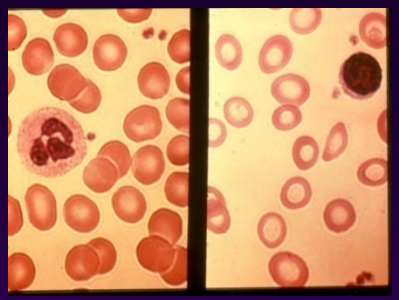


Anemia and Peripheral Smears

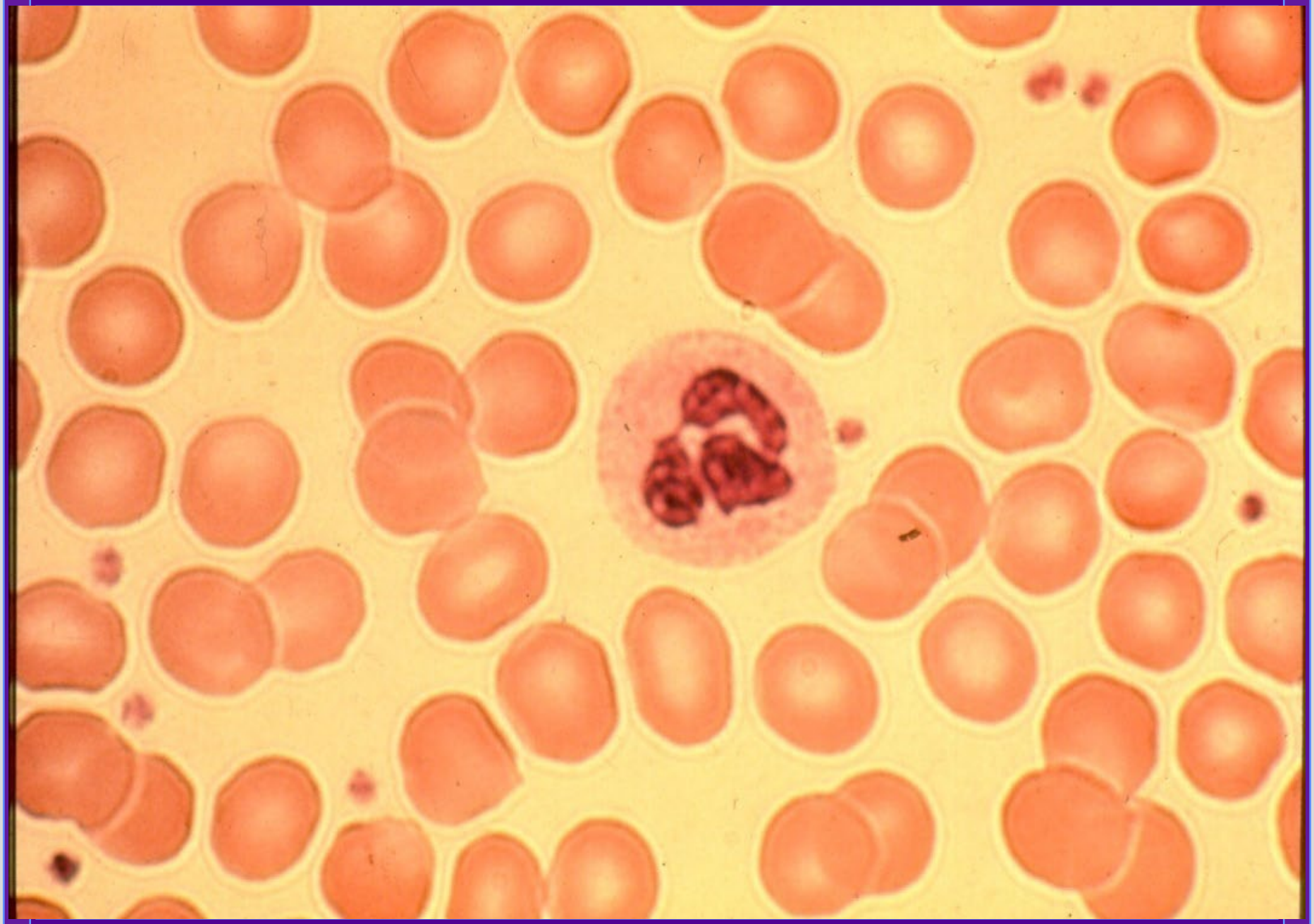
July 19, 2023

ACP Internal Medicine Board Review

Rachel Safran, MD, FACP, AAHIVS

MultiCare Rockwood Clinics, Spokane WA

Slides adapted from Joyce Wipf, MD, MACP



ANEMIA

- *Definition:* anemia represents a decrease in O-2 carrying capacity; not a dx but a sign of underlying disease
- Peripheral smear is an important tool in diagnosis of type of anemia

- Symptoms will vary depending upon:
  - Extent to which the O2 carrying capacity of the blood is compromised
  - Total change in blood volume/ rapidity of onset
  - Manifestations of the underlying disorder that caused the anemia
  - Coexistent disease that limits CV/pulm function

Case 1.

The most common cause of anemia in women in the US is:

A. Anemia of chronic disease
B. Iron deficiency anemia due to low dietary intake
C. Iron deficiency due to blood loss
D. Macrocytic anemia due to alcohol
E. Vitamin B12 deficiency

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B. Iron deficiency anemia due to low dietary intake
C. Iron deficiency due to blood loss
D. Macrocytic anemia due to alcohol
E. Vitamin B12 deficiency

ETIOLOGY OF ANEMIA

- Most common cause in US:
  - Women and children: Fe deficiency
    - Blood loss in women, nutritional in children
  - Men: anemia of chronic disease
    - Fe deficiency is second

ETIOLOGY OF ANEMIA

- 1/3 of teens are anemic
- Muscles are a prominent user of iron
- Fe deficiency in Athletes:
  - 50-80% of female athletes
  - 10-17% of male athletes
- CNS need for iron
  - Test scores in young women improve after iron repletion

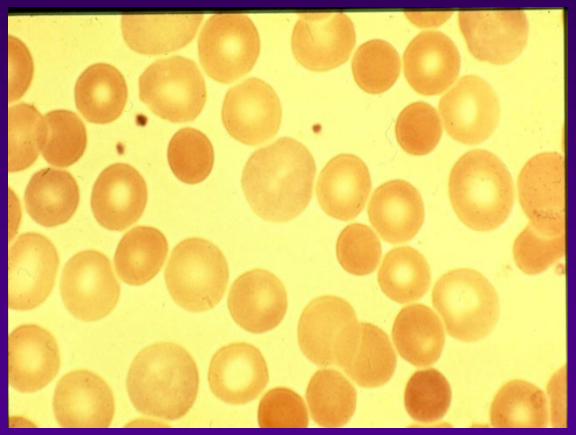
Mr. T is admitted to Medicine with recurrent foot infection and gangrene. Diabetes Type 2, PVD

Labs: Hgb 10 Hct 30 MCV 80

What should be included in work-up of anemia in this pt?

(note 1/3 of patients admitted to acute medicine are anemic)

What should be in the work-up of anemia?

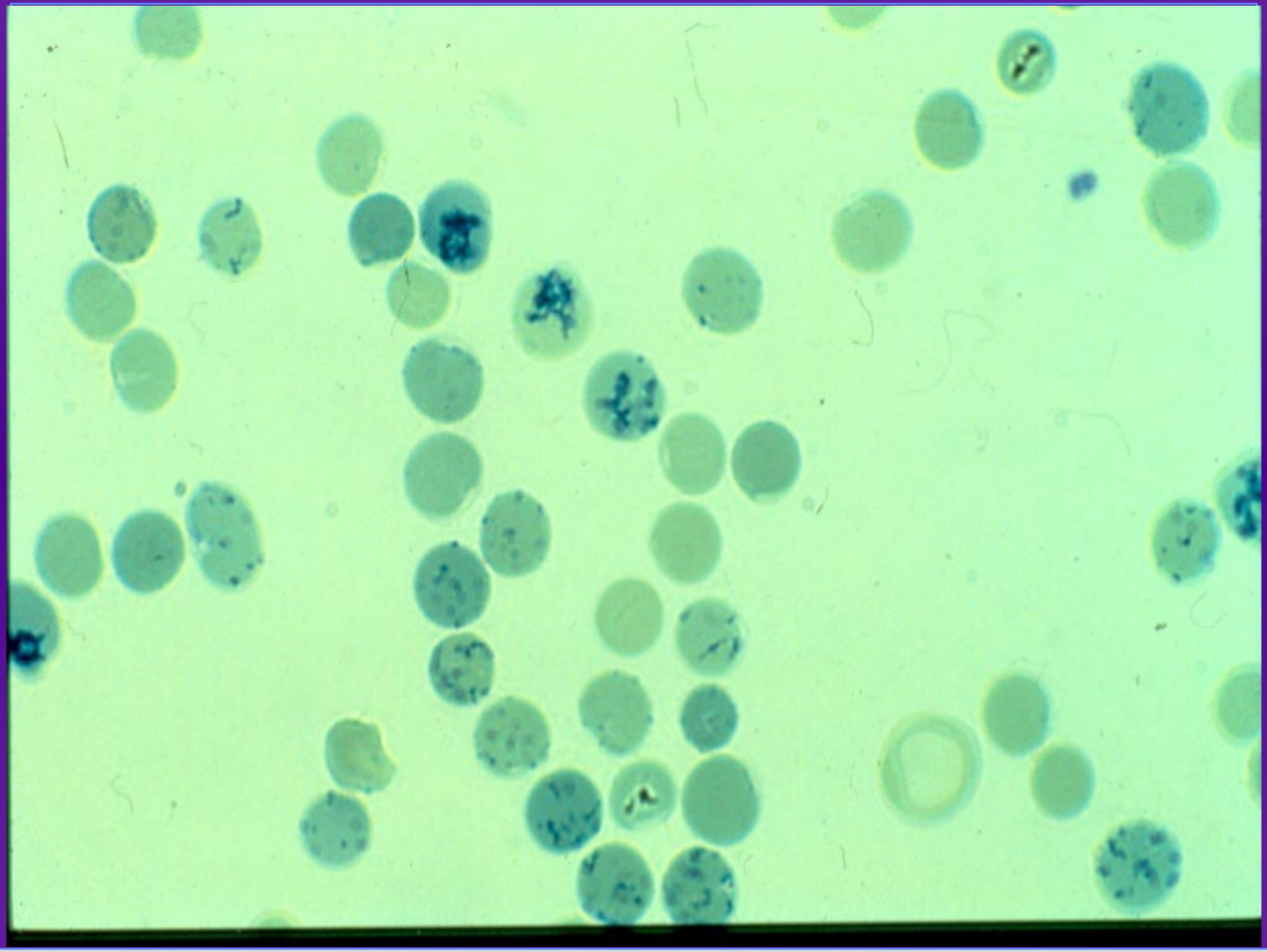


Indices
(MCV)
Retic index
Peripheral smear
Fe studies
? Other (TSH, Bilirubin,
Macrocytic: B12, Folate)

Check other cell lines: wbc, plts

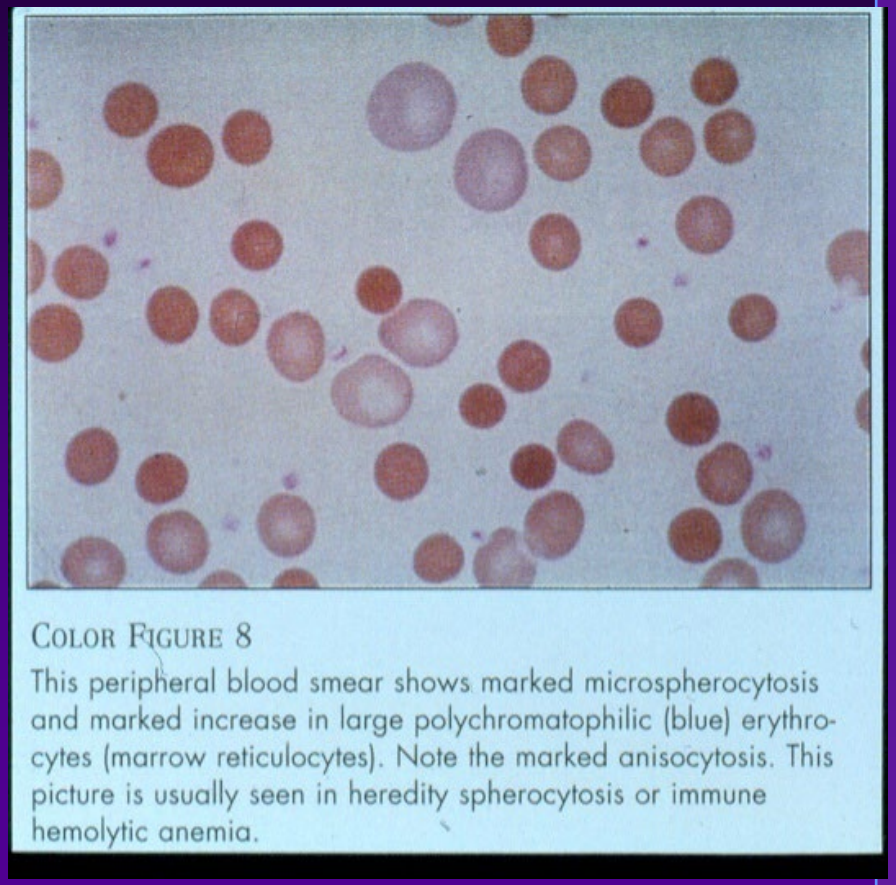
RETICULOCYTE COUNT

- Reticulocytes are immature RBCs recently released into peripheral circulation from the bone marrow
- On peripheral smear appear as larger, slightly blue RBCs (polychromasia)
- Retic count measured with special stain as a percentage
- Must be corrected (indexed) for HCT
  - Elevation suggests hyperproliferative process
  - Decrease suggests hypoproliferative process



Hyperproliferative anemias

- Blood loss
- Hemolytic anemia



COLOR FIGURE 8
This peripheral blood smear shows marked microspherocytosis and marked increase in large polychromatophilic (blue) erythrocytes (marrow reticulocytes). Note the marked anisocytosis. This picture is usually seen in heredity spherocytosis or immune hemolytic anemia.

Hypoproliferative anemias

- Early iron deficiency
- Anemia of chronic disease
- Anemia of renal failure
- Anemia with endocrine conditions
  - ie hypothyroidism, adrenal insufficiency hypogonadism
- Marrow disorders
  - myelofibrosis, myelodysplasia
- HIV
- Megaloblastic anemias

Case 3.

Pt is a 33 yr old woman who comes in for evaluation after turned down for blood donation due to anemia. Last donation 1 unit 6 months ago.

Sx: diminished energy, trouble keeping up with her 3 yr old.

ROS: menorrhagia x ~4 cycles.

Exam: BP 110/56, HR 50, wt 149 lbs

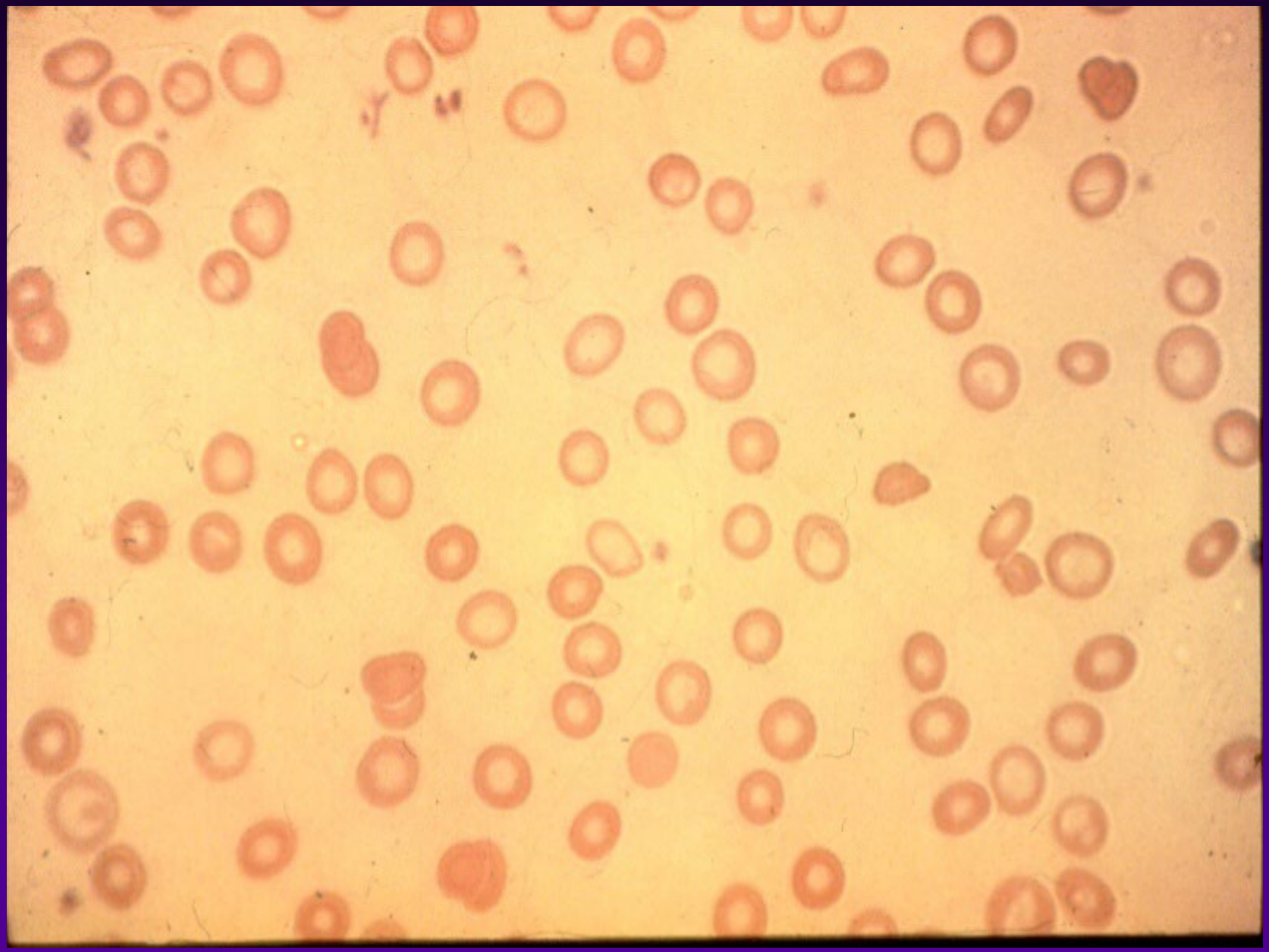
HEENT: pink mucous membranes

GYN exam nl.

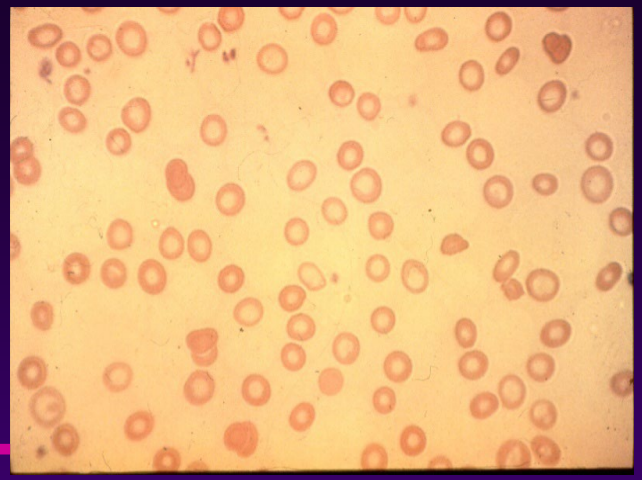
Labs: WBC 6.0 Hgb 9.6 Hct 29% MCV 76

TSH 43

Peripheral smear is shown.



Case 3.
What is the most likely explanation for this anemia and peripheral smear?



A. Menorrhagia→Iron deficiency anemia
B. Excessive blood donations→Iron deficiency
C. Hypothyroidism→anemia of chronic disease
D. Surreptitious alcohol use disorder

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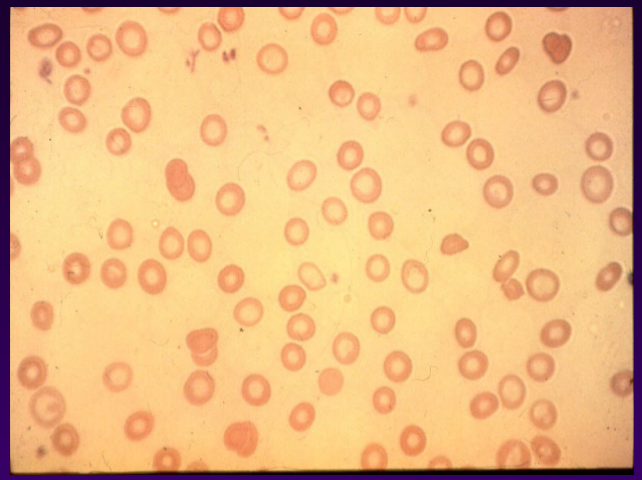

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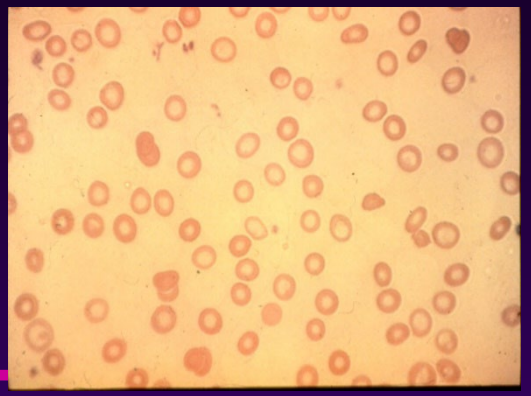
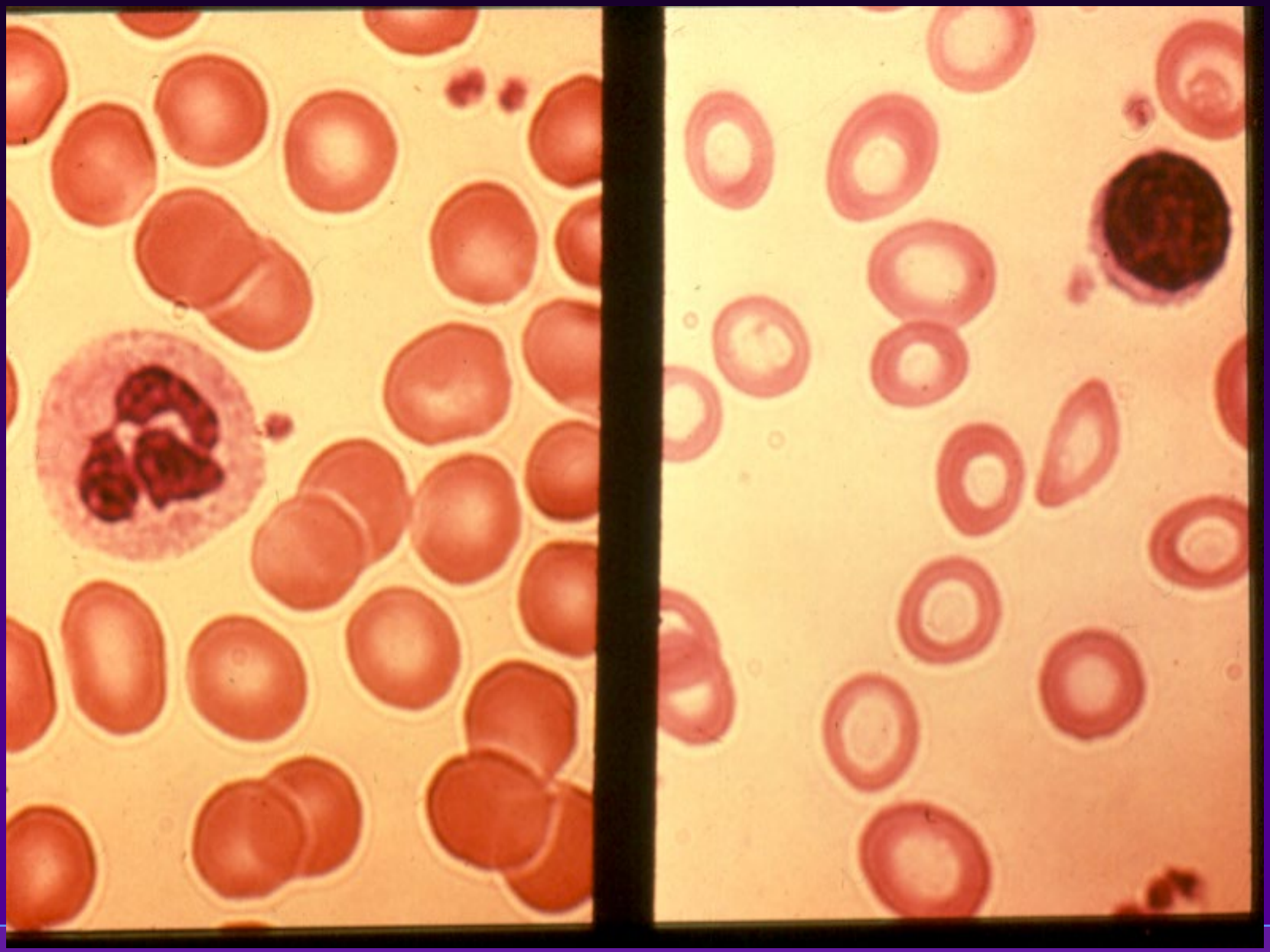
Case discussion



- Smear: microcytic hypochromic RBCs
- Low MCV
- Blood loss hx: Fe deficiency
- Hypothyroidism also present, but is usually associated with normochromic normocytic RBCs, occas micro/macrocytic



IRON DEFICIENCY: Clinical Features

- *Pica:* an unusual desire to eat substances of little nutritional value: clay, ice, starch
- Angular cheilitis
- Glossitis with papillary atrophy of the tongue
- Spoon nails (koilonychia) or brittle nails
- CHF, dyspnea
- New systolic murmur

Case 4.
Pt is a 42 year old male with diabetes, recently started on hemodialysis for ESRD. He is chronically on anticoagulation for recurrent DVT. In routine evaluation, the patient notes six episodes of BRBPR x 3months. No postural sx.
Exam: BP 138/88, pulse 84, alert, NAD. Abdomen benign
Rectal: brown stool, heme negative; no external hemorrhoids, no mass palpable

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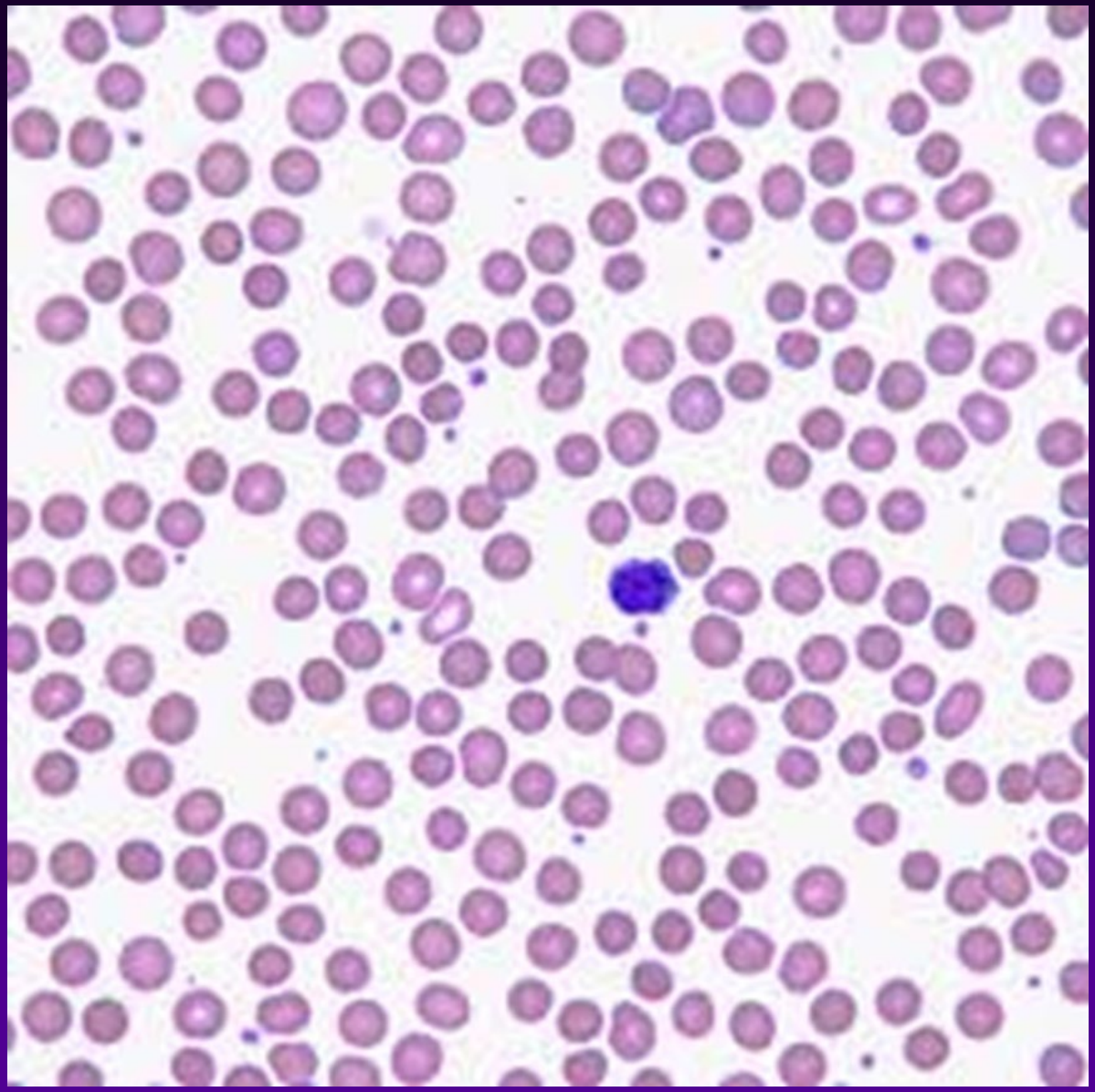
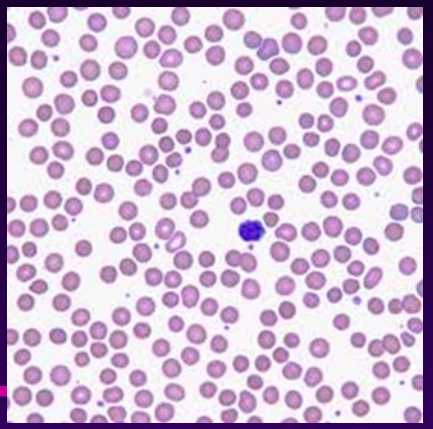
Labs: Hgb 10.2, hct 31%, WBC 6.2, plts 386K
Fe 42/ TIBC 199/ Sat 18%/ Ferritin 188
Peripheral smear is viewed.



Case 4.

The most likely cause of this patient's anemia and smear findings:



A. Iron deficiency anemia secondary to GI blood loss
B. Anemia of chronic disease
C. Vitamin B12 deficiency
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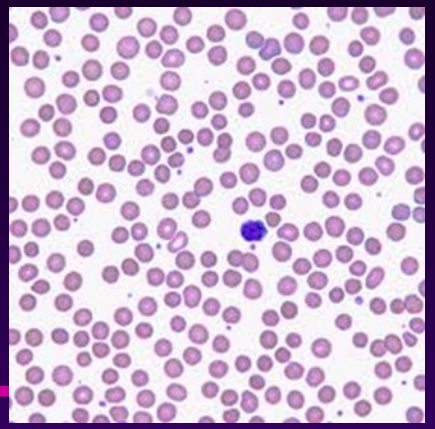

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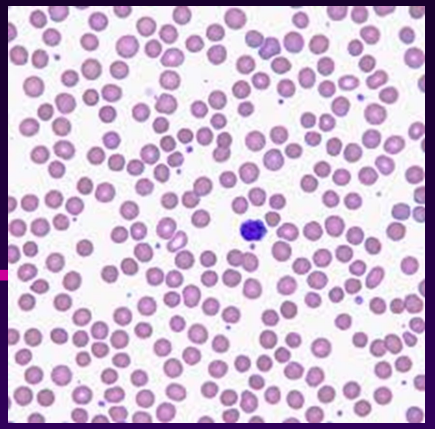

- Smear: normochromic normocytic RBCs
- Fe studies c/w anemia of chronic disease
- Other etiologies of anemia possible (has some blood loss, etc) but smear and MCV don’t fit Fe deficiency

Comparison of Fe def and ACD

Test	Fe Deficiency	ACD
Serum Iron *(nl 50-150)*	Very low (<25)	Low
- bound iron transported by transferrin		
TIBC	High nl or high	Nl or low
- measures available transferrin binding sites		
% Saturation	<15%	Slightly low
- Percent of transferrin sites bound by iron		
*Ferritin**	Low (<50 mcg/L)	Nl or high
- intracellular storage form of iron		
Transferrin receptor	High	Normal
- not acute phase reactant		

Case 5.
Which symptom is associated with ferritin levels <50?

A. Leg cramps
B. Numbness of the feet
C. Foot pain
D. Restless legs

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Restless Leg Condition

- Check a ferritin level (is the only useful blood test in patient with restless legs)
- Rx for iron deficiency if ferritin <50
  - IV iron increasingly used if ferritin <100 (no current Sleep Medicine practice guidelines however)
- Anemia may or may not be present

Treatment of Iron Deficiency

- Target Ferritin level? (>50)
- Fe Gluconate or Fe Sulfate
  - If can tolerate, Fe Sulfate better absorbed
  - Takes 6 wks to correct anemia, 6-12 m to replete Fe Stores
- Dose recommendations?
  - Daily or QoD (not TID)
  - Affects other meds, less Fe absorption with higher dose
- Do you give with Vitamin C? (common practice, not strong evidence)
- When to use IV Fe? Severe Fe def, sx

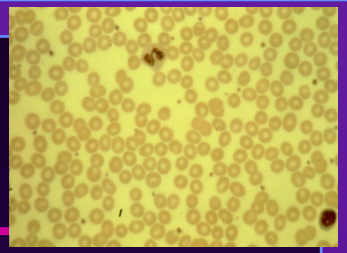
Ferritin levels: What is normal?

- No physiologic reason why women would have lower ferritin levels than men
- Normals set by lab
- Study (*BMJ* 2003) of non-anemic women:
  - Randomized to Fe Rx or none
  - Energy level signif improved in treated group if ferritin <50
- Consider Fe deficiency if ferritin <50 (regardless of lab setting normal at 10 or 30…)

Low Ferritin: GI disease?

- Study of older patients with ferritin <50 (*Am J Gastroenterol* 1998)
  - Serious GI pathology in over half
  - Cancer 10%
- Important to rule out GI disease in older patients, and in younger who have persistent sx

Anemia of Chronic Disease



- ACD most common anemia among hospitalized patients; #1 cause in elderly US men
- 3 classic conditions: infection, inflammation, neoplasia
  - Other: trauma, liver dz, renal dz, endocrine
  - 70% pts with severe CHF have ACD
  - COPD, DM
- May coexist with other types of anemia
- Anemia typically develops over months, but abnormalities in Fe studies over 2-3 wks
- Labs: Anemia usually mild, Hgb 7-8, Hct >25%, occas severe;

  1/3 microcytic

Anemia of chronic renal disease

- ESRD: Erythropoetin Rx→
  - Be sure not also Fe deficient: Rx Ferritin <100 in ESRD
  - Recommend Hgb 10-12, partial correction
- *RCTs showed increased CV events/ CKD progression if correct anemia to normal*
  - *NEJM* 1998 (Besarab)
  - CHOIR trial *NEJM* 2006 (Singh)
  - CREATE trial *NEJM* 2006 (Dureke)

Transfusion

- Expect Hgb/Hct to rise by 1 and 3 points respectively per unit
- When to Transfuse: General rule is when Hgb <7/ Hct <21%; (vs <25%)
  - Some situations where want to achieve higher levels

    - if actively bleeding
    - highly symptomatic
    - severe cardiovascular disease (ie angina precipitated)
    - planned surgery with anticipated significant blood loss

Case 6.
A 27 yr old man with stated SE Asian ethnicity comes in for a routine exam required for employment. He is in good health, without weight loss, fatigue or bleeding symptoms. Exam is unremarkable and the pt has no hepatosplenomegaly. Negative stool FIT test. FH negative for anemia

---

Labs:

WBC 5.3, Hgb 11.4, Hct 35%, MCV 65,

Plts 330K.

Retic index 0.8%.

Case 6.

What is the best test to confirm the most likely cause of this patient's anemia?

A. Obtain CBC on siblings
B. Perform ultrasound for spleen size
C. Measure serum ferritin and iron studies
D. Check glucose-6-phosphate dehydrogenase screen
E. Perform hemoglobin electrophoresis

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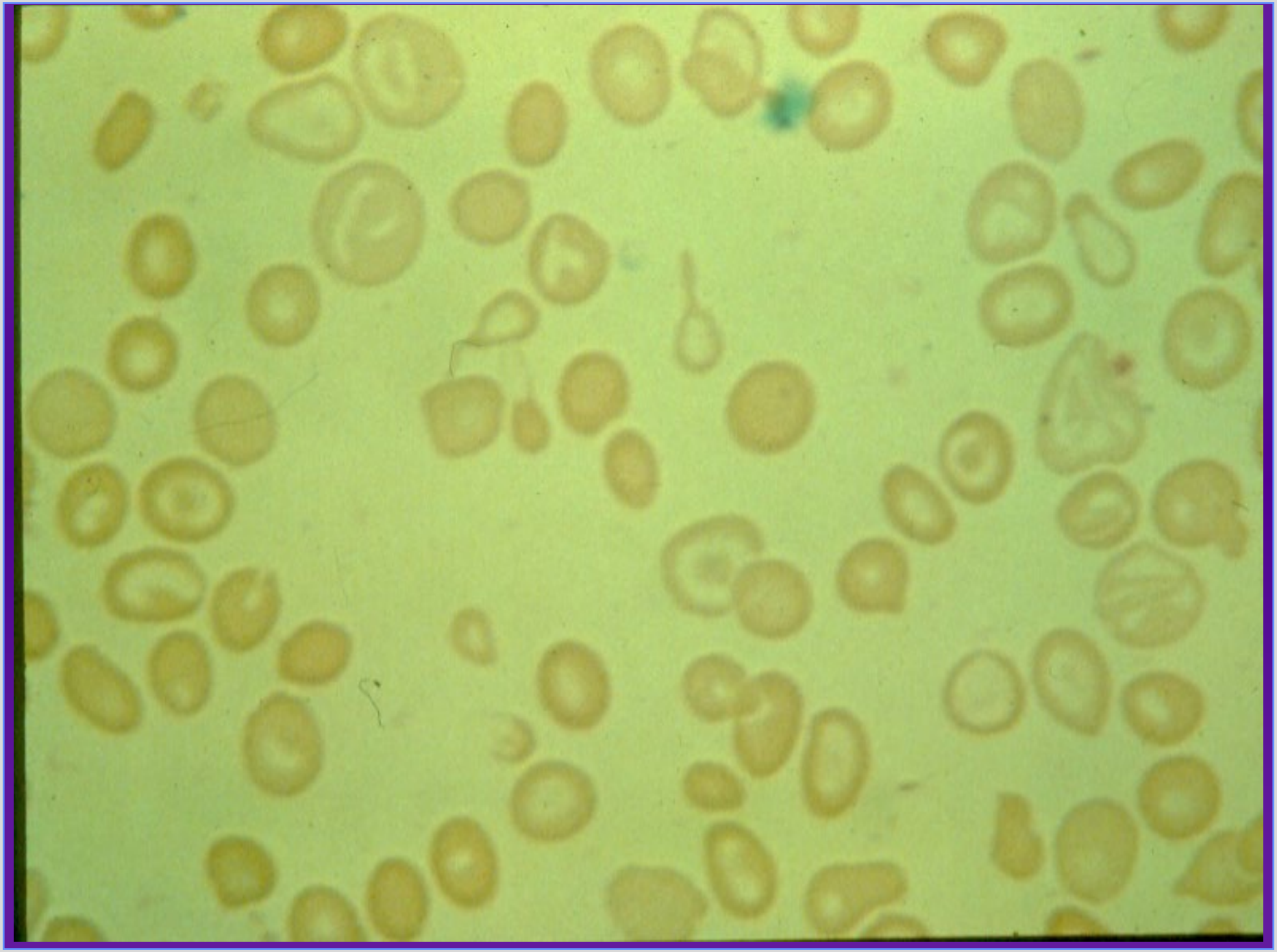
Microcytic anemia

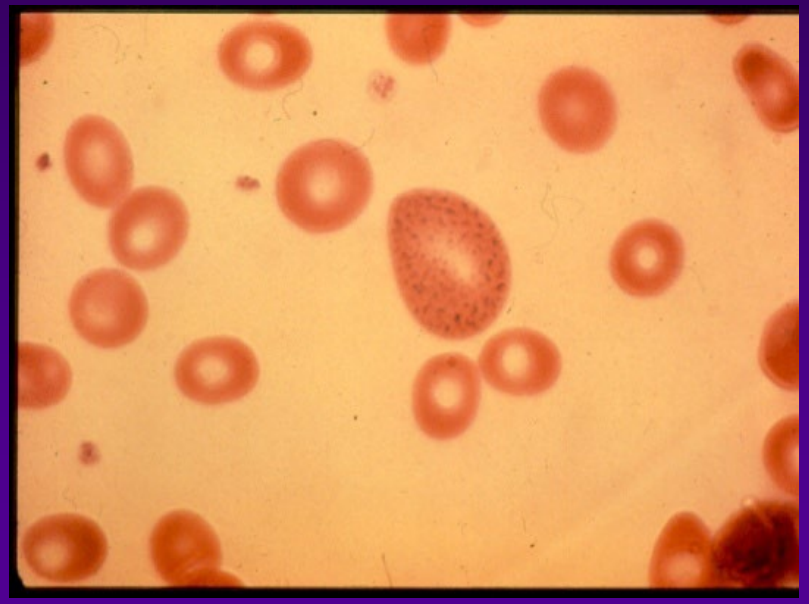
Evaluation of microcytic anemia

- Thalassemia trait: *suspect when mild anemia and marked microcytosis (MCV <70)*
  - Clues: ethnicity (Mediterranean, Asian)
    lack of symptoms
    (often negative FH)
  - Dx thal trait: Hemoglobin electrophoresis
- Thalassemia:
  - splenomegaly, abnormal smear, high retic
- Iron deficiency anemia: *usually more pronounced microcytic anemia than thal trait*
  - sx with exertion, bleeding hx, menorrhagia/metorrhagia



Case 7.
The peripheral smear showed numerous abnormal speckled red cells.
What is this patient's diagnosis?

A. Mercury toxicity
B. Lead toxicity
C. Arsenic toxicity
D. Cadmium toxicity



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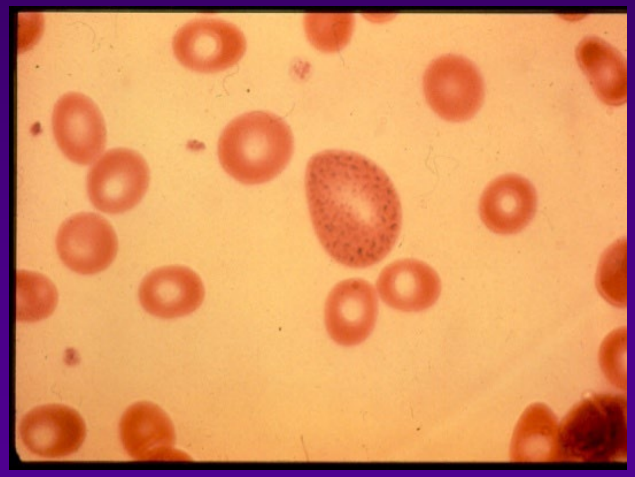

Basophilic Stippling

Case 8.

What percentage of outpatients >age 65 have macrocytosis without anemia?

A. 3%
B. 5%
C. 10%
D. 15%
E. 20%

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A. 3%

B. 5%

C. 10% (MCV to 96; 2-4% MCV >100)

D. 15%

E. 20%

Evaluation of *macrocytosis in outpatient setting*

- ? Anemia present
- Mild: Consider hypothyroidism
- MCV > 110: vitamin B12/folate

Case 9.
You are working up a 74 yr old woman for anemia and mild cognitive impairment:
Labs: Hgb 9.9, hct 31%, MCV 118 with 2+ anisocytosis, 2+ poikilocytosis. Vitamin B12 level is 210 (nl 200-900); Folate level is normal. Methylmalonic acid is high. Homocysteine level is high.
What is the most likely diagnosis?

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B. Vitamin B12 deficiency
C. Neither Vitamin B12 or folate deficiency

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B12, Folate, MMA and Homocysteine: challenges

- Low normal B12 levels are nonspecific
- Serum folate levels return to normal after several good meals, and RBC folate levels may be unreliable
- Decreased folate may cause low B12 concentrations due to metabolic blocks
- Deficiency of either Vitamin B12 or folate can increase homocysteine, an amino acid
  - Low B12 or folate and high homocysteine may be assoc with increased CV risk (Framingham data, other)
- High Methylmalonic acid levels helpful in Dx Vit B12 deficiency: high MMA strong association with low or low normal (150-300 ng/ml) Vitamin B12 levels.
  - MMA levels drop after 3m of Rx B12
- If elevated Homocysteine and normal MMA→dx folate def.

Klee, *Clin Chem* 2000; 46:1277-83

Cochrane Review 2008

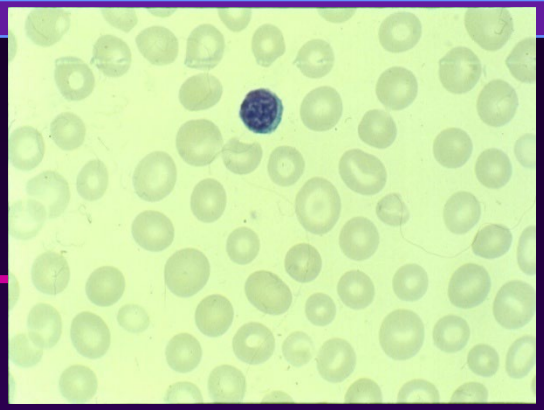
Vitamin B12 deficiency

- Macrocytic anemia, MCV typically 110-140
- Smear: macro-ovalocytes, hypersegmented PMNs
- Neurologic sx (presenting sx in 30%):
  - Stocking/glove paresthesias, poor proprioception & vibratory
  - Dementia
  - Loss of perception of smell
- Glossitis with a beefy smooth-appearing tongue
- Anemia may not be present or may be mild

Vitamin B12 deficiency - 2

- B12 Deficiency common!
  - One study of patients >60:
  - 6% B12 deficiency
  - 16% marginal stores
- Causes: rarely dietary (vegan); usually decreased production of Intrinsic factor (autoimmune, gastrectomy), decreased ileal absorption
  - Medications to decrease stomach acid can contribute to B12 deficiency (PPIs, antacids)
  - Metformin Rx assoc with B12 deficiency

Folate deficiency



- Macrocytic anemia
- Smear: macro-ovalocytes, hypersegmented PMNs
- Neurologic sx may be due to high homocysteine
- May seen mucosal changes and glossitis
- Causes: usually dietary; relatively low tissue stores, develops over several months.
    - Folate in Fruits (citrus, melon, bananas), leafy green vegetables, and fortified grain products

  Meds: TMP/SMX, phenytoin, sulfasalazine. Increased demand seen in pregnancy, chronic hemolytic anemia, exfoliative skin disease
- Rx Oral Folate 1mg q D

Case 10.
A 46 yo woman presents with severe jaundice and mild RUQ abdominal pain. She denies alcohol use.

Meds: Multivitamin, anti-histamines

PMH: Non-smoker, no substance use.
FH: Neg for Cancer or liver disease

Exam: Pt alert, normal MS
Marked icterus
Hepatomegaly to 16cm,
Spleen not palpable
No fluid wave or shifting dullness

Labs:

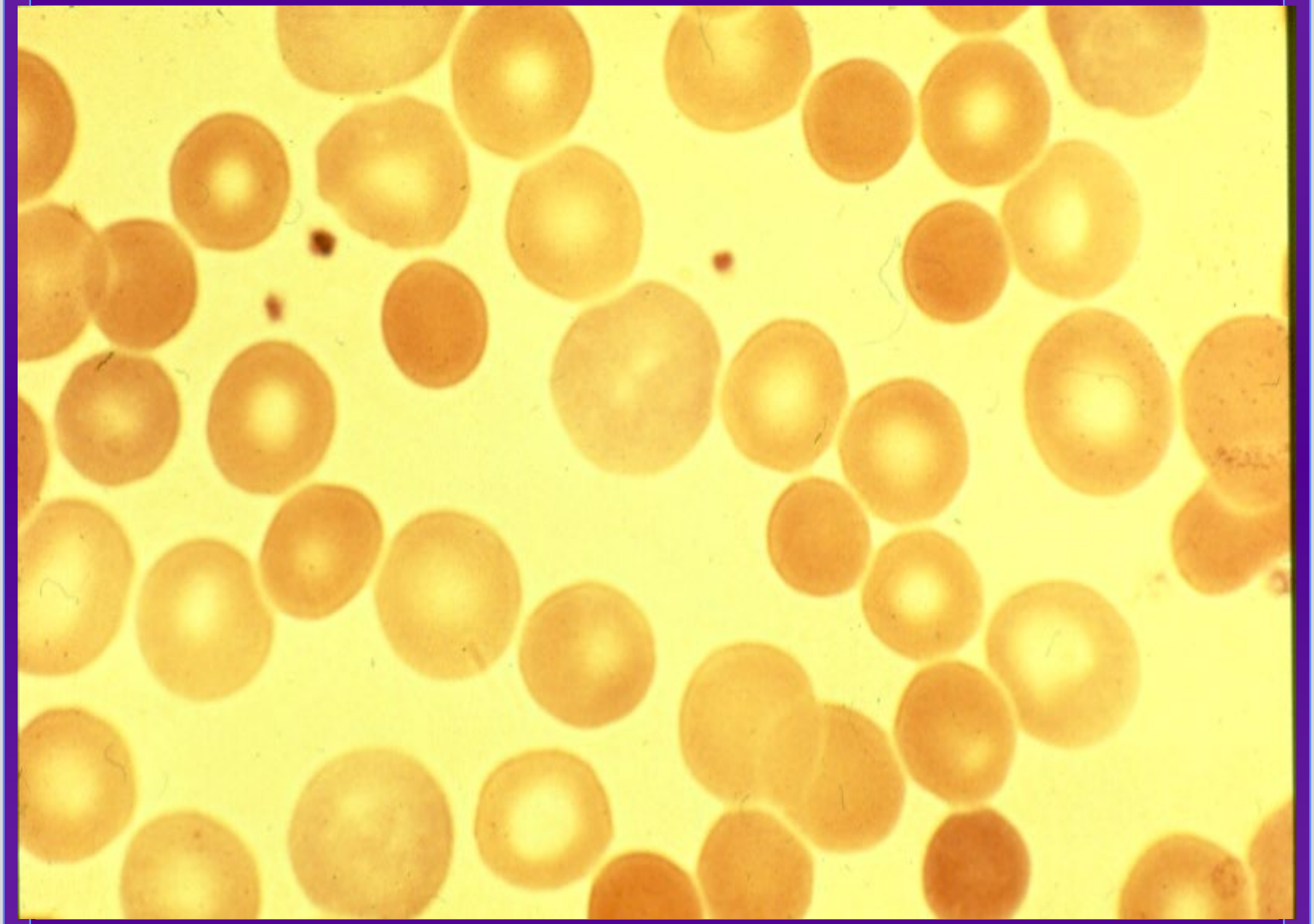
WBC 7.3

Hgb 10.5, Hct 32% MCV 86
Plts 86K
Total Bili 51 (direct 18)
AST 650

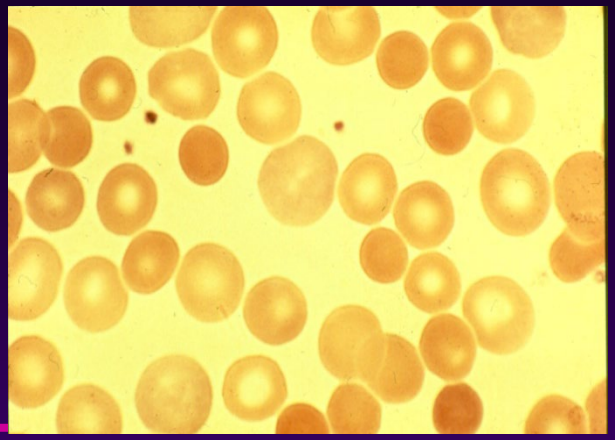
ALT 588

Alk phos 350

Smear shown.



Case 10.
What type of hemolytic process shown on smear does this patient most likely have?



A. Intravascular hemolysis due to transfusion reaction
B. Intravascular hemolysis due to G-6-PD deficiency
C. Intravascular hemolytic anemia due to DIC
D. Extravascular hemolysis due to autoimmune process
E. Extravascular hemolysis due to alcohol

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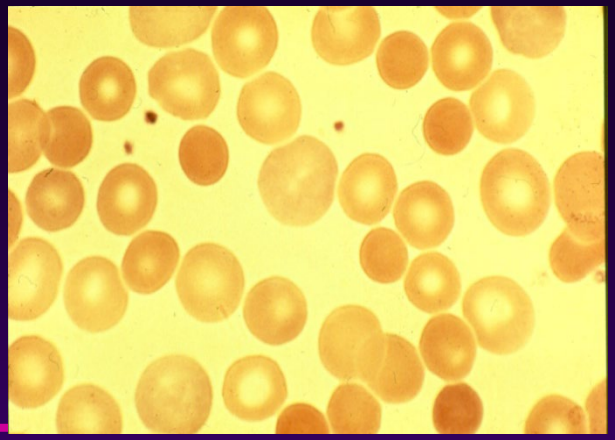

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Hemolytic anemia

- *Extravascular hemolysis*

  More common than intravascular hemolysis

  RBCs sequestered in spleen and liver, then destroyed by macrophages

  RBCs abnormal:

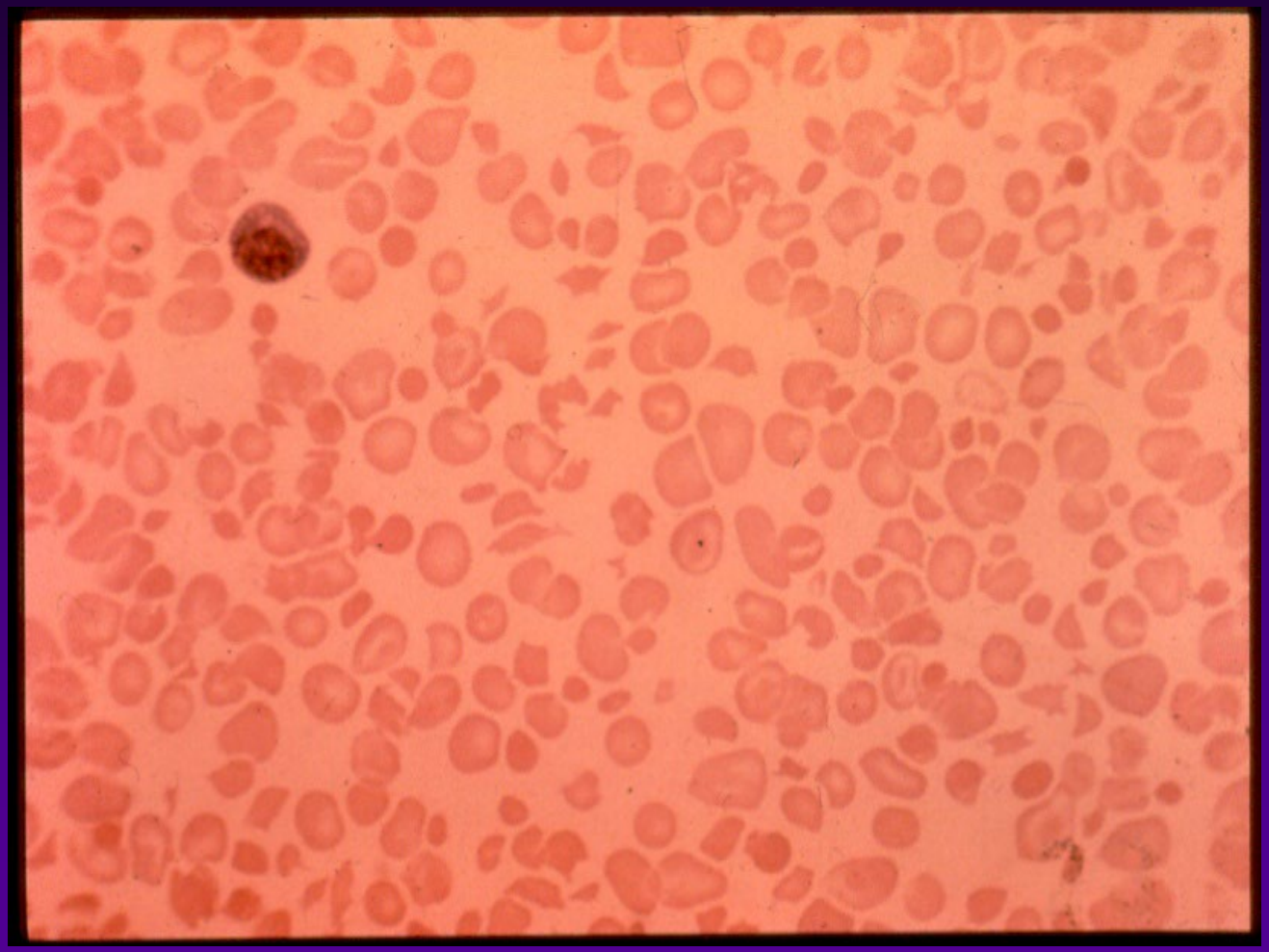
  Coated with AB or structurally abnl and not released by the spleen

  Haptoglobin declines, but detectable

  NO hemosiderinuria or hemoglobinuria

  Mild elevation of LDH

Intravascular hemolysis



Hemolytic anemia

- Common features:
  - Splenomegaly
  - Jaundice
  - Elevated unconjugated bilirubin
  - Marked reticulocytosis
- *Intravascular hemolysis*

  RBCs destroyed directly in the circulation

  Hgb released and binds haptoglobin-->

  low or absent serum haptoglobin

  Renal filtration of hgb-->urinary hemosiderin

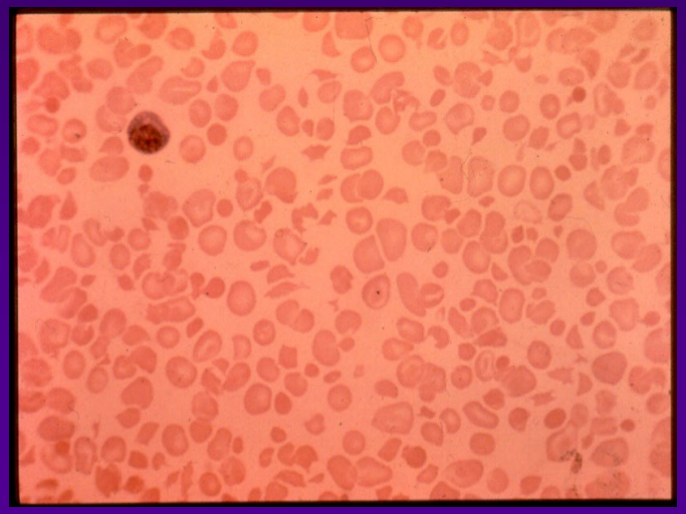
  Hemoglobinuria

  Very high serum LDH levels

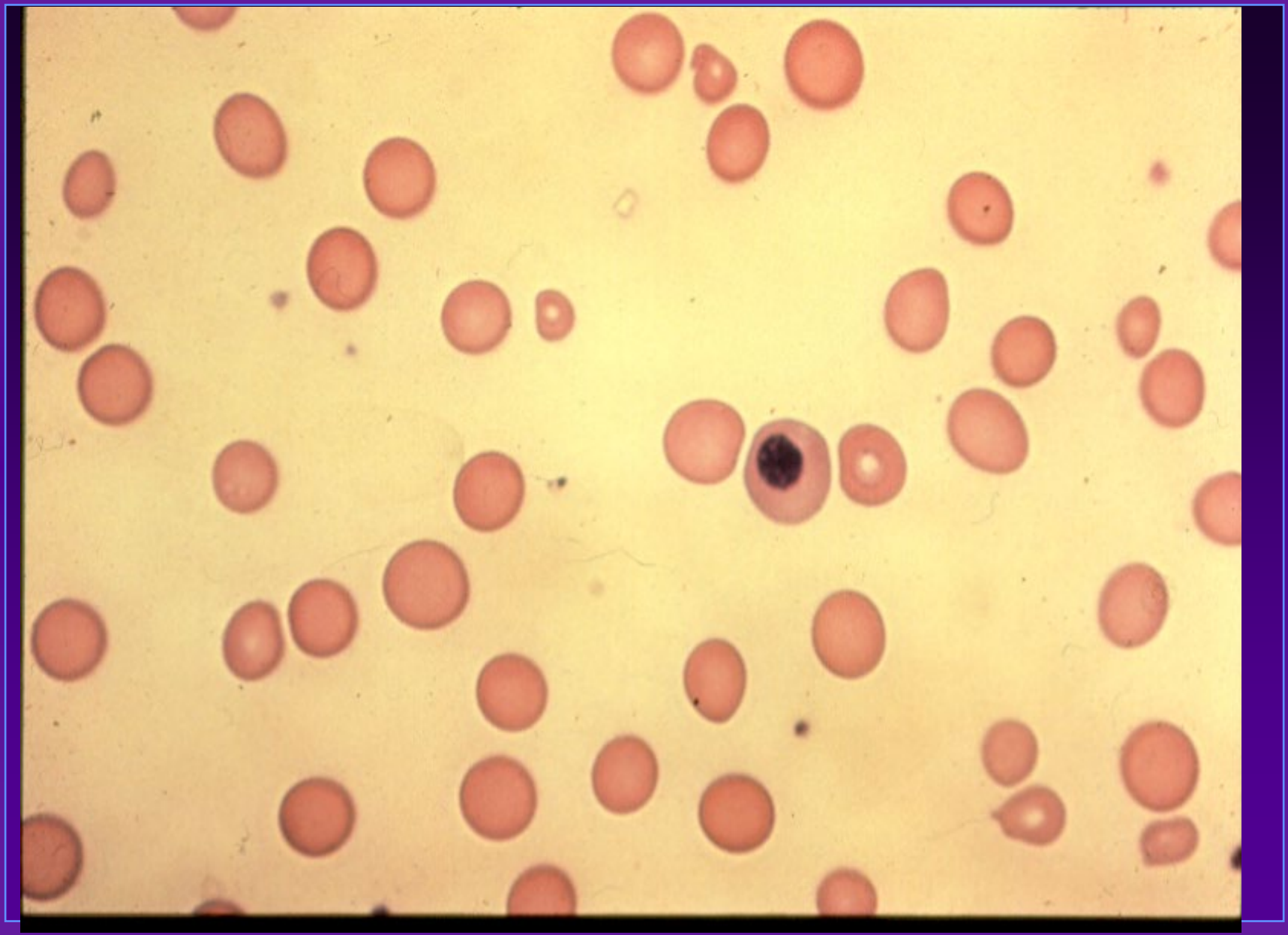
Hemolysis: Peripheral Smear

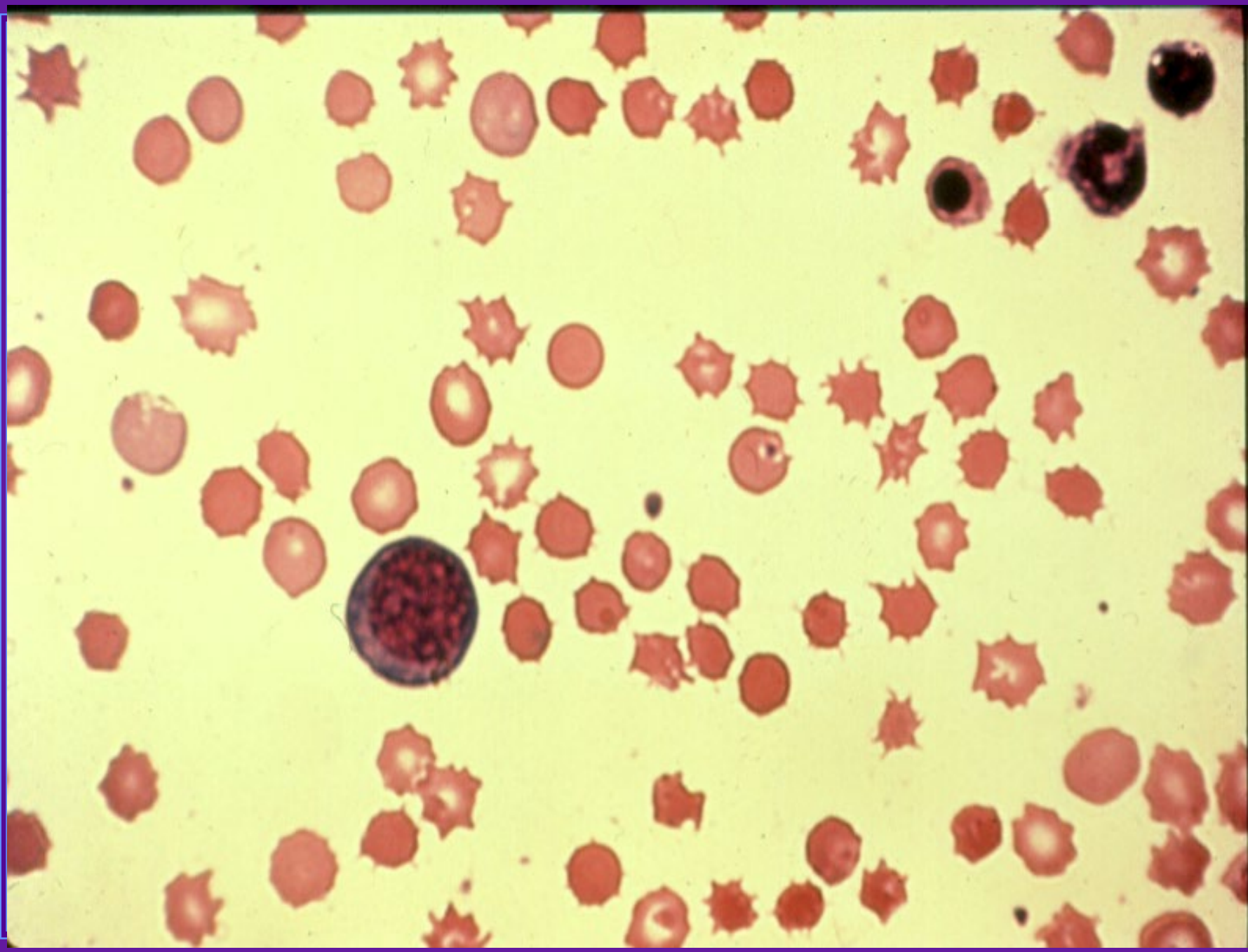
- *Extravascular hemolysis*
  - Subtle
  - Spherocytes (small round RBCs without central pallor)

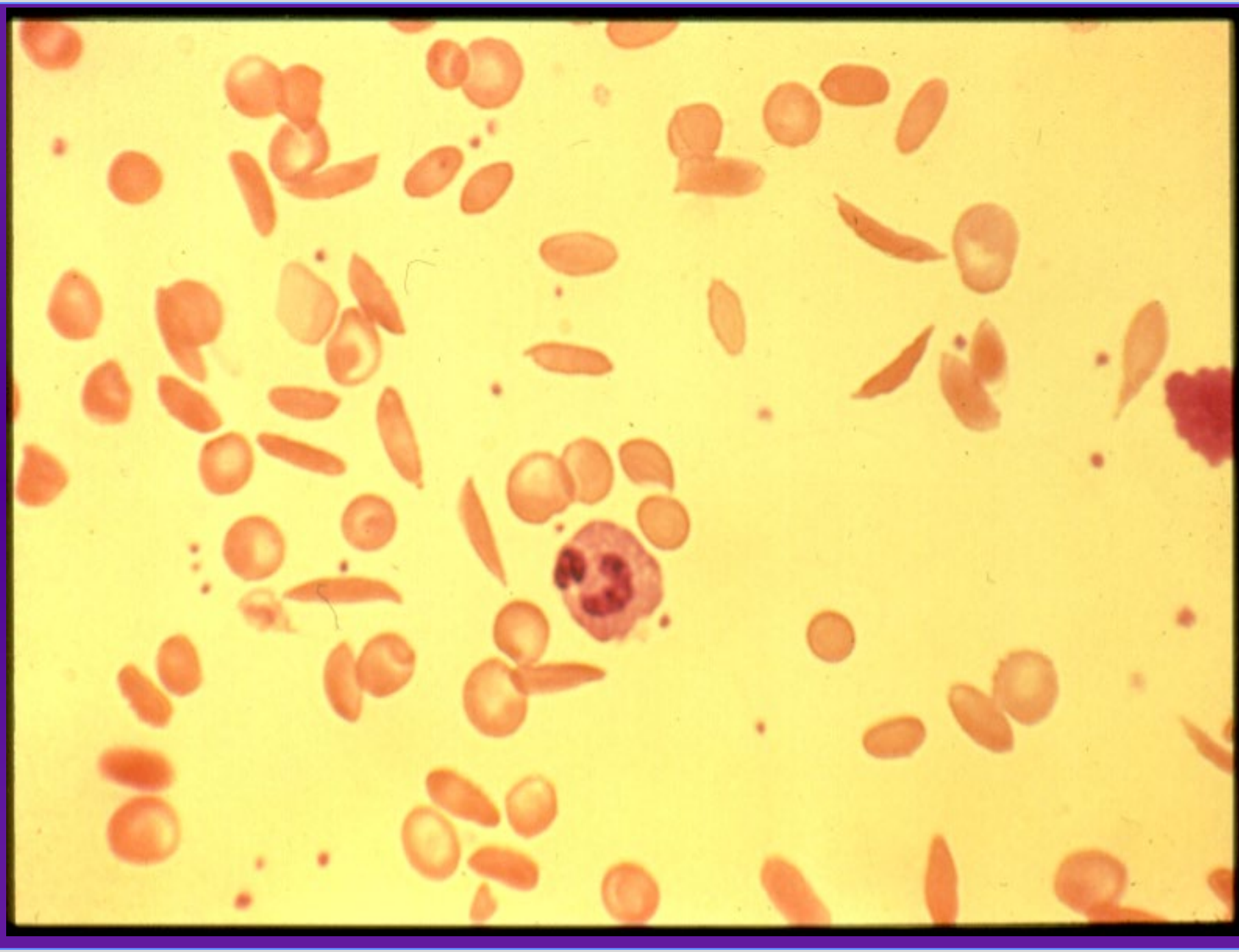
  (as in case)

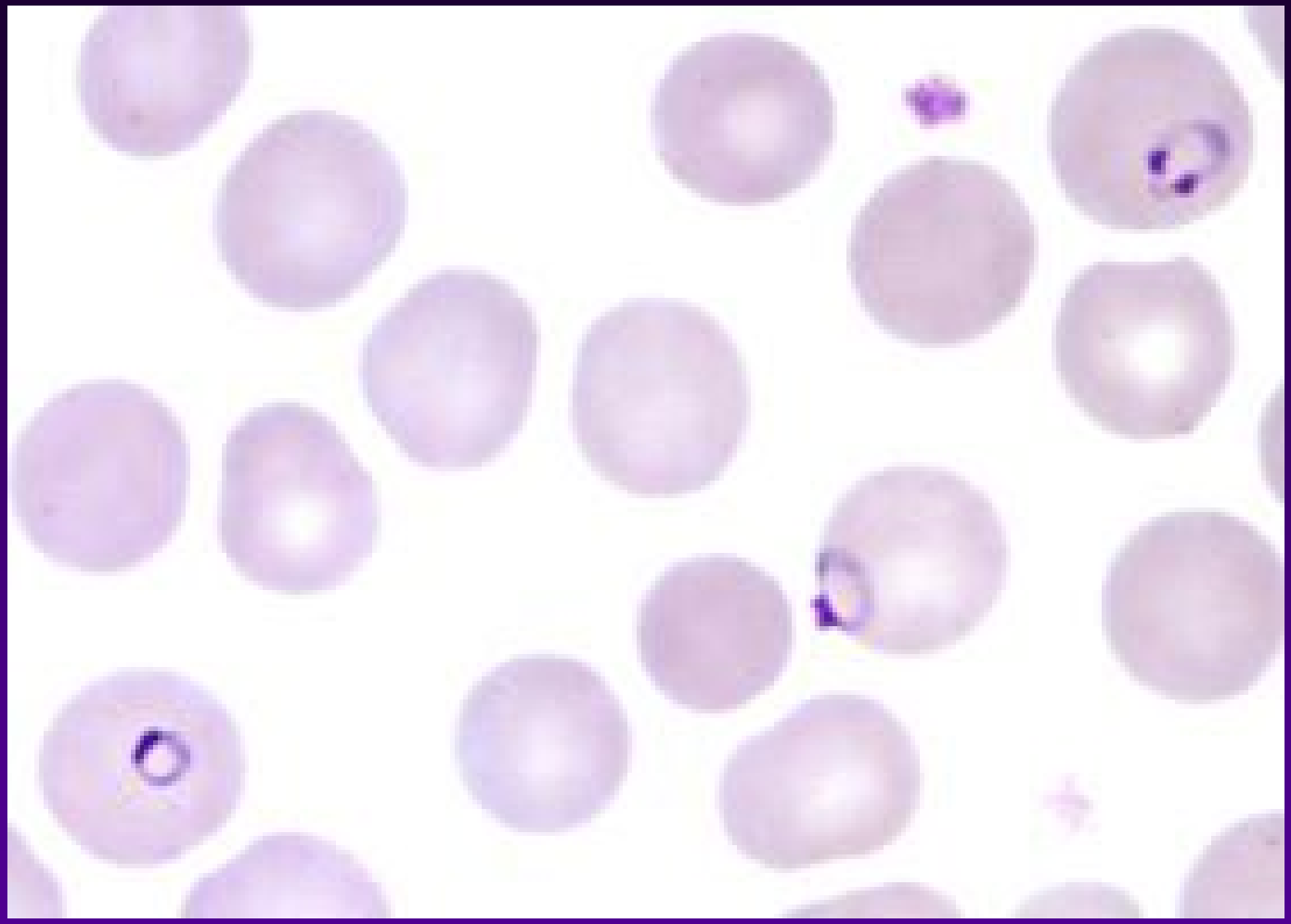


- *Intravascular hemolysis*
  - Dramatic
  - Fragmented RBCs









Google image, CDC website

Anemia Summary

- Use MCV, retic, and smear to help identify cause of anemia
- Common to have more than one cause of anemia co-existing
- Iron studies important, may be hard to interpret
  - Ferritin best readily available test, but has limitations
  - Fe, TIBC and % sat helpful in ACD
- B12 deficiency common in elderly; absorption affected by meds
- Check other cell lines to be sure not pancytopenia

Anemia Answer Sheet

Case 1. C
Case 2. A
Case 3. A
Case 4. B
Case 5. D
Case 6. E
Case 7. B
Case 8. C
Case 9. B
Case 10. D

Good luck!