Pathophysiology of Blood

ERSLEV AND GABUZDA

Second Edition

Pathophysiology of Blood

ALLAN J. ERSLEV, M.D.

Cardeza Research Professor of Medicine, Jefferson Medical College of Thomas Jefferson University; Attending Physician, Thomas Jefferson University Hospital, Philadelphia

THOMAS G. GABUZDA, M.D.

Professor of Medicine, Jefferson Medical College of Thomas Jefferson University; Chief, Department of Hematology, Lankenau Hospital, Philadelphia

1979

W. B. SAUNDERS COMPANY / Philadelphia / London / Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Cover: Fenestrated basement membrane of venous sinus in rat bone marrow. Micrograph courtesy of Pierre F. Leblond (Nouv. Rev. Franç. d'Hémat., *13*:771, 1973).

Pathophysiology of Blood

ISBN 0-7216-3403-6

 Library of Congress catalog card number 78-24813.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

CONTENTS

PREFACE

The first edition of *Pathophysiology of Blood* was published in 1975 to meet a need for a small, readable, and profusely illustrated paperback on the normal and abnormal physiology of blood cells and their supporting plasma components. Now, four years later, the explosive addition of new information has necessitated the publication of a second edition. All the chapters have been updated and to a great extent rewritten. New illustrations have been added, and we have attempted to present a current review of hematologic physiology and the mechanisms of disease. The text was prepared as one chapter for the sixth edition of the textbook *Pathologic Physiology: Mechanisms of Disease,* published by W. B. Saunders Company, and we are indebted to the editors, Dr. William A. Sodeman, Jr., and Dr. William A. Sodeman, Sr., for permitting us to publish these chapters as a separate monograph.

In the second edition of *Pathologic Physiology,* the corresponding chapters were written by Dr. William B. Castle and Dr. James H. Jandl, investigators renowned for their role in transforming hematology from a static morphologic art to a dynamic metabolic science. We have striven to live up to the standards of scholarship and lucid prose set by these investigators. This monograph is aimed at preparing students for courses in hematology and oncology, house staff for board examinations, and internists for postgraduate programs or recertification. However, it is also hoped that the monograph will be read generally as an enjoyable exposure to hematology and as a help in modern therapy, which is based increasingly on an understanding of disease processes at a molecular level.

As in the first edition, we would like to thank our medical artist, Andrew S. Likens, for his excellent illustrations and photomicrographs. In order to maintain a uniform style, all graphs have been redrawn and all legends on the ordinate have been turned for a more readable horizontal presentation. Our secretaries, Rosemarie Silvano, Doris Riso, and Rosemary McGlynn, have provided valiant support; our associates at the Cardeza Foundation, helpful criticisms; and our wives, patient endurance. For all of this we are most grateful.

ALLAN J. ERSLEV, M.D.
THOMAS G. GABUZDA, M.D.

Introduction

Hematology is traditionally defined as the study of the formed elements of blood. The combined mass of these elements constitutes an organ of considerable size and complexity. On the average, it measures 30 ml. per kg. body weight or about the same as the liver. The inclusion of active bone marrow, spleen, lymph nodes, and mononuclear macrophage tissue further adds to the size of the hematologic system and to the importance of hematology. Hematology also has close ties with the fluid phase of blood and with the function and kinetics of other organ systems and it has been increasingly difficult to establish its pathophysiologic limits. The erythrocytes need the cooperation of the heart, lungs, vessels and kidneys in order to bring oxygen to the tissues; the granulocytes need a host of supporting plasma factors for their phagocytic mission; the lymphocytes produce and react with immunoglobulins; and the thrombocytes cannot be functionally separated from the coagulation factors. With this in mind, an attempt will be made here to correlate structure, function, and kinetics of the formed elements of blood with those of other organ systems and with over-all human pathophysiology. This correlation and its documentation must of necessity be of an introductory nature, but it is hoped that it will stimulate the reader to seek more information from the monographs and key references listed.

1

Bone Marrow

With the exception of lymphocytes, blood cell formation in the normal adult is the exclusive prerogative of bone marrow. Even lymphocytes, however, both T and B cells, are bone marrow derived, and multipotential stem cells in the bone marrow cavities are probably directly or indirectly responsible for all blood cell formation. Other areas can support hematopoiesis, but the bones appear to provide an optimal environment for differentiation and multiplication of blood cells. Before bone cavities form during the fifth fetal month, blood cell formation takes place first in the yolk sac and then in the liver and spleen (Fig. 1–1). During the brief yolk-sac phase the erythrocytes produced are nucleated and contain an embryonic hemoglobin but the subsequent crops of fetal erythrocytes produced by the liver, spleen, and bone marrow are non-nucleated and contain fetal hemoglobin with $\alpha_2\gamma_2$ polypeptide chains. Although the spleen in the human fetus plays only a brief role in hematopoiesis between the third and the seventh months, the splenic microcirculation appears to be well suited for blood cell formation, and the spleen serves as the principal back-up organ for the bone marrow. At time of birth the splenic and hepatic phases have ceased, the slow transformation from fetal to adult hemoglobin production is under way, and all bone cavities are actively involved in blood cell formation.

For the first few years of life there is a precarious balance between the need for blood cells of a rapidly growing infant and the available bone marrow space, and reactivation of hepatic and splenic hematopoiesis takes place whenever there is an increased demand for blood cell forma-

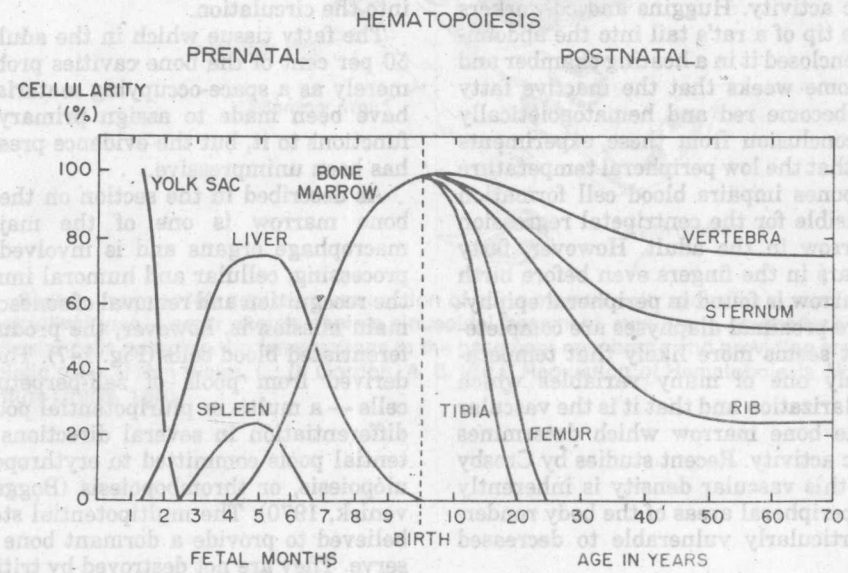

Figure 1–1 Expansion and regression of hematopoietic tissue during fetal and adult life.

tion. At about the age of 4 the growth of bone cavities has outstripped the growth of the circulating blood cell mass, and fatty reserve bone marrow becomes noticeable. Fatty replacement occurs first in the diaphysis of the peripheral long bones, then slowly creeps centripetally until at the age of about 18 hematopoietically active bone marrow is found only in the vertebrae, ribs, sternum, skull, and proximal epiphyses of the long bones. This obviously must mean that the available bone marrow space has continued to grow faster than the circulating blood cell mass, since the ratio between progenitor cells in the marrow and mature cells in the circulation is the same at all ages. In support of this assumption are measurements by Hudson which indicate that the volume of bone marrow cavities increases from about 1.5 per cent of body weight at birth to about 4.5 per cent of body weight in the adult, while the blood volume actually decreases from about 8 per cent of body weight at birth to about 7 per cent of body weight in the adult. During adult life the expansion of bone cavities continues, owing to bone resorption, and there is a gradual increase in the amount of fatty tissue present in all bone marrow areas. Because of the abundant bone marrow space, compensatory reactivation of extramedullary sites rarely takes place in later life, even during periods of accelerated hematopoietic activity. When present, extramedullary hematopoiesis often indicates inappropriate rather than compensatory blood formation.

Measurements of blood flow and hematopoietic activity have shown a close relationship between cellular production and blood supply, and some interesting experiments by Huggins suggest that this relationship goes in both directions and that induced vascularization is followed by increased hematopoietic activity. Huggins and co-workers implanted the tip of a rat's tail into the abdominal cavity or enclosed it in a heating chamber and found after some weeks that the inactive fatty marrow had become red and hematopoietically active. The conclusion from these experiments was initially that the low peripheral temperature in the long bones impairs blood cell formation and is responsible for the centripetal regression of active marrow in the adult. However, fatty marrow appears in the fingers even before birth and active marrow is found in peripheral epiphyses when more proximal diaphyses are completely inactive. It seems more likely that temperature is merely one of many variables which control vascularization and that it is the vascular density of the bone marrow which determines hematopoietic activity. Recent studies by Crosby suggest that this vascular density is inherently lower in the peripheral areas of the body rendering them particularly vulnerable to decreased temperature.

Structurally, the bone marrow is highly organized with a spokelike pattern of venous sinuses and cords of hematopoietic tissue (Fig. 1–2). The cords are percolated by arterial blood draining into the central venous sinuses through a fenestrated basement membrane (Fig. 1–3) partly covered on the inside by endothelial cells and on the outside by reticular cells. Projections from the reticular cells subdivide the cords and provide support for hematopoietic cells (Fig. 1–4). They also control available hematopoietic space by gaining or losing lipid globules. Within the cords, the megakaryocytes lie close to the outside of the sinus wall and appear to reel off strings of cytoplasmic platelets directly into the sinus. The erythroblasts also lie close to the venous sinuses in distinctive clusters or islands. Each island consists of a central macrophage, or nurse cell, with maturing and dividing erythroblasts nestled in cytoplasmic pockets (Fig. 1–5). When mature enough for independent existence, the erythroblasts squeeze through the sinus apertures usually losing their pyknotic and non-deformable nuclei (Fig. 1–6). The maturing and dividing granulocytic precursors are situated deep in the hematopoietic cords and do not move toward the sinus wall until they reach a motile metamyelocytic stage.

The nervous supply to the bone marrow is quite extensive, as everyone having experienced a bone marrow aspiration can attest. Some of the nerves are in close contact with the hematopoietic islands and may sense pressure changes caused by cellular proliferation. If such signals are transmitted to the nerves attached to the vessel walls, an autoregulatory system may well exist, adjusting the flood flow to permit undisturbed proliferation and maturation before the cells are released into the circulation.

The fatty tissue which in the adult fills about 50 per cent of the bone cavities probably serves merely as a space-occupying material. Attempts have been made to assign primary regulatory functions to it, but the evidence presented so far has been unimpressive.

As described in the section on the spleen, the bone marrow is one of the major lymphomacrophage organs and is involved in antigen processing, cellular and humoral immunity, and the recognition and removal of senescent cells. Its main mission is, however, the production of differentiated blood cells (Fig. 1–7). These cells are derived from pools of self-perpetuating stem cells — a multi- or pluripotential pool capable of differentiation in several directions and unipotential pools committed to erythropoiesis, granulopoiesis, or thrombopoiesis (Boggs and Chervenick, 1970). The multipotential stem cells are believed to provide a dormant bone marrow reserve. They are not destroyed by tritiated thymi-

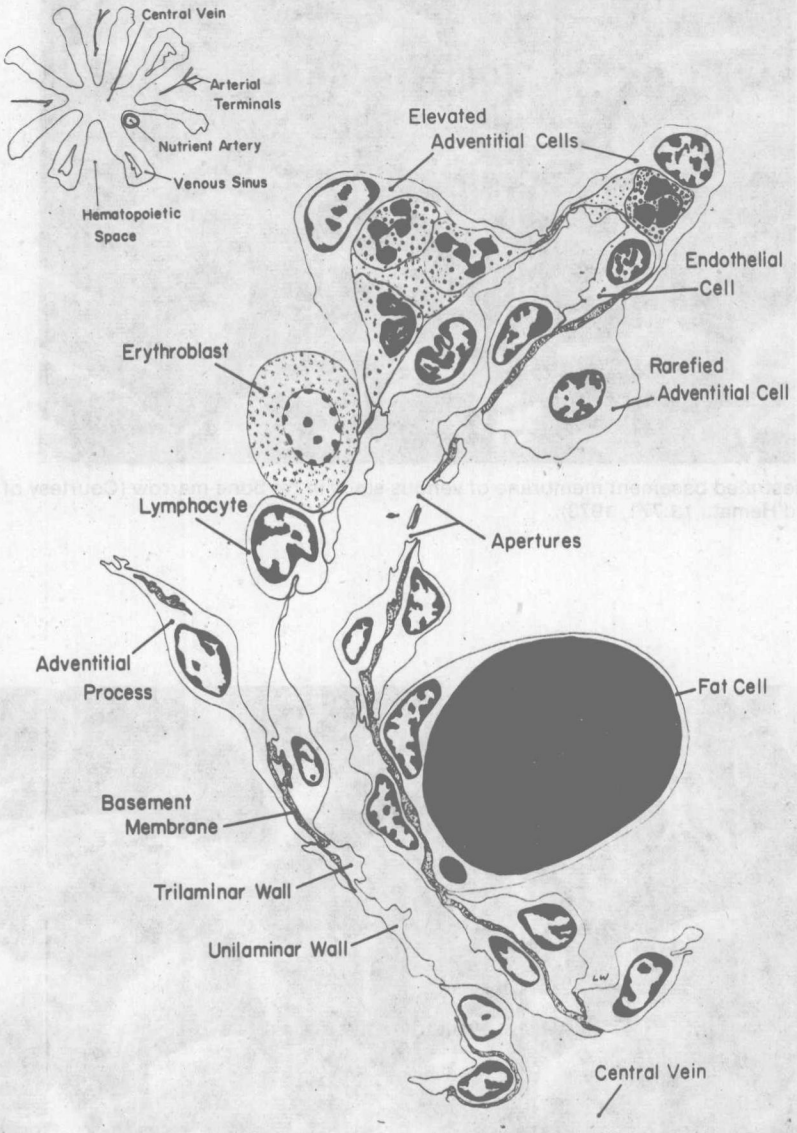

Figure 1–2 Sketch in upper left depicts cross section of bone marrow with spokelike sinusoids draining into a central longitudinal vein. Larger sketch depicts sinusoidal basement membrane covered on the outside by adventitial reticular cells guarding the fenestrations in the basement membrane and providing structural support for hematopoietic cells. (From Weiss, L.: *In* Gordon, A. S. (Ed.): Regulation of Hematopoiesis. Vol. 1. New York, Appleton-Century-Crofts, 1970.)

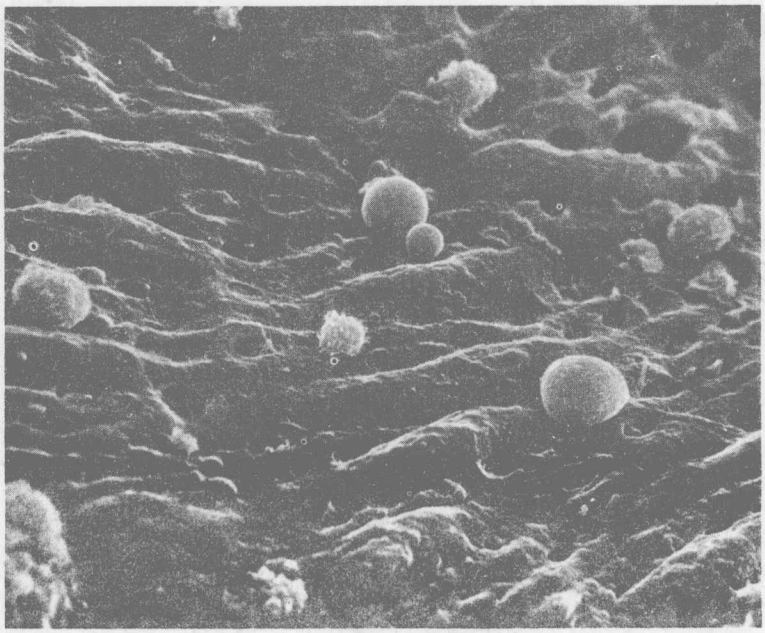

Figure 1–3 Fenestrated basement membrane of venous sinus in rat bone marrow (Courtesy of LeBlond, P.-F., Nouv. Rev. Franc. d'Hemat., *13*:771, 1973).

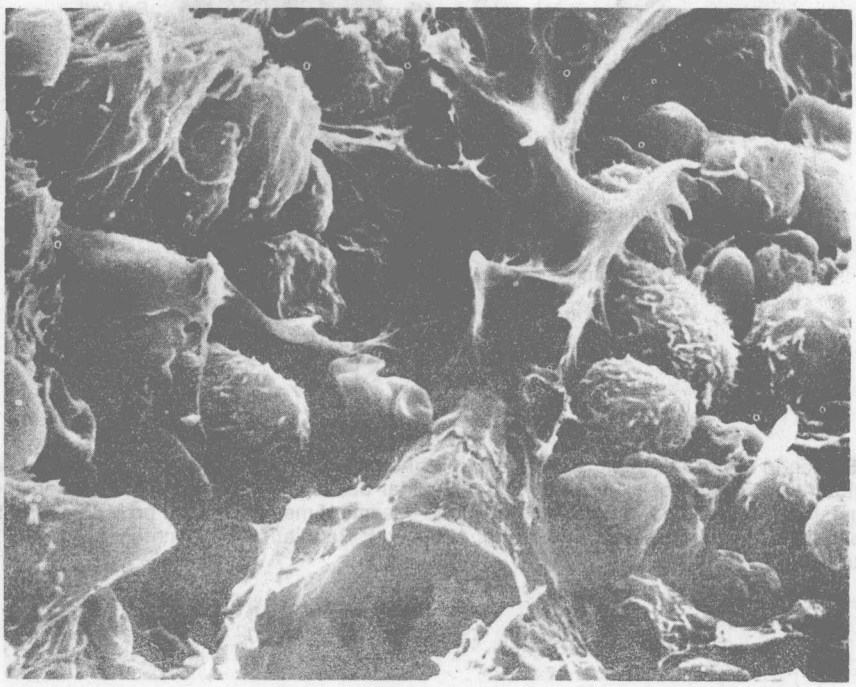

Figure 1–4 A venous sinus crossing the field with luminal endothelium exposed to the right but otherwise covered by adventitial reticular cells. The cytoplasm of these cells extends far into the hematopoietic compartment and provides structure and support for hematopoietic cells. (Courtesy of Weiss L.: Anat. Rev., *186*:161, 1976.)

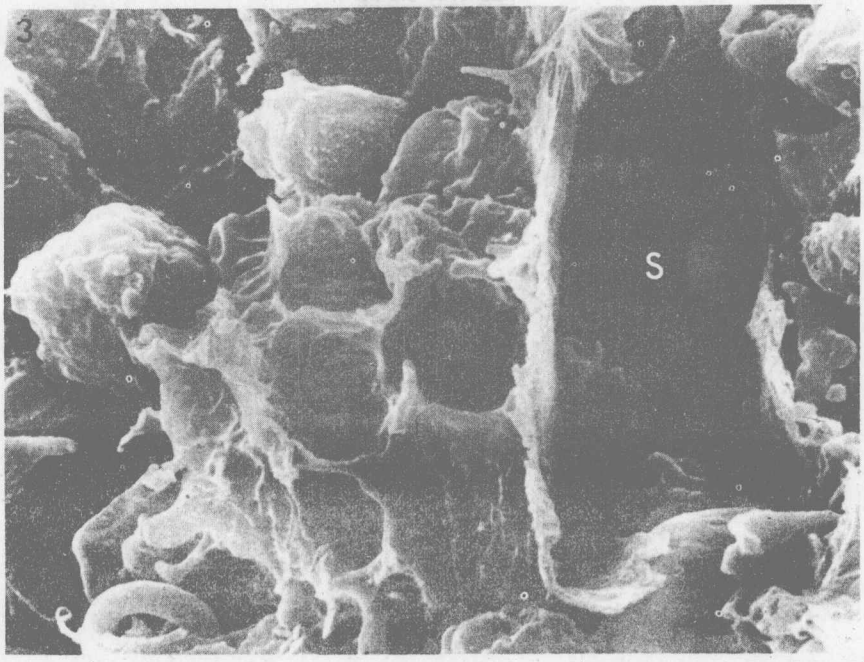

Figure 1–5 An erythropoietic island lying on the wall of a sinusoid (s) in rat bone marrow. The erythroblasts, nestled in the pockets of the island, were removed during the preparation of this scanning electron microscopic picture. (Courtesy of Weiss, L. Anat. Rev., *186*:161, 1976.)

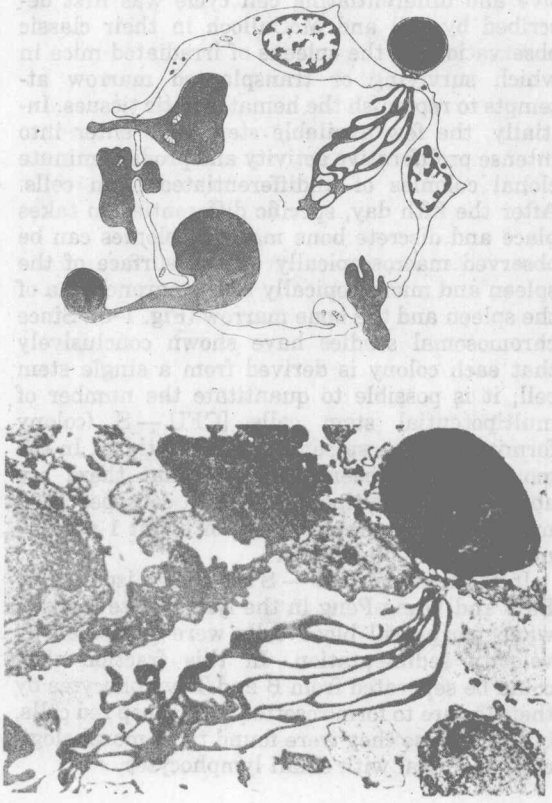

Figure 1–6 Nucleated and non-nucleated red blood cells squeezing through basement pores into a venous sinusoid. The nucleus is incapable of the necessary deformation and is snared off. (Courtesy of Bessis M. Life Cycle of the Erythrocyte. Sandoz Pharm., 1966.)

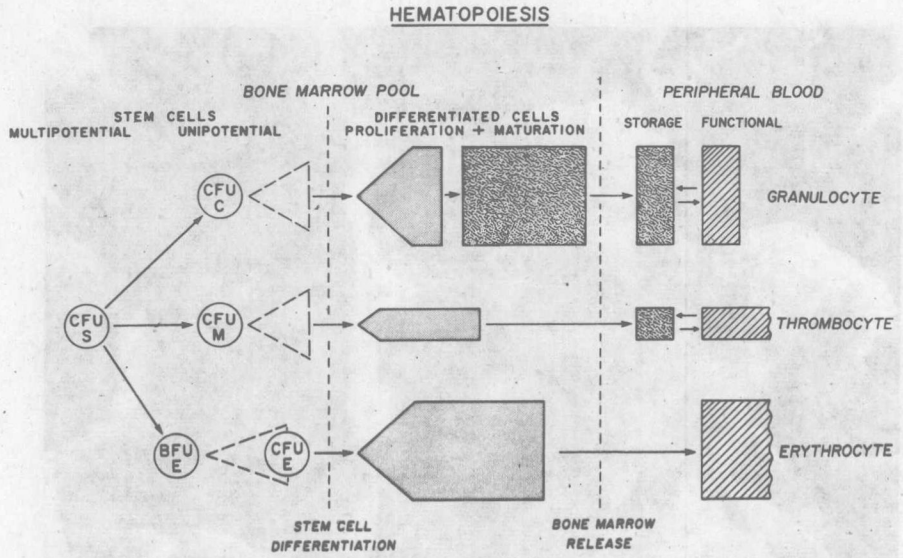

Figure 1–7 A dynamic model of hematopoietic activity.

dine when given in doses which will cause radiation-induced "suicide" of all cells using thymidine in the synthesis of DNA, unless they first have become activated by bone marrow depletion or injury. Such activation into a regenerative and differentiating cell cycle was first described by Till and McCulloch in their classic observations of the spleens of irradiated mice in which surviving or transplanted marrow attempts to replenish the hematopoietic tissues. Initially, the few available stem cells enter into intense proliferative activity and produce minute clonal colonies of undifferentiated stem cells. After the fifth day, specific differentiation takes place and discrete bone marrow colonies can be observed macroscopically on the surface of the spleen and microscopically in the parenchyma of the spleen and the bone marrow (Fig. 1–8). Since chromosomal studies have shown conclusively that each colony is derived from a single stem cell, it is possible to quantitate the number of multipotential stem cells [CFU — S (colony forming units — spleen)] present initially. In the mouse, it has been estimated that there are about 1 to 3 multipotential stem cells per 1000 nucleated bone marrow cells, or about 1 per 100 nucleated red blood cells.

In the human, CFU — S have been isolated by Barr and Wang-Peng in the lymphocyte fraction when peripheral blood cells were separated by velocity sedimentation. In this fraction they could be separated from B and T lymphocytes by their failure to form rosettes with sheep red cells, but otherwise they were found to be morphologically identical with small lymphocytes.

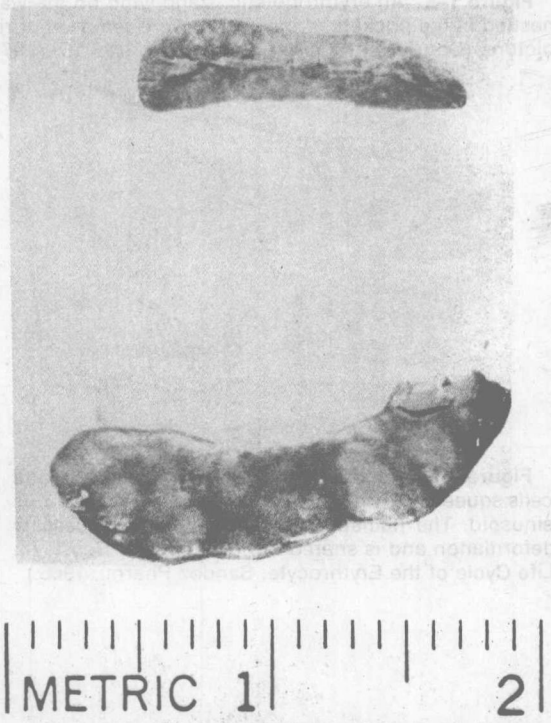

Figure 1–8 Each white raised plaque on the surface of the lower mouse spleen contains a colony of bone marrow cells. These colonies were found 7 days after total body radiation immediately followed by a transfusion of bone marrow cells obtained from an isogeneic donor. Each colony is derived from a single sequestered multipotential stem cell. The upper spleen is a normal control.

Studies on the distribution and composition of bone marrow colonies in the spleen have provided valuable information about the interrelationship between parenchymal structure and cellular differentiation. Each colony is made up of a mixture of hematopoietic cellular elements, usually with one cell type dominating. Although the specific differentiation probably is determined by humoral stimuli, it has been demonstrated by Trentin that the immediate cellular environment or HIM (hematopoietic inductive microenvironment) modifies the effectiveness of the stimuli. Colonies derived from stem cells lodged on the surface of the spleen are primarily erythroid, while colonies from cells lodged in the center of the spleen or in the bone marrow are primarily granulocytic and megakaryocytic. This effect of the microenvironment on cellular differentiation is undoubtedly of major importance for normal hematopoiesis but it is not known whether it is caused by a modification of the activities of stem cells or of differentiated cells.

The unipotential stem cells have been shown, by the use of "suicide" techniques, to be in active cell cycle and capable of self-renewal for a considerable period of time. However, they need the stimulus of a humoral "poietin" in order to undergo blast transformation and further differentiation. Erythropoietin is known to be the specific "poietin" for stem cells committed to erythropoiesis but there is also mounting evidence for the existence of a leukopoietin and a thrombopoietin responsible for the differentiation of stem cells committed to granulocytopoiesis and thrombopoiesis.

In the presence of even small amounts of erythropoietin, bone marrow suspensions plated on fibrin clots or on methyl cellulose plates will form tiny erythroid colonies consisting of from 8 to 64 hemoglobin-containing erythroblasts (Fig.

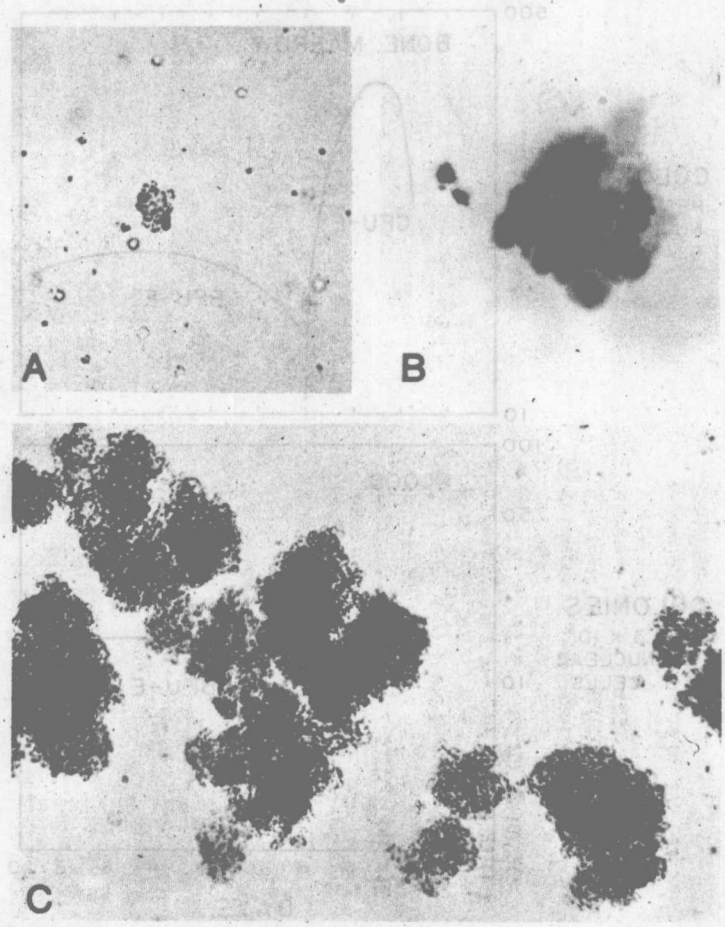

Figure 1–9 The appearance of a single CFU-E (*A*) and a single BFU-E (*C*) grown on a methyl cellulose medium (× 120) (courtesy of Gregory C. J. and Eaves A. C.: Blood, *49*:855, 1977) and of a single CFU-E (*B*) × 1,000.

1–5). The responsible cell has been identified by Clarke and Housman as a small mononuclear "lymphocyte." It has been designated as a CFU-E (colony forming unit-erythroid) and it is probably identical with the unipotential, erythropoietin-responsive stem cell. In addition to these early occurring CFU-E, a second kind of colony begins to appear after eight to ten days of culture if the medium contains large amounts of erythropoietin. These colonies grow to macroscopic size and may contain thousands of erythroblasts. Because of their irregular outline with many CFU-E subcolonies they are called "bursts," and the responsible cell is called a "burst forming unit-erythroid" or BFU-E. BFU-E have been demonstrated both in peripheral blood and bone marrow while CFU-E have been found only in the bone marrow (Fig. 1–10).

Apparently, erythropoietin promotes both stem cell proliferation and blast transformation. Whether this dual effect is accomplished by a single effect of erythropoietin on stem cells or by multiple sequential actions (or multiple erythropoietin species) is not known. A current hypothesis envisions BFU-E as early descendants of CFU-S (Fig. 1–7). They contain a few erythropoietin receptors enabling them to respond to large concentrations of erythropoietin with proliferation and maturation. According to Gregory and Eaves, the progeny will contain an increasing number of erythropoietin receptors until at a certain point of maturation the stem cells acquire the properties of CFU-E and undergo blast transformation to hemoglobin-producing erythroblasts. A problem with this hypothesis is that erythropoietin-responsive stem cells appear to be in

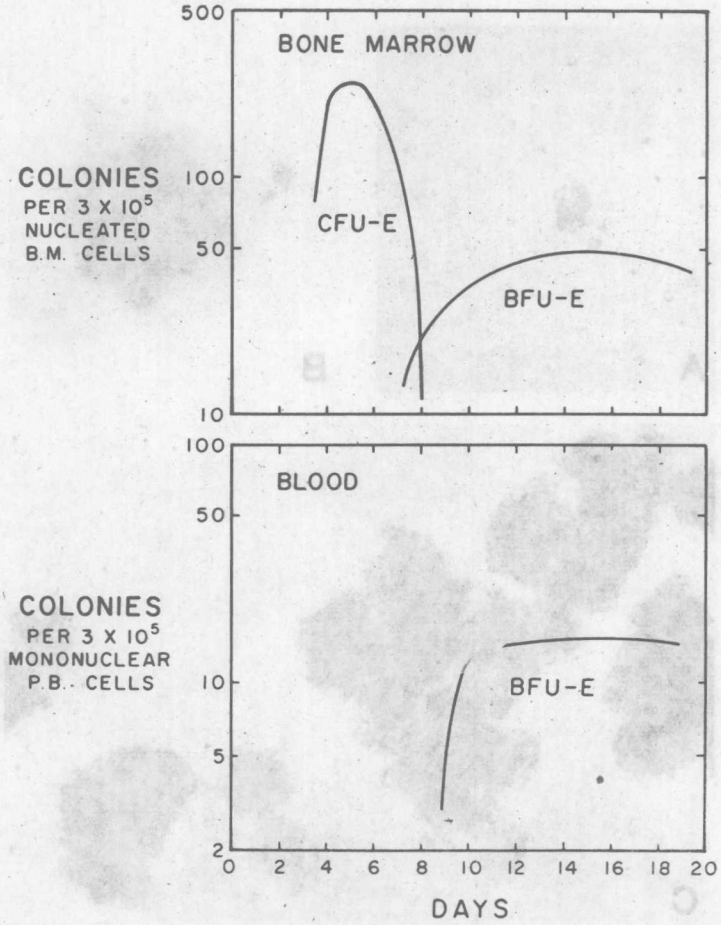

Figure 1–10 The sequential appearance and disappearance of erythroid colonies in bone marrow and peripheral blood suspensions plated on a methyl cellulose medium. (Slightly modified from Ogawa M. et al., Blood, *50*:1081, 1977.)

TABLE 1–1 NORMAL BLOOD CELL KINETICS

Cell Type	Marrow			Blood		
	Number (cells/kg)	Transit time (days)	Production (cells/kg/day)	Number (cells/kg)	Transit time (days)	Production (cells/kg/day)
I. Red cells						
Normoblasts	5.3×10^9	≈5.0	3.0×10^9	–	–	–
Reticulocytes	8.2×10^9	2.8	3.0×10^9	3.1×10^9	1.0	2.56×10^9
Erythrocytes	–	–	–	3.07×10^{11}	120.0	2.56×10^9
II. Megakaryocytes	15×10^6	≈7	2.0×10^6	–	–	–
Platelets	–	–	–	2.5×10^{10}	9.5	2.5×10^9
III. Granulocytes						
Proliferation pool	2.1×10^9	≈5.0	0.85×10^9	–	–	–
Postmitotic pool	5.6×10^9	6.6	0.85×10^9	–	–	–
Circulating	–	–	–	0.4×10^9	0.3	0.85×10^9

(Courtesy of Finch C. A., et al., Blood, *50*:699, 1977.)

active cell cycle even in the absence of erythropoietin. An explanation may be that these stem cells have a certain slow base line rate of proliferation with wastage and death of cells not exposed to erythropoietin. Studies, summarized by Craddock and co-workers, provide some support for this explanation by demonstrating the presence of short-lived "lymphocytes" in the bone marrow.

Bone marrow plated on agar plates has also been shown to grow large granulocytic colonies when exposed to a "colony stimulating factor, CSF." These colonies have been designated CFU — C (C for culture). The CSF originates from monocytes or macrophages and apparently is capable of transforming granulocyte-committed unipotential stem cells to myeloblasts. Although it acts as a leukopoietin in vitro, its physiologic significance, if any, for in vivo granulopoiesis has not been resolved. Megakaryocytic colonies (CFU-M) originating from bone marrow plated on fibrin plates have been described by Nakeff and Daniels-McQueen, but their relationship to physiologic thrombopoiesis is also unknown.

The newly formed proerythroblasts and myeloblasts will subsequently undergo three to five mitotic divisions, resulting in an eight to 32-fold multiplication (Fig. 1–7). The nucleus of the megakaryoblast will undergo the same number of endomitotic divisions, resulting in the formation of a few huge cells with multilobed nuclei. Concomitant with nuclear proliferation the cytoplasm will undergo specific maturation and three to five days after the initial differentiation the cells are almost completely mature and functional.

The maturing reticulocytes and the maturing granulocytes remain in the bone marrow for some days before they are released into the circulation. The length of this delay appears to be responsive to the immediate needs for circulating blood cells. However, because the circulating granulocyte mass is much smaller than the circulating red cell mass, a premature release of the marrow reserve of maturing cells is of importance only for the functional adjustment of the peripheral granulocyte count. After the release from the bone marrow, the erythrocytes are all in active use in circulating blood, while about 50 per cent of the granulocytes and 30 per cent of the thrombocytes are sequestered in the microvasculature or in the spleen as functional reserves. Figure 1–11 and Table 1–1 give a summary of the cellular morphology and composition of the hematopoietic tissue. The apparent discrepancy between the 2:1 ratio between erythroid and granulocytic cells and the 1:3 ratio found in bone marrow smears is caused by the fact that the bone marrow reticulocytes are included in Table 1 but usually not in bone marrow differential counts.

Figure 1–11 The normal morphology of the hematopoietic cells.

REFERENCES

Baikie, A. G., Court Brown, W. M., Buckton, K. E., Harnden, D. G., Jacobs, P. A., and Tough, I. M.: A possible specific chromosome abnormality in human chronic myeloid leukaemia. Nature (London), *188*:1165, 1960.

Barr, R. D., and Whang-Peng, J.: Hemopoietic stem cells in human peripheral blood. Science, *190*:284, 1975.

Boggs, D. R., and Chervenick, P. A.: Hemopoietic stem cells. *In* Greenwalt, T. J., and Jamieson, G. A. (Eds.): Formation and Destruction of Blood Cells. J. B. Lippincott Co., Philadelphia, 1970, p. 240.

Clarke, B. J., and Houseman, D.: Characterization of an erythroid cell of high proliferative capacity in normal human peripheral blood. Proc. Nat. Acad. Sci. USA, *74*:1105, 1977.

Craddock, C. G., Longmire, R., and McMillan, R.: Lymphocytes and the immune response. N. Engl. J. Med., *285*:324, 1972.

Crosby, W. H.: Experience with Injured and Implanted Bone Marrow: Relation of Function to Structure. *In* Stohlman, F. Jr. (ed.): Hematopoietic Cellular Proliferation. Grune & Stratton, New York, 1970, p. 87.

Ebbe, S.: Thrombopoietin. Blood, *44*:605, 1974.

Erslev, A. J.: Feedback circuits in the control of stem cell differentiation. Am. J. Pathol., *65*:629, 1971.

Finch, C. A.: Pathophysiologic aspects of sickle cell anemia. Am. J. Med., *53*:1, 1972.

Finch, C. A., Harker, L. A., and Cook, J. D.: Kinetics of the formed elements of human blood. Blood, *50*:699, 1977.

Gregersen, M. I., and Rawson, R. A.: Blood volume. Physiol. Rev., *39*:307, 1959.

Gregory, C. J., and Eaves, A. C.: Human marrow cells capable of erythropoietic differentiation in vitro. Definition of three erythroid colony responses. Blood *49*:855, 1977.

Hudson, G.: Bone marrow volume in the human foetus and newborn. Br. J. Haematol., *11*:446, 1965.

Huggins, L., and Blockson, B. H.: Changes in outlying bone marrow accompanying a local increase of temperature within physiologic limits. J. Exp. Med., *64*:253, 1956.

Killmann, S. A., Cronkite, E. P., Fliedner, T. M., and Bond, V. P.: Mitotic indices of human bone marrow cells. III. Duration of some phases of erythrocyte and granulocytic proliferation computed from mitotic indices. Blood, *24*:267, 1964.

Kretchmar, A. L.: Erythropoietin: Hypothesis of action tested by analog computer. Science, *152*:367, 1966.

Nakeff, A., and Daniels-McQueen, S.: In vitro colony assay for a new class of megakaryocyte precursor: Colony-forming unit megakaryocyte (CFU-M). Proc. Soc. Exp. Biol. Med., *151*:587, 1976.

Ogawa, M., Grush, O. C., O'Dell, R. F., Hara, H., and MacEachern, M. D.: Circulating erythropoietic precursors assessed in culture: Characterization in normal men and patients with hemoglobinopathies. Blood, *50*:1081, 1977.

Reissmann, K. R., and Udupa, R. B.: Effect of erythropoietin on proliferation of erythropoietin-responsive cells. Cell Tissue Kinet., *5*:481, 1972.

Robinson, W. A., and Mangalik, A.: The kinetics and regulation of granulopoiesis. Seminars Hematol., *12*:7, 1975.

Till, J. E., and McCulloch, E. A.: A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat. Res., *14*:213, 1961.

Trentin, J. J.: Determination of bone marrow stem cell differentiation by stromal hemopoietic inductive microenvironment (HIM). Am. J. Pathol., *65*:621, 1971.

Weiss, L.: The hemopoietic microenvironment of the bone marrow: An ultrastructural study of the stroma in rats. Anat. Rev., *186*:161, 1976.

Weiss, L.: The histology of the bone marrow. *In* Gordon, A. S. (Ed.): Regulation of Hematopoiesis. Appleton-Century-Crofts, New York, 1970, p. 79.

Weiss, L., and Chen, L. T.: The organization of hematopoietic cords and vascular sinuses in bone marrow. Blood Cells, *1*:617, 1975.

Wu, A. M., Till, J. E. Siminovitch, L., and McCulloch, E. A.: A cytological study of the capacity for differentiation of normal hemopoietic colony-forming cells. J. Cell. Physiol., *69*:177, 1967.

2

Spleen

STRUCTURE

The mature normal spleen — no longer involved in hematopoiesis — is the largest of the lymphoid organs. Yet it is also a unique filtration bed for the circulating blood well equipped with macrophages to remove undesired particles from the circulation. The parenchyma or "pulp" is partitioned by fibrous trabeculae, through which run the arteries, veins, and lymphatics. Arterioles run out from the trabeculae into the white pulp, branch at right angles into the marginal zone, and then terminate in the red pulp (Fig. 2–1). The venous drainage system originates in the sinus system of the red pulp. The blood then flows out through the trabecular veins and on into the portal system. The efferent lymphatic drainage runs into the thoracic duct.

In the white pulp, a sleeve of T lymphocytes — the "periarterial lymphatic sheath" — is wrapped around the central artery (Fig. 2–2). Nodular accumulations of lymphocytes, often at the sites of the right angled vascular branches, form follicles along the course of the central arteriole. These contain germinal centers rich in B lymphocytes surrounded by mantle zones of T lymphocytes and macrophages. The cellular structure is held together by a network of fibrillar reticular cells.

The marginal zone is an ill-defined boundary between the white and red pulp. Into its interstices, also held together by fibrillar reticular cells, empty many arteriolar branches filling the spongy network with blood cells. Under provocative stimuli, macrophages readily migrate into this area.

Blood from the marginal zone as well as from central arterial terminals drains into the red pulp, either directly into venous sinuses and on out through the efferent veins, or into the cords that lie between the sinuses (Fig. 2–3). The blood cells that enter the cords must pass through the fenestrated wall separating the cords from the sinuses before gaining access to the venous drainage system. They are thus delayed to varying degrees in their transit. The fenestrations in the wall separating the cords and sinuses are about 3 μ in diameter, so small that erythrocytes must be squeezed through with effort. They pass through because their pliability and deformability is normally very great (Fig. 2–4). The sinus side of the wall is lined by reticular endothelial cells lying

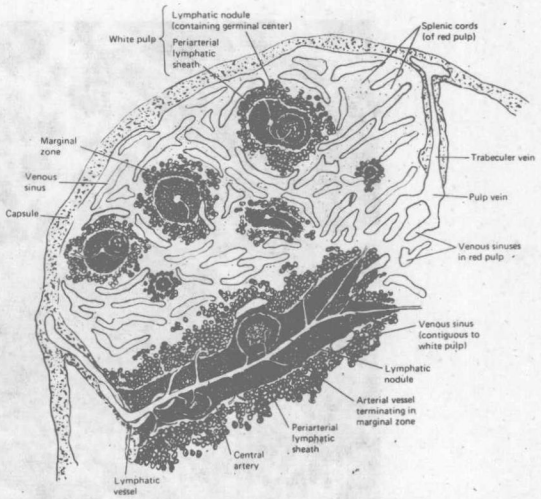

Figure 2–1 The structure of the spleen. The white pulp consists of the periarterial lymphatic sheath and lymphatic nodules with germinal centers. The red pulp contains the splenic cords and sinuses. The marginal zone is interposed between white and red pulp. The central artery sends branches out into the marginal zone and then terminates in the red pulp. Blood from the splenic cords passes through a fenestrated wall into the sinuses and is then collected into the splenic veins. (From Weiss, L., and Tavassoli, M.: Sem. in Hematol., 7, 372, 1970, Reprinted from Histology, by L. Weiss, and R. O. Greep, Copyright © 1977, McGraw-Hill Book Company.

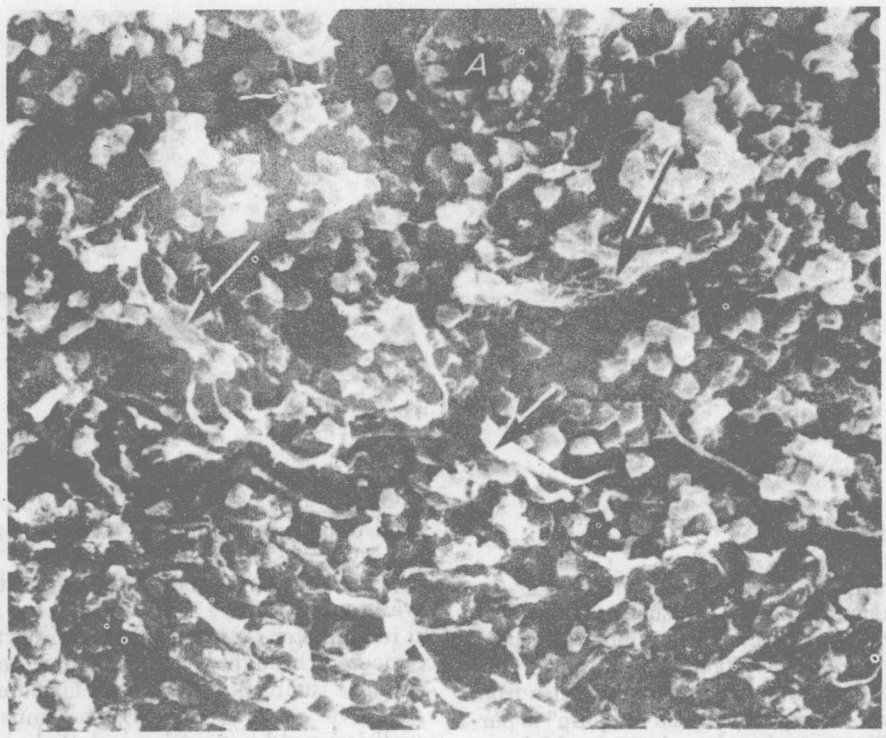

Figure 2–2 Scanning electron micrograph of the splenic white pulp in the region of the periarterial lymphatic sheath. A sea of lymphocytes is held together by reticular cells and their associated fibrils (shown by arrows). The central arteriole (A) is shown in cross section near the upper margin. (From Weiss, L. Blood *43*:665, 1974.)

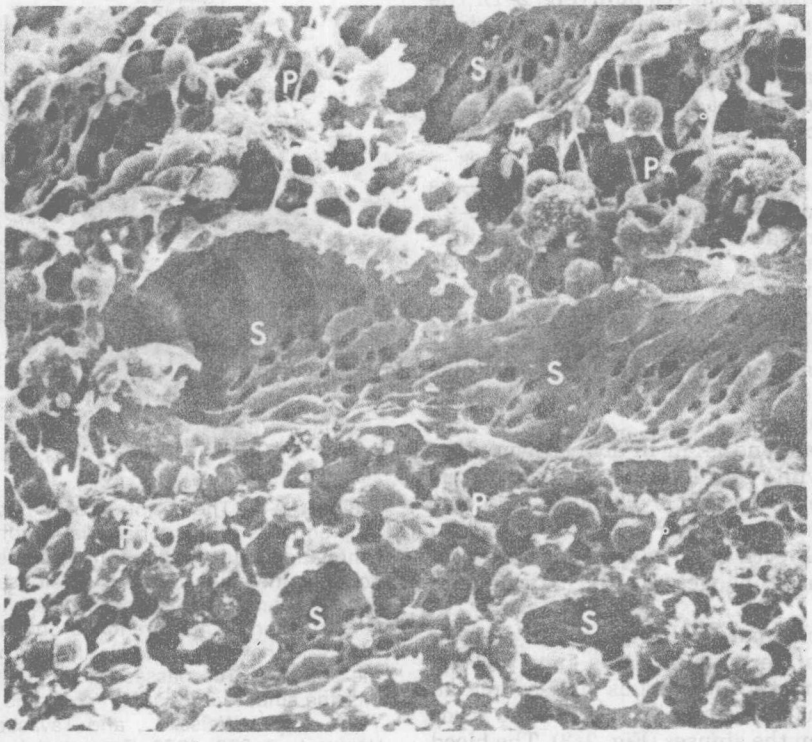

Figure 2–3 Scanning electron micrograph of the splenic red pulp, showing the fenestrated sinuses (S) and the spongy cords (P) that lie between the sinuses and consist of hematogenous cells enmeshed in an adventitial reticular network. (From Miyoshi, M., and Fujita, T. Arch. Histol. Japan *33*:225–246, 1971.)