Megakaryocyte or Precursor, Normal

SYNONYMS
none

VITAL STATISTICS

size	20-160 µm in diameter
N:C ratio	varible, depending on maturation of cell; early forms have a high N:C rato which decreases as cell matures and acquires cytoplasm; at the end of cell lifespan, the cytoplasm is discharged as platelets and the N:C ratio increases again
cell shape	variable; may be round or have irregular cytoplasmic contours; platelets may form at the periphery producing a fragmented sillouette
nuclear shape	young cells: round or horseshoe shaped; mature cells: irregularly lobed, ring-shaped or doughnut-shaped; lobes are connected; not multinucleated
chromatin	dense; stains dark purple-blue; less clumped in young cells
nucleoli	immature cells only
cytoplasm	young cells: basophilic and agranular or a few granules; mature cells: abundant light blue and packed with fine azurophilic granules that cluster producing a checkerboard pattern

KEY DIFFERENTIATING FEATURES
- mature cells: low N:C ratio, large cell size, highly lobed nucleus, light blue cytoplasm packed with pink granules, platelets sometimes at periphery
- young cells: moderate N:C ratio, moderately clumped chromatin, basophilic cytoplasm with irregular boarder, para-nuclear early granule formation
- blasts: high N:C ratio, round nucleus, evenly distributed chromatin, nucleoli, basophilic cytoplasm

POTENTIAL LOOK-ALIKES
- histiocytes and macrophages (Langerhans and Touton giant cells, Gaucher's and other storage disease cells)
- osteoclast and osteoblast
- lymphoma (hyperlobated cell, Reed-Sternberg cell)
- granulocytic precursors (mimic micromegakaryocytes)
- metastatic tumor cells

ASSOCIATED DISEASE STATES AND CONDITIONS
normal finding in bone marrow

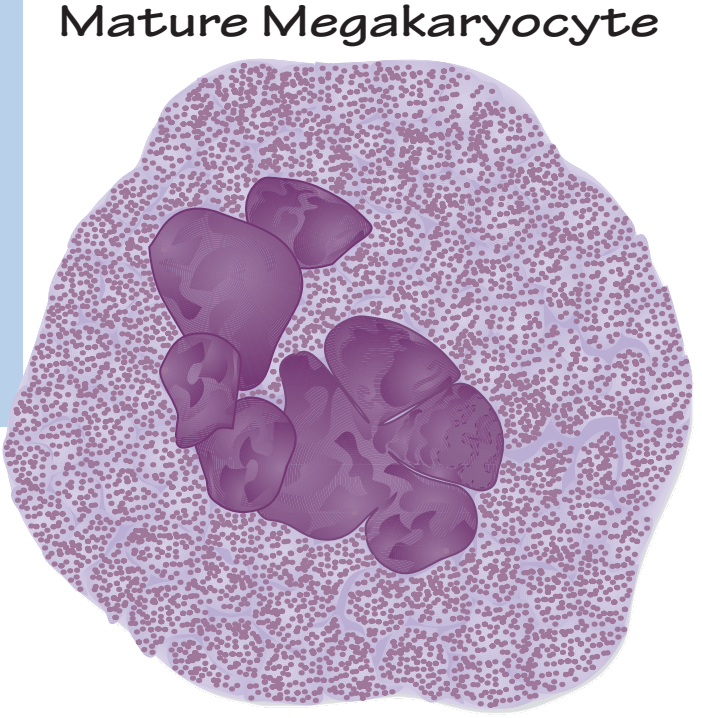
Megakaryocytes develop from a series of committed stem cells, the last one designated CFU-MK. The committed cell goes through a sequence of nuclear duplication without cell division called *endomitosis* or *endoreduplication*. The result is a large cell with abundant cytoplasm and a hyperdiploid nucleus. The cytoplasm then matures, dividing into territories which eventually become mature platelets. The entire maturation sequence is detailed in the following *A Closer Look At…Megakaryocyte Maturation* discussion on page 190.

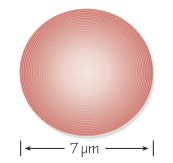
The CFU-MK stem cell is a mononuclear lymphoid-like cell with megakaryocyte-specific cell markers but no morphologic distinguishing features. As the cell develops, three stages are recognized:

Stage I: megakaryoblast
Stage II: promegakaryocyte
Stage III: granular or mature megakaryocyte

The mononuclear megakaryoblast is at least 15 µm in size. The nucleus is round or a slightly indented with evenly distributed chromatin. Nucleoli are generally visible and may be prominent. The nucleus is surrounded by a small rim of basophilic cytoplasm.

The promegakaryocyte, also knows as basophilic megakaryocyte, is at least 20 µm in size and has a lobated or horseshoe-shaped nucleus. Chromatin starts to show significant clumping. There is a moderate amount of intensely basophilic cytoplasm that may be irregular in shape with blebs and extensions. The earliest site of platelet production occurs next to the





nucleus. Here, azurophilic granules form. Later stages may have a patchy eosinophilic cytoplasm. This stage marks the end of DNA duplication.

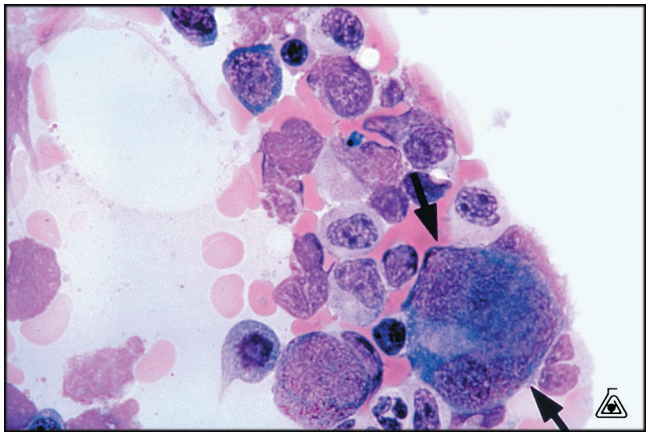
Granular megakaryocytes are capable of platelet production. They are the largest bone marrow hematopoietic cell, meauring at least 25-50 µm. They are normally pleomorphic and a spectrum of cell shapes and sizes is typical. The numerous nuclear lobes are of various sizes, connected by large bands or fine chromatin threads. The chromatin is initially coarse and clumped and later pyknotic in the fully mature megakaryocyte. The abundant cytoplasm stains pink or wine-red and contains fine azurophilic granules which may be clustered due to formation of demarcation lines. This produces a checkered pattern.

Increased numbers of megakaryocytes are seen in chronic myeloproliferative disorders, myelodysplastic syndromes, acute megakaryoblastic leukemia (M7), ITP, hypersplenism, infections, blood loss (intra or extravascular), and some malignancies.

Decreased numbers of megakaryocytes are seen in acute leukemia, infiltration of the marrow by neoplastic cells (histiocytes, lymphoma, carcinoma, etc.), occasional myelodysplastic syndromes, amegakaryocytic thrombocytopenia, viral infections, aplastic anemia, and radiation or toxic-drug treatments.

HE-44, 1992 (Bone Marrow, Wright-Giemsa, X300)

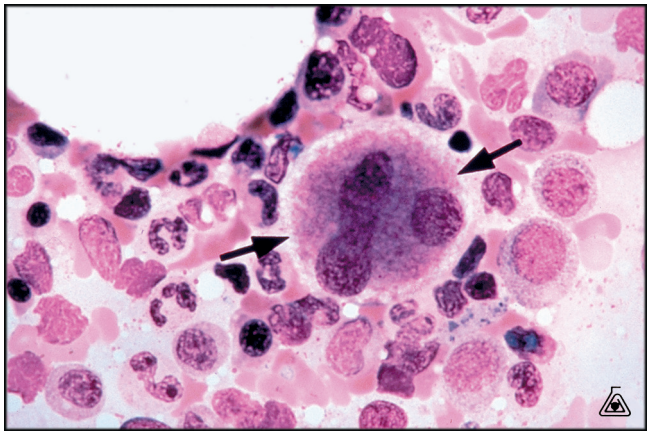
Identification	Referee %	Participant %
Megakaryocyte or precursor, normal	47.4	39.7
Megakaryocyte or precursor, abnormal	52.6	48.0



The arrowed cell is a normal megakaryocyte precursor (promegakaryocyte). The nucleus is lobated and the chromatin is coarse but relatively evenly distributed. No nucleoli are visible. The cytoplasm is basophilic and lacks the marked granularity associated with mature megakaryocytes. Early granule production is seen near the golgi region. Many of the participants and referees incorrectly identified this cell as an abnormal megakaryocyte. Such cells are generally too small (micromegakaryocytes), gigantic, or have too few or too many nuclear lobations. None of these dysplastic features are seen in the arrowed cell. Its only "aberration" is immaturity.

HE-43, 1992 (Bone Marrow, Wright-Giemsa, X300)

Identification	Referee %	Participant %
Megakaryocyte or precursor, normal	100	83.5
Megakaryocyte or precursor, abnormal	-	11.4



The arrowed cell is a normal mature megakaryocyte. The large cell has multiple, overlapping nuclear lobes and abundant granulated cytoplasm. Three nuclear lobes are visible; one appears separate from the other two which are overlapping. The chromatin is clumped. No nucleoli are visible. Notice how the cytoplasm is divided into smaller platelet territories. Soon it will fragment into thousands of small platelets. The remaining nucleus will condense and be digested by bone marrow macrophages.

A Closer Look At...

Megakaryocyte Maturation

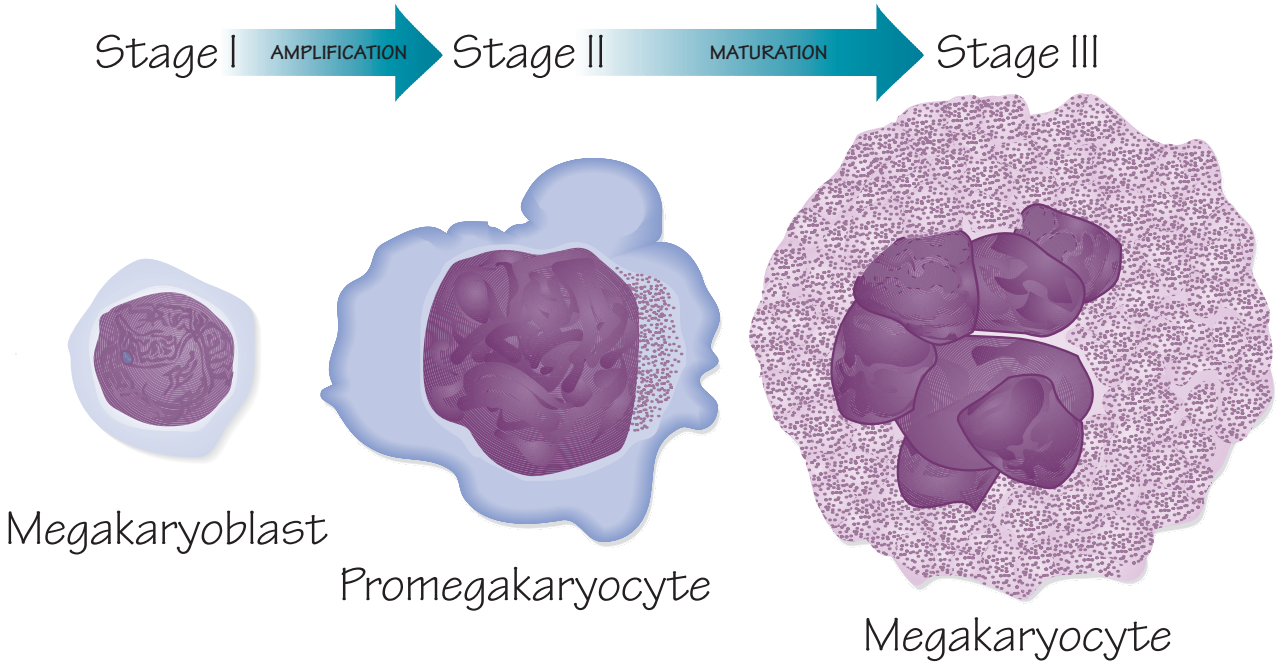
Megakaryopoiesis is a complex process that involves maturation, nuclear development, and platelet production. The illustrations below and on the next page portray these events in a stylized fashion.

Bone marrow stem cells undergo normal cell division and sequence through several stages, eventuating in the CFU-MK cell. This committed stem cell (called a promegakaryoblast) develops into morphologically-recognizable megakaryocytes in a three-stage process.

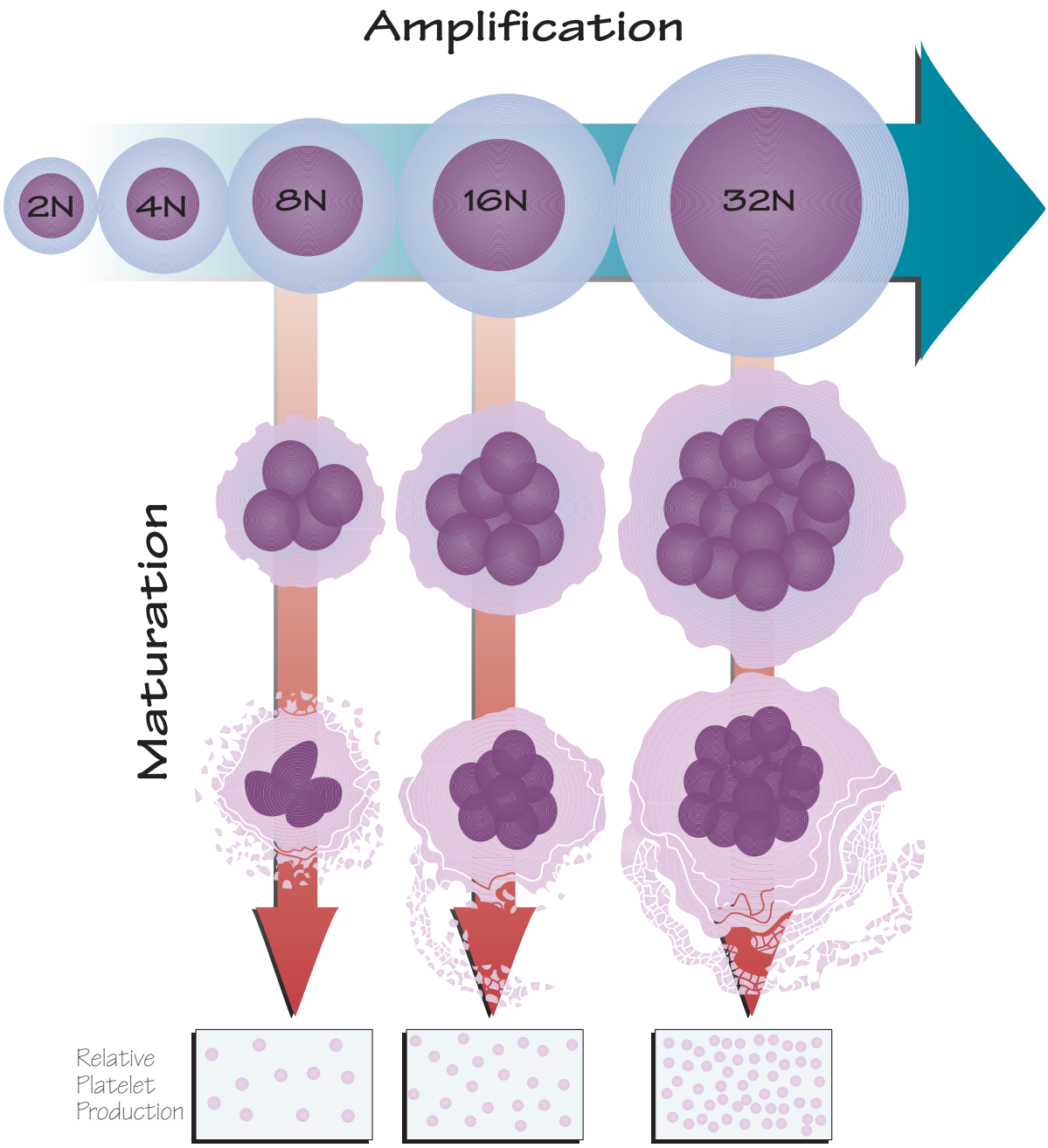
In stage I, megakaryoblasts form. These cells measure 15 µm or more in size and have a round nucleus with a small to moderate amount of slightly basophilic cytoplasm. Nuclear chromatin is coarse, without much clumping. This cell has a normal amount of DNA (2N).

Stage II begins after a series of amplification steps. The megakaryoblast becomes a promegakaryocyte. The cell stops dividing and instead DNA doubles in amount, forming cells with 4, 8, 16, 32, and rarely 64 sets of chromosomes. This unusual process of polyploidization goes by either the term *endomitosis* or nuclear *endoreduplication*.

In stage III, granular megakaryocytes form. Sometime during endoreduplication, the cell stops doubling the DNA content and instead focuses on cytoplasmic maturation. There is no direct associaton between the amount of DNA in the cell and when maturation is



triggered. Some cells with 8N begin to mature, while others do not start the process until the 32N stage. This is illustrated in the drawing below. The nucleus develops lobes, with each lobe roughly containing a single complement of chromosomes. Cells with 16N nuclei are the most common and these have 8 lobes. The cytoplasm, which has approximately doubled in amount with each nuclear multiplication, also begins to mature. Proteins and other biochemical constituents of platelets are produced giving the cytoplasm a pink granular appearance. Demarcation membranes develop, dividing the cell into territories that will eventually become platelets. Cells with increased ploidy—and therefore increased cytoplasm— produce platelets that are smaller and less dense. Lower ploidy cells produce fewer numbers of platelets that are larger, denser and more functionaly active. The process of platelet release is illustrated on page 201. The pyknotic nucleus is left behind to be phagocytized by marrow histiocytes.



Megakaryocyte or Precursor, Abnormal

SYNONYMS
dysplastic or atypical megakaryocyte

VITAL STATISTICS

size	micromegs 15-39 µm (most <20 µm); very large megs 160 µm or more
N:C ratio	highly variable; micromegs 1:1 to 1:2; larger cells lower ratio
cell shape	micromegs irregular with cytoplasmic budding or blebs common; large cells highly pleomorphic
nuclear shape	micromegs round, oval, bilobed or trilobed; large cells are hyper- or hypolobated
chromatin	dense or puddled; naked nuclei may be pyknotic (apoptosis)
nucleoli	usually none; micromegs may have small nucleoli
cytoplasm	pale blue or pink with minimal or very abundant granularity; platelet production may be visible

KEY DIFFERENTIATING FEATURES
clustering
paratrabecular location (visible on bone biopsies only)
small size (micromegakaryocytes) or markedly enlarged
mononuclear and hyperlobated forms
cytoplasmic hypogranularity
dyspoiesis present in other cells lines (granulocytes and nucleated red blood cells)
striking variability from cell to cell and field to field

POTENTIAL LOOK-ALIKES
histiocytes and macrophages (Langerhans and Touton giant cells, Gaucher's and other storage disease cells)
osteoclast and osteoblast
lymphomas (large cell types, Reed-Sternberg cells)
granulocytic precursors (micromegakaryocytes)
metastatic tumor cells

ASSOCIATED DISEASE STATES AND CONDITIONS
newborns (micromegs a normal finding in cord blood)
chronic myeloproliferative disorders (CML, PRV, AMM, ET)
myelodysplastic sydromes
5q- syndrome
acute megakaryocytic leukemia (M7)
other variants of AML
B_{12} and folate deficiency

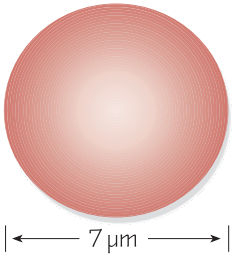
Dysplasia in bone marrow megakaryocytes may manifest as abnormalities in cell size, nuclear shape, and cell location. *Micromegakaryocytes* are the most common example. These cells, also known as dwarf megakaryocytes, are abnormally small megakaryocytes that usually measure 15 to 39 µm in diameter (most are <20 µm). The N:C ratio is 1:1 or 1:2. They are morphologically mature but have impaired polyploidization. The nucleus may be hypolobated or may have multiple small lobes reminiscent of the pmn's in megaloblastic anemia. The cytoplasm is pale blue and may contain pink granules. Micromegakaryocytes are usually found in the marrow in myelodysplastic syndromes. They may also circulate in the blood. When they lack any significant cytoplasm, they are best termed *megakaryocyte nuclei* or fragments.

Larger abnormal megakaryocytes are highly variable in morphology. Some show marked nuclear lobation while others are hypolobated or mononuclear. Normal megakaryocyte nuclei are connected in series. Dysplastic nuclei may be separated. The finding of triple nuclei forming a pawn-ball pattern is a particularly useful marker of dysplasia.

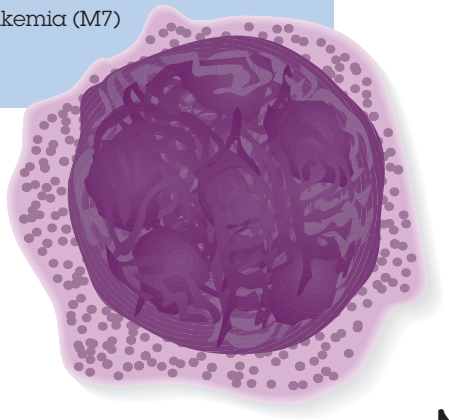
Normally, megakaryocytes are single cells, well separated from each other and from the bony trabeculae. Dyspoiesis may be manifested by cell clustering and a paratrabecular location. Large sheets of highly pleomorphic cells may be found. This feature is best seen on bone marrow biopsies and clot specimens rather than aspirate smears.

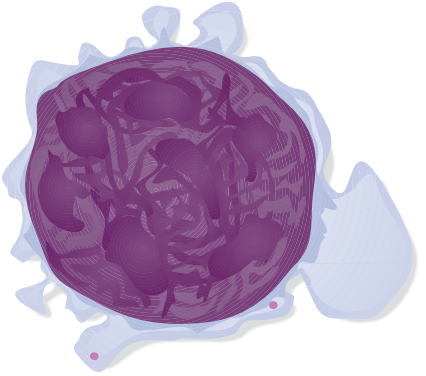
Uniform hypolobated megakaryocytes are a feature of 5q- syndrome. This subtype of myelodysplasia occurs most commonly in elderly females. Patients have a macrocytic anemia with normal or elevated platelets. The prognosis is better than other subtypes of myelodysplasia.

Circulating micromegakaryocytes in adults are abnormal; they are seen most commonly in myeloproliferative conditions, especially agnogenic myeloid metapalsia. They are a normal finding in cord blood.



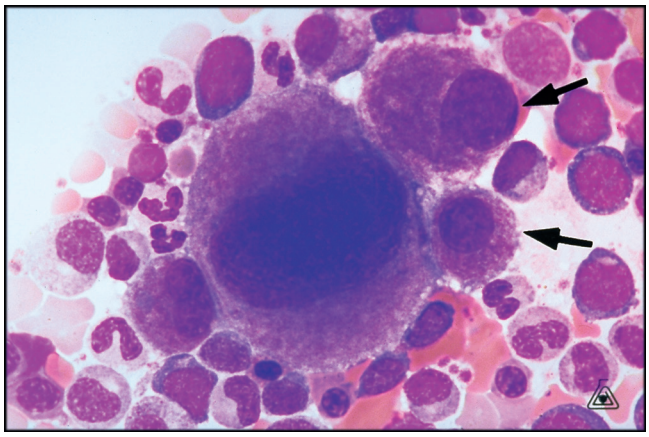
size of normal red blood cell





Micromegakaryocytes

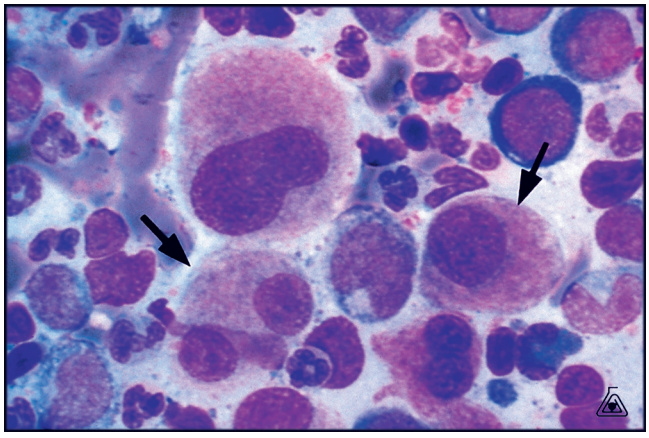
HE-45, 1995 (Bone Marrow, Wright-Giemsa, X313)



Identification	Referee %	Participant %
Megakaryocyte or precursor, abnormal	73.9	58.8
Megakaryocyte or precursor, normal	21.7	24.6
Megakaryocyte nucleus	4.2	0.3
Osteoblast	-	2.6
Plasma cell, immature	-	2.7

The bone marrow is from a patient with myelodysplasia. The large central cell and the surrounding three smaller cells, two of which are arrowed, are all dysplastic megakaryocytes. The cytoplasm is heavily granulated but the nucleus is round or minimally lobated. The small cells are best designated micromegakaryocytes. Megakaryocyte nuclei are stripped of most of their cytoplasm, unlike these cells. Osteoblasts have blue cytoplasm and a prominent clear zone (Golgi) a short distance away from the nucleus. Plasma cells have blue cytoplasm and a clear zone adjacent to the nucleus.

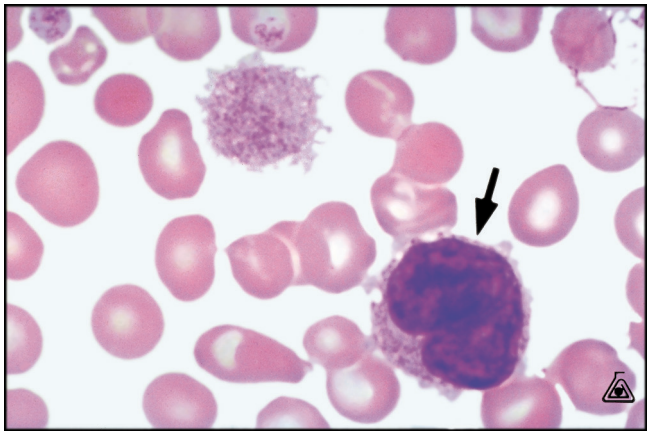
H1-31, 1988 (Bone Marrow, Wright-Giemsa, X330)



Identification	Referee %	Participant %
Megakaryocyte or precursor, abnormal	70	49
Megakaryocyte or precursor, normal	20	11.3
Myelocyte	10	24.7

This is a case of chronic myelogenous leukemia. The bone marrow is hypercellular with markedly increased megakaryopoiesis. In this field, there are four recognizable abnormal megakaryocytes, two of which are arrowed. The arrowed cells are abnormally small (micromegakaryocytes) and have a single round nucleus. The cytoplasm exhibits varying degrees of granularity. The small bilobed cell beneath them is a heavily granulated megakaryocyte beginning to shed platelets. The larger megakaryocyte above them is hypolobated for the degree of cytoplasmic maturity. The size of the arrowed cells far exceeds that of myelocytes; in addition, no cytoplasmic granules suggestive of myelocytes are seen.

HE-11, 1994 (Blood, Wright-Giemsa, X400)



Identification	Referee %	Participant %
Megakaryocyte or precursor, abnormal	48.1	28.3
Megakaryocyte or precursor, normal	18.5	16.8
Megakaryocyte nucleus	11.1	10.8

The arrowed cell is a micromegakaryocyte circulating in the peripheral blood of an adult. The N:C ratio is high. The nucleus is attempting to lobate. Chromatin is smudged. The pink granular cytoplasm forms small projections from the cell that are similar in appearance to the giant platelet above it. Circulating micromegakaryocytes are abnormal in adults but they are a normal finding in cord blood. For CAP proficiency testing purposes, the term *megakaryocyte nucleus* refers to cells that have very little or no cytoplasm. This cell has too much cytoplasm for that designation. (See page 196 for a discussion of megakaryocyte nuclei).