APPROACH TO ANEMIA

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Definition

- Males Hgb 14-17
- Females Hgb 12-16

Causes

- Blood loss
- Decreased production
- Increased destruction (hemolysis)

RBC FORMATION

- Production requires:
- erythropoietin
- iron (red meat, poultry, fish)
- B 12

History

- Family hx of anemia
- Drugs, use or abuse
- Last Hgb?

Symptoms

- Asymptomatic
- Tachycardia
- DOE, chest pain
- Fatigue, malaise
- pallor

Exam

- Pallor
- Lymphadenopathy
- Petichiae
- Heme + stool
- Glossitis
- Stomatitis

Reticulocyte count

- Key to initial classification of anemia
- Residual RNA in newly made RBC
- Normal is 23,000 – 90,000
- > 110,000 suggests normal marrow response to anemia
- 2-3 x normal is expected within 10 days of onset of anemia.

Reticulocyte production Index

- Retic count x (measured Hgb/14)/2

Divided by 2 for maturation time correction, in the face of anemia, reticulocytes are released from the marrow prematurely, so this additional correction may be needed

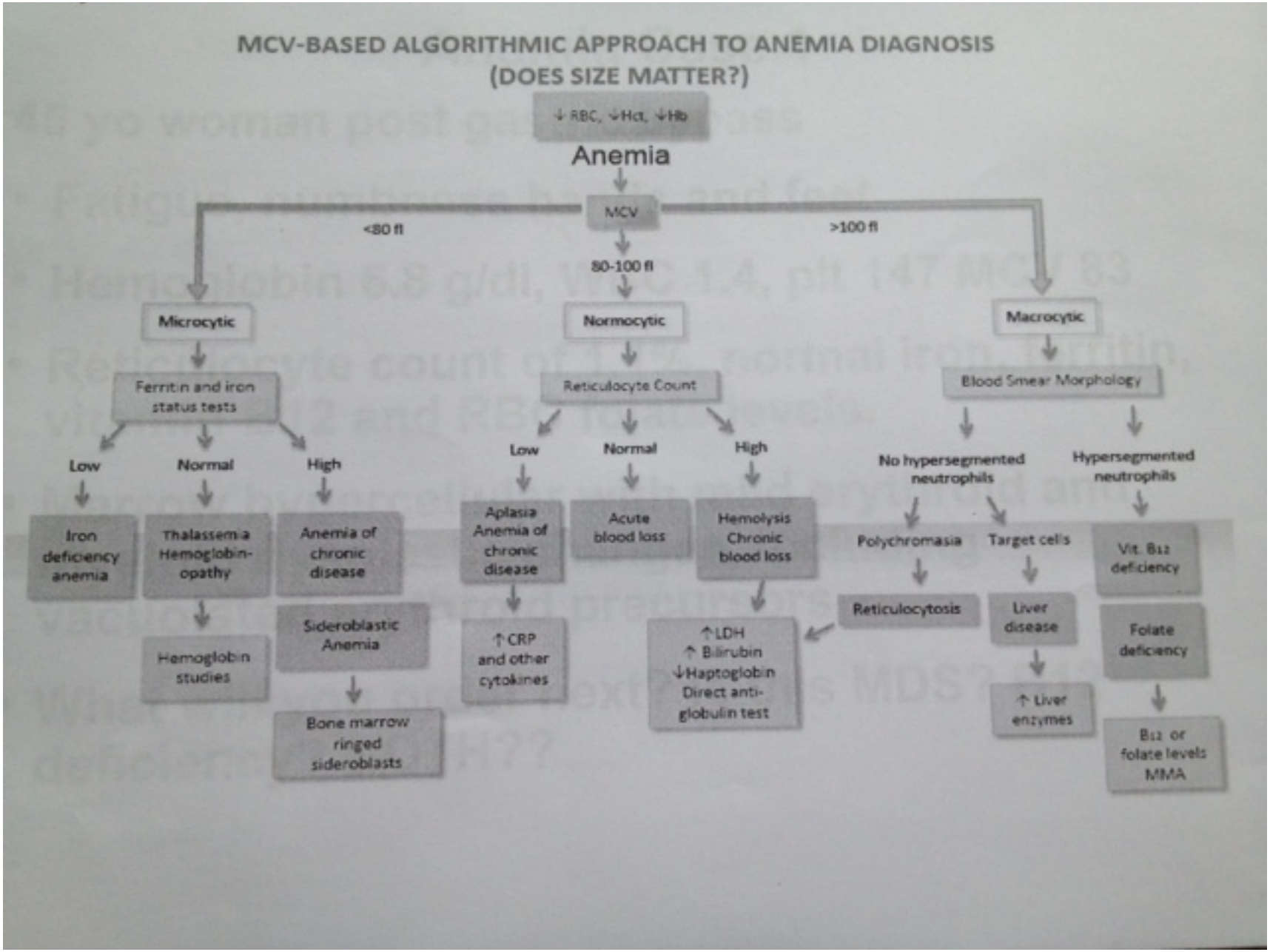
- If polychromasia (normoblasts) are not seen on smear, this correction is not needed

Physiologic Classification of Anemia

High ---------- Retic count ----------Low or NL

Bleeding---yes---Blood loss		Smear	
no			
Smear	Micro	Normo	Macro
Schistocytes	IDA	Aplasia	B12
Spherocytes	Thal	Marrow infilt	Folate
Sickle cells	sideroblast	Renal dx	MDS
Bite cells	Inflammation	Drug Tox	
Target cells	Chronic dx	Etoh	
Inclusions			

MCV-BASED ALGORITHMIC APPROACH TO ANEMIA DIAGNOSIS (DOES SIZE MATTER?)



HYPOCHROMIC MICROCYTIC

- Iron Deficiency
- Thalassemia
- Chronic Disease, Inflammatory (usually normo, normo)
- Myelodysplastic syndrome (ringed sideroblasts seen on bone marrow)

Iron Deficiency

- Low Fe , high TIBC, low Ferritin. High RDW
- Reduced transferrin saturation (Fe/TIBC)
- If ferritin < 15, essentially no Fe stores
- Iron absorbed proximal small bowel: celiac dx, IBD, resection can affect
- May see accompanying thrombocytosis

Iron Deficiency

- Signs and symptoms
- fatigue, malaise
- headaches
- pallor
- pagophagia (ice chewing)
- pica
- glossitis
- stomatitis
- koilonychia (spooning of nails)
- chronic blood loss is always suspect in adults

Iron Deficiency Treatment

- Correct underlying problem if blood loss
- $FeSO_4$ 325 mg tid is least expensive, watch for nausea and constipation
- Slow Fe preparations not advised as absorption is markedly reduced
- Parenteral Fe therapy available for the rare patient who does not tolerate oral
- Duration: when Hgb normalizes, treat for additional 3-6 months to replenish the Fe stores

Thalassemia

- Hgb has 2 alpha chain globin and 2 B chain globin
- Ineffective erythropoiesis, intravascular hemolysis and decreased Hgb production
- Microcytic, hypochromic RBC and target cells on smear
- Dx with Hgb electrophoresis
- RDW usually normal in Thal but elevated in IDA

Thalassemia

A single gene deletion is an asymtomatic carrier state that is normal clinically and hematologically

Alpha Thal Minor or Alpha Thal trait is a two gene deletion and is usually asymptomatic, mild anemia, microcytosis

- African, Mediterranean, SE Asia, Middle Eastern descent
- No treatment is needed

Thalassemia

- Hemoglobin H disease is caused by deletion of 3 alpha genes
- Severe anemia with CHF and hypoxia
- Hydrops fetalis or Hemoglobin Bart is caused by 4 gene deletion of the alpha chain and usually causes intrauterine demise

Thalassemia

- B Thal more prevalent in Mediterranean, SE Asian, Indian and Pakistan descent
- B Thal trait: mild anemia, microcytosis, hypochromia, target cells, increase A2 Hgb and sometimes also Hgb F
- No tx needed

- B Thal Intermedia: hemolytic anemia moderate to severe, can have massive extramedullry erythro in liver and spleen and in children in the facial bones causing chipmunk facies and frontal bossing
- Often develop Fe overload
- Increased Hgb A2, F or both

Thalassemia

- B Thal major: Cooley's anemia, almost complete absence of B globin
- Unbalanced alpha and B chains causes accumulation of insoluble alpha chains in the marrow which kills developing erythroblasts
- Severe anemia
- Growth retardation
- Iron overload
- Tx with transfusions and chelation therapy

Macrocytic Anemia

No Hypersegmented neutrophils	Hypersegmented neutrophils
I	I
Polychromasia, think	B 12 def
possible hemolysis	Folate def

B 12 (cobalamin) Deficiency

- B12 sources: calf liver, sardine, shrimp, scallop
- Effective enterohepatic uptake, deficiency takes years to develop, stores generally good for 3-4 years

B 12 deficiency

- Decreased absorption:
- Pernicious anemia (antibody directed destruction directed at parietal cells)
- Aging with achlorhydria
- Celiac disease
- Pancreatic insufficiency
- Bacterial overgrowth

B12 deficiency exam

- Glossitis
- Pallor
- Jaundice possible due to ineffective erythropoiesis
- Neuropathy
- Spastic ataxia
- Dementia
- Psychosis

B 12 Smear

- Hyperchromic macrocytic RBC's
- Oval macrocytes with basophilic stippling
- Hypersegmented neutrophils with > 5 lobes
- Decreased platelets
- Decreased WBC

B 12 Diagnosis

- B12 level
- Methylmalonic acid level is more sensitive than measuring the B 12 level and will be high with B 12 deficiency (expensive test)
- Homocysteine level should be high
- Haptoglobin level may be decreased
- LDH may be high
- Indirect Bili may be high

B 12 Treatment

- B12 1000 mcg IM per month, 6 injections spaced every 3-7 days should replenish stores
- Oral replacement has been shown to be as effective and less costly at 1000-2000Mcg/ day
- Hemoglobin levels may take several months to normalize, if they do not, consider alternative diagnosis such as MDS
- Neuropsychiatric disorders take longer to resolve and ultimately may not

Folate Deficiency

- Sources: green leafy vegs., melons, lemons, bananas, fortified grains
- Dietary deficiency is unusual
- Stores are only 3-4 months
- Triamterene, Phenytoin accelerate folate metabolism
- Alcohol decreases folate absorption
- It is best to measure erythrocyte folate levels, serum folate may go up quickly with a meal

Folate Deficiency Diagnosis

- Folic acid levels
- Homocysteine level increased but are not used for diagnosis
- Methymalonic acid level is NOT increased contrasting with B 12 deficiency

Folate Deficiency treatment

- Folic acid 5-15 mg daily
- Will take about 4 months to treat
- Always check B 12 level before giving the Folic acid, if this is low and not corrected, the anemia will improve but not the Neuropsych symptoms
- Long term therapy may be needed for patients with a degree of hemolysis or those on dialysis

INFLAMMATORY ANEMIA

- Inflammation
- Infection
- Tissue injury
- Other conditions (cancer for one) causing release of inflammatory cytokines such as TNF alpha, IL 6, IL 1, and interferon

INFLAMMATORY ANEMIA DIAGNOSIS

- Normochromic normocytic or microcytic, hypochromic
- Fe is normal or decreased
- TIBC is decreased
- Ferritin is normal or increased

INFLAMMATORY ANEMIA TREATMENT

- No treatment needed in general
- Use Epo carefully as this may cause Htn and increase risk of thrombosis

ANEMIA WITH NORMOCHROMIC NORMOCYTIC INDICES

- Renal disease: level of anemia correlates with degree of renal failure
- Normo, normo
- Fe levels, TIBC, ferritin all normal
- Those on dialysis may also develop Fe deficiency
- Epo levels low

ANEMIA WITH NORMOCHROMIC NORMOCYTIC INDICES

- Liver disease
- Smear: spur cells, stomatocytes
- If Alcoholic, may have also Folate deficit and may have blood loss so check the Iron levels also

HEMOLYTIC ANEMIA

- Signs: DOE, pallor, jaundice, gallstones, splenomegaly
- Labs: LDH increased

  Indirect Bili increased

  Haptoglobin decreased

HEMOLYTIC ANEMIA

CONGENITAL

- Erythrocyte membrane – spherocytosis
- Erythrocyte enzyme – G6PD
- Defective Hgb structure – Sickle, Thalassemias

HEMOLYTIC ANEMIA CONGENITAL

- G6PD deficiency – Male > Female, AA most common
- Episodic hemolysis in response to stressors (infection, TMP-SMX, Nitrofurantoin), fava beans
- Heterozygotes protected to some degree against P. falciparum
- Smear : Bite cells
- Tx: supportive, withdraw offending agent

HEMOLYTIC ANEMIA ACQUIRED

Autoimmune: Warm – IgG 80%
mild splenomegaly
Direct Coombs + 90%, weakly + C3
spherocytes may be seen

Treatment: Prednisone 1 mg/kg
splenectomy
Rituximab
Cytoxan

HEMOLYTIC ANEMIA ACQUIRED

- Autoimmune: Cold agglutinin– IgM 20%
  Direct Coombs neg, positive C3
  clumped RBC
  may develop weeks after EBV or
  mycoplasma infection

Treatment: Warm clothes
Chlorambucil, Cytoxan, Rituxan
Steroids and splenectomy not effective
Plasmapheresis for acute

HEMOLYTIC ANEMIA ACQUIRED

- Microangiopathic smear shows helmet cells or schistocytes
- TTP, DIC, HUS, aged mechanical heart valve
- Plasma exchange may be lifesaving for TTP and HUS

HEMOLYTIC ANEMIA ACQUIRED

PNH

- stem cell disorder with hemolytic anemia, pancytopenia and atypical thrombosis (mesenteric, cerebral).
- Dx based on flow cytometry
- Tx with anticoagulants, Eculizimab helpful, steroids may help occasionally but ultimately require immunosuppressants or allogeneic BMT
- Median survival 10-15 years

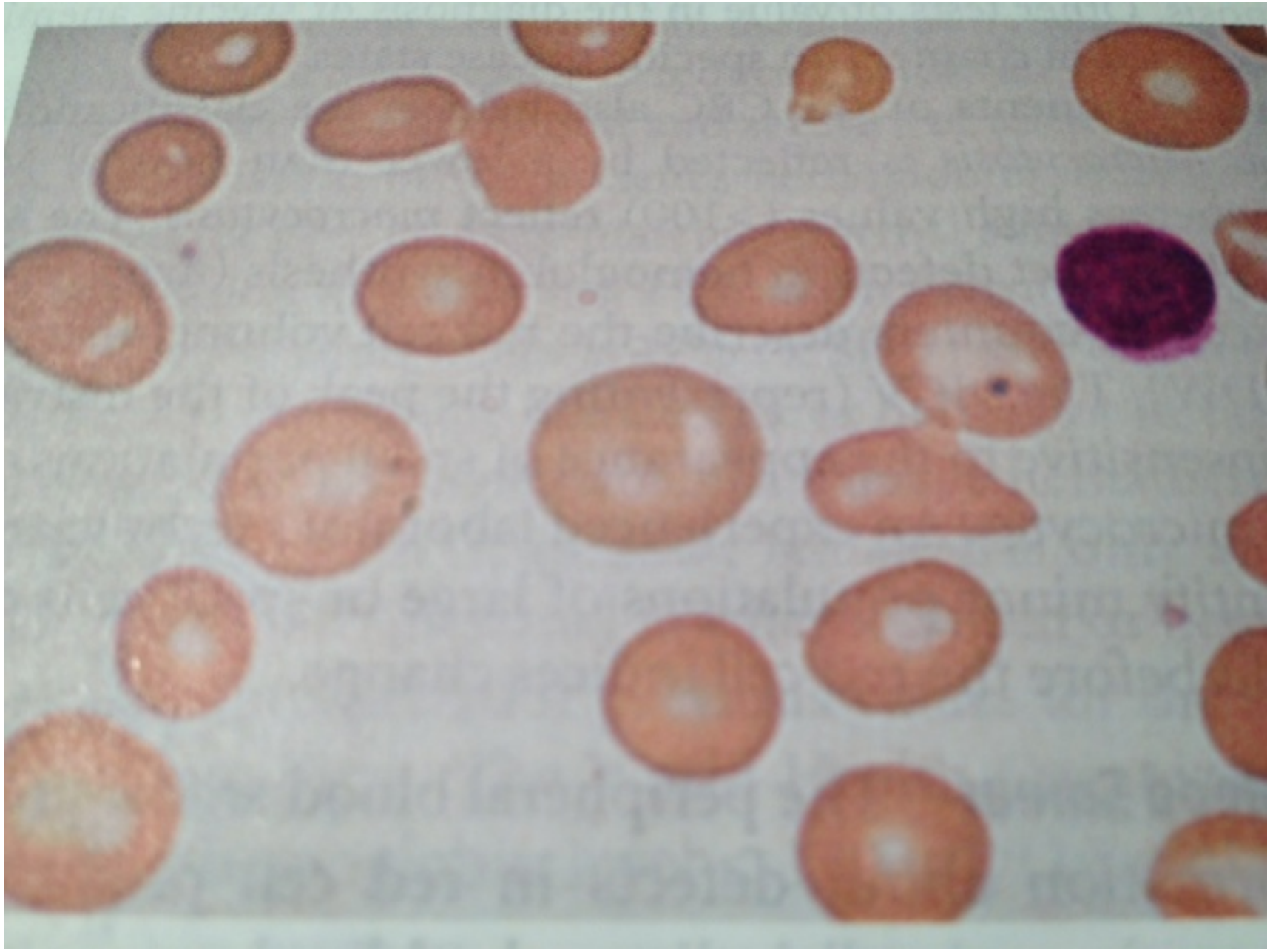
HEMOLYTIC ANEMIA ACQUIRED

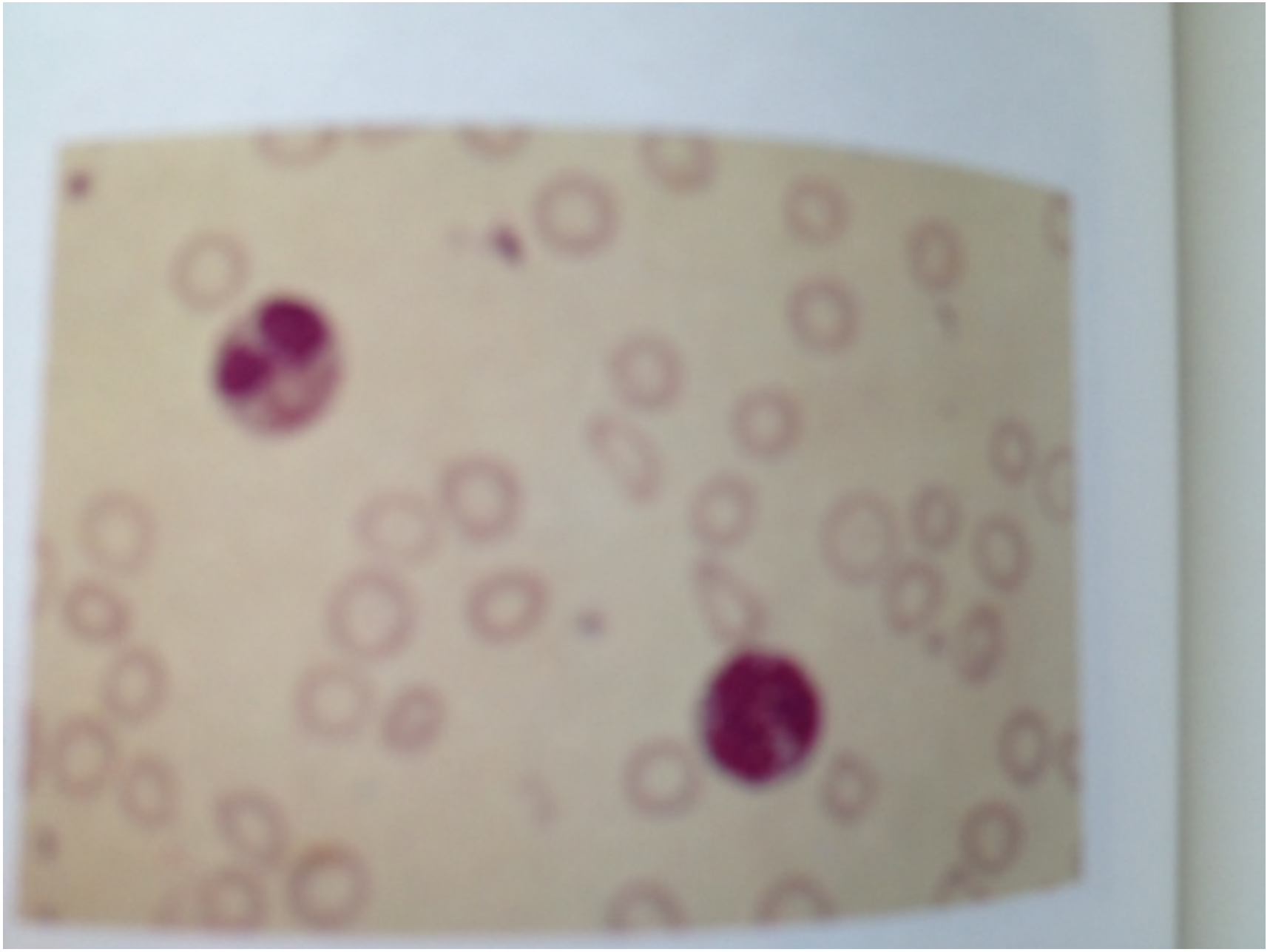
- Exposures – Malaria, Arsine gas, Babesiosis (Nantucket, Cape Cod, NC), Clostridial sepsis
- Venoms – brown recluse spider bite, snakes, massive wasp or bee stings
- Drugs – Cyclosporine, Tacrolimus, Clopidogrel, Ticlopidine
- Copper toxicity – Wilson's disease
- Severe burns, Radiation

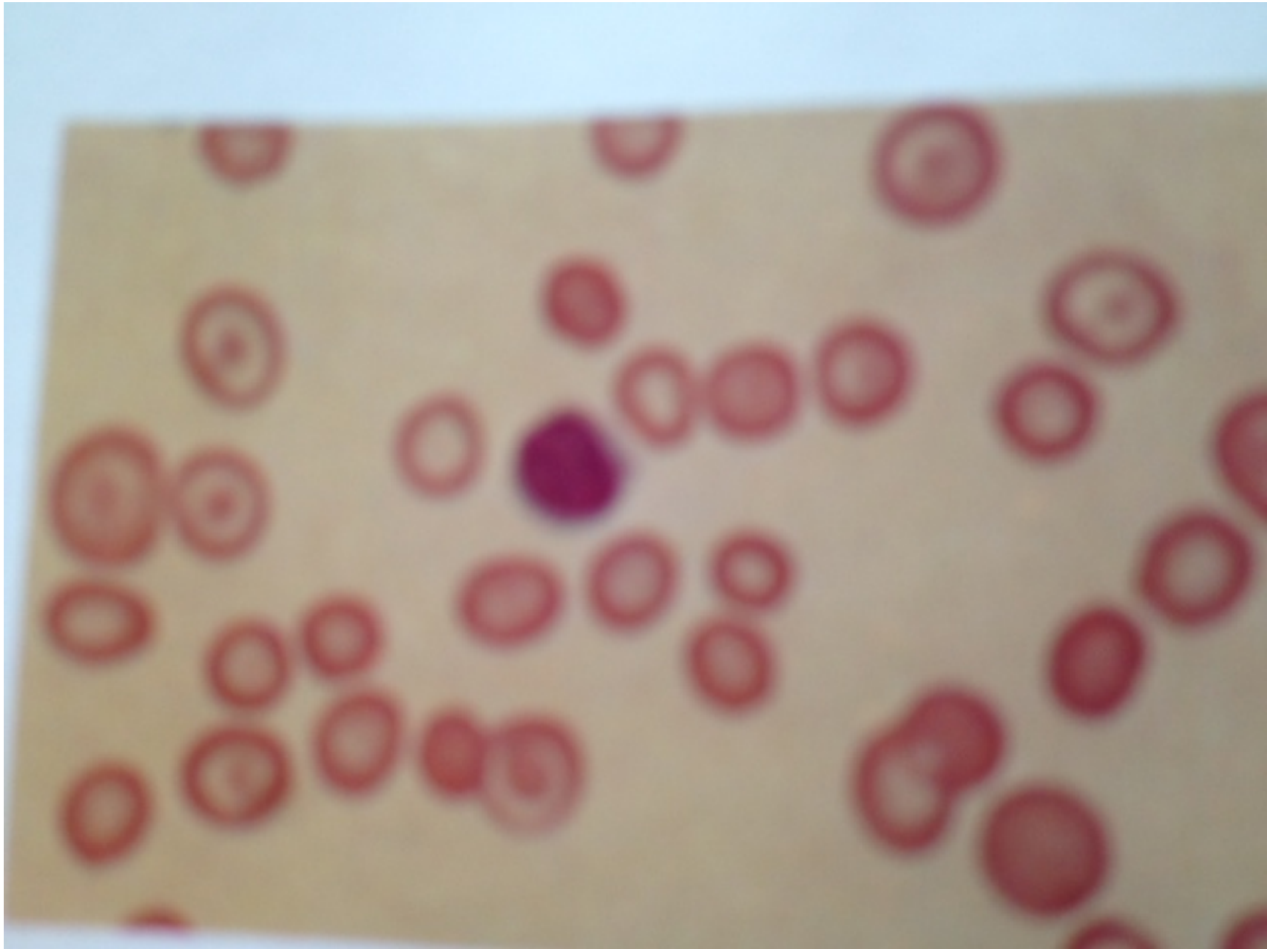
SMEARS

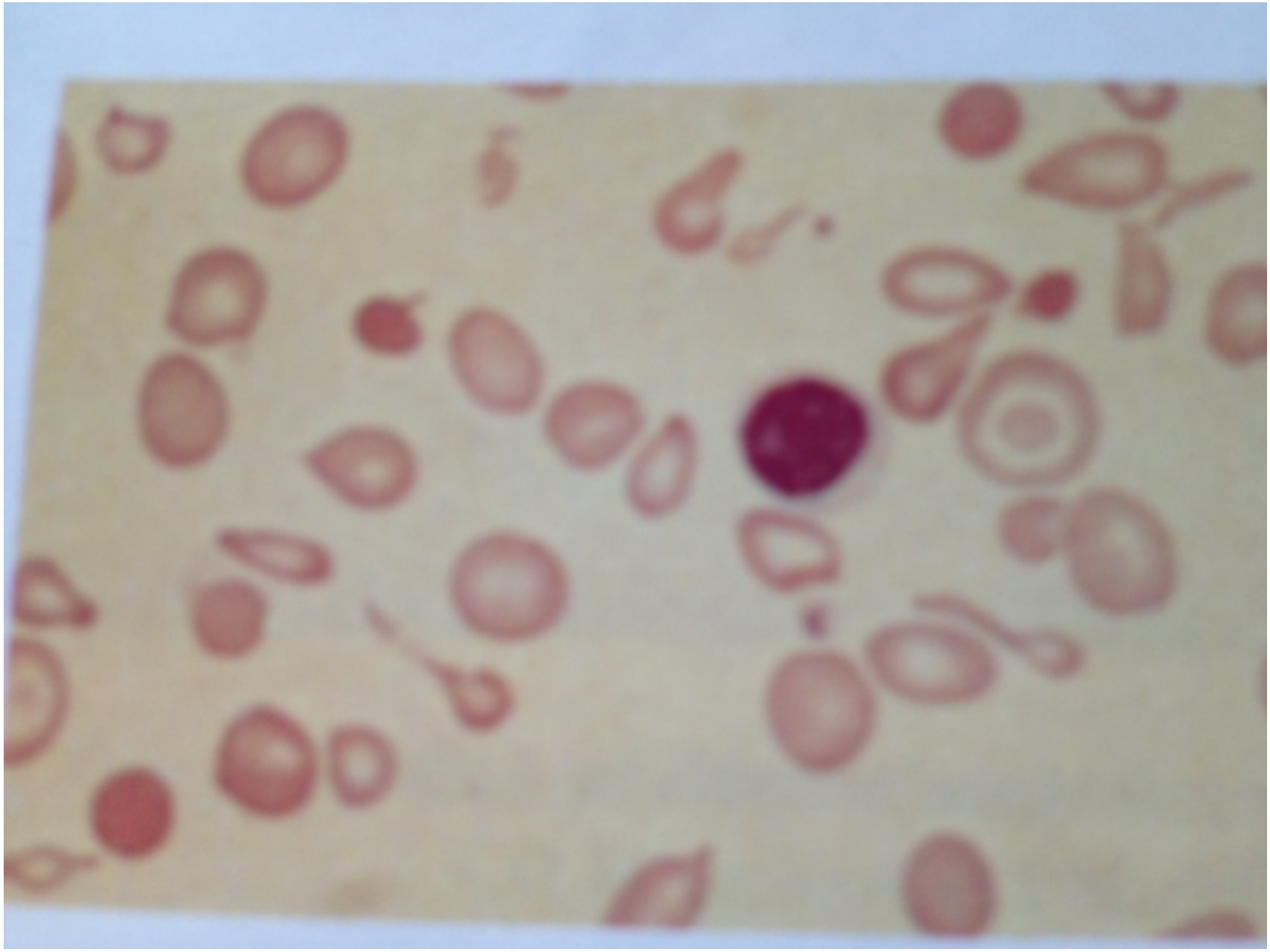
- Microcytosis : Fe def, Inflammatory, Thal
- Macrocytes: B12, Folate, MDS
- Spherocytes: Hereditary Spherocytosis
- Target cells: Hemoglobinopathy, Liver disease, splenectomy
- Burr cells: Kidney dx
- Bite cells: G6PD
- Spur cells: severe liver dx
- Sickle cells: SCD
- Nucleated RBC: marrow stress (hemolysis, hypoxia)
- Teardrop cells: Fibrosis, infiltrative marrow dx, marrow granuloma

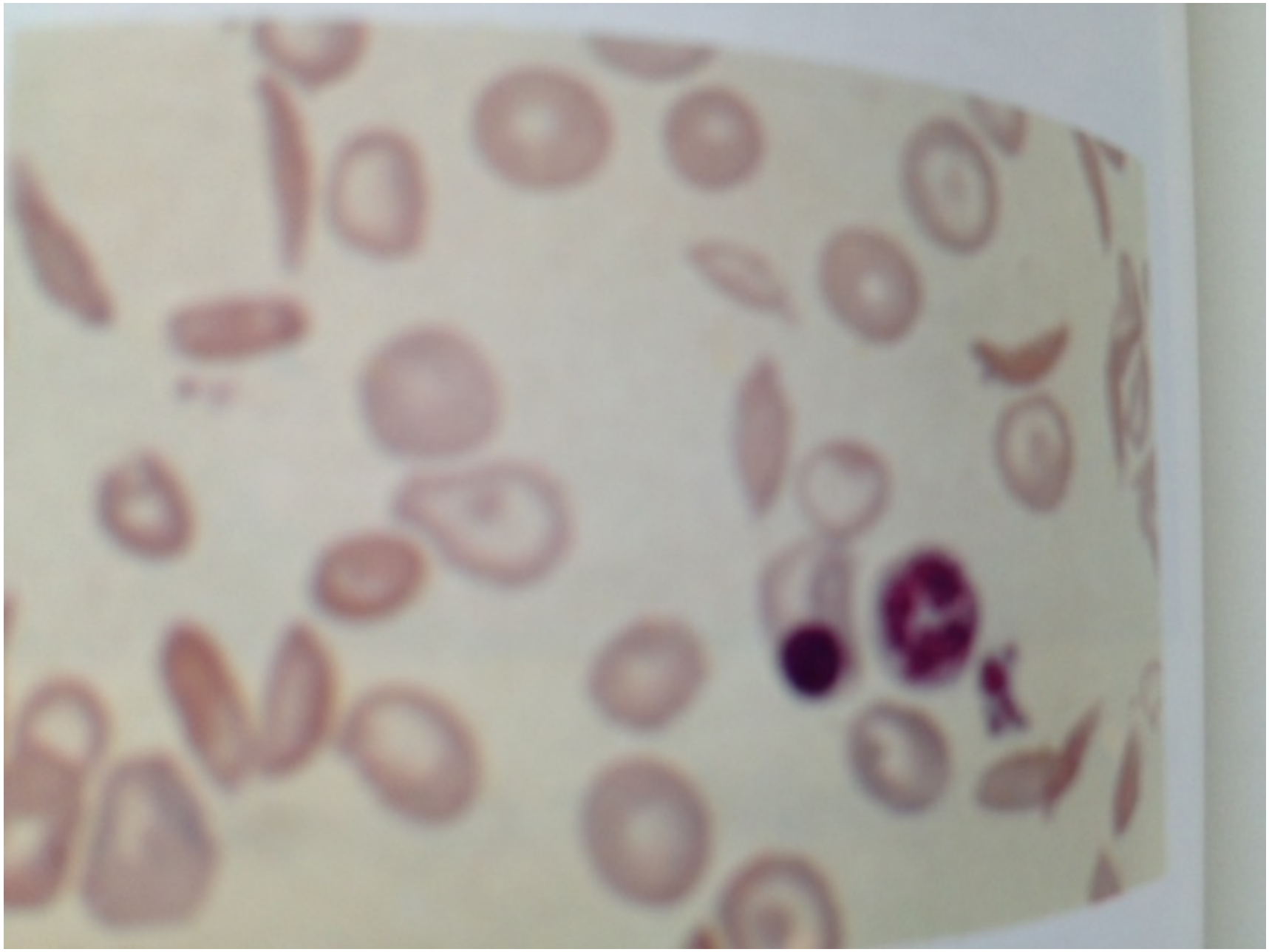
(from Harrison's Principles of Internal Medicine)

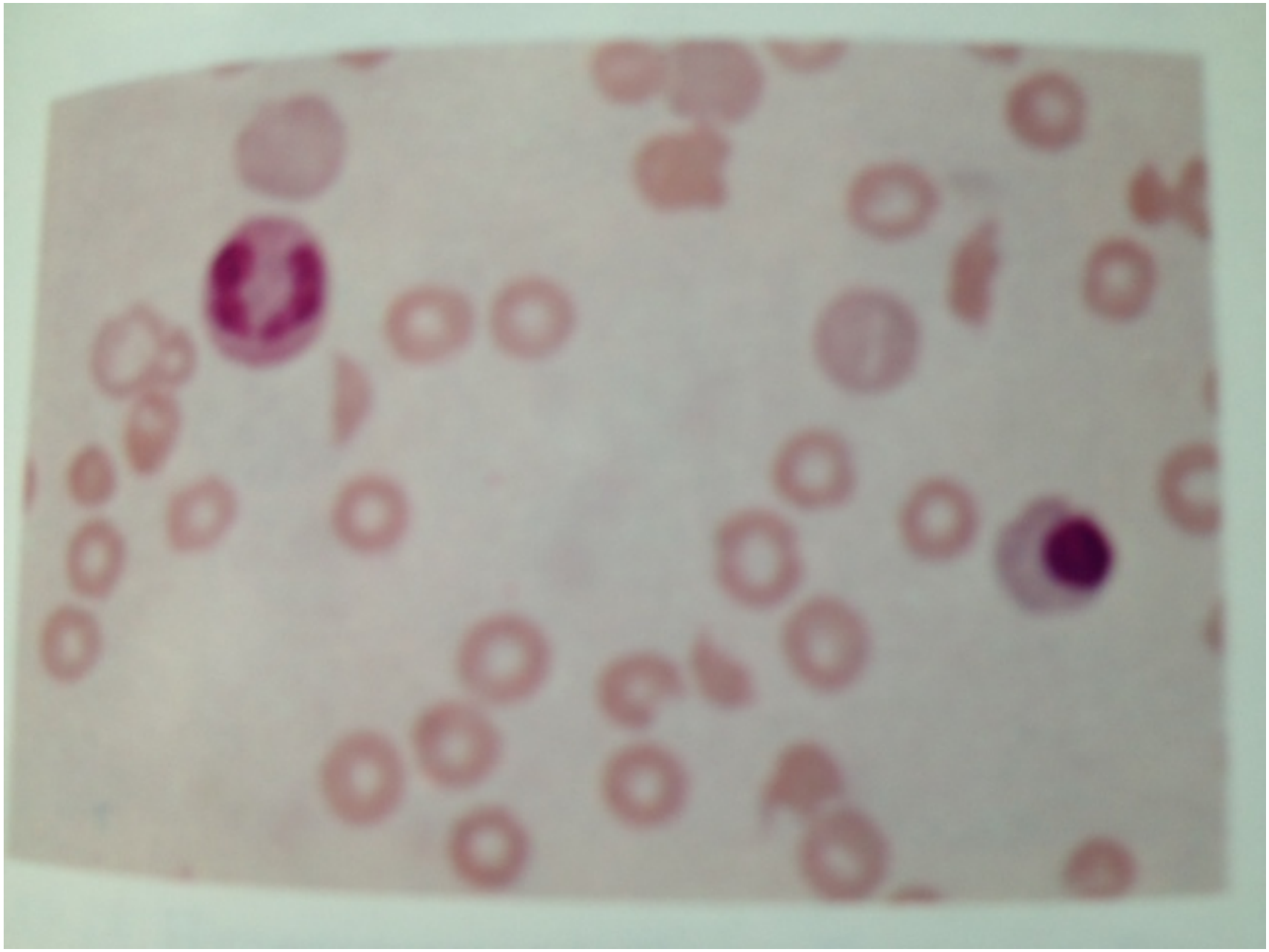


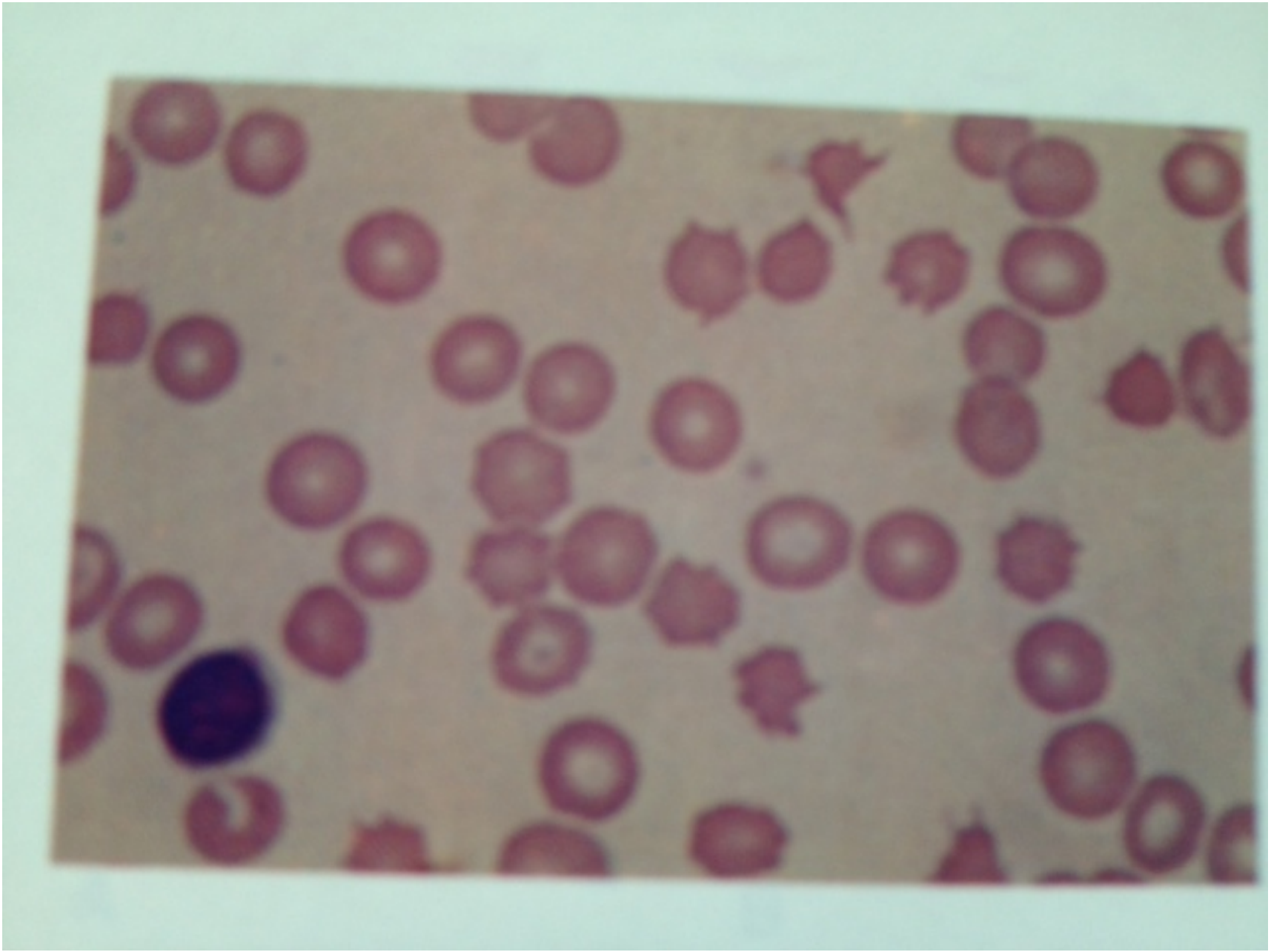


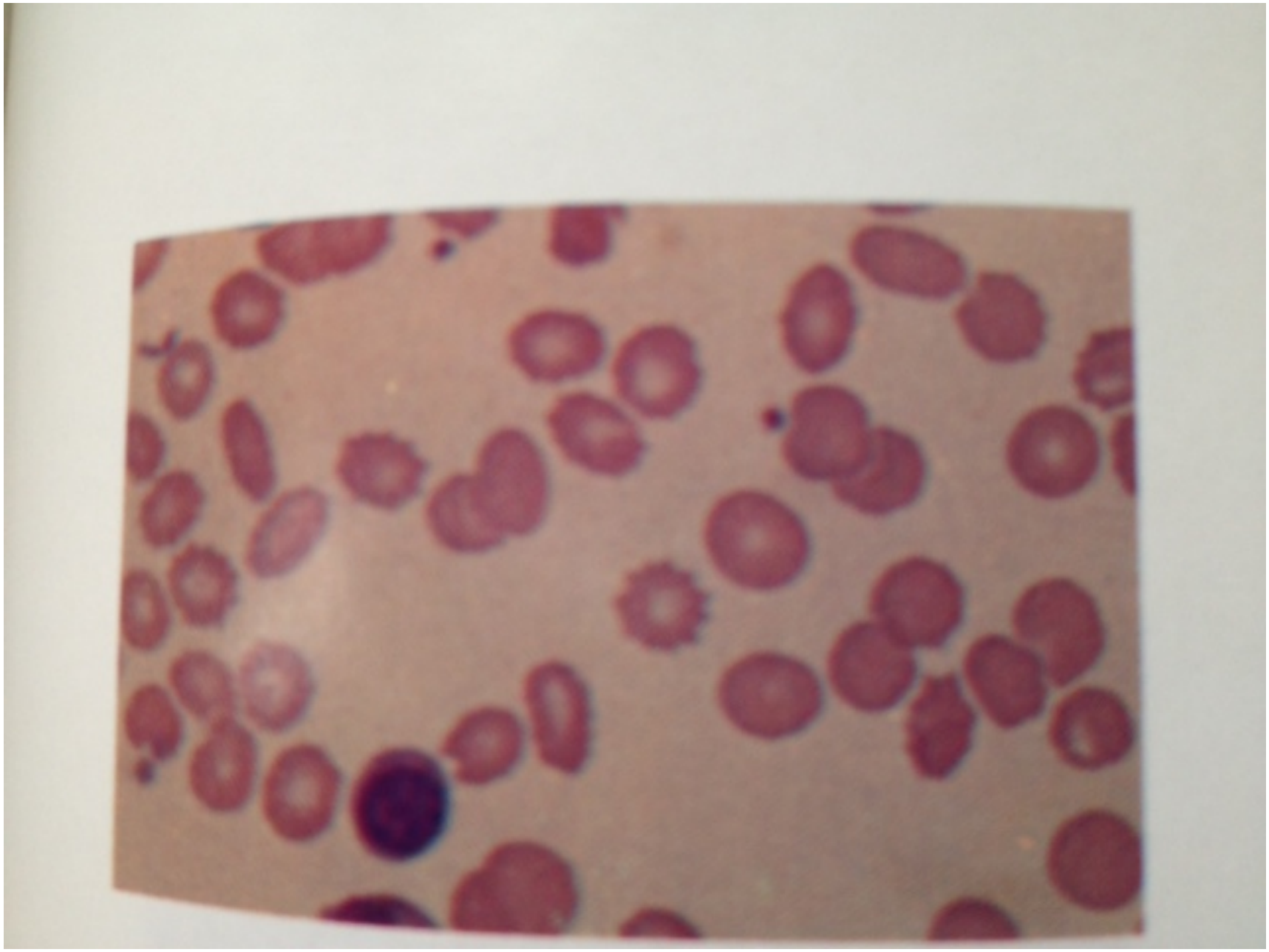


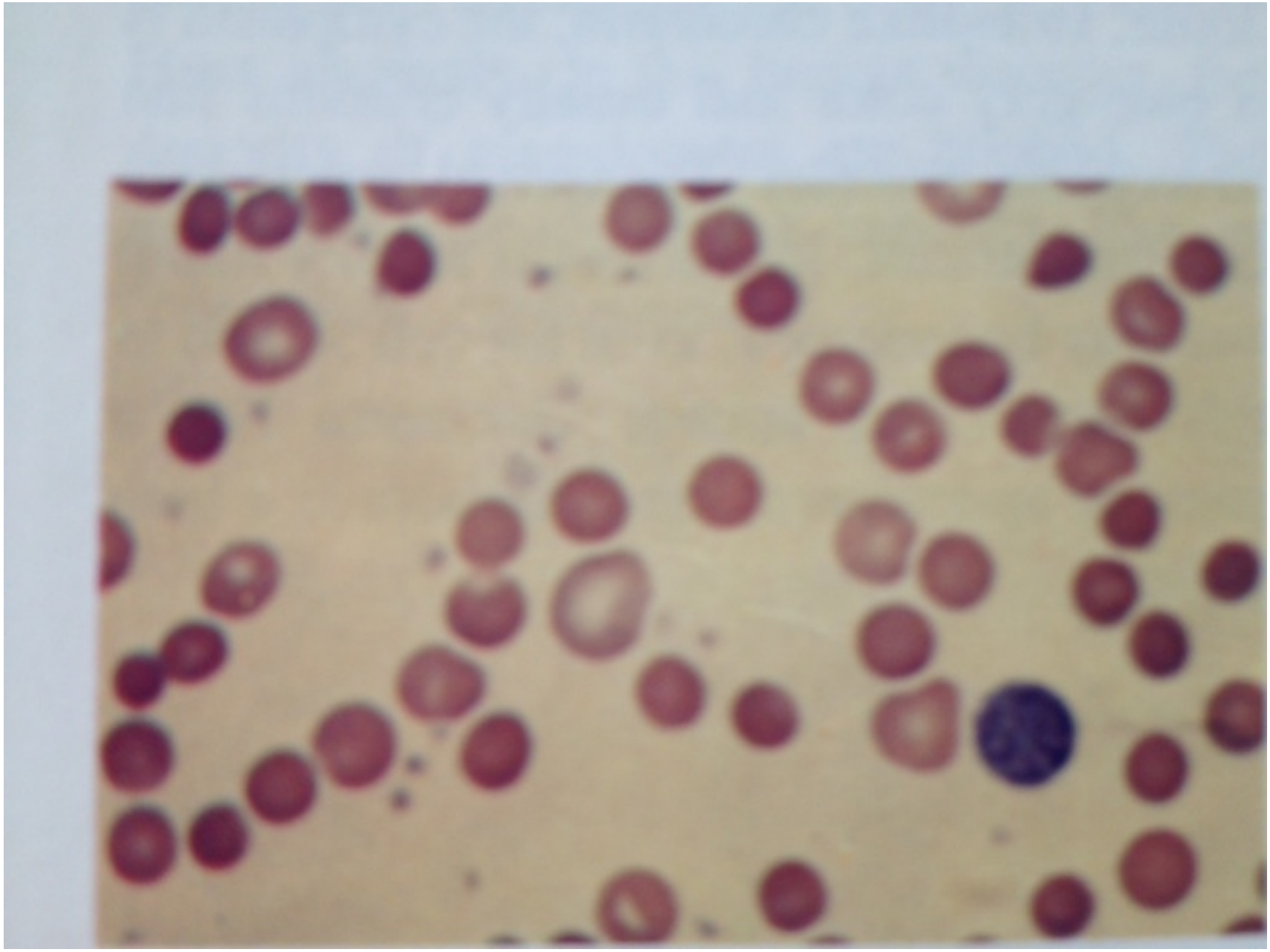


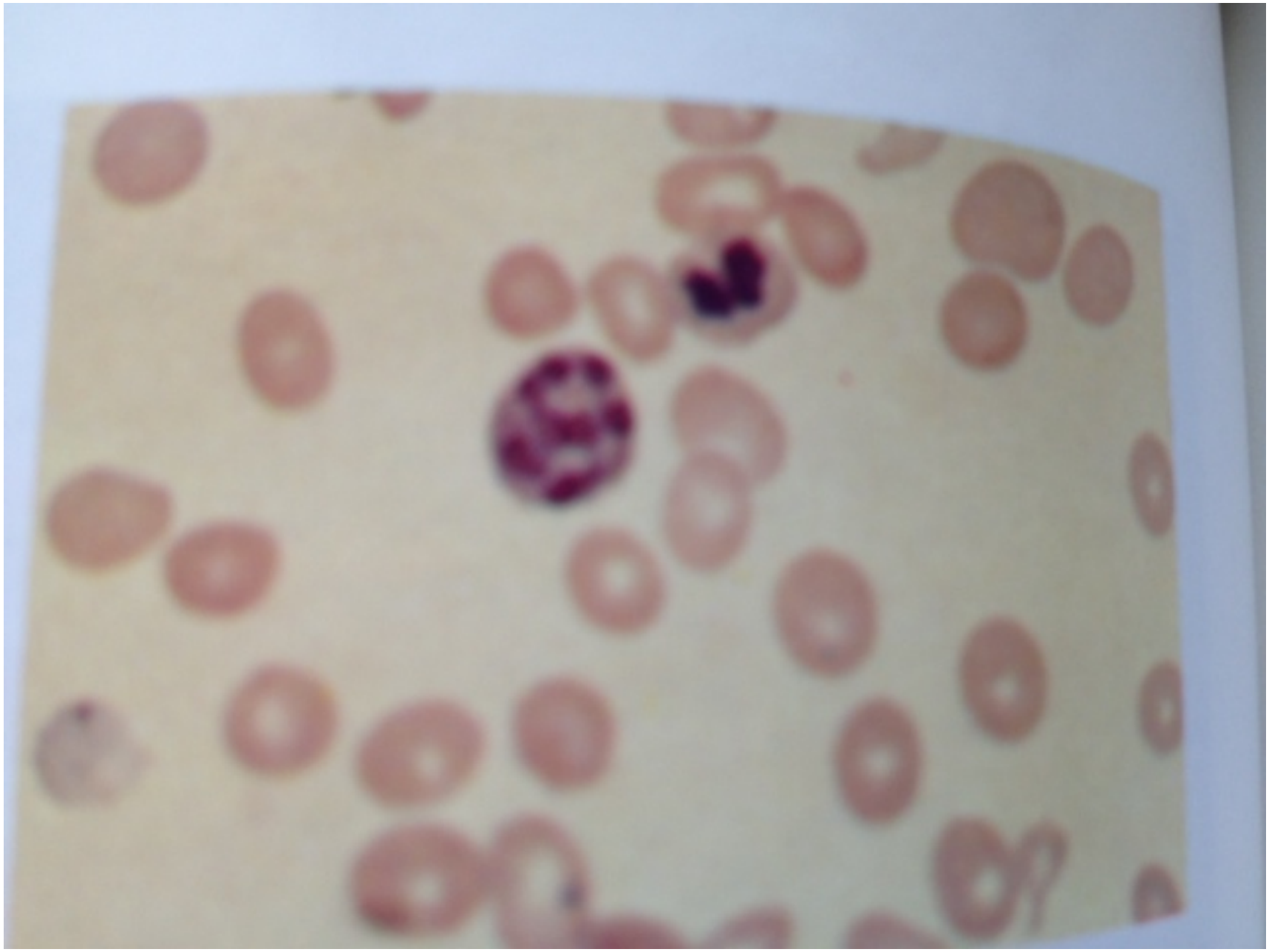












HEMATOLOGIC CAUSES OF SPLENOMEGALY

- Hemolytic anemia
- Spherocytosis
- Thallesemia
- SCD (early)
- Myelofibrosis
- Leukemia

HEMATOLOGIC CAUSES OF MASSIVE SPLENOMEGALY

>1000 grams

Thallesemia
CML
CLL
Lymphoma
Hairy Cell Leukemia
P. Vera
Myelofibrosis
Autoimmune Hemolytic Anemia

QUESTIONS

- 1. In B12 Deficiency, the Haptoglobin level may be decreased
- A. True
- B. False

QUESTIONS

2. In Fe deficiency anemia:

- A. it will take 3-6 months after the Hgb is normalized to replace Fe stores
- B. Slow Fe is preferred replacement
- C. Thrombocytosis is often present
- D. RDW is usually normal

1. A, B, C 2. A, C 3. B,D 4. all of the above

QUESTIONS

3. In Inflammatory Anemia

- A. cells are Normo/normo or micro/hypo
- B. Fe is normal or decreased
- C. TIBC is decreased
- D. Ferritin is low
- 1. A,B, and C 2. A and C 3. B and D 4. All of the above.