost their nucleoli and which demonstrate a characteristic pattern of chromatin-clumping. Basophilic normoblasts are seen to undergo cell division. Evidence has been presented to suggest that the number of cell divisions or the rate of maturation occurring in the proerythroblast and normoblast compartments may be influenced by erythropoietin.[11-13] On well-prepared marrow films, these cells average about 15 microns in diameter; approximately 2% of the cells in a normal marrow specimen are basophilic normoblasts. As with all species of marrow cells, wide ranges of normal values are recorded, partly because most cytologists have difficulty identifying every marrow cell with certainty, and partly because erythroblasts occur in islands rather than diffusely and uniformly throughout the