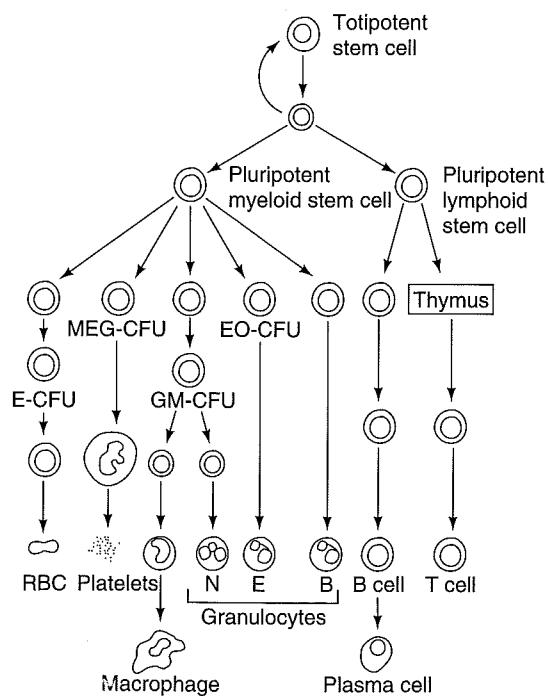
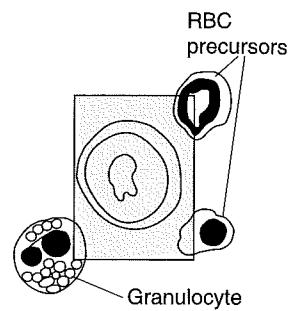


HEMATOPOIESIS

The development of blood cells (**hematopoiesis**) is a complex sequence of events in which a single totipotent stem cell gives rise to eight very different mature cell types with functions that range from carrying oxygen to producing antibodies. The process of hematopoiesis is continuous throughout a lifetime and operates to replace 3.7×10^{11} blood cells that are normally lost each day. In addition to its routine capacity, this system is very sensitive to increased demands related to environmental changes. For example, during severe infection, the number of granulocytes increases from 5,000 to 50,000/ μl within a few days.

Many of the cells in bone marrow are similar to the one shown in the micrograph. These cells cannot be morphologically classified into any particular developmental lineage, but they contain features that are characteristic of a relatively undifferentiated **stem cell**: a large euchromatic nucleus (N) with a prominent nucleolus (n), and a cytoplasm packed with free polyribosomes. Activity is directed toward protein synthesis for internal use, such as for proteins involved in cell division, which is the most common event for stem cells. As differentiation proceeds, the nucleus becomes smaller and more heterochromatic and the cytoplasm acquires differentiation products such as hemoglobin or granules. Beginning with the **totipotent stem cell**, a hierarchy of **pluripotent stem cells** exists. These progressively lose their ability for self-renewal as they become more restricted in lineage.

Early progenitor cells are not identified by their morphology but instead by the type of progeny they produce within clonal colonies. Cells referred to as erythrocyte-colony-forming units (E-CFUs) form only erythrocyte colonies. Progenitors of granulocyte (refers only to neutrophils in this case) and monocyte colonies are referred to as GM-CFUs. The growth and differentiation of CFUs in vitro is sensitive to specific growth factors, proteins including erythropoietin and many colony-stimulating factors (CSFs). Some of these factors have been produced using recombinant technology and are being used successfully in clinical trials. Results include (1) reduction of the need for transfusion in anemic patients when administered erythropoietin, and (2) the restoration of the white cell count in AIDS patients following GM-CSF treatment.



Modified from S. C. Clark and Robert Kamen, *Science* 236:1229(1987).



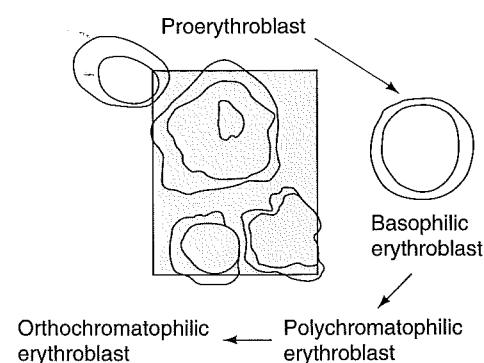
ERYTHROPOIESIS: Early Development

Red blood cell development (**erythropoiesis**) occurs in 4–6 days and is characterized by the gradual synthesis and accumulation of hemoglobin to the exclusion of all organelles, including the nucleus. The large cell (P) on the micrograph is probably a **proerythroblast**, the first morphologically recognizable stage in the red cell line. The proerythroblast is formed from its precursor, apparently following stimulation by erythropoietin. Even though hemoglobin is being synthesized at this early stage, it is not concentrated enough to observe the electron density associated with iron. As differentiation proceeds to the **basophilic** (not shown in micrograph), **polychromatophilic** (PE, micrograph), and **orthochromatophilic** (OE, micrograph) erythroblast stages, hemoglobin concentration and electron density increase. Along with this, there is a reduction in free ribosomes and a progressive chromatin condensation from the euchromatic nucleus of the proerythroblast to the extreme condensation of the orthochromatophilic erythroblast.

The synthesis and assembly of **hemoglobin** is tightly controlled within different parts of the cell. Protoporphyrin is synthesized within the mitochondria (arrowheads, micrograph) in a complex series of reactions. Iron is transported into the mitochondria, where it combines with protoporphyrin to form heme. The globin chains (2α and 2β), synthesized on polysomes, are then assembled into the mature hemoglobin.

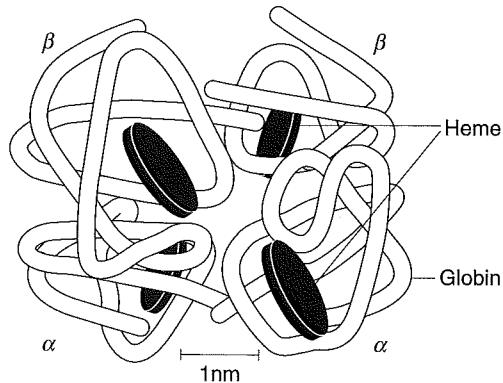
Iron–transferrin complexes are brought into the cell by receptor-mediated endocytosis. Iron is released and transferrin is recycled to the surface along with the receptor. In the early stages of red blood cell (RBC) development, such as the proerythroblast stage, the number of transferrin receptors within the cell membrane is large. With progressive development this number diminishes along with the other organelles important to hemoglobin synthesis.

Bone marrow preparations such as that used for this micrograph show developing cells isolated from one another and other supporting cells. Actually, all blood cells develop in microniches in intimate contact with some type of bone marrow **stromal cell**. Stromal cell contact is essential for long-term blood cell development in culture. In vitro studies and biopsy specimens show many developing RBCs in the same stage enclosed in processes of a single stromal cell, forming an **erythropoietic unit**.



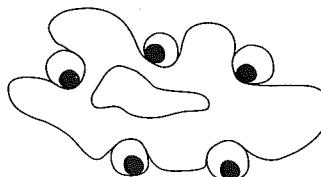
Orthochromatophilic erythroblast

Polychromatophilic erythroblast



Modified from H. A. Harper et al.,
Physiologische Chemie, Springer-Verlag, New York, 1975.

Stromal cell

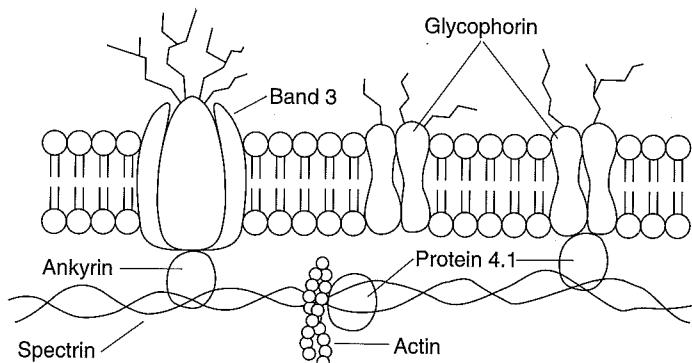
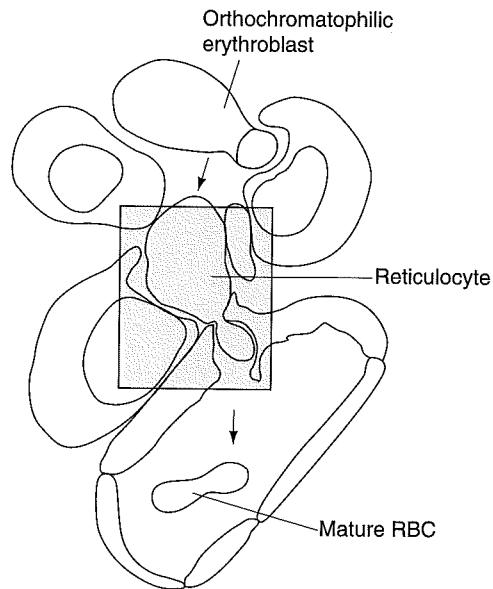




ERYTHROPOEISIS: Reticulocyte

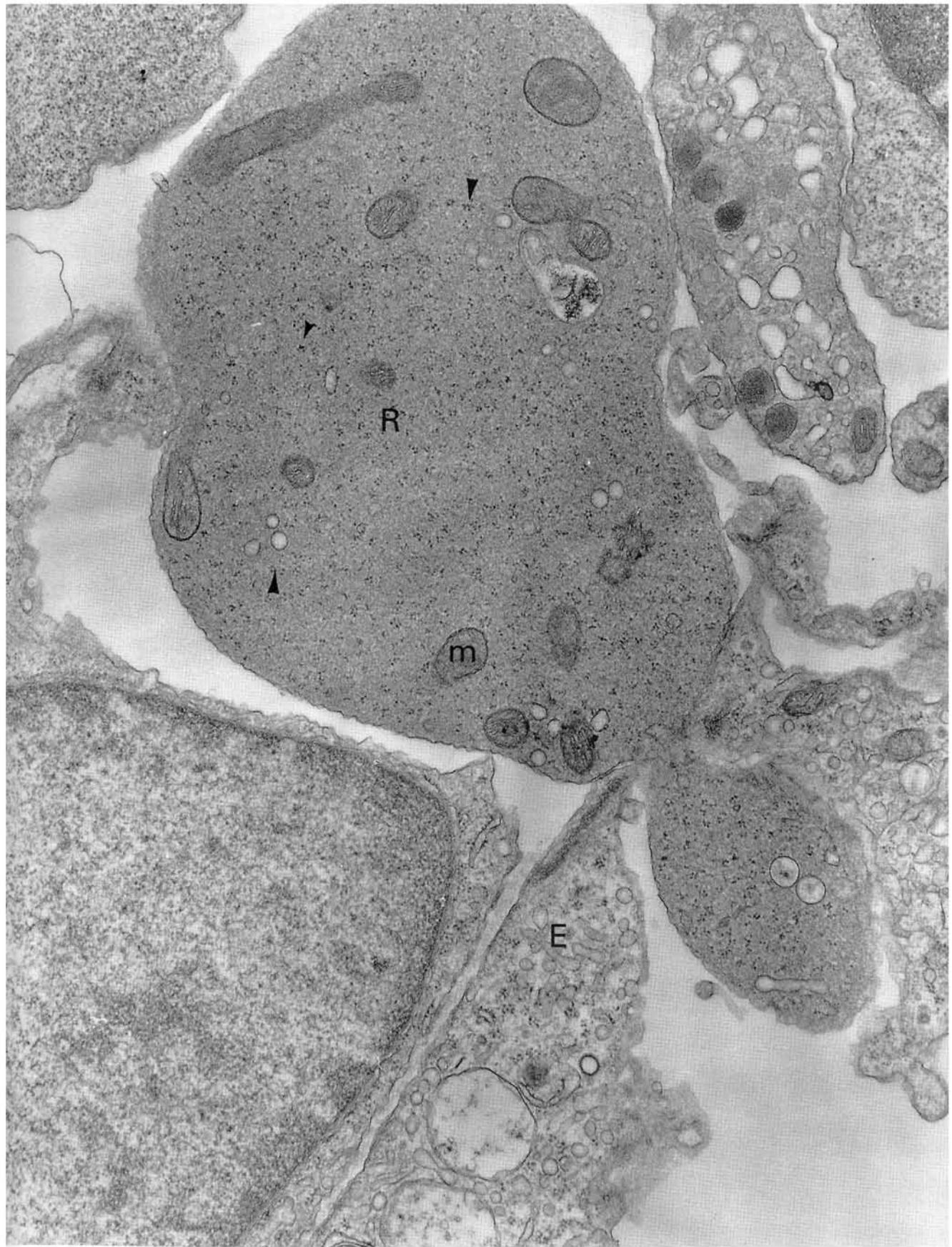
Orthochromatophilic erythroblasts (normoblasts) extrude their nuclei, which are immediately phagocytosed by associated macrophages. The remaining cytoplasm repairs quickly to form an immature red blood cell, the **reticulocyte** (R, micrograph). Normally one third of reticulocytes leave bone marrow and complete their differentiation in peripheral blood. The reticulocyte in the micrograph is in the process of squeezing between endothelial cells (E) lining the bone marrow sinusoid. The polysomes (arrowheads) and mitochondria (m) still present continue to be involved in hemoglobin synthesis as the cell completes maturation. The gradual loss of these structures as reticulocytes mature does not occur within lysosomes, but occurs within the cytoplasm when the polypeptide ubiquitin binds to organelle proteins, initiating their enzymatic destruction. Reticulocytes develop in one to two days into mature RBCs, biconcave discs tightly packed with hemoglobin.

The synthesis of the red blood cell **cytoskeleton** and associated unique membrane components occurs along with hemoglobin synthesis and is significant to RBC functioning. Spectrin, a protein dimer of two nonidentical rod-shaped polypeptides, binds to membrane proteins such as Band 3 and glycophorin via other proteins such as ankyrin and protein 4.1. This membrane–cytoskeleton network maintains the discoid shape that provides the large surface: volume ratio that is critical to the soft, pliable nature of the red cell. Mature cells are continually deformed as they travel through narrow capillaries. Even the reticulocyte demonstrates considerable flexibility as it enters the peripheral blood (micrograph).



Modified from S. B. Shoket & S. E. Lux, *Hosp. Pract.* 19 (1984). In L. Stryer, *Biochemistry*, Freeman, New York, 1988.

Erythroid cells depend upon an **attachment to fibronectin** in the stromal cell matrix for proper differentiation. Unattached cells grown in suspension are fragile and fail to assemble a stable cytoskeleton. As differentiation progresses, the number of fibronectin receptors on erythroid cells decreases, and cells normally detach at the reticulocyte stage. A constant number of reticulocytes leave the marrow and populate the peripheral blood as they detach from fibronectin.



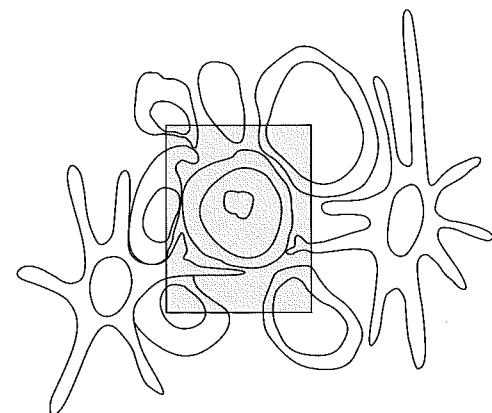
GRANULOPOIESIS: Promyelocyte

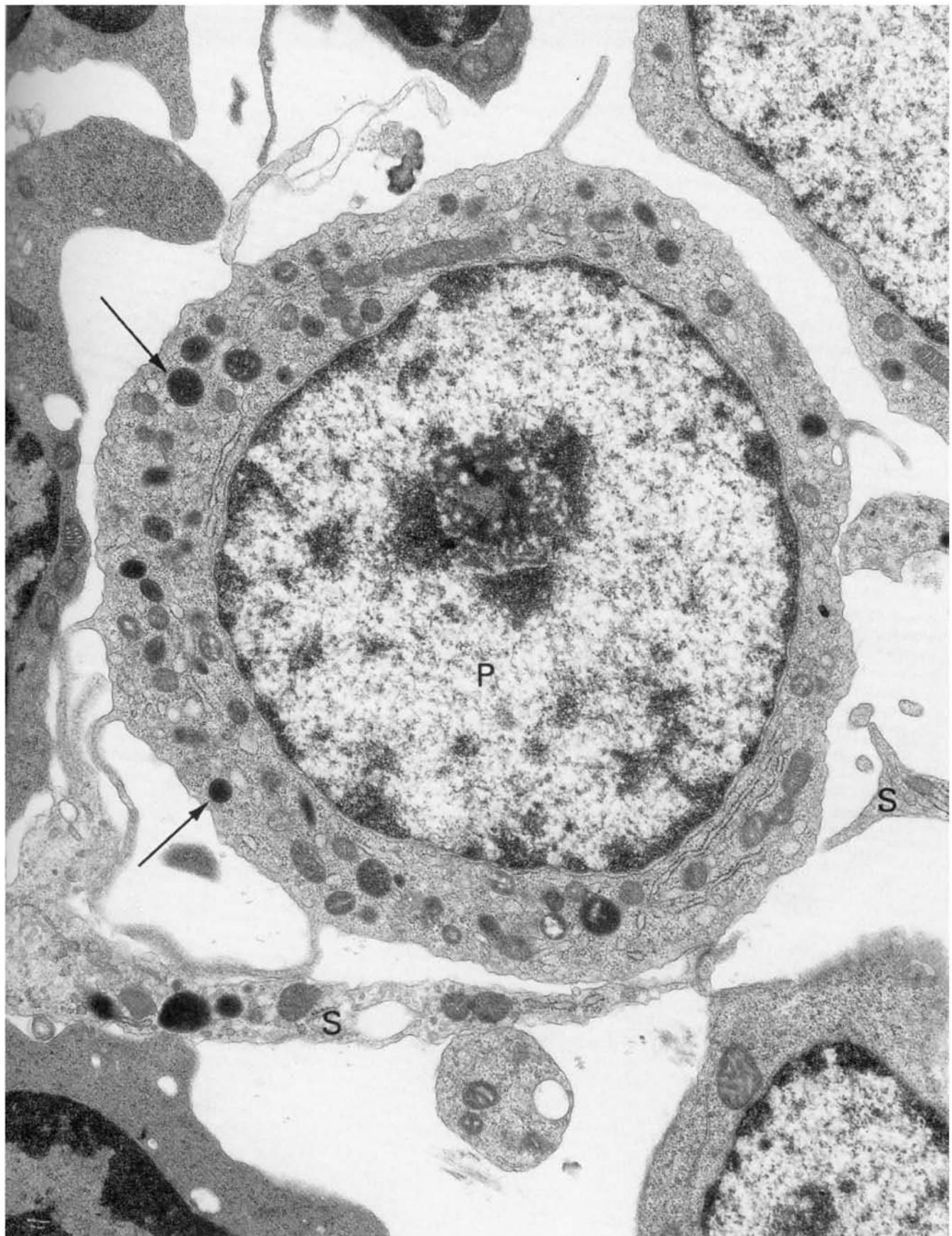
Granulopoiesis is the process of differentiation of neutrophils, eosinophils, and basophils, white blood cells (leukocytes) characterized in morphology and function by unique granules. The immediate precursor to these granulocytes, the **promyelocyte** (P, micrograph), is a large cell with a euchromatic nucleus and well-developed nucleolus. The granules synthesized at this stage are called primary since they are the first to be synthesized during development, and are called azurophilic due to their affinity for azure dyes in light-microscope preparations. **Primary granules** produced in the promyelocyte stage are distributed to all granulocytes as development proceeds. **Secondary or specific granules** of mature granulocytes are synthesized in subsequent stages. Many of the large, dense primary granules (arrows, micrograph) are similar to lysosomes in their content of acid hydrolases (e.g., β -glucuronidase), but others contain components such as neutral proteases (e.g., elastase) and microbial enzymes (e.g., lysozyme, myeloperoxidase).

Promyelocytes, identified as a single cell-type in bone marrow smears, are actually different in their developmental potential. In culture some promyelocytes form colonies that give rise to (1) neutrophils and monocytes, (2) eosinophils, or (3) basophils. The development of these clones seems to depend upon separate colony-stimulating factors.

Myeloperoxidase (MPO), a heme-containing microbial enzyme synthesized during this stage and sequestered in the primary granules, has received considerable attention due to its role in the formation of hypochlorous acid and other toxic oxygen species that function during the respiratory burst of phagocyte killing (see Cell, page 20). This enzyme is synthesized as a large precursor on the rough ER, processed in the Golgi, and transported to primary granules. The gene that encodes MPO, localized to chromosome 17, is translocated (partially or completely) to chromosome 15 in acute promyelocytic leukemia. Such malignant promyelocytes exhibit increased numbers of abnormal granules and unusually high concentrations of MPO.

The processes of **stromal cells** (S) are seen in this micrograph adjacent to the promyelocyte. Stromal cell glycosaminoglycans adsorb colony-stimulating factors and concentrate them in specific microenvironments in which they act to stimulate clonal expansion of precursor cells.





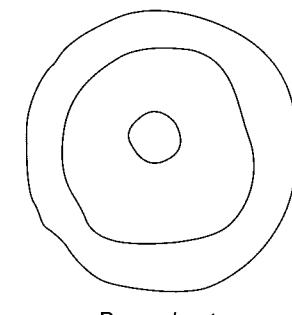
GRANULOPOIESIS: Myelocyte and Band Neutrophil

Promyelocytes divide and differentiate to form **myelocytes** (micrograph 1). Myelocytes and earlier stages are capable of division and form a mitotic pool of precursor cells within the bone marrow. Cells within this pool are only seen in peripheral blood in disease states. During the myelocyte stage, **secondary (specific) granules** are formed that contain at least one component unique to the granulocyte type (e.g., lactoferrin in neutrophils, histamine in basophils, major basic protein in eosinophils). In the neutrophil stages in the micrographs, the specific granules (arrows) are generally smaller and less dense than the larger primary granules (arrowheads) inherited from the promyelocyte. Specific granules, initially synthesized in the myelocyte stage, are also synthesized during subsequent stages. The prominent Golgi (G) in the **band neutrophil** in micrograph 2 is critical to granule formation.

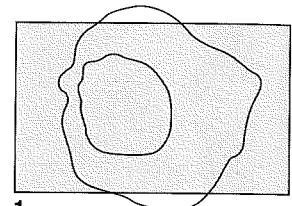
Evidence suggests that several different kinds of specific granules are synthesized during neutrophil development, each containing different substances. In mature neutrophils they are released at different times and are under different control mechanisms. Contents of neutrophil specific granules include (1) lactoferrin, a glycoprotein that facilitates the formation of the hydroxyl radical in respiratory burst activity, (2) chemoattractants, opsonins, and activators of complement synthesis, and (3) collagenase, an enzyme important to the migration of neutrophils in loose connective tissue.

The membranes of specific granules concentrate many receptors and enzymes. Following initial exposure to the bacterial chemoattractant N-formyl-methionyl-leucyl phenylalanine (FMLP), granule membranes fuse with the cell membrane, resulting in the immediate exposure of concentrated FMLP receptors ("up regulation"). An activated human neutrophil has up to 50,000 FMLP receptors.

During differentiation into a mature neutrophil, the nucleus undergoes a series of changes, from large, round, and euchromatic to band-shaped and less euchromatic to a small, heterochromatic nucleus with 3–5 lobes in the mature cell. At the same time the cell becomes smaller. Both band and mature neutrophils are normally released into peripheral blood in a ratio of 1:3.

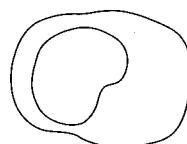


Promyelocyte

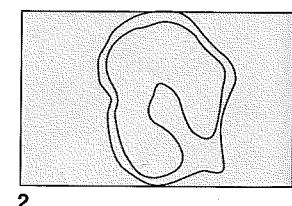


1

Myelocyte

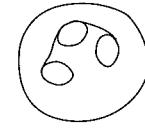


Metamyelocyte

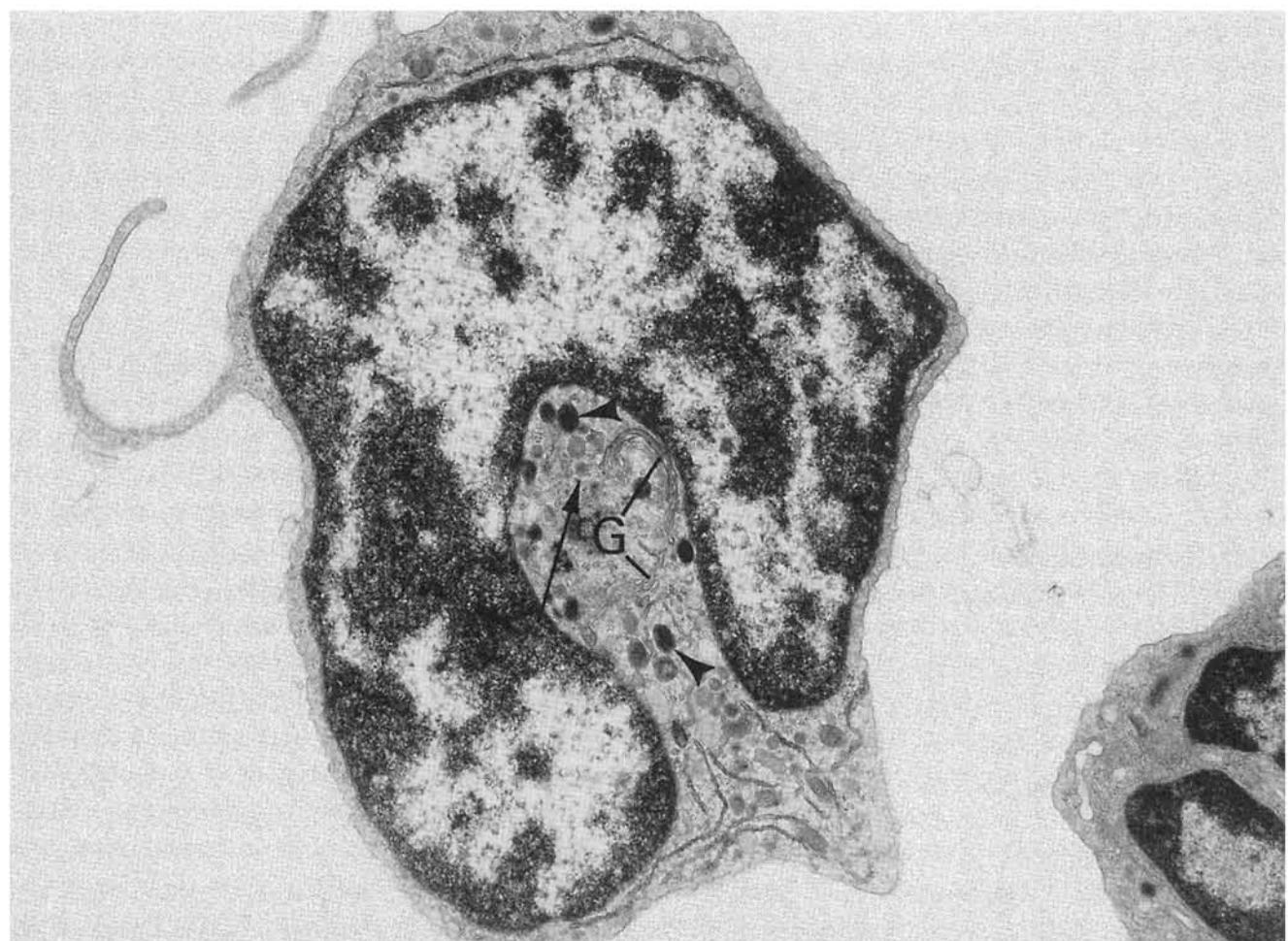
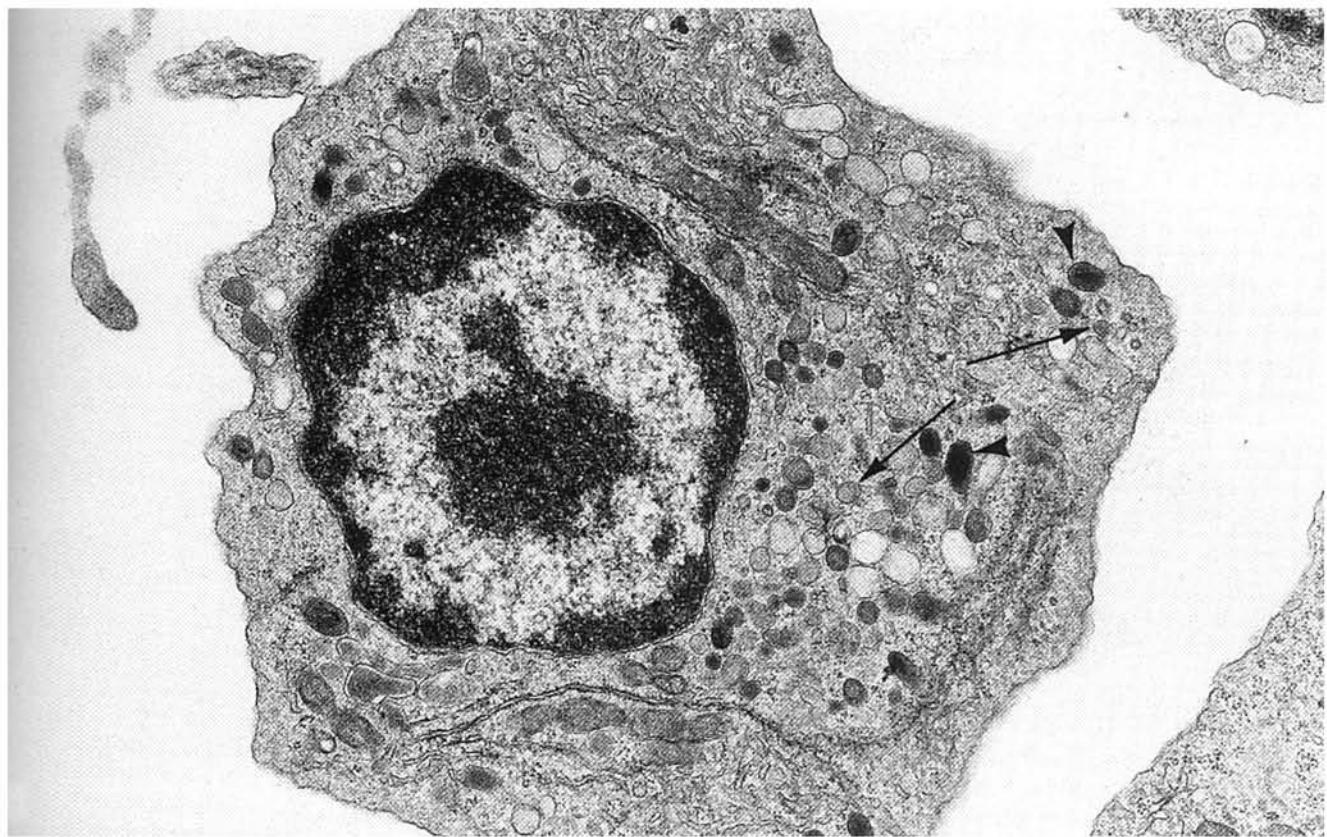


2

Band neutrophil

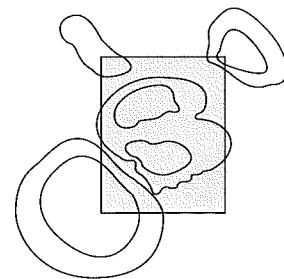


Mature neutrophil



GRANULOCYTE: Neutrophil

Neutrophils have a relatively heterochromatic nucleus (N) divided into three to five lobes (section shown in micrograph passes through only two) and a cytoplasm packed with **primary** and **secondary granules** (arrows). In the mature cell, the rough ER (arrowheads, micrograph) and Golgi (G, micrograph) remain active in the production and packaging of secondary granules. Following 10 days of postmitotic development in bone marrow, mature segmented neutrophils (segs, polymorphonuclear leukocytes, or PMNs) leave bone marrow and travel in peripheral blood for approximately 10 hours before they squeeze between endothelial cells (diapedesis) and migrate to infected regions.

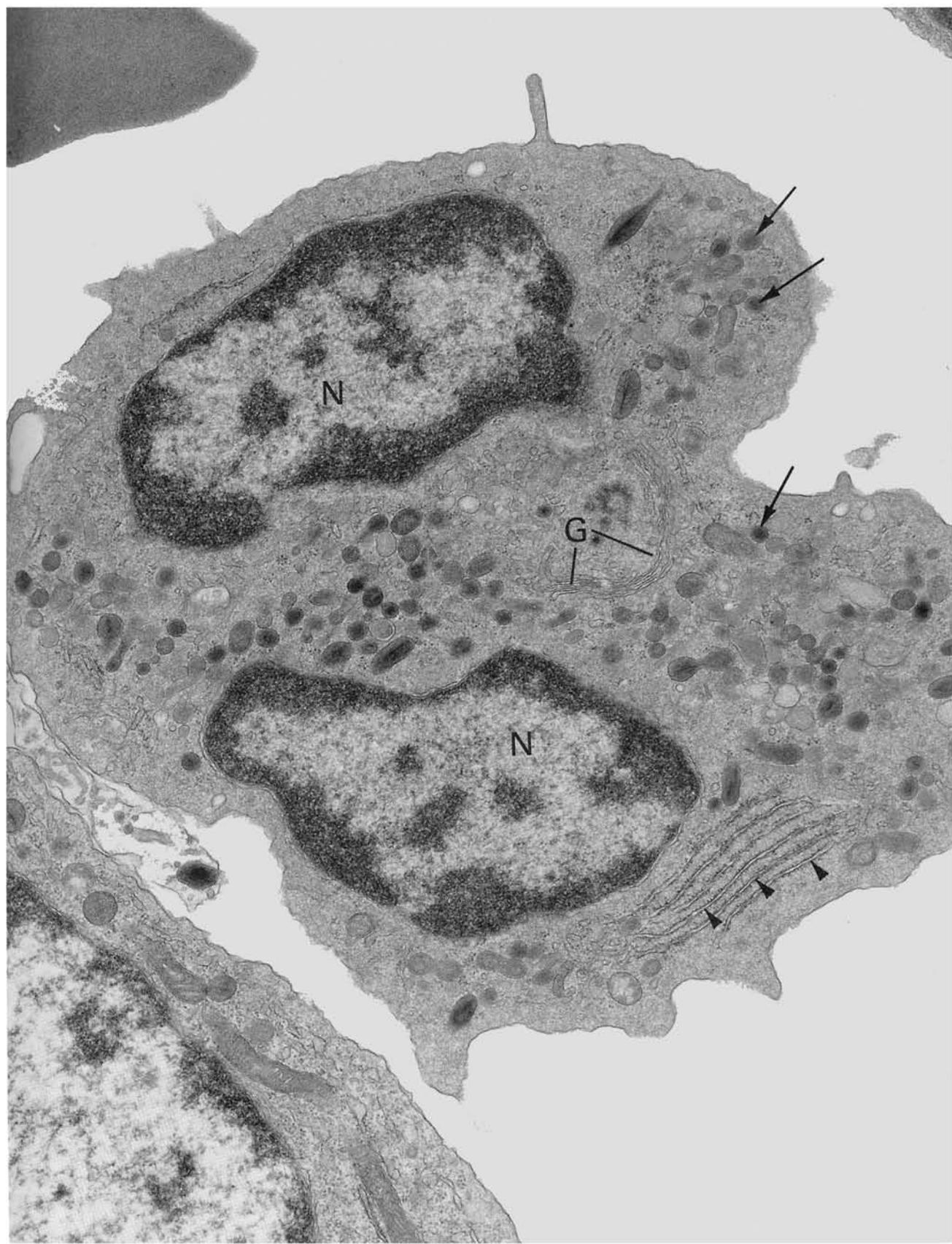


Neutrophils are the initial phagocytes at the site of infection. In comparison to their companion phagocytes, the macrophages, neutrophils are quicker and more specialized. They reach a site of infection first and concentrate on the phagocytosis of opsonized bacteria. Macrophages arrive later and clear the battlefield remains. In both of these cell types, receptor contact with the coated antigenic material initiates increased enzyme activity in the cell membrane and granules.

A variety of types of granules are produced by neutrophils, but it is impossible to distinguish them by ultrastructure and even difficult using histo- or immunochemical techniques. Some of the granules are associated with the phagocytic role of neutrophils, while others release substances involved in migration and cell interaction. Many are involved in the respiratory burst that kills phagocytosed bacteria. When opsonized bacteria bind to neutrophil receptors, oxygen consumption increases 100-fold and toxic oxygen species are formed. One of these, hypochlorous acid, is capable of altering nucleotides and cytochromes as part of the killing action. How these events are coordinated in subcellular compartments is not precisely known; however, one of the initial steps involving NADPH oxidase occurs on the cell membrane.

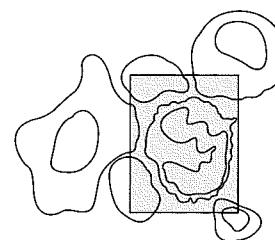
In a rare X-linked disorder, chronic granulomatous disease, neutrophils are unable to undergo a respiratory burst, and affected individuals are subject to recurrent, sometimes fatal, infections. The defective gene in this disease has been found to code for a part of a cytochrome that may act as an electron carrier in association with NADPH oxidase activity.

Aside from the role of oxidants in defense against microorganisms, their release can also cause tissue injury and contribute to such diseases as adult respiratory distress syndrome and arthritis. In addition, products of phagocyte oxygen metabolism have recently been implicated in carcinogenesis.



GRANULOCYTE: Eosinophil

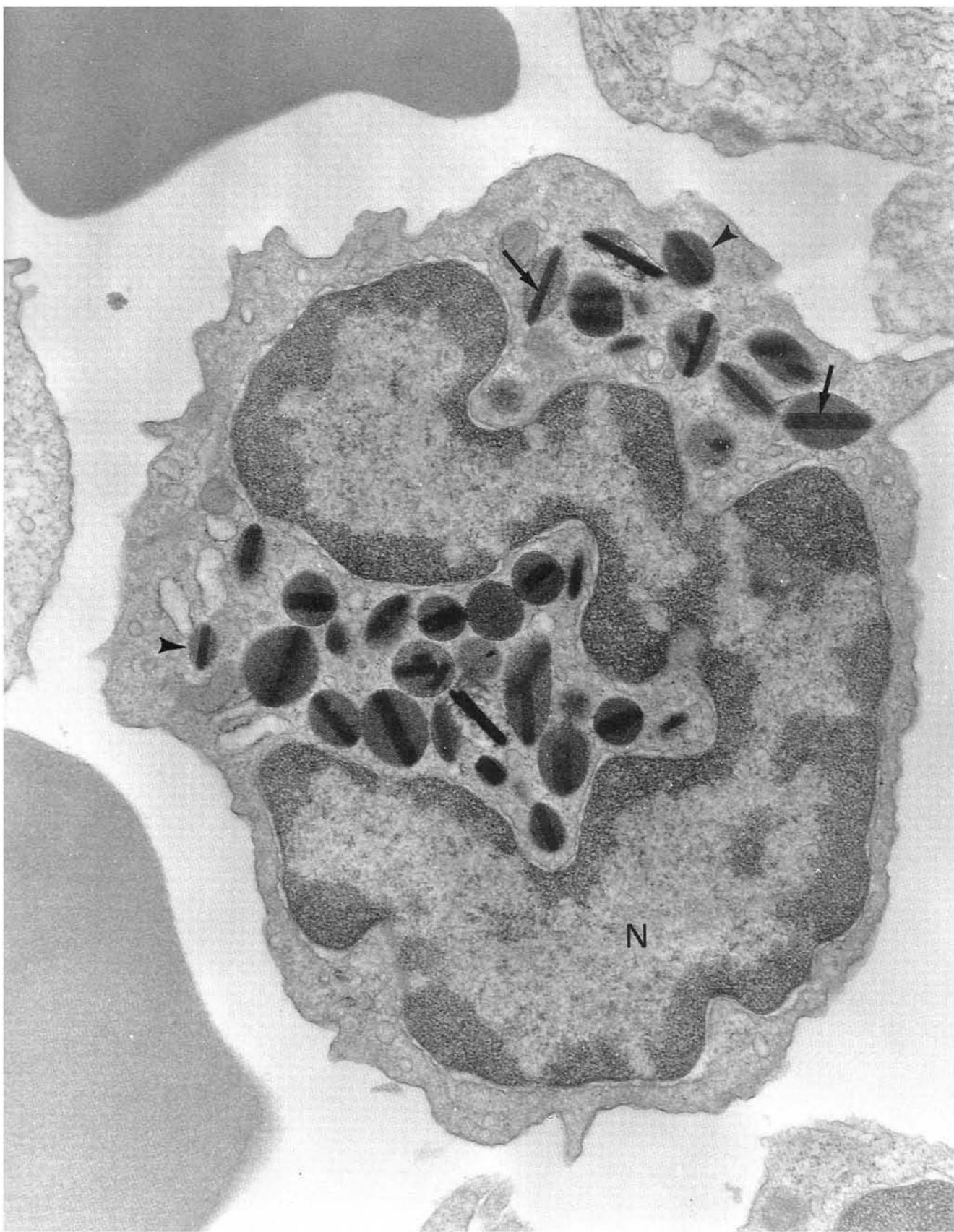
Eosinophils (micrograph) contain characteristic large specific granules (arrowheads). These specific granules contain several **cationic proteins**, of which the most abundant and well characterized are eosinophilic cationic protein, major basic protein, and eosinophil peroxidase. Major basic protein differs from eosinophilic cationic protein in many respects, including its tendency to aggregate and form the insoluble crystalline cores (arrows, micrograph) that give eosinophils their unique appearance on electron micrographs. The band-shaped nucleus (N, micrograph) shown here will separate into two to three lobes as the cell completes maturation.



Eosinophils are attracted to sites of infection and function to dampen the effects of mast cell degranulation (see Connective Tissue, page 78). In addition, they are the principal defense against **schistosomiasis**, a parasitic helminthic disease that kills more than 800,000 people per year throughout the world.

In schistosomiasis, the number of eosinophils in larval-infected tissues reaches 100,000/mm³. Eosinophil receptors attach to the Fc portion of antibodies that coat the larvae. Receptor binding activates the release of granule contents directly onto the larval surface. Both **eosinophilic cationic protein** and **major basic protein** are capable of causing damage; however, eosinophilic cationic protein seems to be the most potent and is effective *in vitro* at a concentration as low as 10⁻⁷ M. Eosinophilic cationic protein acts by altering membrane permeability by creating transmembrane pores. This type of membrane damage is also caused by complement and cytotoxic T cells, and may be a common killing mechanism in immune defense.

Like neutrophils and macrophages, eosinophils depend upon a respiratory burst for their functioning. Peroxidase activity within the eosinophilic granules is part of a sequence leading to the formation of toxic oxidants. In contrast to other cell types, however, the eosinophil peroxidase preferentially oxidizes bromide instead of chloride to form hypobromous acid (HOBr), a more toxic and faster acting agent. In addition to the role of peroxidase in killing, this enzyme, along with eosinophil histaminase, helps regulate the effects of mast cell activity at sites of antigen invasion.



AGRANULOCYTE: Monocyte

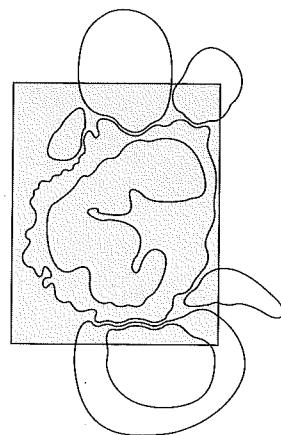
In contrast to granulocytes, a major part of the differentiation of the **agranular leukocytes** (monocytes and lymphocytes) occurs after they leave bone marrow. These cells leave the marrow as relatively immature cells capable of mitosis and travel to other tissues and organs where they divide and undergo critical differentiation changes.

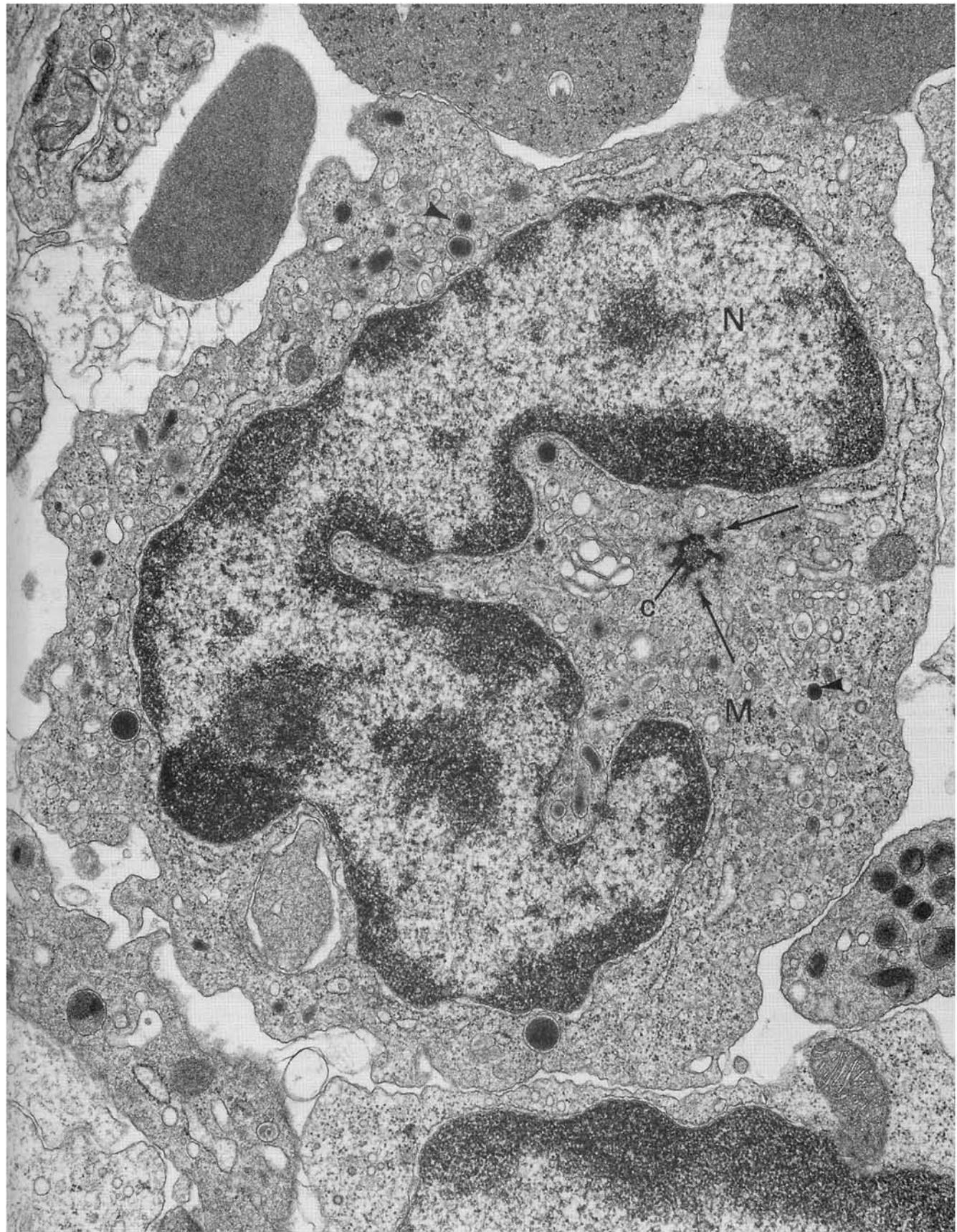
Monocytes (M, micrograph), often recognized by their euchromatic indented nucleus (N, micrograph), are the largest cells normally found in peripheral blood. They circulate for approximately 14 hours and then migrate into tissues throughout the body where they differentiate into a variety of cell types. The most ubiquitous is the **macrophage**, which is found in many different regions where it functions in defense (secondary lymphoid regions, connective tissue, liver, lung) and in removing old and diseased red blood cells (spleen and liver) and platelets (spleen). Monocytes also fuse to form specialized cells such as osteoclasts in bone, giant foreign body cells in certain types of inflammation, and Reed–Sternberg cells in the malignant lymphoma of Hodgkin’s disease.

Many of the organelles seen within the monocyte in the micrograph will become particularly important during the division and differentiation into these varied cell types. The centriole (c) and its associated microtubule-organizing centers (arrows) will play major roles as organizers of the mitotic spindle during division, and the primary lysosomes (arrowheads) will increase in number to perform their function either in phagocytosis (macrophages) or secretion (osteoclasts).

Monocytes are attracted to areas of injury by bacterial components, products associated with tissue injury (e.g., fragments of elastin and fibronectin, platelet-derived growth factor), and many cytokines released from activated cells involved in defense. One such cytokine chemoattractant is granulocyte–macrophage colony-stimulating factor (GM-CSF) produced by T lymphocytes at the site of injury. CSFs seem not only to promote growth during blood cell development in bone marrow but also to affect the differentiation and the activity of certain blood cells during activation.

Monocytes (and macrophages) are important secretory cells. One significant secretion released in response to infection is interleukin 1, a protein with far-ranging effects. This protein acts locally on T cell activation and systemically on (1) the enhancement of liver cell synthesis of proteins associated with inflammation (the hepatic acute phase reaction) and (2) the release of glucocorticoids that regulate immune function during stress. Interleukin 1 released by monocytes stimulates the synthesis of corticotropin-releasing factor (CRF) in the hypothalamus, which, via adrenocorticotrophic hormone (ACTH) from the pituitary, increases glucocorticoid release.





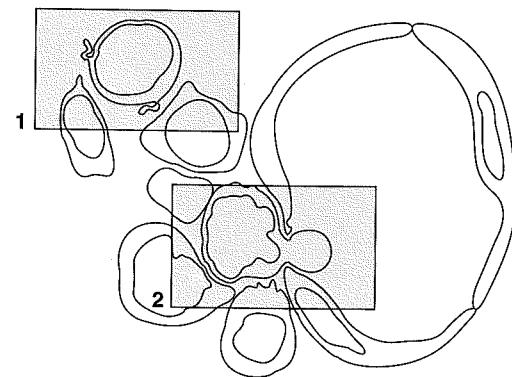
AGRANULOCYTE: Lymphocyte

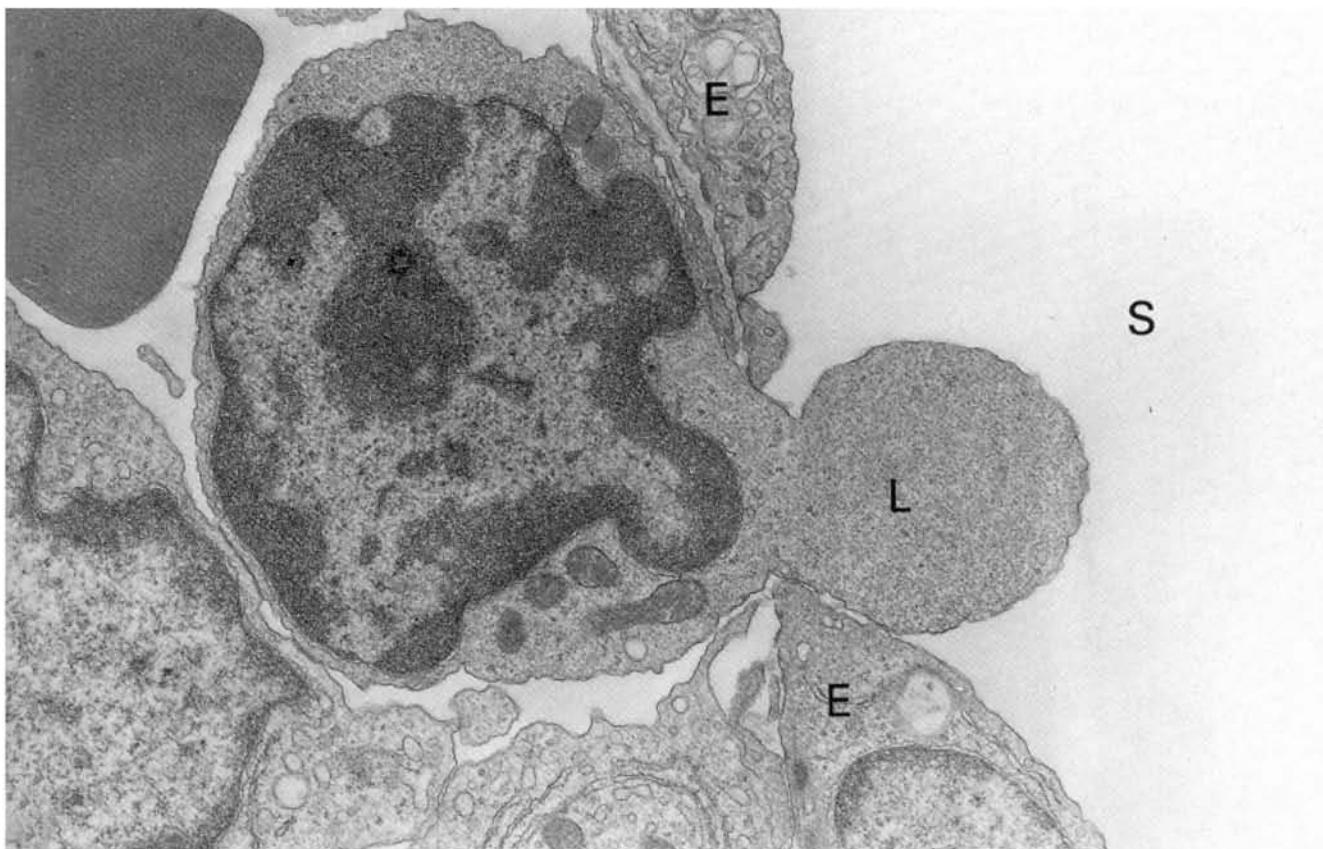
Most lymphocytes (L, micrograph 1) are small ($10\text{ }\mu\text{m}$), with a thin rim of cytoplasm and surface projections. These cells, like monocytes, leave bone marrow in a relatively undifferentiated stage and enter the peripheral blood, where they travel to lymphoid organs (spleen, lymph nodes, thymus) and tissues (Peyer's patches in the intestine and connective tissue underlying most luminal surfaces). The lymphocyte (L) in micrograph 2 is in the process of squeezing between two endothelial cells (E) to enter a bone marrow sinusoid (S). Peripheral blood lymphocytes represent less than 5% of the total lymphocyte pool. Since lymphocytes periodically enter and leave peripheral blood during their life span, this traveling 5% represents an extremely **heterogeneous population**. Some of those that have recently left bone marrow are not yet immunocompetent; others are memory cells that have undergone a previous activation by antigen in a peripheral organ and are migrating to another peripheral site.

Two major classes of lymphocytes develop from a pluripotent lymphoid stem cell in the bone marrow, the **B cells** involved in humoral immunity and the **T cells** involved in cell-mediated immunity. Lymphocytes destined to become T types leave the bone marrow and travel to the thymus, where they differentiate and develop immunocompetence. In contrast, B lymphocytes remain in bone marrow and seem to develop immunocompetence in this region before traveling to the peripheral lymphoid organs.

The first committed B precursors to be recognized contain small amounts of cytoplasmic immunoglobulin which is probably a type of IgM. There is no surface expression of this immunoglobulin at this early stage, but these cells are committed to respond to a single antigenic determinant. In the next stage of B cell development IgM is expressed on the surface. It is not clear whether this occurs in bone marrow or in peripheral lymphoid tissues and organs.

Acute lymphocytic leukemia, the most common leukemia in children, is a result of a deficiency of the enzyme adenosine deaminase in a bone marrow lymphocyte stem cell. Purine synthesis is impaired and a toxic metabolite, deoxyadenosine, accumulates. As in other leukemias, increasing numbers of abnormal cells crowd out other developing blood cells and spill into the peripheral blood.





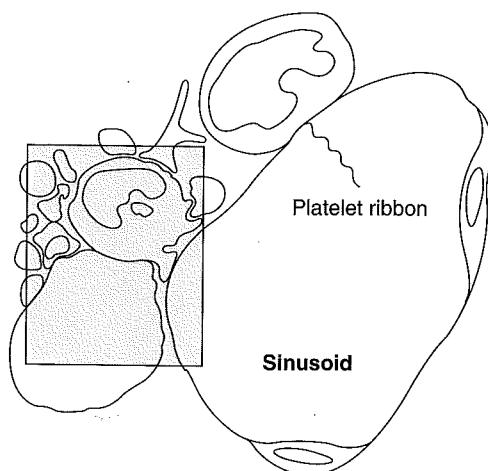
PLATELETS: Megakaryocyte

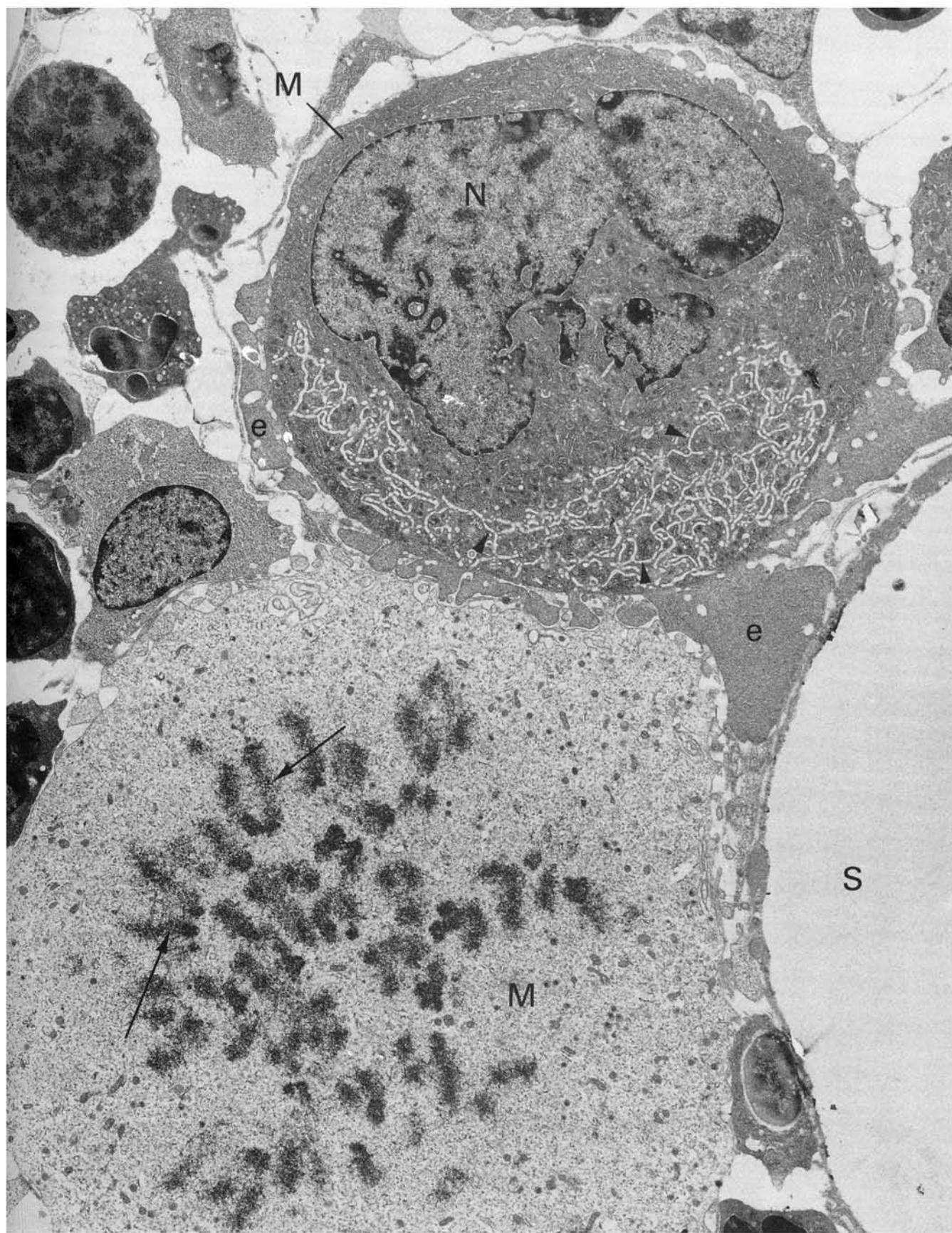
Megakaryocytes (M, micrograph) are large, polyploid cells that give rise to **platelets**. They develop from small pluripotent stem cells that undergo first cellular division, then a subsequent series of chromosome divisions without cytoplasmic division (endomitosis). During endomitosis several metaphase plates are formed and chromosomes separate and move apart. The section of the dividing megakaryocyte in the facing micrograph is probably a polar view through one of these metaphase plates (arrows designate chromosomes).

Following division the different chromosome groups come together enclosed by the same nuclear membrane. Endomitosis results in cells with large multilobed nuclei (N, micrograph) that are 8N, 16N, 32N, or 64N. The greater the number of chromosomes in a megakaryocyte, the greater the amount of cytoplasm that is synthesized and the greater the number of platelets formed. Megakaryocytes can form up to 8000 platelets.

During the cytoplasmic maturation of megakaryocytes, the cell membrane invaginates to form channels separating cytoplasmic islands about $3-4 \mu\text{m}$ in diameter. These **platelet demarcation channels** (arrowheads, micrograph) eventually coalesce to release platelets. During early cytoplasmic maturation the outer rim of megakaryocytes is frequently devoid of organelles and forms a kind of ectoplasm (e, micrograph).

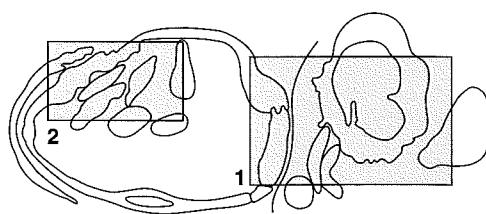
Megakaryocytes typically rest next to bone marrow sinusoids (S, micrograph) and extend cytoplasmic projections between endothelial cells into the sinusoids. Many platelets appear to be released together as a “ribbon” from these extensions, with the actual formation of individual platelets usually occurring after the ribbon separates from the megakaryocyte.





PLATELETS: Mature Platelets

Platelets (P, micrographs 1 and 2) are small (2–4 μm) **biconvex cell fragments** that repair blood vessels. These cell fragments reach concentrations of approximately 250,000/ mm^3 . At a site of injury they respond to substances as diverse as thrombin, adenosine diphosphate (ADP), and basal lamina proteins. The glycocalyx covering platelets contains many receptors for such agonists. Once activated, platelets change shape, acquire surface stickiness, aggregate, release mediators (both newly synthesized and stored), and contract. This sequence, which usually repairs a damaged vessel surface and maintains blood homeostasis, can also lead to vessel wall thickening and result in disease states such as arteriosclerosis.

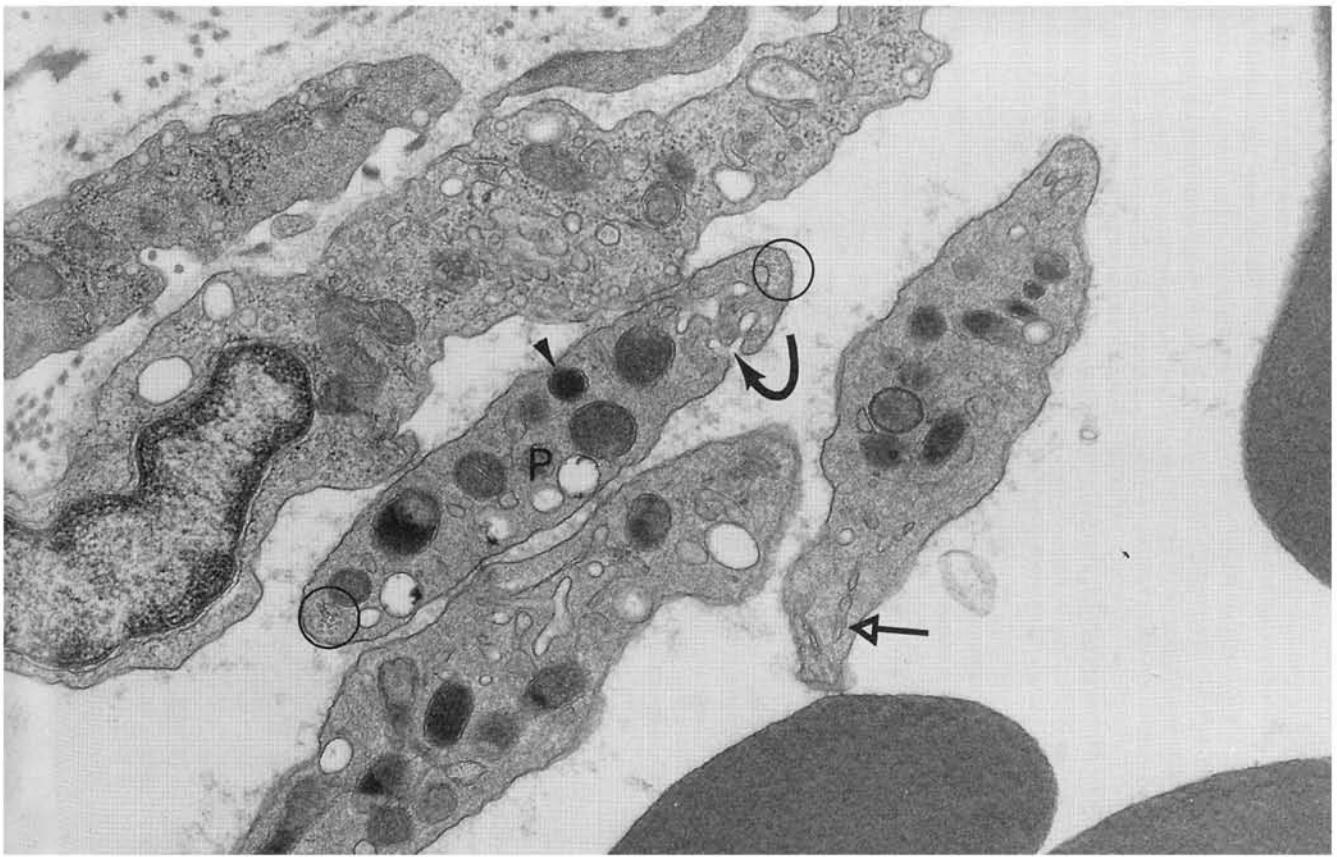
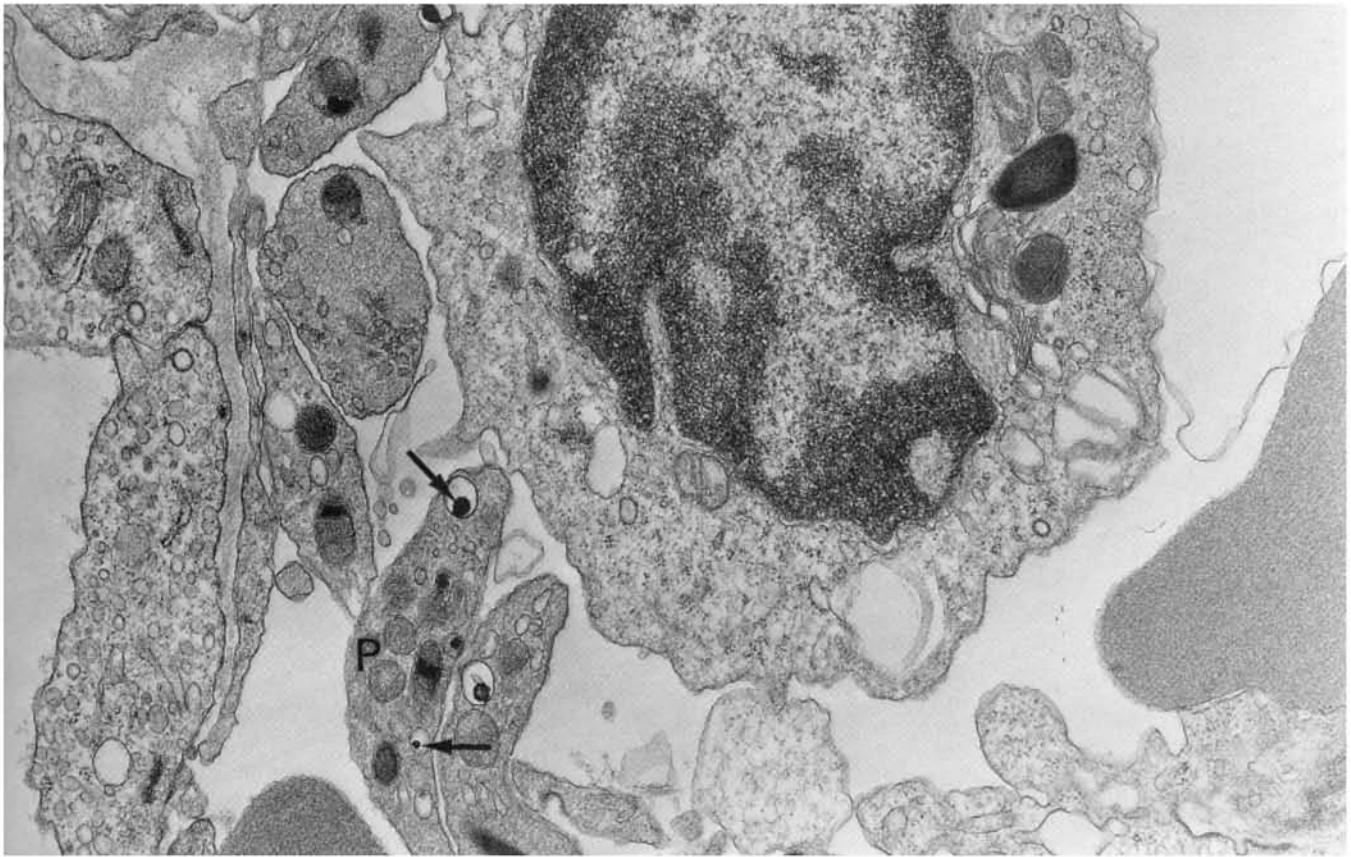


During the initial stage of activation platelets adhere to exposed basal lamina. Attachment activates the release of components from two types of granules, those with a dense core (arrows, micrograph 1) usually separated from the granule membrane, and those with variable form and less dense contents (arrowhead, micrograph 2). The **dense core granules** contain products, including adenine nucleotides and serotonin, that are picked up from other cells and temporarily stored. ADP is an important platelet aggregator, and serotonin causes the contraction of smooth muscle in damaged vessels, minimizing blood loss.

The less dense granules consist of at least two types, **lysosomes** with acid hydrolases, and **α -granules** that contain molecules active in coagulation including platelet factor-4 and fibrinogen. Alpha granules also contain platelet-derived growth factor, which, due to its effect on vascular smooth muscle proliferation and migration and its ability to attract monocytes, is often considered a key element in vascular disease.

When platelets are activated, both the α - and dense core granules release their contents either directly onto the surface or into the **open canalicular system**, which forms snakelike channels that open onto the platelet surface. One region where the open canalicular system is continuous with the platelet surface is shown at the curved arrow in micrograph 2. A second system of channels, the **dense tubular system** (open arrow), is a separate organelle derived from megakaryocyte smooth ER that concentrates calcium and plays an important role in platelet activation.

Even though actin is the most abundant cytoskeletal element in platelets, the most prominent in most electron micrographs is the ring of **microtubules** near the cell membrane, seen in cross section in micrograph 2 (circles). These microtubules maintain the integrity of platelets even when they undergo the pronounced shape change from discoid to the spiky spheres characteristic of activation.



BONE MARROW

These low-magnification micrographs of bone marrow help to emphasize the diversity of cells in this organ. In micrograph 1, a striking comparison can be made between the small heterochromatic nucleus of the **orthochromatophilic erythroblast** (OE), the lobed nucleus of the mature **neutrophil** (N), and the small round nuclei of the **lymphocyte** (L) and **plasma cell** (P). The cytoplasm of these four cells is equally distinct. Each characteristic provides insight into the function of the cell, from the electron-dense hemoglobin in the RBC precursor (OE) to the bactericidal granules in the neutrophil to the thin rim of cytoplasm with surface extensions in the motile lymphocyte to the rough ER dilated with antibody in the plasma cell.

In micrograph 2, the **macrophage** (M), with its primary and secondary lysosomes and irregular euchromatic nucleus, stands out from the **polychromatophilic erythroblast** (PE) and the developing **granulocyte** (G). As shown in micrograph 3, macrophages (M), which in connective tissue are considered relatively large cells, are dwarfed in bone marrow by **megakaryocytes** (ME). With their small size and dense nuclei and cytoplasm, the polychromatophilic (PE) and orthochromatophilic (OE) erythroblasts in this micrograph provide even more contrast.

All of the cells identified in these micrographs originated from a single precursor cell during a rapid sequence of mitosis and differentiation. The severity of bone marrow disease relates to the far-reaching effects of a defect in a single stem cell. Acute myelocytic leukemia, one of the most severe bone marrow disorders, with a median survival time of two months, is probably a disease of the pluripotent myeloid stem cell (see Blood, page 164). This cell continues to divide, but differentiation is impaired and immature cells accumulate in bone marrow and peripheral blood. The reduction in the number of mature erythrocytes, granulocytes, and platelets results in anemia, infection, and bleeding disorders. In severe cases, some of the malignant precursor cells settle in blood vessels in the brain and form tumors, leading to cerebral hemorrhage.

