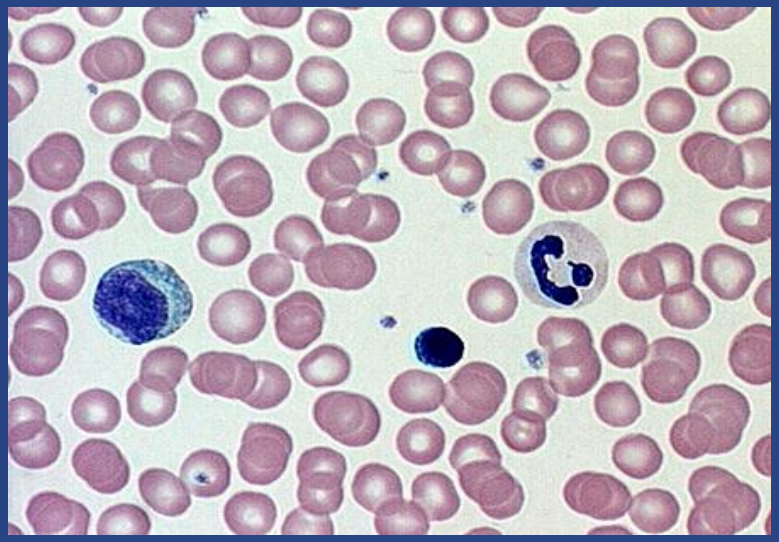
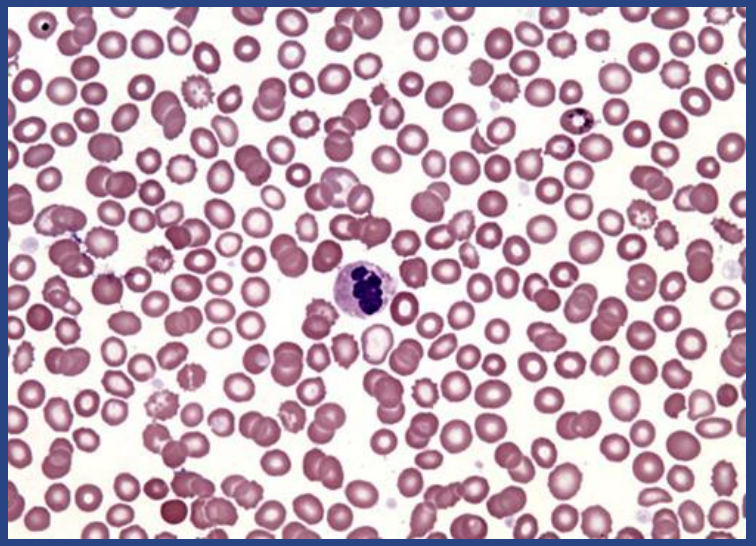
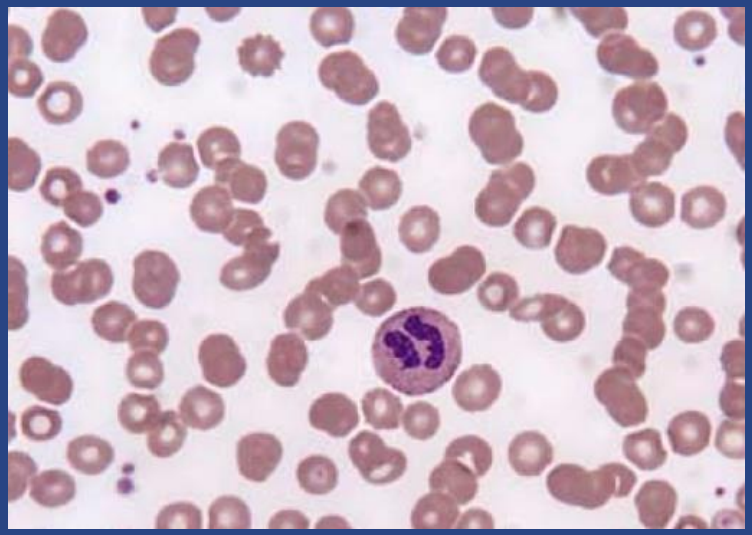




Evaluation of the Anemic Patient



Brenda Shinar, MD

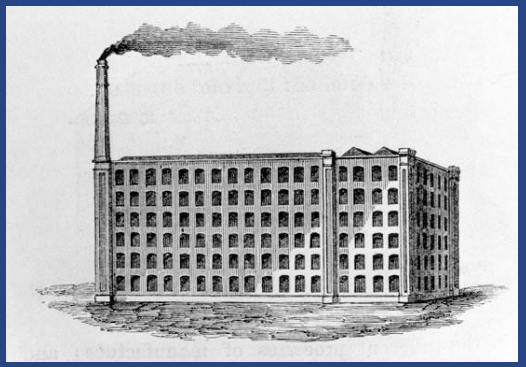
Banner University Medical Center- Phoenix

September 18, 2018

Objectives:

- Understand the basics of hematopoiesis.
- Define anemia and understand how to classify it based on the kinetic model and the morphologic model.
- Define the red cell distribution width and understand how its value helps to narrow the differential.
- Understand how to calculate the absolute reticulocyte count and reticulocyte index and what these values mean.
- Understand the differentials of microcytic, normocytic, and macrocytic anemias and how to appropriately evaluate them to make a diagnosis.

Red Blood Cell Factory: What is Required?



- Work space
- Task master
- Building blocks
- Instructions
- Distribution
- Survival

- Bone marrow
- Erythropoietin
- Precursor cell, heme, iron, B12, folate
- Cytokines
- Exit out of bone marrow
- No lysis, sequestration, or loss

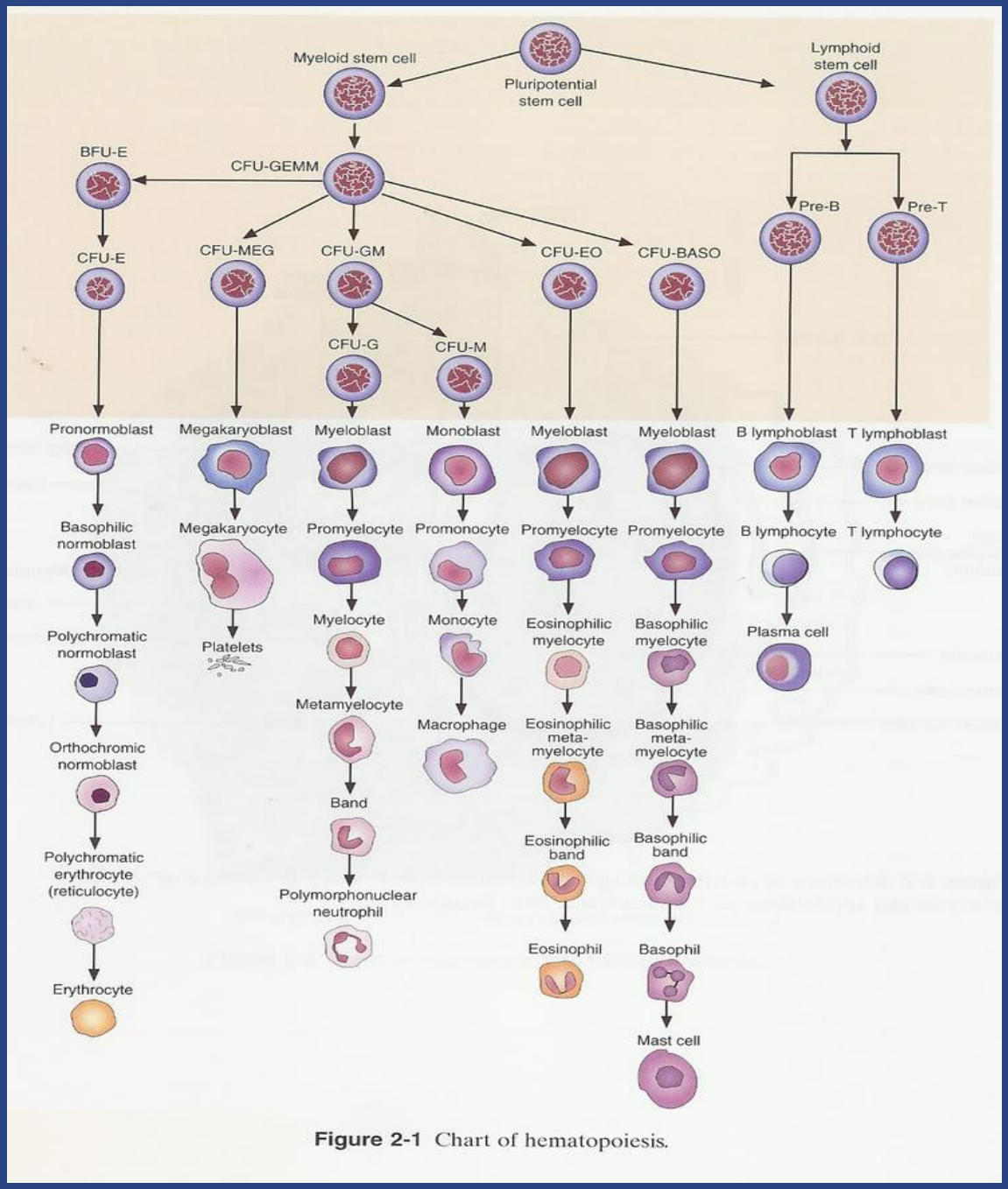
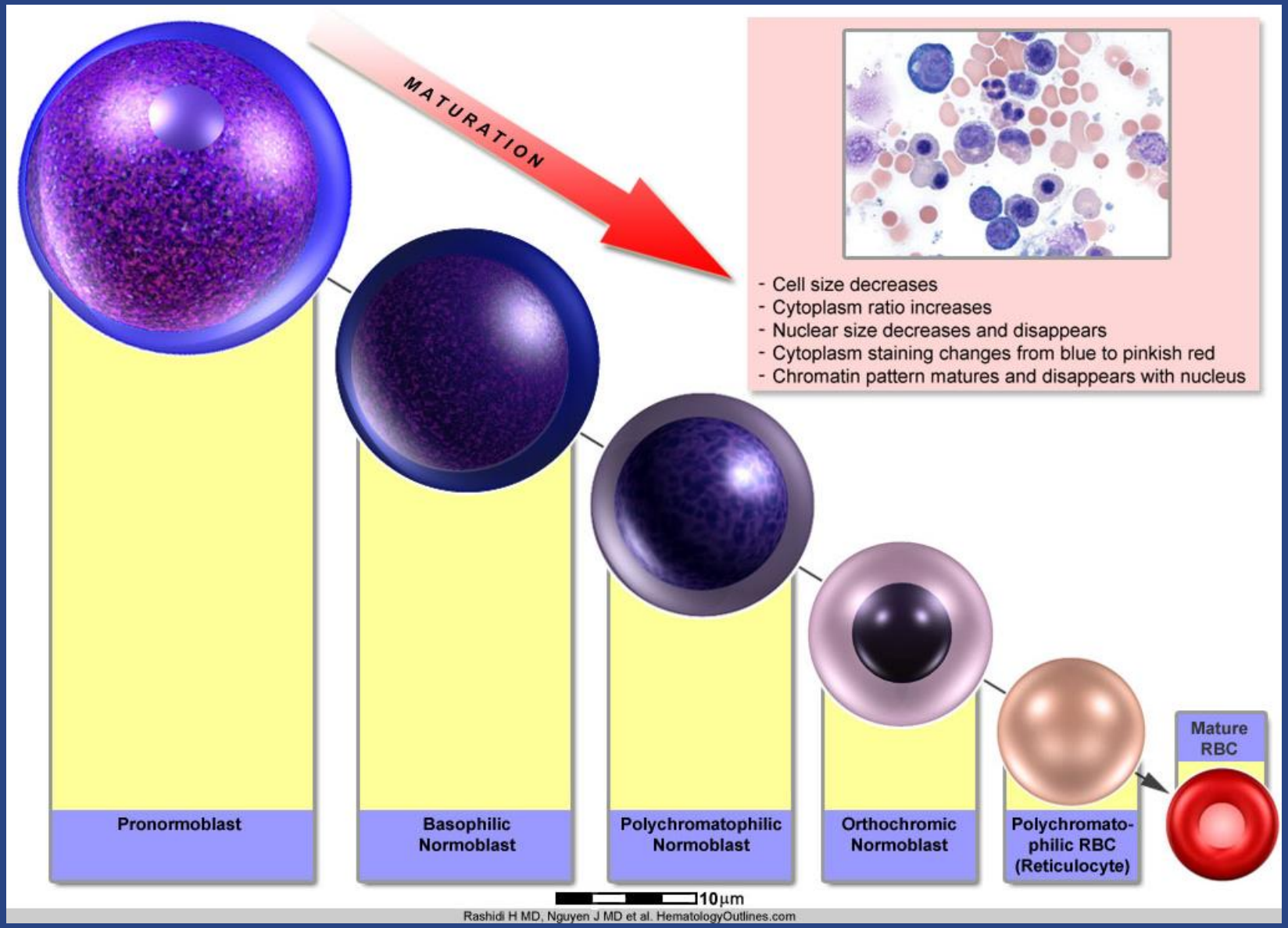


Figure 2-1 Chart of hematopoiesis.

The Red Cell Family Tree

The Red Cell Maturation: Benjamin Button



The Complete Blood Count (CBC)

- Hemoglobin (g/dL)
- Hematocrit (percent)

- Red Blood Cell Count (RBC) (million/mm3)

- Mean Cell Volume (MCV) (fL)
- Red Cell Distribution Width
  - Standard deviation of MCV/Mean MCV x 100
  - CV: coefficient variation
  - SD: standard deviation

- MCH: mean cell hemoglobin (pg)
- MCHC: mean cell hemoglobin concentration (g/dL)

LABORATORY	07/27/2015 09:10 MST	07/27/2015 05:18 MST
CBC		
WBC		10.6
RBC		2.03 (low)
HGB		6.4 (low)
HCT		18.9 (low)
MCV		93
MCH		31.5
MCHC		33.9
RDW-CV		18.6 (high)
RDW-SD		63.4 (high)
Platelet		65 (low)

Normal values for red blood cell parameters in men and women

Red cell parameter	Adult men		Adult women
Hemoglobin, g/dL	15.7 ± 1.7		13.8 ± 1.5
Hematocrit, percent	46.0 ± 4.0		40.0 ± 4.0
RBC count, million/µL	5.2 ± 0.7		4.6 ± 0.5
Reticulocytes, percent	1.6 ± 0.5		1.4 ± 0.5
Mean corpuscular volume, fL		88.0 ± 8.0	
Mean cell hemoglobin, pg/RBC		30.4 ± 2.8	
Mean cell hemoglobin concentration, g/dL of RBC		34.4 ± 1.1	
Red cell volume distribution width, percent (RDW)		13.1 ± 1.4	

Values are mean ± 2 standard deviations.
Adapted from Williams' Hematology, 6th ed, Beutler, E, Lichtman, MA, Coller, BS, et al (Eds), McGraw-Hill, New York, 2001.

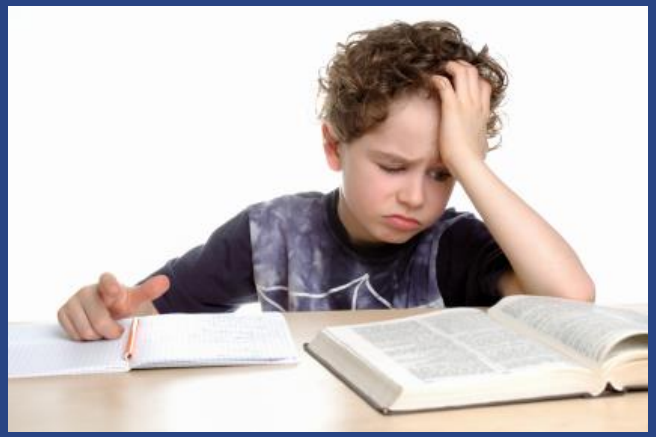
Measurement Caveats: **Ratio** of RBCs to Plasma Determines Hgb, Hct, and RBC count

- *Acute bleeding* will cause orthostatic change but gives falsely normal values of Hgb, Hct, and RBC count because ratio of RBCs and plasma lost is the same

- *Pregnancy* increases plasma volume by 20-25% and therefore lowers the Hgb, Hct, and RBC count

- *Dehydration* decreases the plasma volume and artificially increases the Hgb, Hct, and RBC count

Is the bone marrow responding to the anemia?



1) **Reticulocyte Count**= 2.8%
2) **Absolute Retic Count**=
   2.8 x pt's hct/nl hct=
   2.8 x 30/45 = 1.24
3) **Absolute Retic Index**=
   Absolute Retic Ct / Maturation factor
   1.24/1.5= 0.83

Maturation Factor corrects for the length of time a reticulocyte is in circulation so as not to count it twice or more. This factor varies with the degree of anemia.

HCT > or =35% = 1.0
25-35% = 1.5
20-25%= 2.0
< 20% =2.5

Evaluating the Anemic Patient: Kinetic Model

Decreased Production

Absolute Reticulocyte Index < 2

- Bone marrow disorders or suppression
- Lack of erythropoietin
- Lack of iron, B12, or folate
- Anemia of chronic disease

Increased Destruction or Blood Loss

Absolute Reticulocyte Index > 2

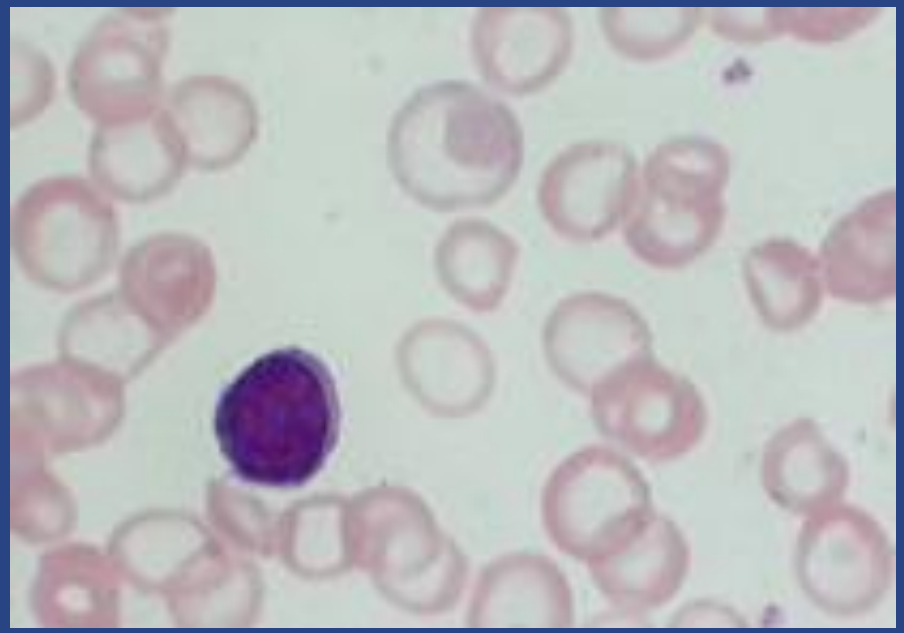
- Congenital
  - Membrane defects
  - Hemoglobinopathies
  - Enzyme deficiencies
- Acquired
  - Autoimmune HA
  - Microangiopathic HA
  - Infections (Malaria)
  - Paroxysmal Nocturnal Hemoglobinuria

Evaluating the Anemic Patient: The Morphologic Model

Microcytic Anemia :

MCV <80 fL

- Reduced iron availability
  - Iron deficiency
  - Anemia of chronic disease
- Reduced heme synthesis
  - Lead poisoning
  - Congenital or acquired sideroblastic anemia
- Reduced globin production
  - Thalassemias
  - Other hemoglobinopathies



Case 1

ID and CC:

22 year old Caucasian female with fatigue and dyspnea with exertion

Labs:

Hemoglobin 5.8 g/dL

MCV 68 fL

RDW 18 (11-16)

- What important questions do you ask her in the ROS?
  - Menstrual history
  - GI complaints
- What is the most important lab test to order to make the diagnosis?
  - Ferritin
- What is the next step in her management?
  - GI evaluation/colonoscopy
  - Evaluate for celiac disease

What are the positive predictors of GI lesions in iron deficient premenopausal women?

1. Symptoms of heartburn, regurgitation, or dyspepsia (OR 3.76 p=.002)
2. MCV < 70 fL (OR 1.88 p=.04
3. Hemoglobin < 10 g/dL (OR 1.7 p=.05)

NEGATIVE risk factor: Heavy menstrual blood loss

(OR 0.46 p=.002)

Case 2

- ID and CC:

  45 year old man admitted with SIRS due to a UTI and chronic stage 4 sacral decub

- PMH

  Paraplegic due to GSW

  Noncompliance with urinary self-catheterization

  Sacral decubs

  Bipolar disorder

  Anemia

- Labs:

  Hgb 8.0 g/dL

  MCV 75 fL

  RDW 12.0 (11-16)

  Ferritin 250 ng/mL

  Transferrin 100 mg/dL (188-341 mg/dL)

  Percent saturation 8%

What is the most likely cause of his anemia?

Laboratory Tests in Iron Deficiency of Increasing Severity

	Normal	Fe deficiency without anemia	Fe deficiency with mild anemia	Severe Fe deficiency with severe anemia
Marrow reticulo- endothelial iron	**2+ to 3+**	**None**	None	None
Serum iron, µg/dL	60 to 150	60 to 150	**<60**	<40
Iron binding capacity (transferrin), µg/dL	300 to 360	300 to 390	350 to 400	**>410**
Saturation (SI/TIBC), percent	20 to 50	30	**<15**	<10
Hemoglobin, g/dL	**Normal**	**Normal**	**9 to 12**	**6 to 7**
Red cell morphology	Normal	Normal	Normal or slight hypochromia	Hypochromia and microcytosis
Plasma or serum ferritin, ng/mL	40 to 200	**<40**	<20	<10

Serum ferritin ≤ 30 ng/dL = Iron deficient (PPV 83%, PLR= 11)
Serum ferritin ≥ 100 ng/dL = Iron sufficient (NLR .08)

What about if the ferritin is between 30 and 100?

Other Tests to help distinguish IDA from ACD…

- Transferrin:
  - Low or low normal in ACD

- Increased soluble transferrin receptor (sTfR)
  - Specificity 84% and PPV 58%

- Soluble transferrin receptor – ferritin index
  - Still need inflammatory markers/ acute phase reactants for interpretation

- **Low reticulocyte-hemoglobin concentration (RET-He)**
  - Does not distinguish between ACD and IDA but can improve in 2-3 days after IV iron supplementation to prove response to iron therapy

Retic %		1.4
Retic #		51
Immature Retic Fraction (IRF)		21.2 * H
Retic Hgb Equivalent [RET-He]		21.0 * L
Iron		23 L
Transferrin		185 L
Trans % Sat		9.8 L

Distinguishing between ACD and IDA in NON-dialysis patients

- A ferritin of > 100 makes iron deficiency statistically unlikely even in patients with chronic inflammation!
- A transferrin level that is low gives further evidence of anemia of chronic disease.
- A low serum iron level and percent saturation *cannot distinguish between ACD and IDA!*
- The reticulocyte-Hgb content may be a new way to determine response to IV iron therapy.

Case 3

- ID and CC:

  A 42 year old black woman with a history of iron deficiency on iron therapy comes to see you as a new patient.

- Labs:

  Hemoglobin 10.5 g/dL

  MCV 68 fL

  RDW 11 (11-16)

  Ferritin 490 ng/mL

- What important questions do you ask her?
  - Family history
  - Old records to review
- What is the most important laboratory test to make the diagnosis?
  - Hemoglobin electrophoresis
- What is the next step in the management of this patient?
  - Take her off of the iron

Thalassemias

- Found most frequently in the Mediterranean, Africa, Western and Southeast Asia, India, and Burma

- Distribution parallels that of Plasmodium Falciparum

The thalassemias: Genetic, clinical, and laboratory findings

Disorder	Genotype	MCV	Anemia	Hb electrophoresis
Alpha thalassemia				
Silent carrier	α α / α -	NL	None	Normal <3 percent Hb Barts at birth
Trait	α α / - - or α - / α -	Low	Mild	Normal 3-8 percent Hb Barts at birth
Hb H disease (deletional)	α - / - -	Low	Moderate	5-30 percent Hb H present in adults 20-40 percent Hb Barts at birth
Major (fetal hydrops)	- - / - -	Low	Fatal	Hb Barts, Hb Portland, and Hb H present Hb A, Hb F, and Hb A2 are absent
Beta thalassemia				
Trait	β / β°	Low	Mild	Hb A2 increased (3.5-7 percent)
Intermedia	β^{+} / β^{+} and others*	Low	Moderate	Hb F increased in about 50 percent of patients
Major	$\beta^{\circ} / \beta^{\circ}$	Low	Severe	Hb A absent Only Hb A2 and Hb F are present

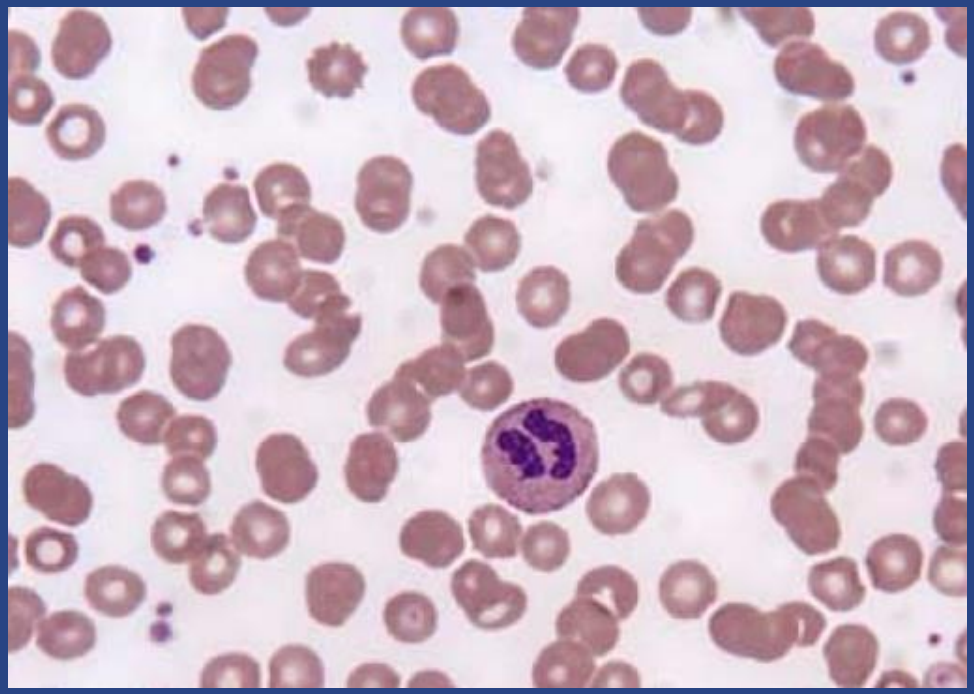
MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; β^{+}: thalassemic gene producing some β -chain; β°: thalassemic gene producing no β -chain.
* See text for multiple other genotypes.
Courtesy of Stephen A Landaw, MD, PhD.

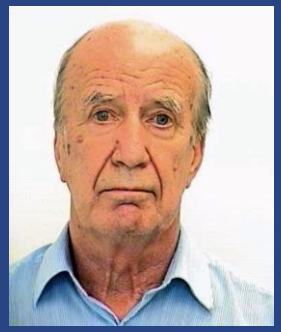
Evaluating the Anemic Patient: The Morphologic Model

Normocytic Anemia: MCV 80-100

- Early iron deficiency
- Anemia of chronic disease
- Bone marrow disease
  - Invasion, aplasia
  - Myeloma, MGUS
- Chronic renal insufficiency
- Endocrine dysfunction
  - Hypothyroid
  - Hypopituitarism

- **Combined disorders in patients with high RDW**
  - ACD or IDA +B12 or folate deficiency





Case 1

- ID and CC

  75 year old man with fatigue and palpitations admitted with anemia and renal failure

- Labs:

  Hemoglobin 6.2 g/dL

  MCV 84 fL

  RDW 12

  Creatinine 3.2 mg/dL

  Urine protein/creatinine ratio: 4.5

  Total Protein 10 g/dL

  Albumin 2.5 g/dL

- What important questions do you ask the patient?
  - Back pain/ Bone pain
  - Recent infections (hypogammaglobulinemia)
- What laboratory tests do you do to make the diagnosis?
  - Peripheral smear
  - SPEP + IFE
  - Free light chains
  - 24 hour UPEP + IFE (optional)
- What do you do NOT give the patient while he is in the hospital?
  - NO IV contrast!

Case 2

- ID and CC:

  35 year-old woman with Crohn's disease is admitted with abdominal pain and bloody stools consistent with a flare of her disease

- Labs:

  Hemoglobin 7.9 g/dL

  MCV 85 fL

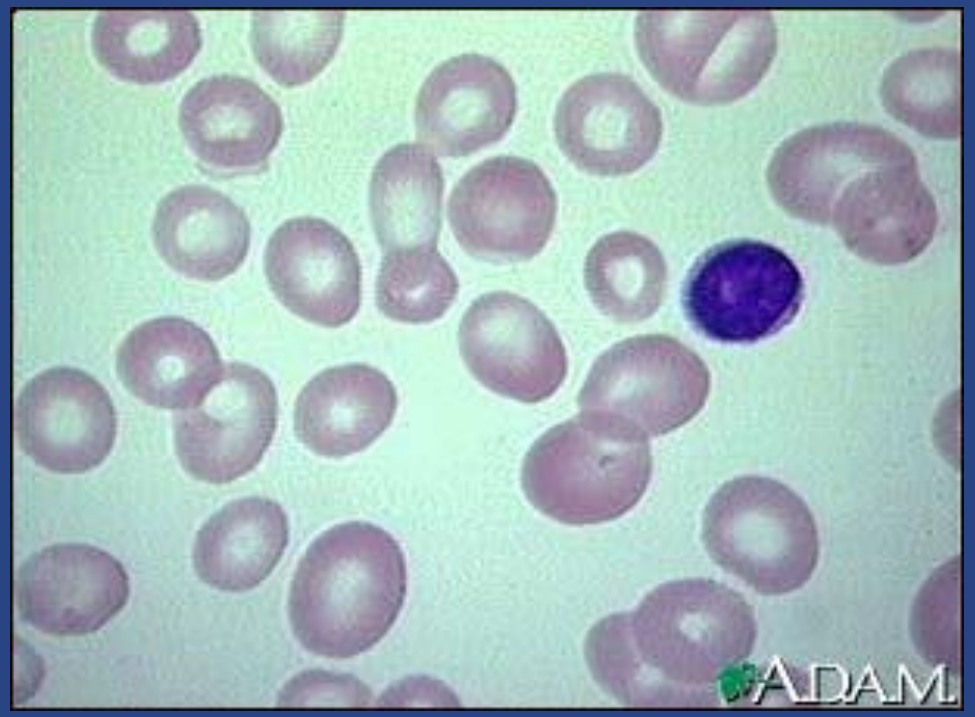
  RDW 19

- What important questions do you ask her?
  - Any bowel resection surgeries?
  - Is she on any supplements of iron, folate, or B12?
- What laboratory tests do you order to make the diagnosis?
  - Peripheral smear
  - Reticulocyte count, ferritin, Iron studies, B12 and folate
  - Possibly methylmalonic acid and homocysteine if the B12 is <300

Evaluating the Anemic Patient: The Morphologic Model

Macrocytic Anemia
MCV > 100

- Ethanol abuse
- Drug-induced
  - AZT, hydroxyurea
- Liver disease
- Reticulocytosis
  - Hemolysis
  - Blood loss
- Myelodysplastic syndromes
- Folate deficiency
- B12 deficiency



Case 1

- ID and CC:

  42 year old man with Hep C and decompensated liver cirrhosis admitted for encephalopathy

- Labs:

  Hemoglobin 7.0 g/dL

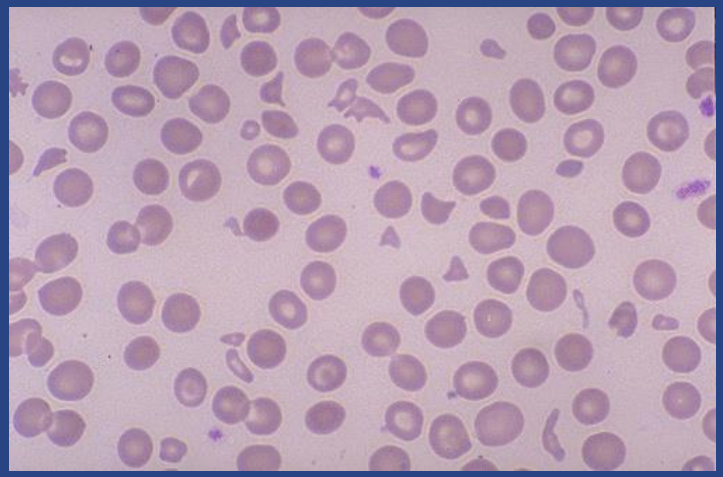
  MCV 107 fL

  RDW 20 (11-16)

- What do you want to know about the patient clinically to determine the cause of his anemia?
  - Orthostatics
  - Melena/Hematocheezia/or Hematemesis
  - History of variceal bleed or other
- What are the most appropriate lab tests to order next?
  - Peripheral smear
  - B12 (normal)
  - Folate (normal)
  - Reticulocyte count 7.5%
  - LDH 222 U/L (high)
  - Haptoglobin <10 (low)
  - Indirect bilirubin predominant
  - Ferritin 1700 ng/mL
- What do you determine the cause of his anemia to be?
  - Hemolysis due to liver disease with inadequate bone marrow response

Hemolytic Anemia

- Combination of normal LDH and haptoglobin rules OUT hemolysis with 92% sensitivity.
- Combination of elevated LDH and low haptoglobin rules IN hemolysis with 90% specificity.



- Peripheral smear can help to guide the work up once hemolysis is confirmed:

- Schistocyte
  - (mechanical shear)
- Spherocyte
  - (autoimmune)
- Acanthocyte
  - (liver disease)
- Bite cell
  - (oxidant damage)

Case 2

- ID and CC:
- 59 year old man with progressive dyspnea with exertion over 3 years

- Labs:

  Hemoglobin 4.7 g/dL

  MCV 118 fL

  Creatinine 1.6 mg/dL

  Platelets 97 K

  WBC 2.3 K

  Retic count 7.5

  LDH 450

  Haptoglobin <10

- What do you want to ask the man in history or review of systems?
  - Alcohol use?
  - Liver disease?
  - Ethnicity?
  - Medications?
  - History of cancer/chemotherapy?

- What do you want to order next to evaluate the cause of his anemia?
  - Peripheral smear
  - B12 (40)
  - Folate (normal)

Causes of vitamin B12 deficiency

Gastric abnormalities
Pernicious anemia
Gastrectomy/Bariatric surgery
Gastritis
Autoimmune metaplastic atrophic gastritis
Small bowel disease
Malabsorption syndrome
Ileal resection or bypass
Crohn's disease
Blind loops
Pancreatitis
Pancreatic insufficiency
Diet
Strict vegans
Vegetarian diet in pregnancy
Agents that block absorption
Neomycin
Biguanides (eg, metformin)
Proton pump inhibitors (eg, omeprazole)
N2O anesthesia inhibits methionine synthase
Inherited transcobalamin II deficiency

Practice Question #1

- 61 year old AA man

WBC		14.8 H
RBC		1.88 L
HGB		5.4 ' C
HCT		15.1 ' C
MCV		80
MCH		28.7
MCHC		35.8
RDW-CV		17.8 H
RDW-SD		51.3 H
Platelet		162
Immature Platelet Fraction (IPF)		
MPV		11.6
Platelet Estimate		
Retic Hgb Equivalent (RET-He)		32.7 *
Diff Type		AUTO
Immature Granulocyte % (IG%)		1.0 *
Immature Granulocyte # (IG#)		0.2 H
Segs %		40
Lymphs %		38
Monos %		11
Eos %		7
Basos %		3 H
Neut#		5.9
Lymph#		5.6 H

- Retic count: 4.7%
- Retic index: 0.7 %
- B12: 910 pg/mL
- RBC Folate: 971 ng/mL
- Ferritin: 7,650 ng/mL

HEMOGLOBINOPATHY EVALUATION			
Helec RBC			2.84 L
Helec HGB			8.3 L
Helec MCV			84
Helec MCH			29.2
Helec RDW-CV			17.1 H
Helec RDW-SD			51.8
Hgb A			92.4 L
Hgb S			5.0 H
Hgb A2			2.6
Helec Interp			Helec Interp
GENERAL COAGULATION			

- Hemoglobin SS disease

Practice Question #1

- Differential diagnosis for a patient with sickle cell disease who presents with Hgb 5 and low retic index?

- Parvo B19
- Aplastic crisis from folate deficiency
- ? Epopoietin deficiency

CHEM GENER		
Specimen Integrity		
Glucose Level		120 * H
BUN		41 H
Creatinine		2.47 * H
Estimated Glomerular Filtration Rate		28 * L
BUN/Creat Ratio		17
Sodium		143
Potassium		4.1
Chloride		111 H
CO2		22
Anion Gap		10
Magnesium		
Calcium		8.2 L
Phosphorus		
Protein, Total		6.5
Albumin		2.3 L
Alb/Glob Ratio		0.5 L
Bilirubin Total		3.4 H
AST		98 H
ALT		49
Alkaline Phos		252 H

- Epo level: 5.0 mIU/mL (2.6-18.5)

Practice Question #2

- 27 yo male
- Abdominal pain and bloody diarrhea x 6 months associated with 40 lb weight loss.

- He was diagnosed with C diff in May and failed flagyl treatment.

- He presents with increasing abdominal pain and diarrhea with new symptoms of vomiting.

WBC	13.3 K/MM3 H
RBC	6.44 M/MM3 H
HGB	13.0 g/dL L
HCT	41.5 %
MCV	64 fL L
MCH	20.2 pg L
MCHC	31.3 g/dL
RDW-CV	17.2 % H
RDW-SD	35.0 fL L
Nucleated RBCs, Automated	0 %
Platelet	303 K/MM3
MPV	10.3 fL

MISC HEMO		
Retic %		1.6 %
Retic #		85 K/ul
Immature Retic Fraction (IRF)		27.9 % * H
Retic Hgb Equivalent [RET-He]		18.7 pg * L
Sed Rate		43 mm/hr H
Iron		53 ug/dL
Transferrin		142 mg/dL L
Trans % Sat		29.4 %
Ferritin		222 ng/mL

Hgb A				95.2 %
Hgb A2				4.8 % H
Helec Interp				Helec Interp

Result type: Helec Interp
Date/Time of Service: July 23, 2017 17:15 MST
Result status: Auth (Verified)
Performed By: ZHOU MD PhD, WENDI on July 25, 2017 14:39 MST
Verified by: ZHOU MD PhD, WENDI on July 25, 2017 14:39 MST
Encounter info: 36902559, BEMC, Observation, 07/23/2017 - 07/25/2017

*** Final Report ***

Elevation of Hemoglobin A2, consistent with beta thalassemia trait.

Reviewed by Dr. Wendi Zhou at Banner -- University Medical Center Phoenix.

Hemoglobinopathy evaluation involves interpretation of high performance liquid chromatography (HPLC) results in the context of red cell indices. Variant hemogolobins such as S, C, E, and others are detected. Some, but not all thalassemic disorders are detected. Consultative assistance is sought when necessary.

Objectives:

- Understand the basics of hematopoiesis
- Define anemia and understand how to classify it based on the kinetic model and the morphologic model.
- Define the red cell distribution width and understand how its value helps to narrow the differential.
- Understand how to calculate the absolute reticulocyte count and reticulocyte index and what these values mean.
- Understand the differentials of microcytic, normocytic, and macrocytic anemia and how to appropriately evaluate them to make a diagnosis.