The ABCs of the LABs: CBCs and Coagulation Studies

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Disclosures

I have no relevant relationships with ineligible companies to disclose within the past 24 months.
(Note: Ineligible companies as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

Objectives

At the conclusion of this presentation, the participant will be able to:

- Interpret complete blood counts and coagulation studies used in making a clinical diagnosis
- Identify correlating disease states indicated by common abnormal hematology and coagulation laboratory results
- Demonstrate the clinical correlation of hematology and coagulation laboratory values to specific patient presentations
- Differentiate unique laboratory specialty tests and when applicable to order for hematologic disease states

Question #1

Of the following laboratory tests, which one is the best test for distinguishing iron deficiency anemia from anemia of chronic disease?

A. Total iron
B. Total iron binding capacity (TIBC)
C. Transferrin saturation
D. Serum ferritin

Question #2

Which of the following conditions would present with macrocytic red blood cells and hypersegmented neutrophils?

A. Vitamin B12 deficiency
B. Sickle cell disease
C. Iron deficiency
D. Chronic disease

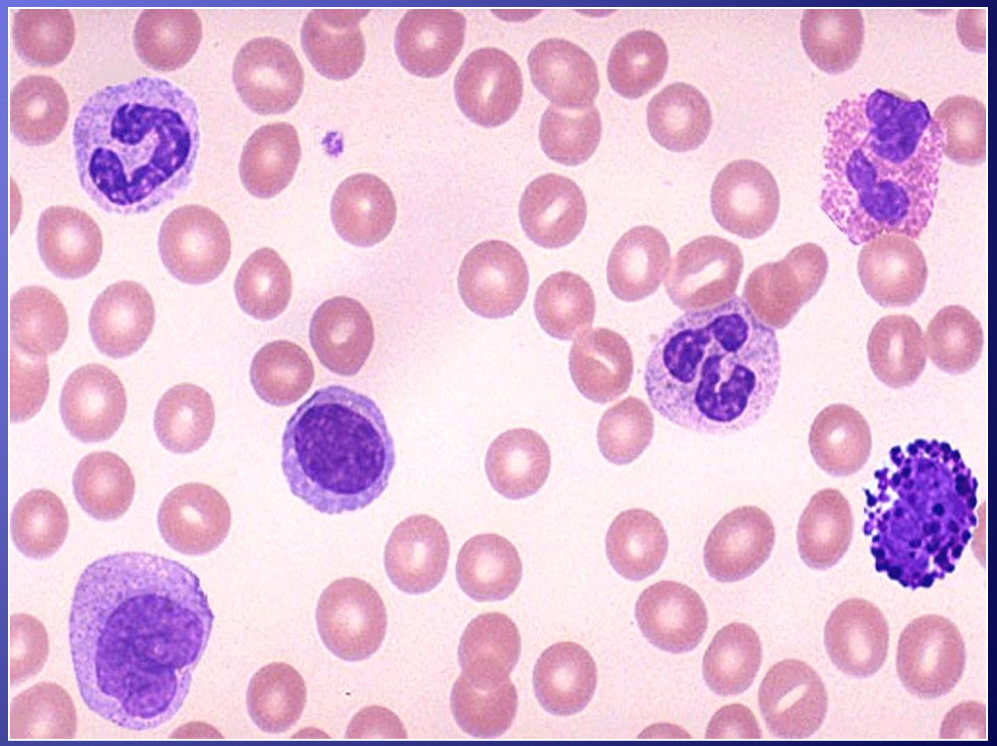
Question #3

In which of the following conditions would a patient present with abnormal bleeding in the presence of an unremarkable physical exam, normal coagulation studies, and a normal CBC with the exception of an extremely low platelet count?

A. Hemolytic uremic syndrome
B. Idiopathic thrombocytopenic purpura
C. Thrombotic thrombocytopenic purpura
D. Disseminated intravascular coagulation

Complete Blood Count (CBC)

- CBC Includes:
  - Hemoglobin
  - Hematocrit
  - RBC count
  - WBC count
  - Platelet count
  - RBC Indices
  - WBC Differential

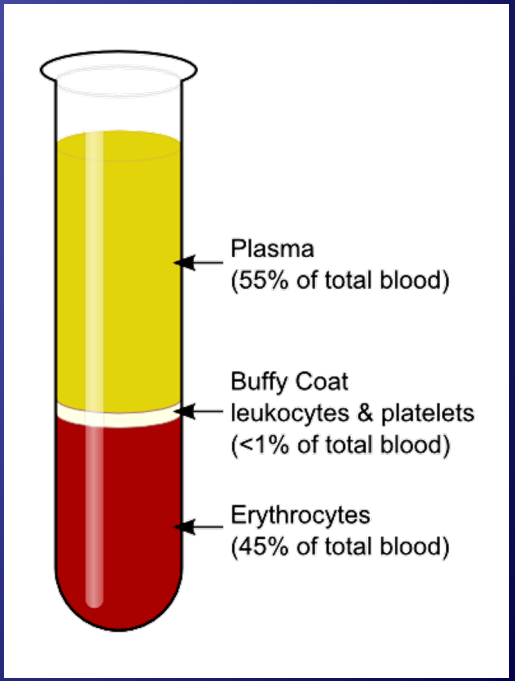


Why Order a CBC?

- Support presence of infectious agents
  - Viruses and bacteria
- Identify white blood cell disorders
  - Acute and chronic leukemia
- Determine presence of anemia
  - Hemolytic, macrocytic, microcytic
- Assess platelets in bleeding disorders

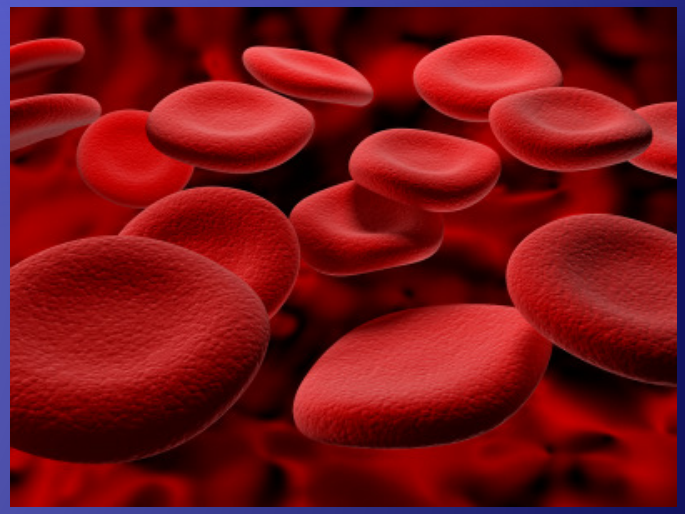
Hemoglobin and Hematocrit

- Hemoglobin
  - 4-globin complex containing heme
  - Normals:
    - 14-18 mg/dL (males)
    - 12-16 mg/dL (females)
- Hematocrit
  - Proportion of RBCs to whole blood
  - Normals:
    - 45-52% (males)
    - 37-47% (females)



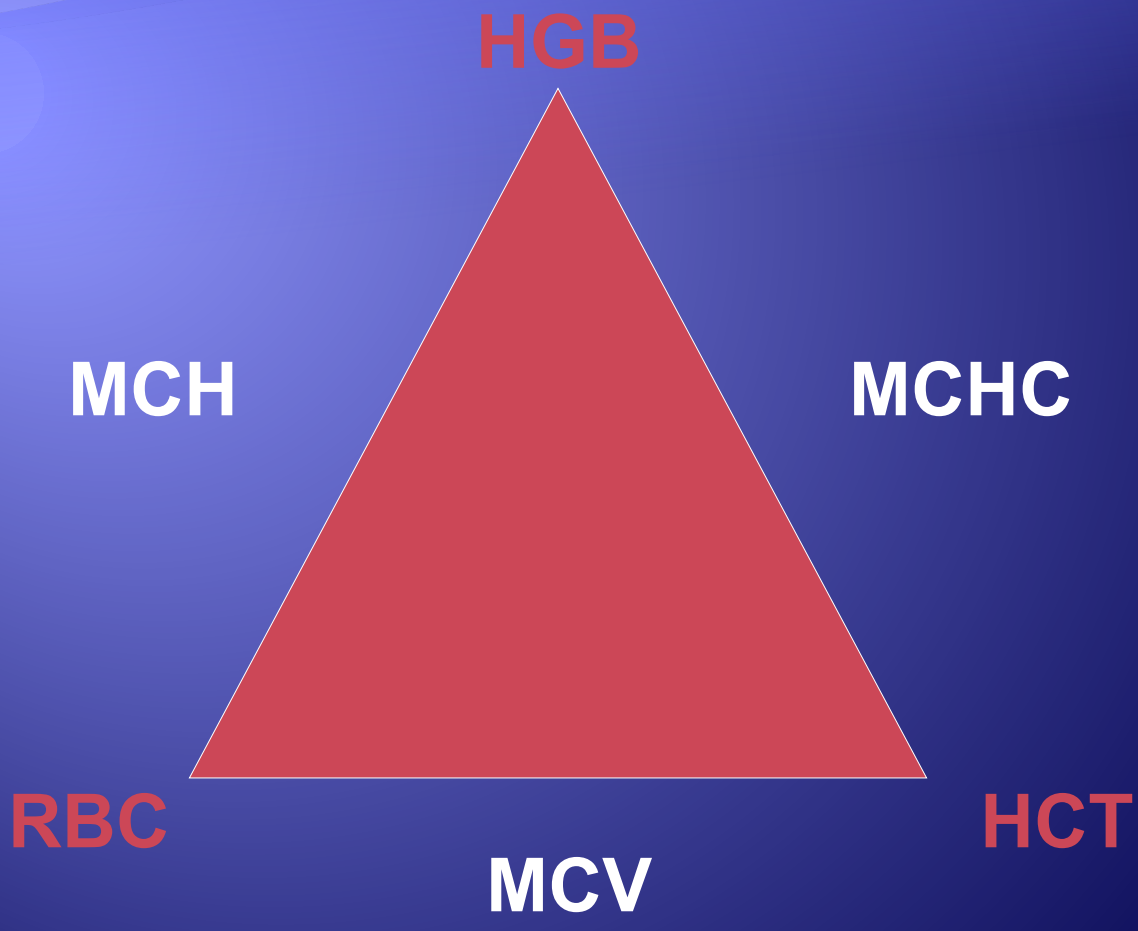
RBCs and RBC Indices

- Red Blood Cell Count
  - Normals:
    - 4.7-6.1 x 10^6/uL (males)
    - 4.2-5.4 x 10^6/uL (females)



- MCV – mean cell volume
- MCH – mean cell hemoglobin
- MCHC – mean cell hemoglobin concentration
- RDW – red cell distribution width

Triangular Relationship



RBC Indices

- MCV = 80-100 fL
  - size of the cells (microcytic, macrocytic)
- MCH = 28-32 pg
  - amount of Hgb present in each RBC
- MCHC = 32-36%
  - proportion of each RBC occupied by Hgb
- RDW = 11.5 – 14.5 %
  - standard deviation of the size of the RBC

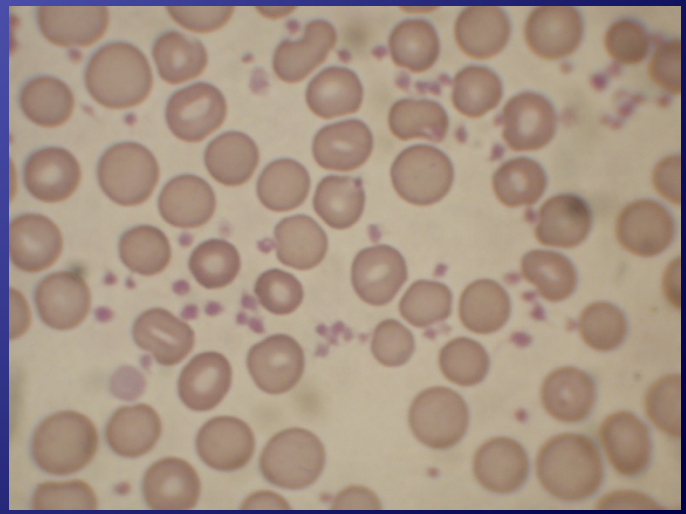
WBCs and Differentials

- White Blood Cell Count
  - Normal: 4.5 – 11.0 x 10^3/uL

Cell type	Relative Normal (%)	Absolute Normal (% x Total WBC)
Neutrophils	54-62%	2000-8000
Lymphocytes	25-33%	1000-4000
Monocytes	3-7%	200-800
Eosinophils	1-3%	100-400
Basophils	0-1%	0-400
Comments included on abnormal WBC Morphology		

Platelets

- Platelet Count
  - Normal = 150 – 450 x 10^3/uL
- MPV = mean platelet volume
  - Normal = 7.4 – 10.4 fL
  - Inverse, non-linear relationship to count

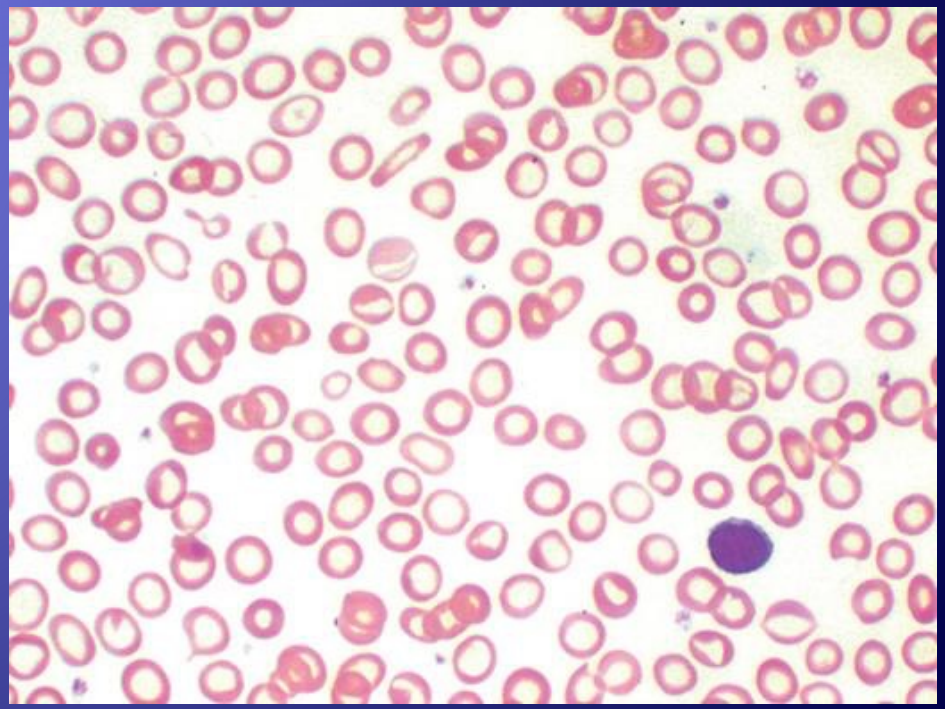


Case 1

A 20-year old female college student presents with complaint of fatigue. She reports she has not been eating much because she does not like the cafeteria food. She reports having normal menstrual periods. Family history is negative for anemia.

Case 1 - CBC Results

Test	Patient Value
CBC	
WBC	7.8 x 10^3/uL
RBC	4.71 x 10^6/uL
Hgb	10.3 g/dL
Hct	33%
MCV	70 fL
MCH	21.9 pg
MCHC	31.2g/dL
RDW	16.4%
PLT	384 x 10^3/uL
WBC Differential	WNL
Retic Count	2.2%



Case 1 Follow-up

What diagnoses are you considering for this patient?

- Iron deficiency anemia
- Anemia of chronic disease

What diagnostic studies would you order to confirm this patient's diagnosis?

- Iron panel – IDA is the most common microcytic, hypochromic anemia and presents with low iron, increased TIBC (transferrin), low % saturation and low ferritin.

ACD versus IDA

	ACD	Fe Defic
Serum Fe	↓	↓
Transferrin	N ↓	↑
% Saturation	↓	↓
Ferritin	N ↑	↓
BM Fe Stores	↑	↓

Case 1 - Follow Up Testing

- Iron
  - 15 ug/dL (normal 30-160 ug/dL)
- Total Iron Binding Capacity (Transferrin)
  - 470 ug/dL (normal 240-450 ug/dL)
- Transferrin Saturation (% saturation)
  - 8% (normal 20-50%)
- Ferritin
  - 10 ng/mL (normal 12-114 ng/mL)

Iron Deficiency Anemia

Food for Thought

- What if iron panel had been normal?
  - Consider other microcytic, hypochromic anemias
    - Lead poisoning
    - Sideroblastic anemia
    - Thalassemia

- Clinical pearl – Always draw anemia labs BEFORE patient receives blood transfusion. Lab can always draw extra tubes to hold for testing if you aren't sure what you want to order.

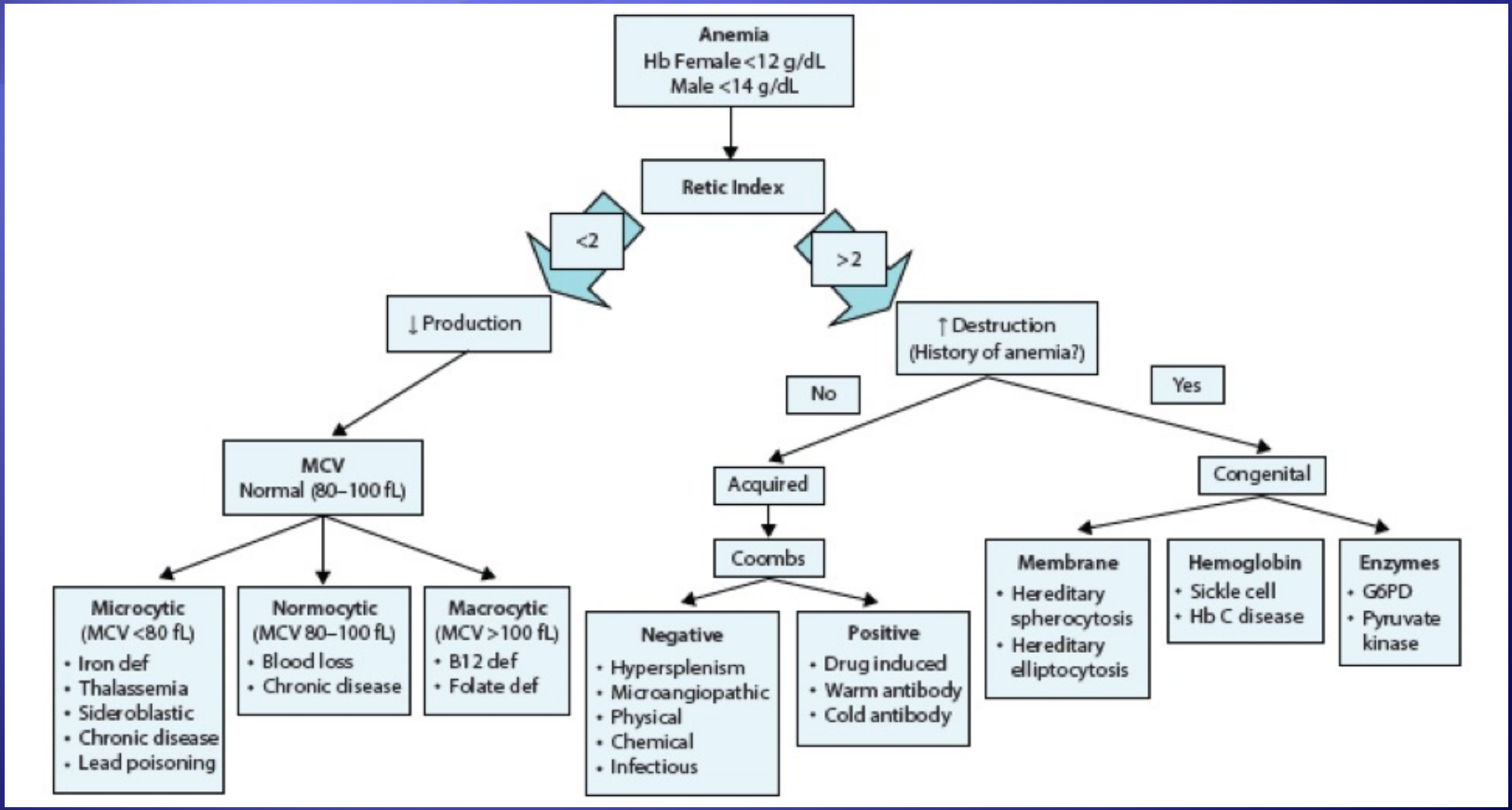
Reticulocyte Production Index

- Retic Ct = % of retics to total RBC count
- To interpret Retic Count in presence of anemia:
  - Reticulocyte Index
    - Corrected Retic = Pt retic/1% x patient Hct/45
    - Corrects for degree of anemia
    - Reflects level of BM production
    - Increased Retic Index
      - Reflects decline in total mature RBCs that normally dilute retics

Assessment of Retic Index

- Reticulocyte Index <2:
  - Inadequate bone marrow response to degree of anemia
- Reticulocyte Index >2:
  - Appropriate bone marrow response to degree of anemia

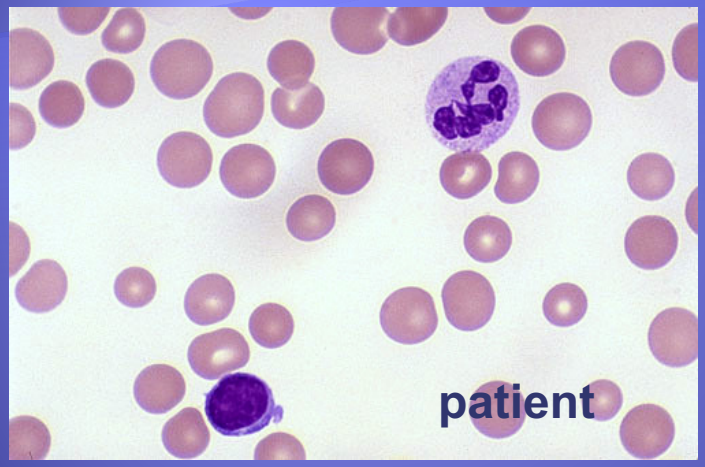
Approach to Anemia Flowchart

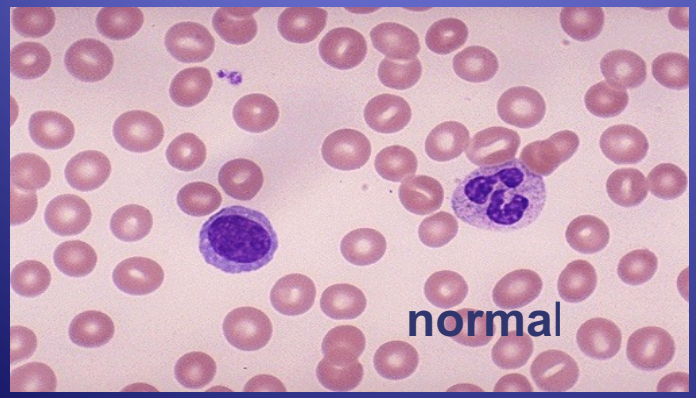


Case 2

- A 75 yr old man is brought to his PCP by his concerned daughter. She states her father has become very forgetful lately and has fallen several times in the past two weeks. He has also lost ~15 lbs in the past month.
- History:
  - Pt states he keeps tripping over things because he can't feel his feet. States food doesn't taste right anymore, and his mouth hurts when he tries to eat
- PE:
  - No major findings except peripheral neuropathy in both feet

Case 2 - CBC Results



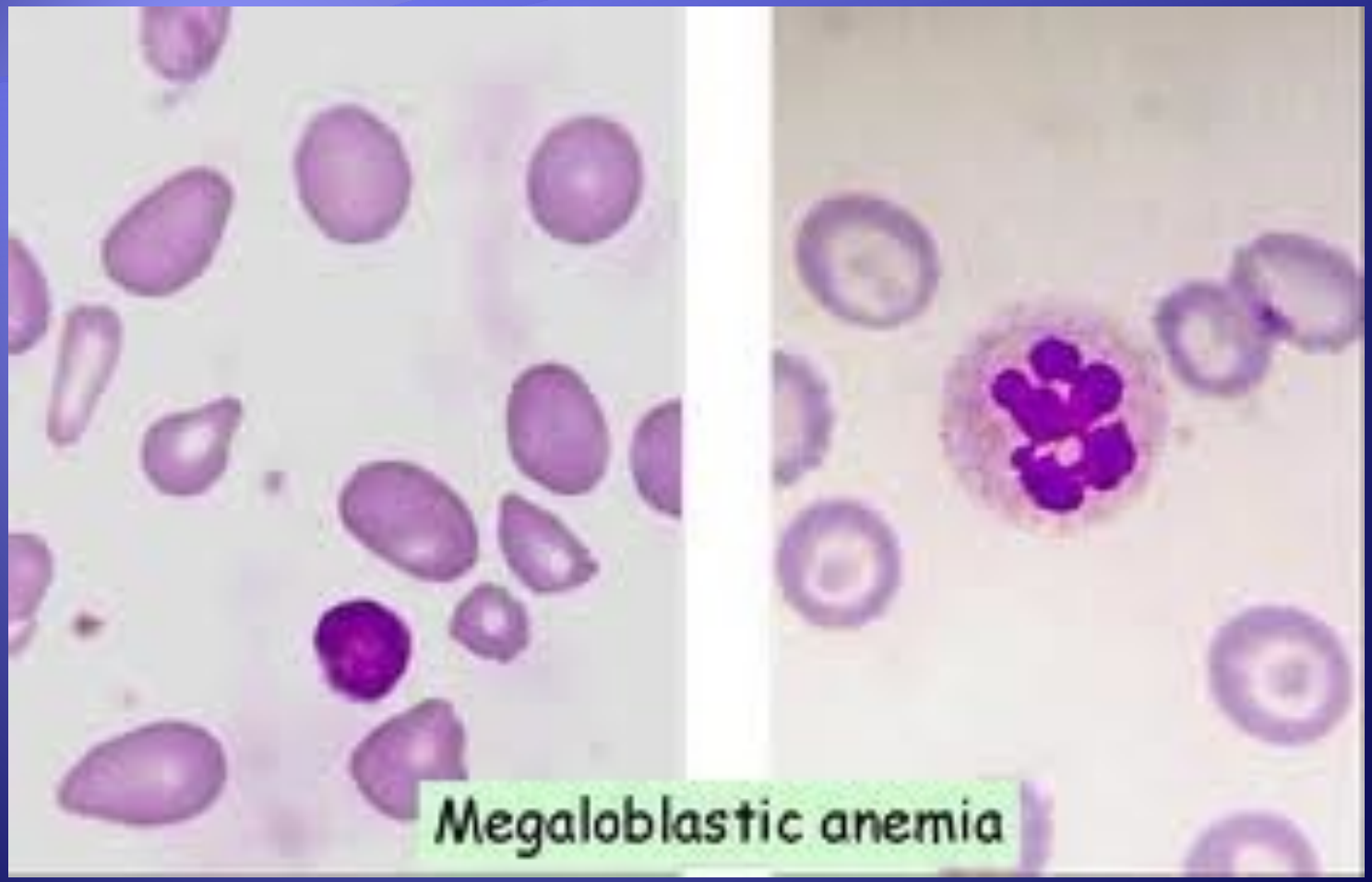


Test	Patient Value
CBC	
WBC	6.2 x 10^3/uL
RBC	2.45 x 10^6/uL
Hgb	8.8 g/dL
Hct	24.3%
MCV	99 fL
MCH	35.9 pg
MCHC	36.2g/dL
RDW	16.4%
PLT	325 x 10^3/uL
WBC Differential	WNL
Retic Count	1.8%

Macrocytic Anemia
B12 vs Folate Deficiency

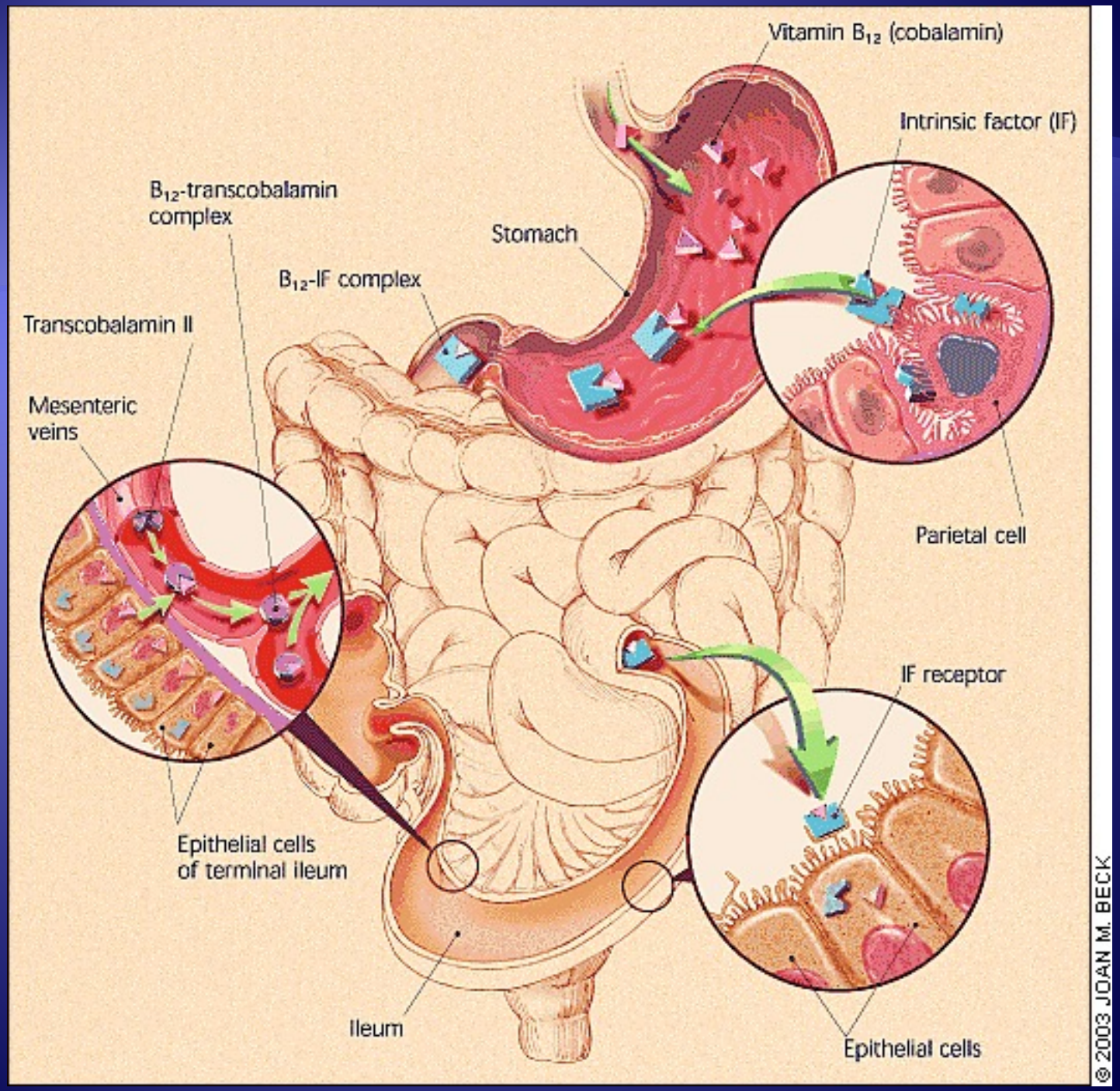
- B12 Deficiency
  - Low Retic Count for degree of anemia
  - RBC morphology
    - Oval macrocytes
  - Decreased serum B12 level
  - **Hypersegmented neutrophils (>5 nuclear lobes per cell)**
- Folate deficiency
  - Low Retic Count for degree of anemia
  - RBC morphology
    - Oval macrocytes
  - Decreased serum folate levels

Macrocytic (Megaloblastic) Anemia



Vitamin B12

- Vitamin B12
  - Functions in DNA synthesis, myelin production, and RBC production
  - Only source is dietary intake
  - Body generally stores ~ 3 years supply of B12
  - Stomach cells produce intrinsic factor protein (IF) that binds to dietary B12, then complex is absorbed in the small intestine


Vitamin B_{12} (cobalamin)
Intrinsic factor (IF)
B_{12}-transcobalamin complex
Stomach
B_{12}-IF complex
Transcobalamin II
Mesenteric veins
Parietal cell
IF receptor
Epithelial cells of terminal ileum
Ileum
Epithelial cells
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Vitamin B12 Deficiency

Causes:

- most common cause is pernicious anemia - lack of intrinsic factor to absorb B12
  - Due to
    - Loss of intrinsic factor secreting cells in stomach
    - Antibodies against intrinsic factor
- Other causes –
  - Loss of terminal ileus
  - Loss of absorption in ileus

Vitamin B12 Deficiency

- Diagnostic tests
  - Initial tests:
    - Vitamin B12 level
    - Newer tests: Homocysteine and Methylmalonate more sensitive as they are dependent on B12 for metabolism and will be increased in B12 deficiency
  - Follow up tests to identify cause:
    - Anti-intrinsic factor Ab test

Folate

- Folate (Vitamin B9) used in DNA synthesis
- Found in many foods, especially greens
- Body generally stores ~ 3-4 month supply
- Folate deficiency
  - Causes:
    - decreased intake
    - decreased absorption
  - Tests:
    - Serum folate level

Case 2 – Follow Up Testing

- Folate
  - 17 mcg/L (normal = 5-25 mcg/L)
- Vitamin B12
  - 212 pg/dL (normal = > 200 pg/dL)
- Methylmalonic acid
  - 5.2 mcg/dL (normal = 0-4.7 mcg/dL)

Vitamin B12 Deficiency

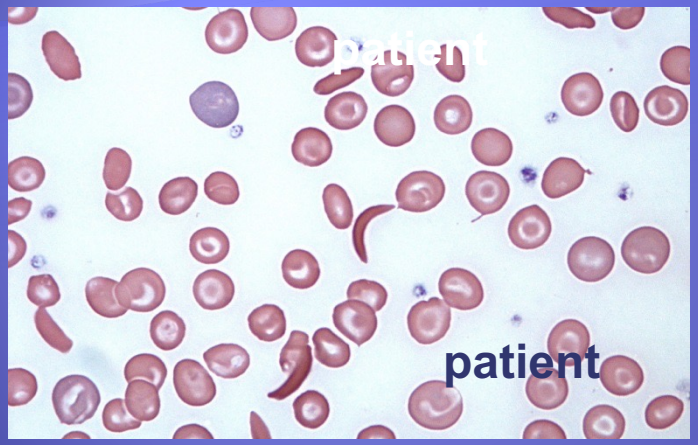
Case 3

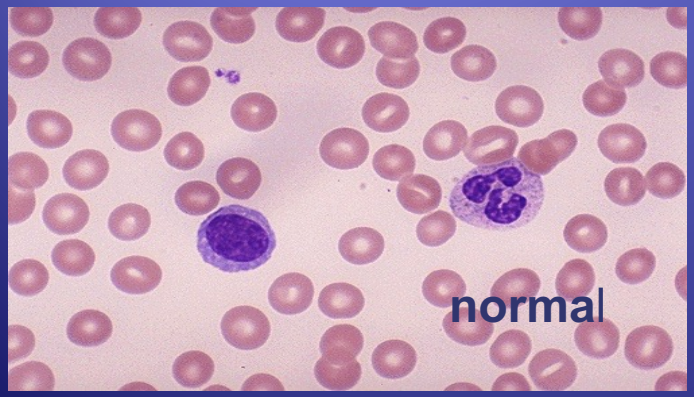
- A 19 yr old AA female comes to the ER with c/o severe right leg and lower abdominal pain after hiking in the mountains

- History:
  - Patient is from Florida and this is her first trip to the mountains. She hiked about 2 miles over strenuous terrain.
  - No injury or trauma to the leg/trunk.
  - Patient has not had similar pain in the past.

- PE:
  - No significant findings – leg is warm, good turgor, 2+ pulses throughout, full range of motion, non-tender to palpation

Case 3 – CBC Results



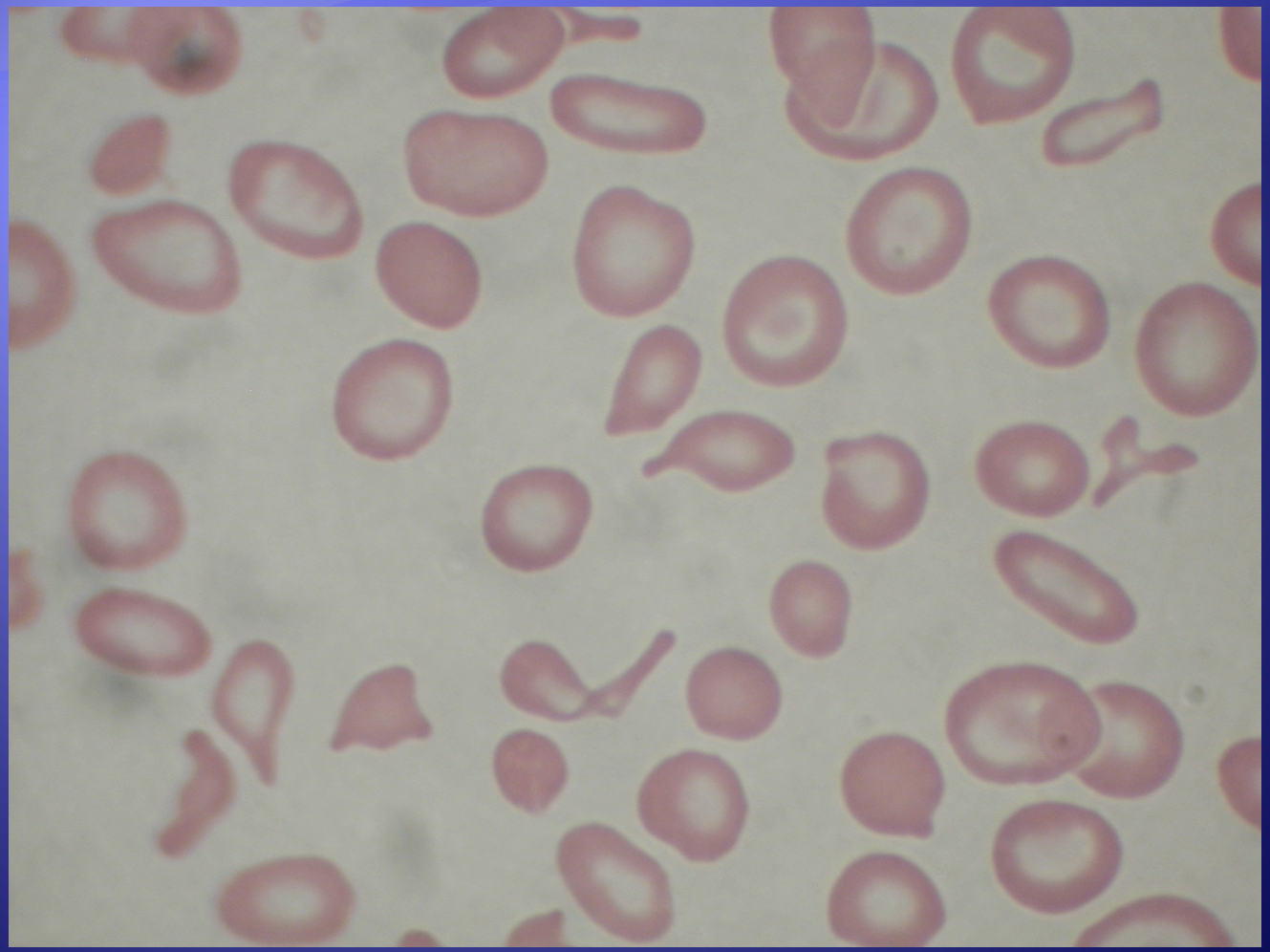


Test	Patient Value
CBC	
WBC	12.8 x 10^3/uL
RBC	2.2 x 10^6/uL
Hgb	6.6 g/dL
Hct	20.2%
MCV	91.8 fL
MCH	30.0 pg
MCHC	32.6 g/dL
RDW	17.6%
PLT	482 x 10^3/uL
WBC Differential	WNL
Retic Count	13.2%

Hemolytic Anemia

- RBCs do not survive 120 days
- Anemia not apparent until RBC life reduced to approximately 20 days
- Causes
  - Intrinsic – inherited
    - Abnormal membrane, enzyme, or hemoglobin
  - Extrinsic
    - Toxins, microangiopathic, infections, autoimmune, mechanical, drug-induced

Schistocytes

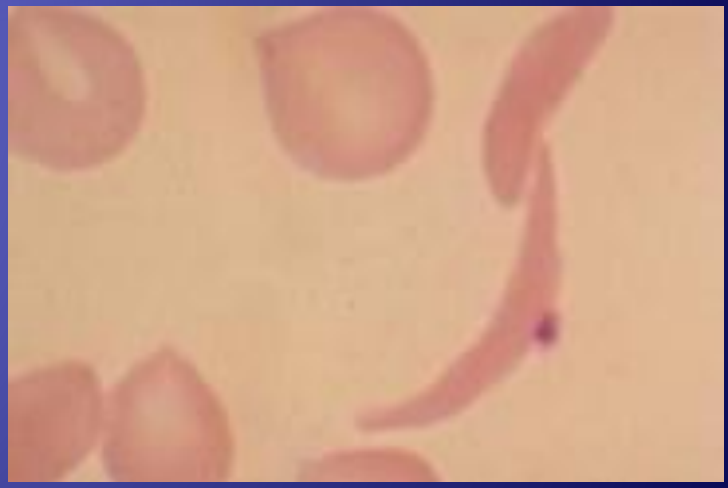


Hemolytic Anemia Intrinsic Defects

- Membrane abnormalities
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
- Hemoglobinopathies
  - Sickle cell anemia
  - Hemoglobin C and SC
- Enzyme deficiencies
  - G6PD deficiency
  - Pyruvate kinase deficiency

Hemoglobinopathies

- Sickle cell anemia
  - Defect in hgb causes hgb to form long chains that precipitate out and cause cell membrane to deform
    - Increased in low O2 environment
    - Sickle cell anemia vs sickle cell trait

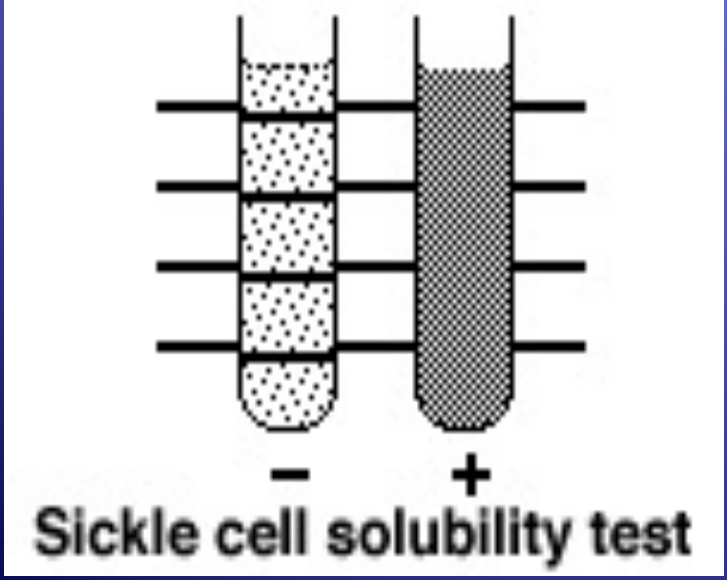


Sickle Cell Anemia
Sickle Cell Disease (SS)

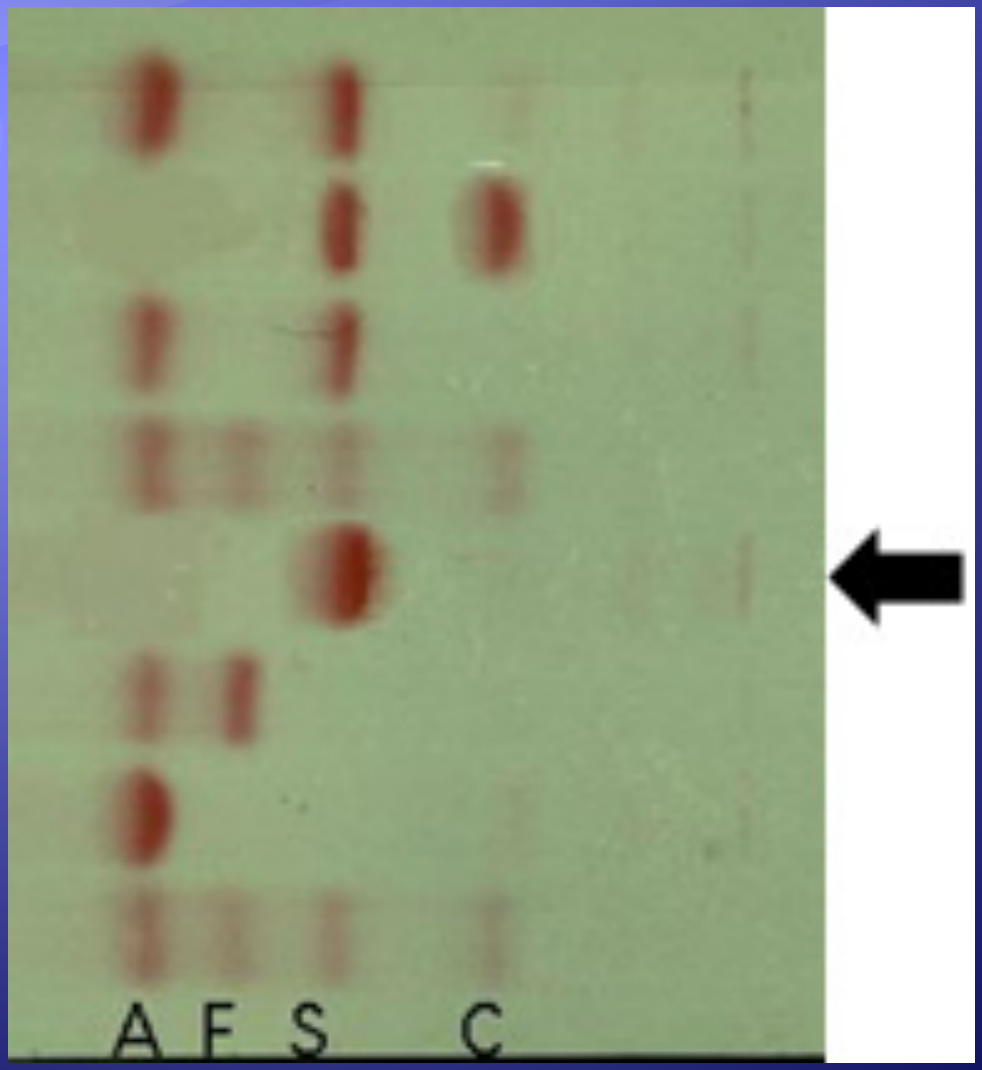
- Lab Results
  - Severe normocytic, normochromic anemia
  - Sickle cells, target cells, nucleated RBCs, Howell-Jolly bodies on smear
  - Increased WBCs and platelets
  - Retic count 10-20%
  - Positive solubility test
  - Hemoglobin electrophoresis shows Hgb S

Sickle Cell Anemia

- CBC with diff
- Sickle cell solubility test
- Hgb Electrophoresis



Hgb Electrophoresis

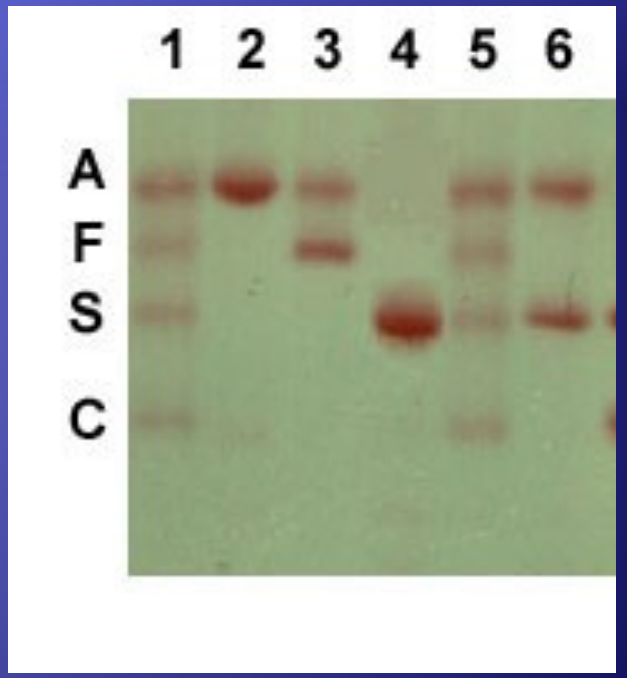


Sickle Cell Trait (AS)

- Lab Results:
  - Normal blood smear
  - Positive solubility test
  - Hemoglobin electrophoresis shows 55-60% Hgb A and 25-45% Hgb S
  - May also have Hgb F and A2

Case 3 – Follow Up Testing

- Hgb electrophoresis
  - Pt is #6

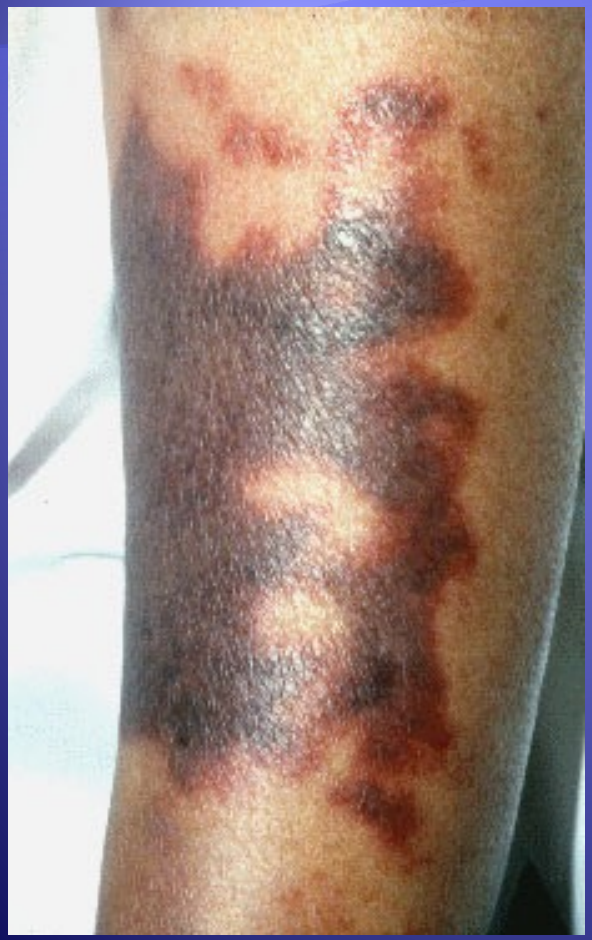


Sickle Cell Trait

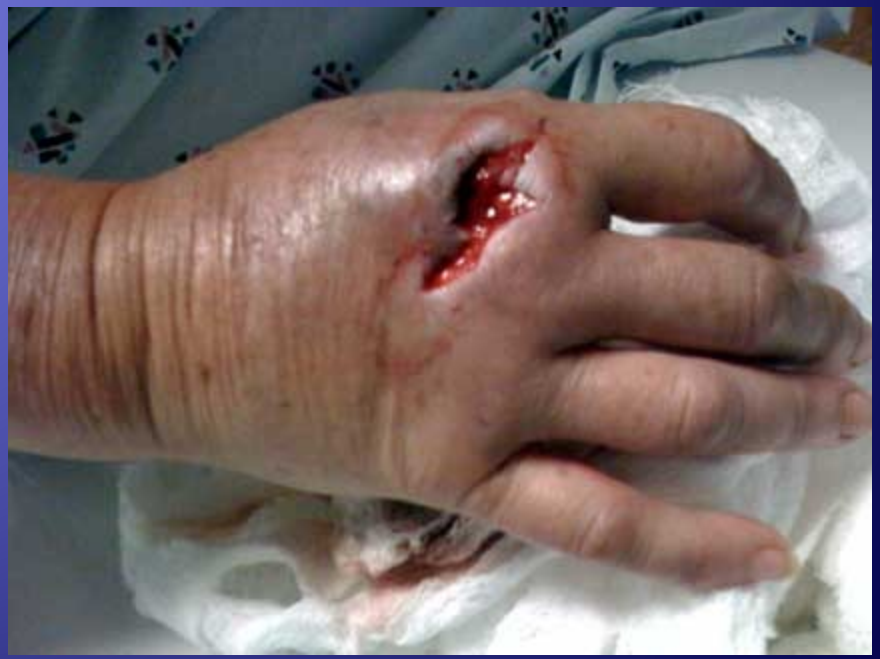
Case 4

- 52 yo male comes into the ER with c/o fever, chills, and a very swollen right hand.
  - PMHx: HTN
  - PSHx: none
  - FHx: non-contributory
  - SHx: non-smoker, occasional beer, no illicit drugs
  - Meds: Lisinopril 5 mg daily
  - Allergies: none
  - PE:
    - WDWN male, appears acutely ill
    - P 110, R 22, BP 72/40, T 104.0
    - LUE – puncture wound noted on the dorsum of right hand with significant erythema and edema to shoulder
    - BLE: multiple non-blanchable purpura noted

Case 4

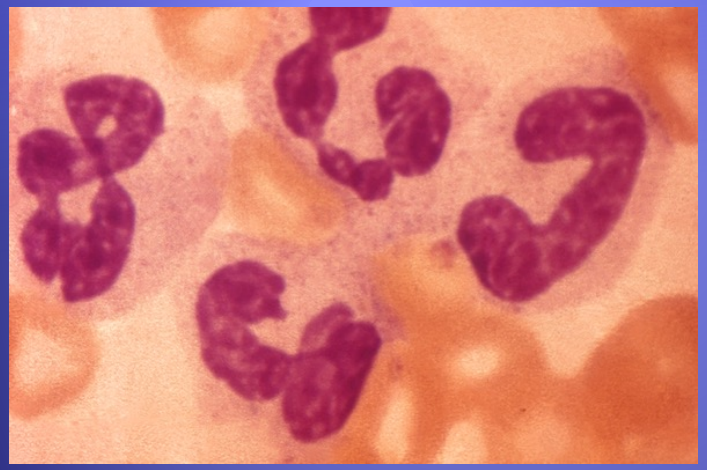


- Patient states he was bitten by his dog 3 days ago.

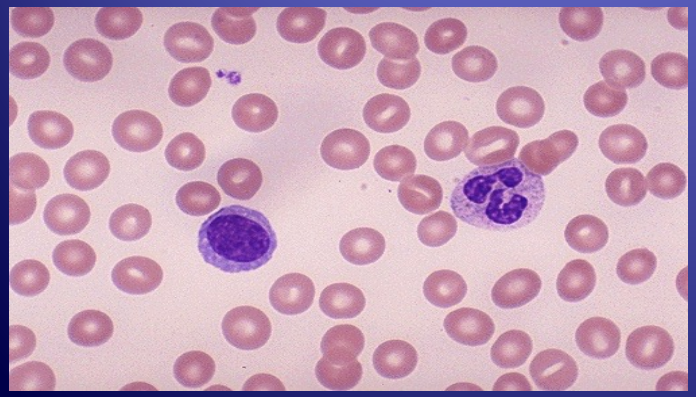


Case 4 – CBC Results

Patient

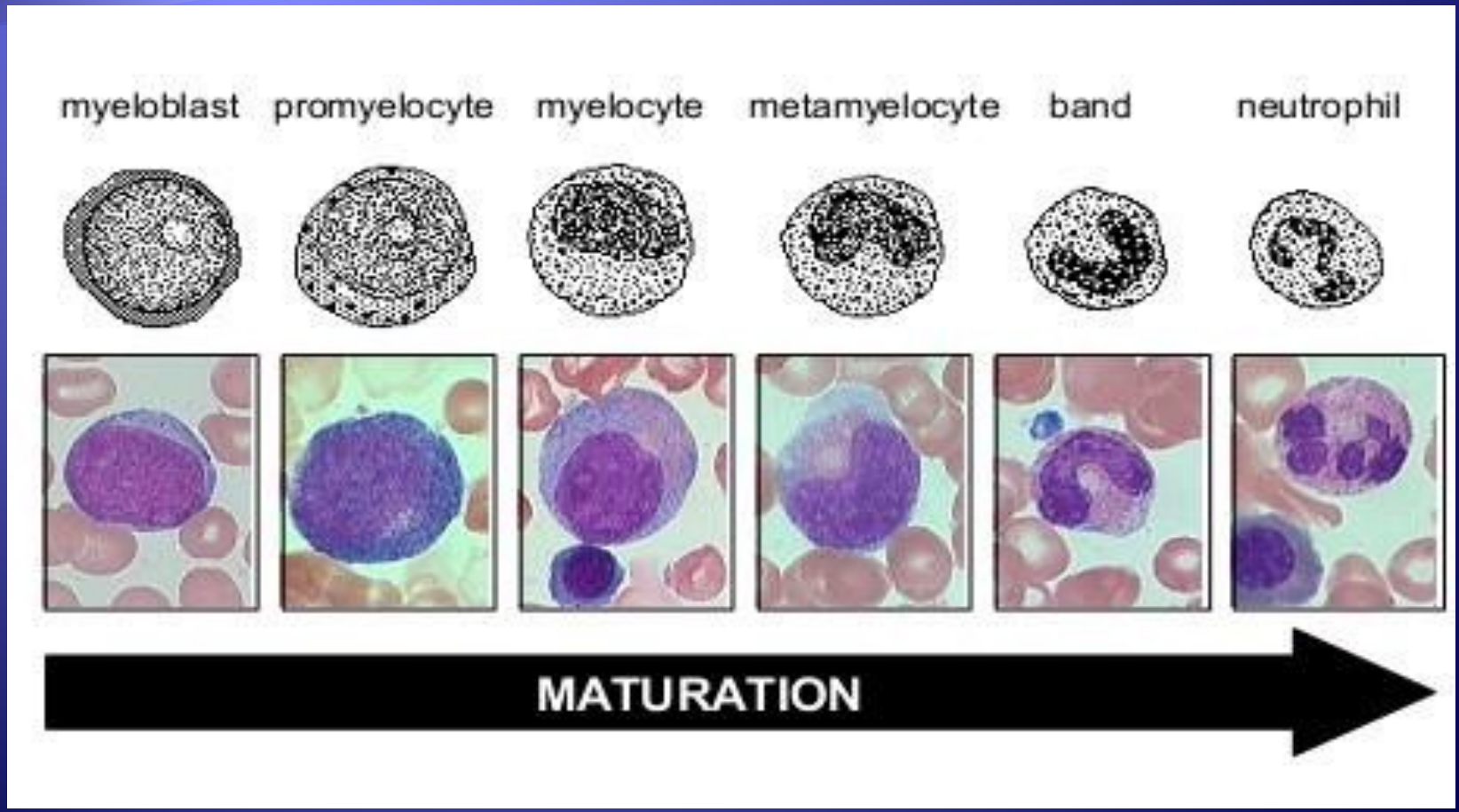


Normal



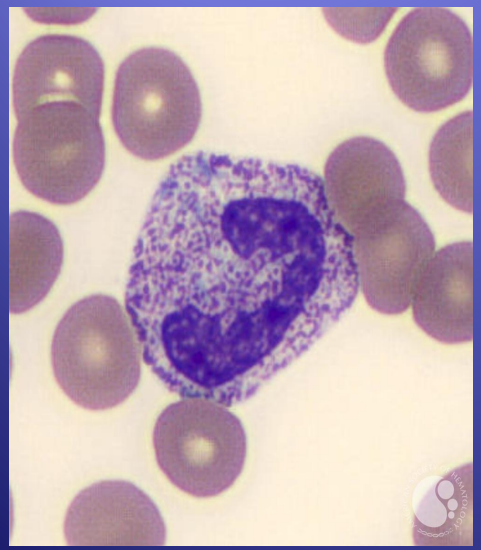
Test	Patient Value	Test	Patient Value
CBC		**WBC Diff and Smear Eval**	
WBC	22.2	PMNs	34%
RBC	4.29	Bands	51%
Hgb	13.8	Lymphocytes	6%
Hct	40.7	Monocytes	1%
MCV	94.9	Eosinophils	0
MCH	32.2	Basophils	0
MCHC	33.9	Meta	6%
RDW	15.5	Myelo	2%
PLT	19	Toxic Gran	+2
		Vac PMNs	+2
		Schistocytes	+1

“Left Shift"

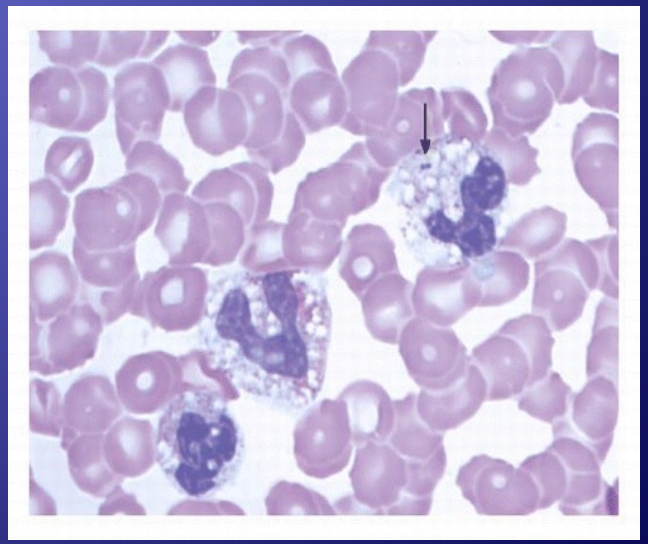

myeloblast
promyelocyte
myelocyte
metamyelocyte
band
neutrophil
MATURATION

WBC Morphology?

- What does toxic granulation and vacuolated PMNs indicate?
  - Severe bacterial infection



Toxic granulation

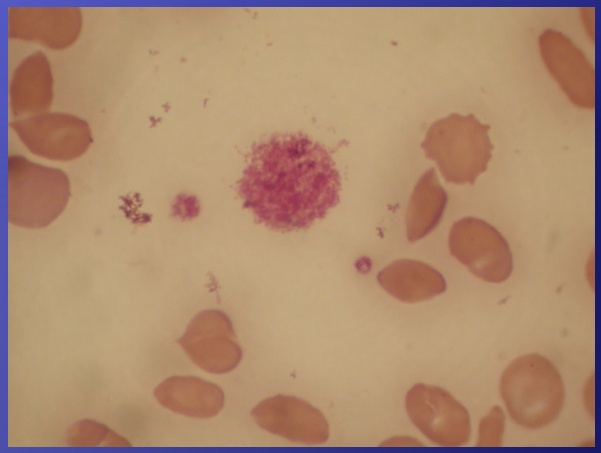


Vacuolated Segs

Additional Lab Results

- Additional tests:
  - Lactate 6.9 (normal < 1.5)
  - CRP 23.6 (normal for this pt < 1)
  - ESR 82 (normal for this pt < 20)

Platelets & RBC Morphology?



- Platelets = 19 x 10^3/uL
- RBC morphology shows schistocytes
- What else is going on with this patient?
  - Coagulation disorder???

Why Order Coagulation Studies?

- To determine if a low hemoglobin is due to a bleeding disorder
- To determine if a bleeding disorder is present, and to help distinguish the etiology of the bleeding disorder
- In order to establish a baseline before beginning anti-coagulation therapies

Coagulation Studies

- PTT or aPTT = Partial Thromboplastin Time
  - Measures intrinsic and common pathway
  - Normal = 25-35 sec
  - Heparin proper dosage = PTT 1.5-2.5 times normal
- PT = Prothrombin Time
  - Measures extrinsic and common pathway
  - Normal = 10-13 sec
  - Coumadin (warfarin) proper dosage = 2-3 times pre-therapy level
    - INR = International Normalized Ratio = 2.0 – 3.0

Coagulation Testing

- ↑PT, ↔PTT = extrinsic pathway
  - Factor VII deficiency, liver disease, vitamin K deficiency,
  - Coumadin therapy
- ↑PT, ↑PTT = common pathway
  - Factors I, II, V, X or multiple factor deficiencies
  - Coumadin therapy
- ↔PT, ↑PTT = intrinsic pathway
  - Factors VIII, IX, XI, XII, or von Willebrand's disease
  - Heparin therapy
- ↔PT, ↔PTT
  - Platelet deficiency, vascular defect or factor XIII deficiency

Coagulation Studies

- Fibrinogen
  - Converted to fibrin by thrombin in common pathway
  - Diagnose fibrin disorders or inhibitors of thrombin
  - Normal = 150-350 mg/dL
- D-Dimer
  - Breakdown product of fibrin clots (fibrinolysis)
  - Elevated levels of Fibrin Degradation Products (FDP) and D-Dimer indicate increased fibrinolysis
  - Normal = < 200 ng/mL

Additional Lab Results

- Additional tests:
  - PT/INR 2.4 (normal 0.9-1.1)
  - aPTT 76.8 (normal 28-40 seconds)
  - Fibrinogen 80 (normal 200-400 mg/dL)
  - D-dimer 13.5 (normal 0-0.4 ug/mL)

  - CMP: labs consistent with liver and kidney failure

ITP vs. TTP vs. DIC

	ITP	TTP	DIC
Pathogenesis	Antiplatelet antibodies	Endothelial defect	Thrombin excess
Clinical	Not sick	Sick	Sick
RBCs	Normal	Schistocytes	Schistocytes +/-
PT	Normal	Normal/Slight increase	Increased
PTT	Normal	Normal/Slight increase	Increased
Fibrinogen	Normal	Normal	Decreased
FDP	Normal	Slight increase	Increased
D-Dimer	Normal	Slight increase	Increased

Case 4

Severe Sepsis with DIC

In disseminated intravascular coagulation (DIC), the patient is in a hypercoagulable state. As fibrin clots are formed, platelets are decreased due to platelet aggregation, coagulation factors are decreased due to their use in the coagulation cascade, fibrinogen is decreased due to the conversion of fibrinogen to fibrin, and D-dimer is increased due to the excessive breakdown of fibrin.

Question #1

Of the following laboratory tests, which one is the best test for distinguishing iron deficiency anemia from anemia of chronic disease?

A. Total iron
B. Total iron binding capacity (TIBC)
C. Transferrin saturation
D. Serum ferritin

Question #2

Which of the following conditions would present with macrocytic red blood cells and hypersegmented neutrophils?

A. Vitamin B12 deficiency
B. Sickle cell disease
C. Iron deficiency
D. Chronic disease

Question #3

In which of the following conditions would a patient present with abnormal bleeding in the presence of an unremarkable physical exam, normal coagulation studies, and a normal CBC with the exception of an extremely low platelet count?

A. Hemolytic uremic syndrome
B. Idiopathic thrombocytopenic purpura
C. Thrombotic thrombocytopenic purpura
D. Disseminated intravascular coagulation

Take Home Points

- Appropriate interpretation of laboratory test results can eliminate unnecessary follow-up testing.
- Consider all laboratory test result abnormalities when establishing a diagnosis.
- Some laboratory test result abnormalities can alter other laboratory test results.

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Questions?

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