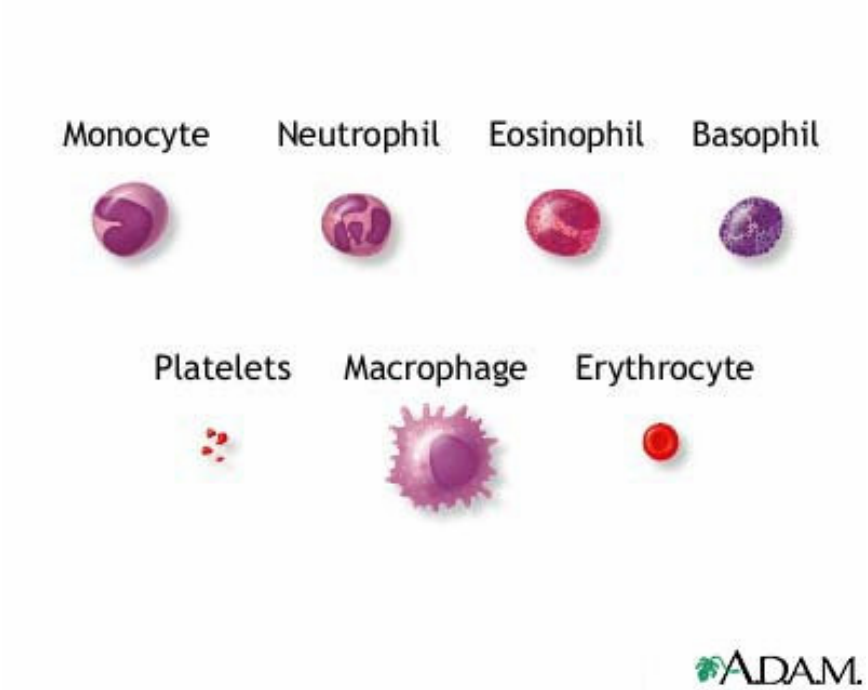
Anemia



Dr. Kenneth Wurtz

Variables which Tend to Raise the Hematocrit

- Dehydration
- Fingerstick (heelstick, earlobe) samples
- Prolonged tourniquet stasis
- Exposure to cold
- Increased muscular activity
- Upright position
- Centrifugation techniques (especially with bizarre cell shapes)

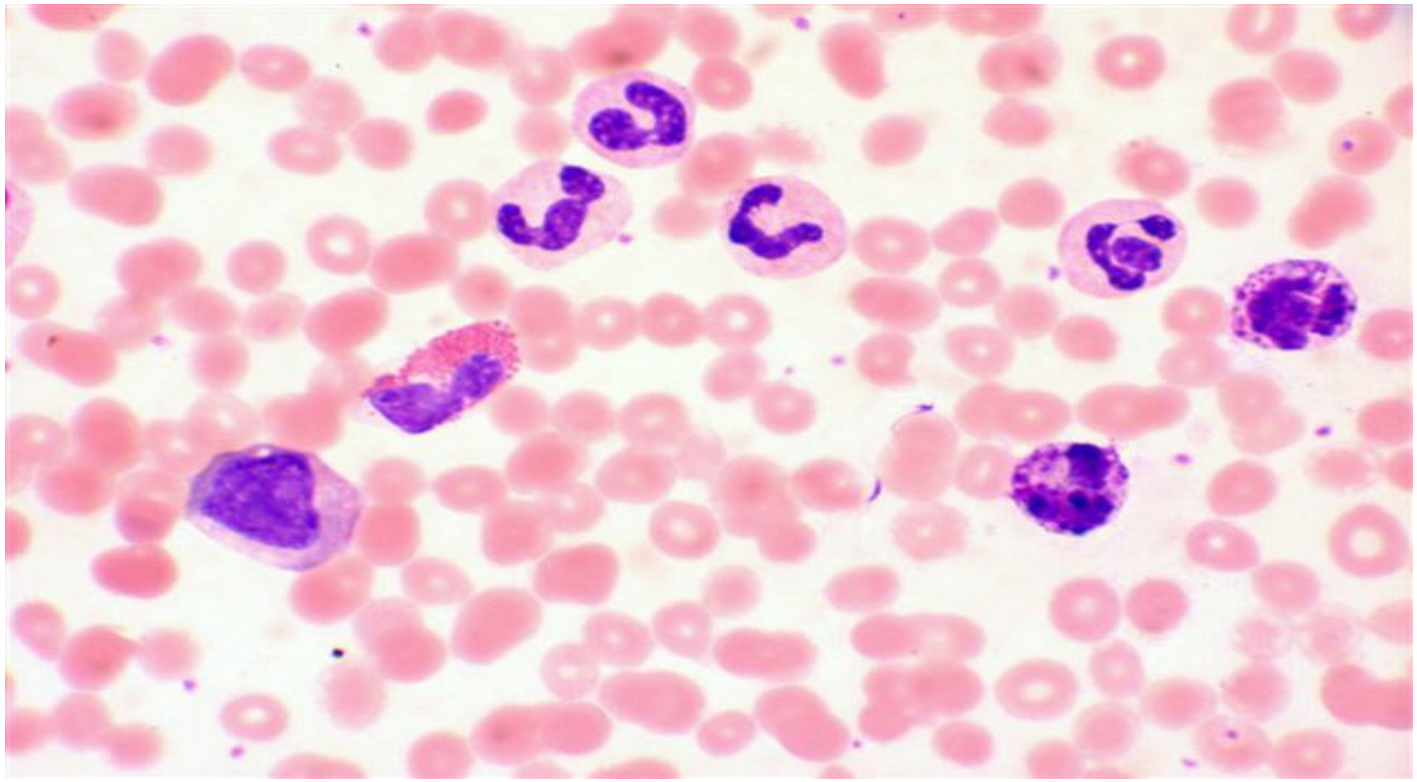
<u>Variables which Tend to Decrease the Hematocrit</u>

- Volume overload
- Supine position
- Capillary tube leakage during centrifugation
- Automated techniques

Representative Normal Values (Coulter S)

	Adult Male	Adult Female
HGB (g/dl blood)	14-18	12-16
HCT (%)	42-54	37-47
MCV (fl)	82-98	82-98
MCH (pg)	27-32	27-32
MCHC (g/dl RBC's)	31.5-36	31.5-36

Peripheral Blood Smear



Help from the Peripheral Smear

- Normal RBC Morphology
  - Anemia of chronic inflammation (malignancy)
  - Chronic renal failure (most patients)
  - Hypoendocrine states (most patients)
  - Early iron deficiency
  - Aplastic anemia
- Abnormal RBC morphology
  - Combined iron and folate deficiency
  - Sideroblastic anemia
  - Leukoerythroblastosis
  - Renal failure (some patients)
  - Hypothyroidism (some patients)

Common Causes of Various RBC Abnormalities

Hypochromia, Microcytosis	•Iron Deficiency •Thalassemia •Sideroblastic anemia •Chronic inflammation
Macrocytosis	•Liver disease (central targeting) •Megaloblastic anemia (macroovalocytes) •Reticulocytosis •Newborn •Preleukemia (mimics megaloblastic morphology)
Marked Anisocytsis and Poikilocytosis	•Marked iron deficiency •Megaloblastic anemia (severe) •Microangiopathic hemolysis •Leukoerythroblastosis •Hemoglobinopathies
Target Cells	•Liver disease •C hemoglobin (AC,CC,SC) •SS Disease •Postsplenectomy •Thalassemia •Artifact

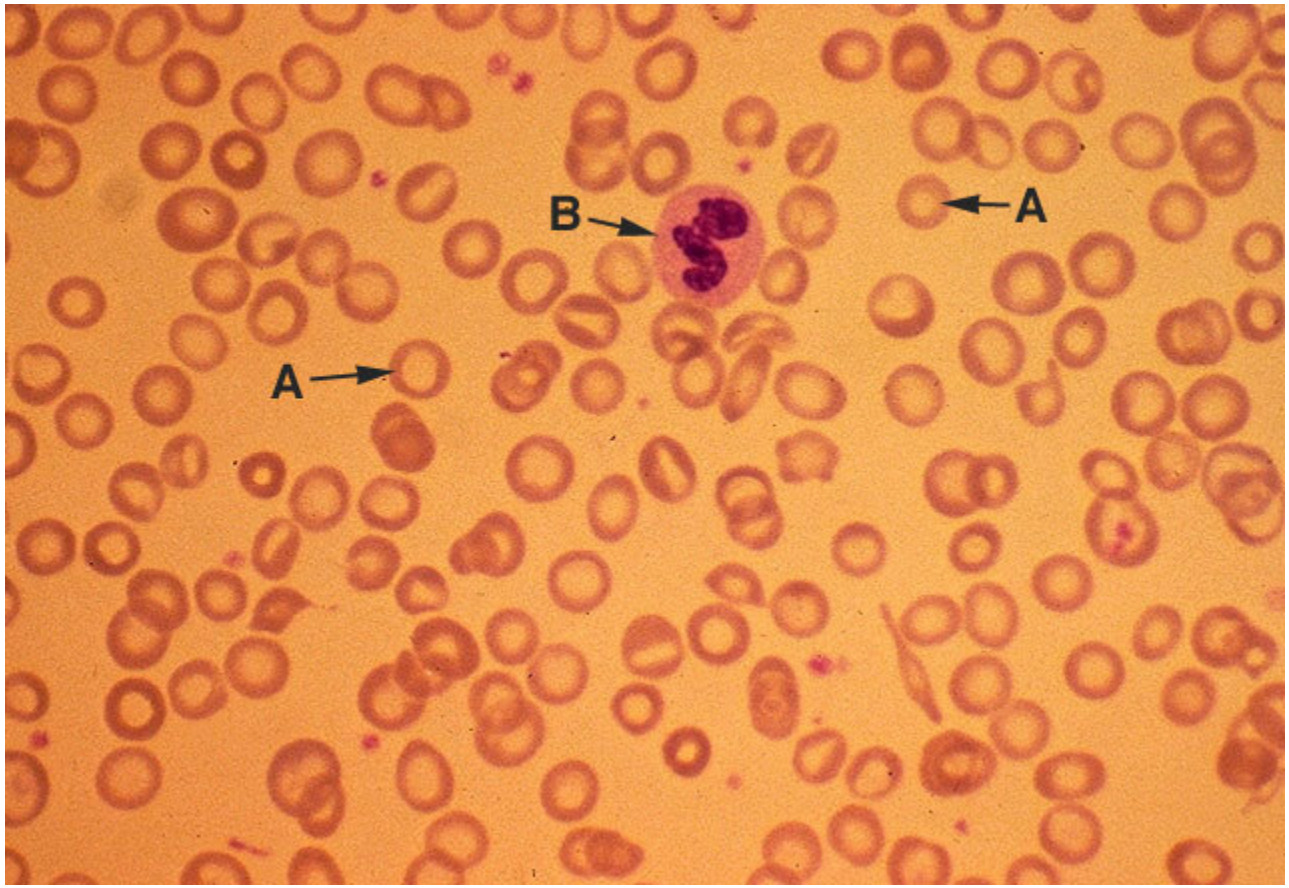
Common Causes of Various RBC Abnormalities Cont.

Spiculated RBC's	•Hereditary acanthocytosis •Liver disease (spur cells) •Renal disease (burr cells) •Post splenectomy •Hypothyroidism •Microangiopathic hemolysis
Tear Drop Cells	•Leukoerythroblastosis •Megaloblastic anemias •Thalassemia
Howell-Jolly Bodies	• Postsplenectomy •Megaloblastic anemia • Erythroleukemia
Pappenheimer Bodies	•Postsplenectomy •Sideroblastic anemia •Megaloblastic anemia •Alcohol •Marked hemolysis •Thalassemia

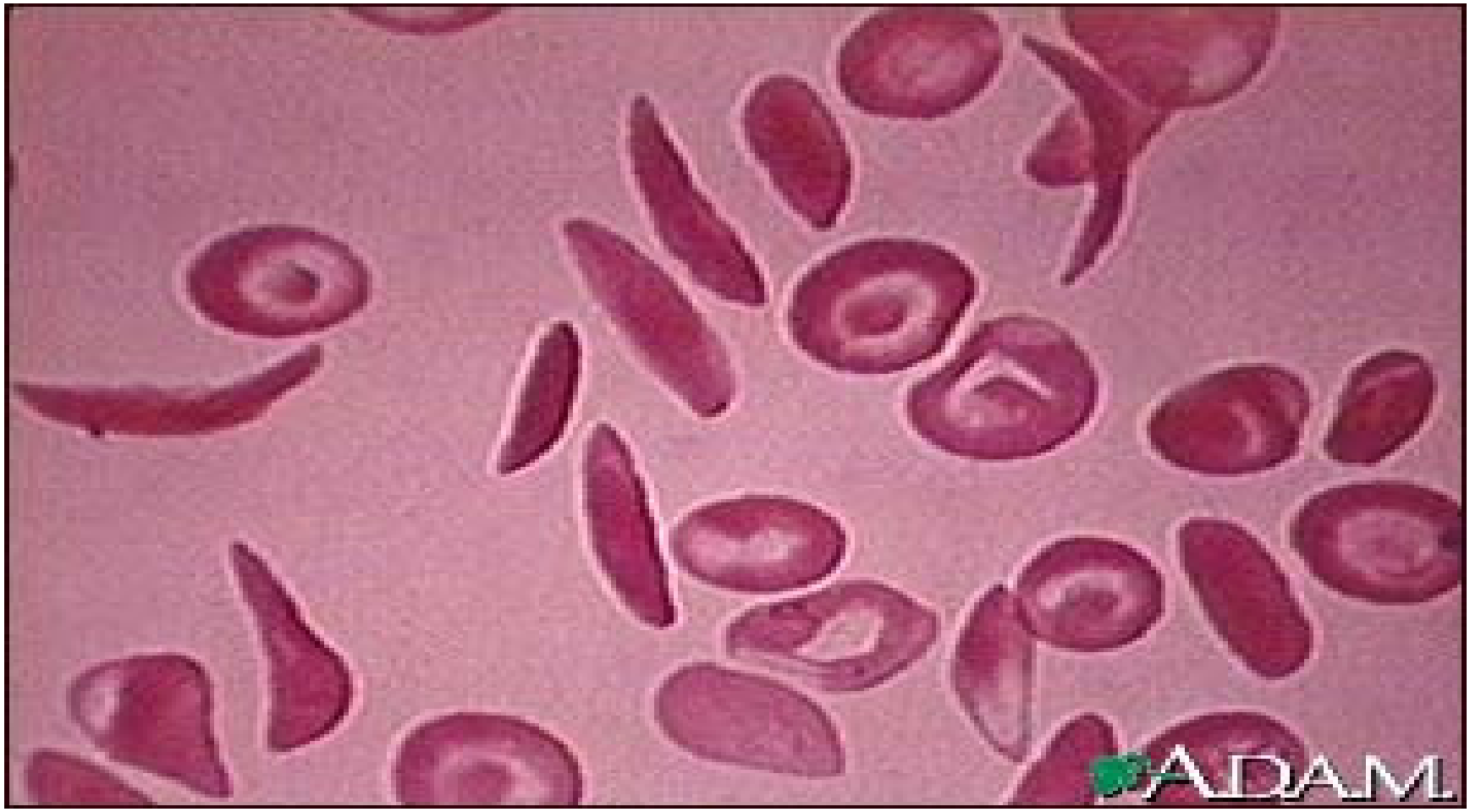
Common Causes of Various RBC Abnormalities Cont.

Spherocytes	•Heredity spherocytosis •Autoimmune hemolysis •Hemoglobin C disorders (CC,SC) •Severe burns
Ovalocytes	•Hereditary ovalocytosis •Megaloblastic anemia •Iron deficiency •Thalassemia

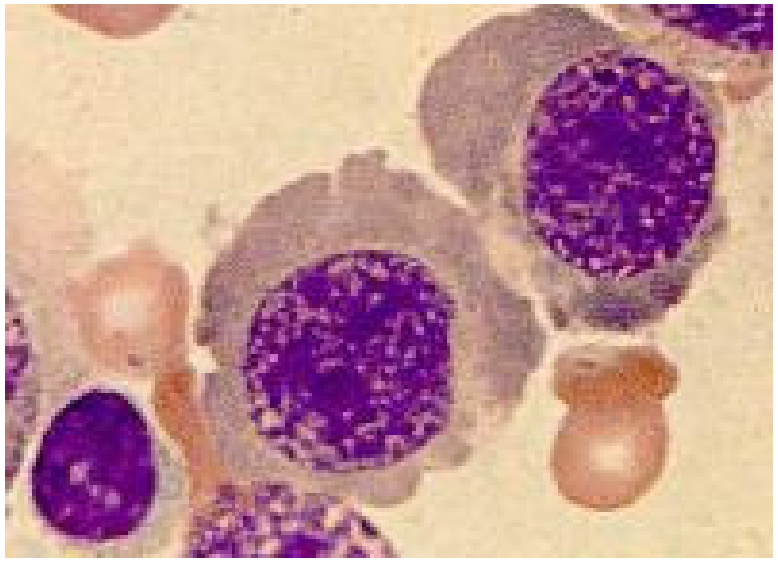
Iron Deficient Anemia

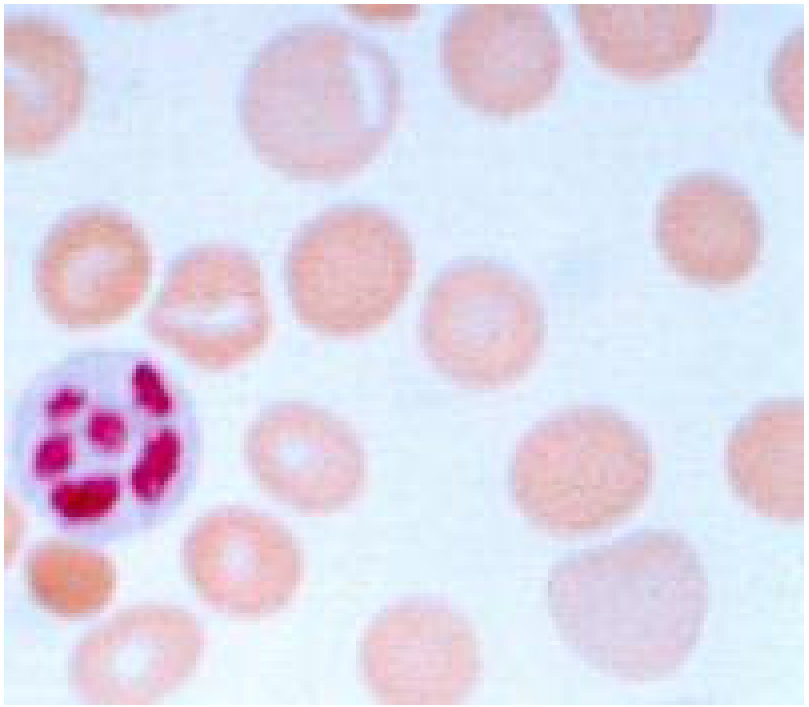


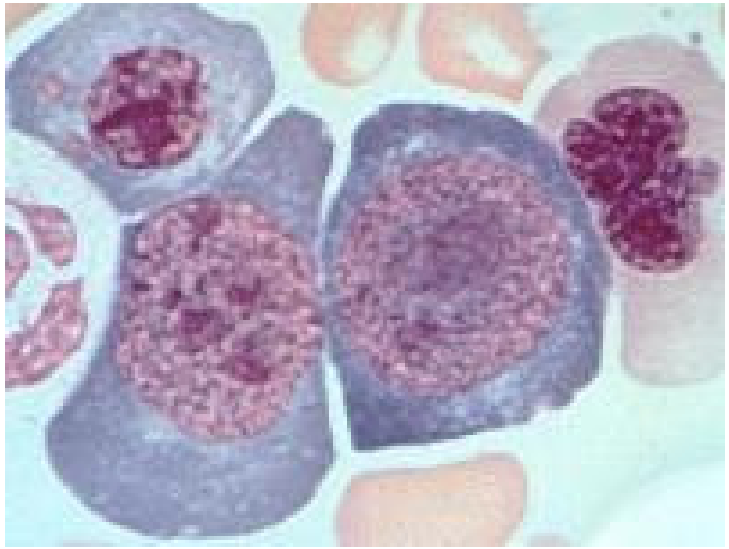
Sickle Cell



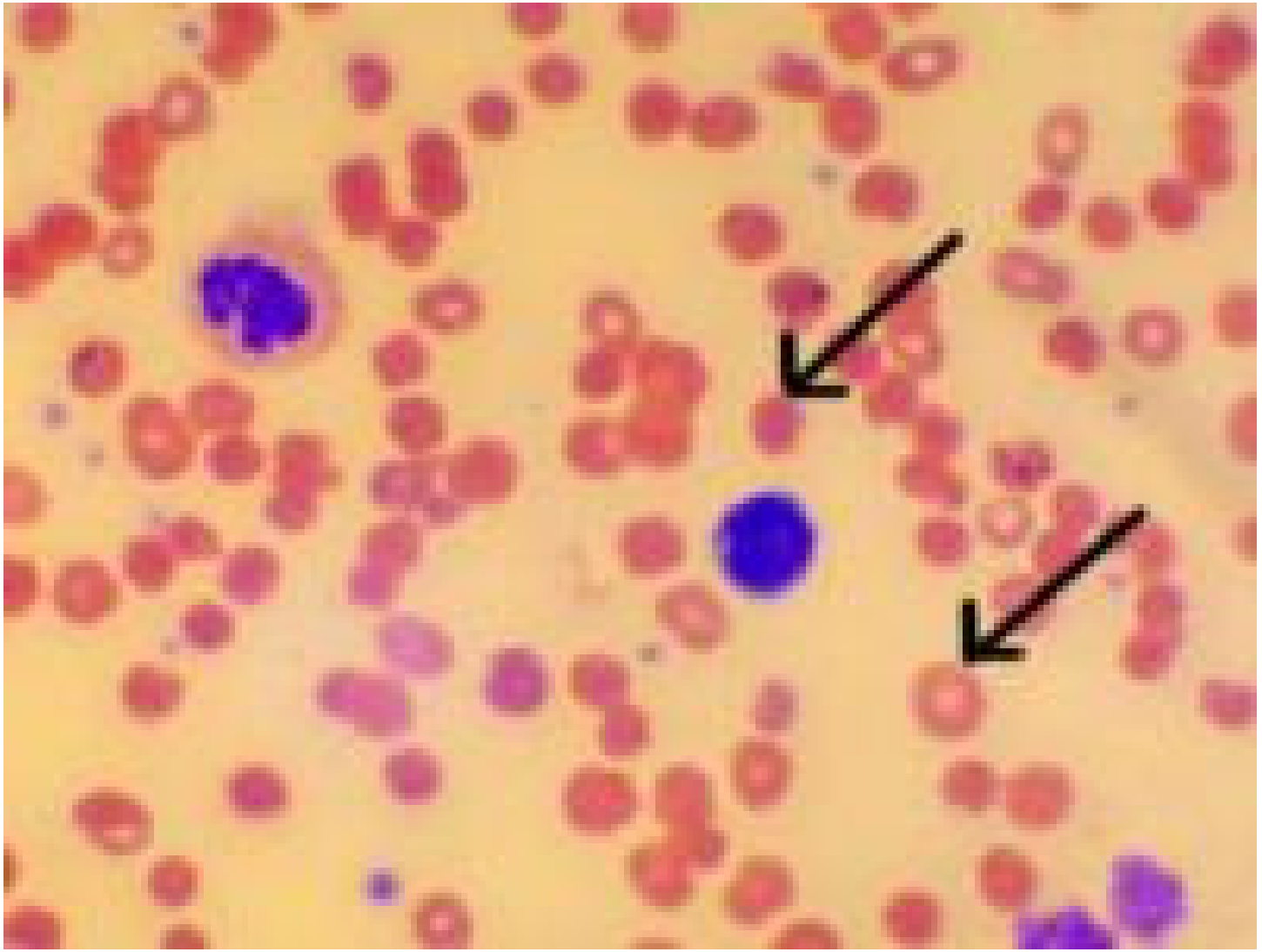
B-12 and Folate Deficiency



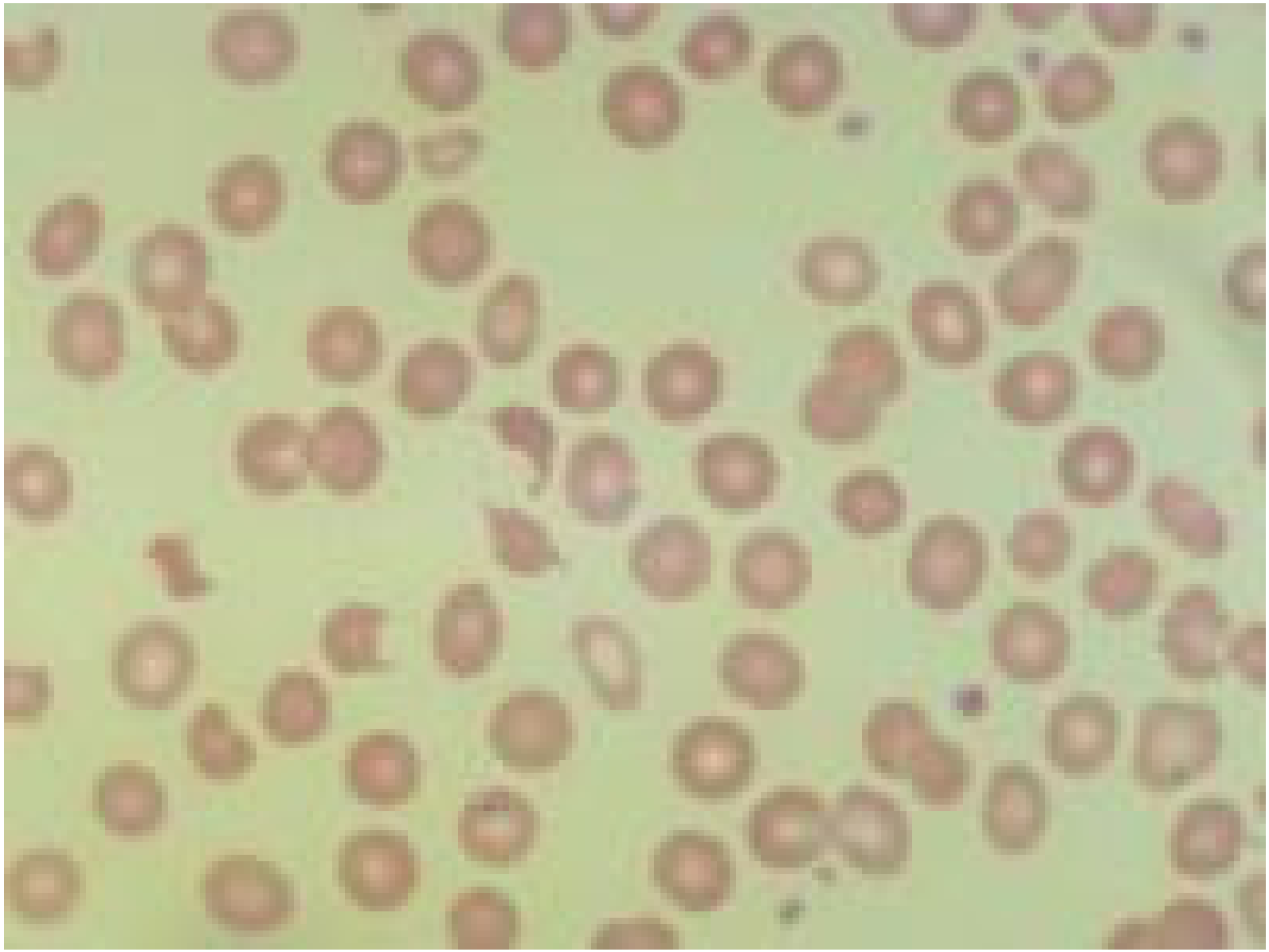




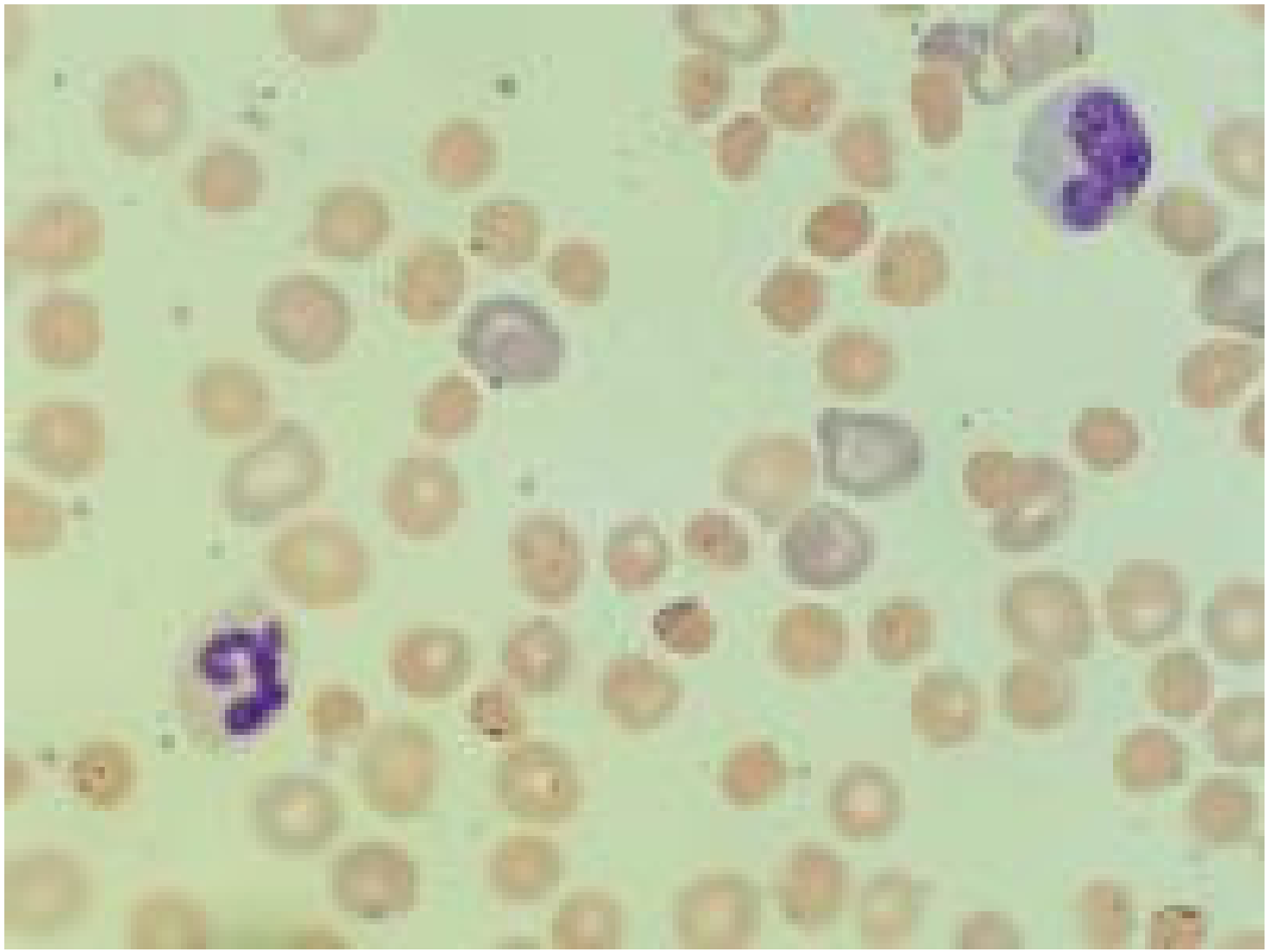
Spherocyte



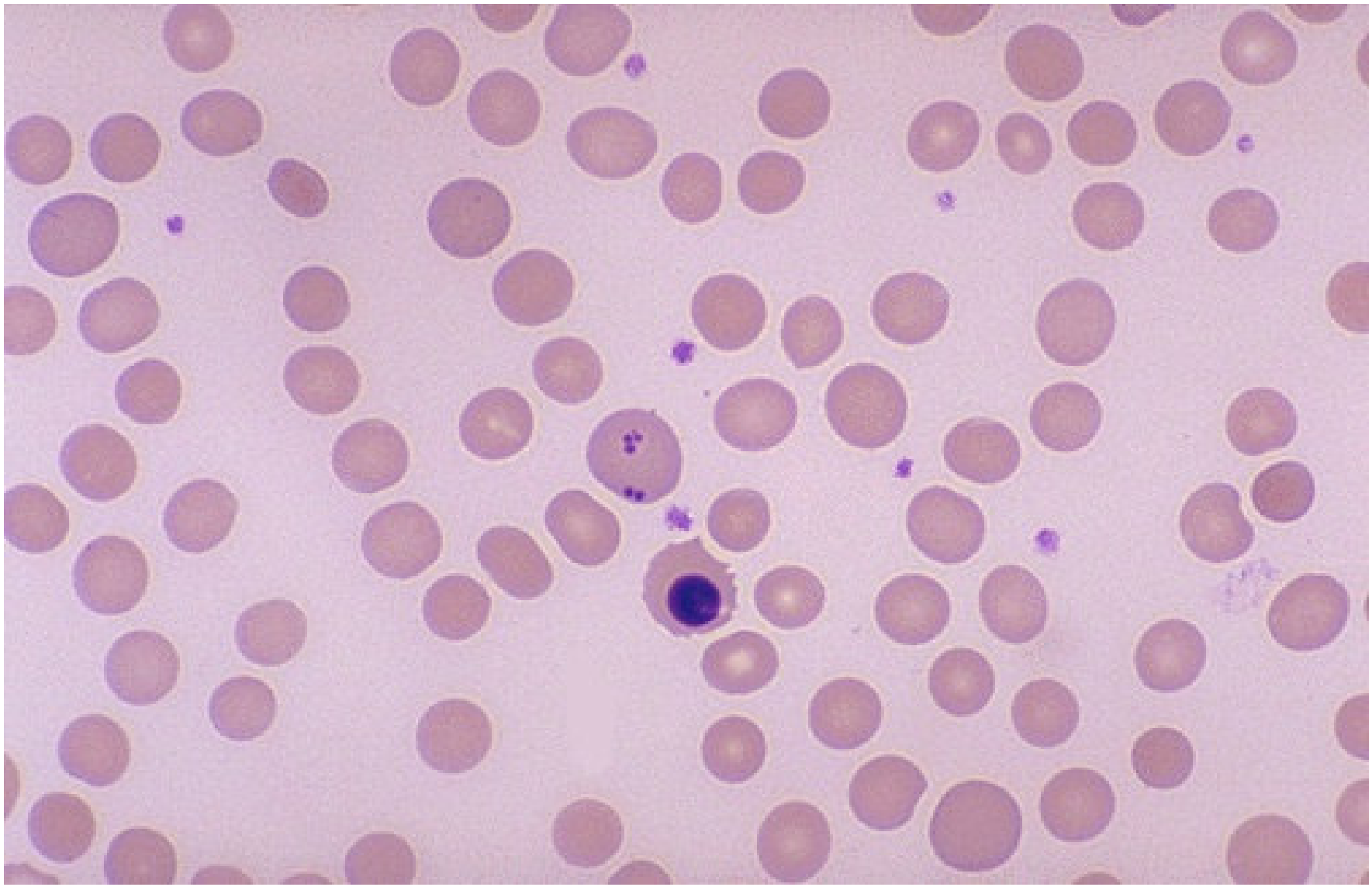
Hemolytic Anemia



Polychromasia



Howell Jolly



Anemia's Associated with Various Clinical States

Female:	Iron Deficiency
Blacks:	G-6-PD Deficiency, Hemoglobinopatheis, Thalassemia
Mediterranian Origin:	G-6-PD Deficiency, Thalassemia
Far East Origin:	Hemoglobinopathies
Viral Infection:	Immune Hemolysis, Decreased Production
Bacterial Infection:	Anemia of Inflammation, Microangiopathic Hemolysis, Oxidative Hemolysis (G-6-PD deficiency), Other Hemolytic Mechanisms
Malignancy:	Microangiopathic hemolysis, Immune hemolysis, Decreased production
Alcoholic Liver Disease:	Bleeding, Hypersplenism, Folate deficiency, Ethanol depression of production, Sideroblastic anemia, Iron deficiency, Hemolysis

Anemia's Associated with Various Clinical States Cont.

Hyper- or Hypothyroidism:	Decreased production, Pernicious anemia, Iron deficiency
Renal Failure:	Decreased production, Hemolysis, Bleeding
Aortic Valve Replacement:	Microangiopathic hemolysis
Malignant Hypertension:	Microangiopathic hemolysis
Rheumatoid Syndromes:	Anemia of inflammation, Iron deficiency, Immune hemolysis
Collagen Vascular Disease	Immune hemolysis, Anemia of inflammation

Drugs:

Aldomet: Immune hemolysis

Quinine/Quinidine:Immune hemolysis

Penicillin: Immune hemolysis (Rare)

Butazolidin/Chloramphenicol: Dose-related marrow depression, Idiosyncratic aplastic anemia

Gold: Aplastic anemia

Antiuberculosis Drugs: sideroblastic anemia

Dilantin: Megaloblastic anemia (folate), pure red cell aplasia

Sulfa: G-6-PD hemolysis

Serum Ferritin

- The bulk of iron in the adult male body is in the hemoglobin of the circulating red cells (approx. 2600mg). Myoglobin (muscle...400mg) Ferritin and hemosiderin (approx. 800mg)(female approx. 200mg) scattered thoughout the body in the RES (monocyte-macropahge system).
- Ferritin is an iron storage protein. You can measure the ferritin.

***Sometimes we correct the anemia with iron, but not correct the iron deficiency. So, give iron for several months.

Transferrin/TIBC, Iron, Iron Saturation

- Transferrin is a transport protein in the plasma which binds the serum iron and then transports the iron to the developing red cells in the bone marrow.
- You can measure the serum iron and transferrin and calculate the % iron saturation.
- FE/transferrin (or TIBC) = %iron saturation
- Iron Absorption Iron is in inorganic (ferric and ferrous) forms and in organic (heme) forms.
- Ferric is common dietary iron.
- Heme iron is present in meats. Animal origin is best absorbed. Phosphates and tannic acid (in tea) may inhibit absorption.
- Duodenum and jejunum are areas or iron absorption.
- Achlorhydria or gastric removal or atrophic gastritis are reasons for lack of iron absorption.

Representative Date Bases at Various Stages in the Slow Development of Severe Iron Deficient Anemia

m=mu

HCT	42	42	35	27	19
MCV (82-98 fl)	92	88	81	75	68
MCHC (32-36g/dl)	33	33	33	33	29
SI (65-175 m g%)	70	60	35	20	20
TIBC 250-375 m g/ml	300	300	300	400	450
Serum Ferritin (10-200 m g/ml)	60	30	5	3	1
Peripheral Smear	Normal	Normal	Normal	1+ poikilocytosis 1+ hypochromia	4+ poikilocytosis 4+ hypochromia
Bone Marrow Stores	Absent	Absent	Absent	Absent	Absent

Anemia-Approach to work-up

1. What is the patients MCV? Cell Size?
2. Mechanism (production, bleeding, hemolysis)
3. Patient problem list.

Example

HCT 10% reticulocyte count 5%

Reticulocyte index= 5% x 10/50 = 1%

-In this example (which uses for ease of calculation an arbitrary normal HCT of 50%) there is an inappropriately low reticulocyte index, indicating that bone marrow production is at least a contributing factor in the etiology of anemia. The elevated reticulocyte count of 5% is misleading. For this degree of anemia an appropriate reticulocyte count would be at least 15%:

reticulocyte index = 15% X 10/50= 3%

Low MCV

- Iron Deficiency
- Thalassemia
- Anemia of Chronic Disease
- Sideroblastic Anemia

Treatment Tips (Dr. Wurtz)

- FESO4 300mg= 60mg Elemental Iron
- Avoid time-release and Enteric coated
- Parenteral iron sometimes necessary if GI intolerance exists or persists.
- Indicated in patients with small and large bowel inflammation, rapid transit GI problems, malabsorption, proven noncompliance, when time to respond is an urgent issue(third trimester of pregnancy, severe anemia). Side effects. Dosing for IM/IV iron.
- Vitamin C- not worth the cost
  - GI side effects

Administration of intravenous iron dextran

MATERIEL

- 2 50cc bags .9 NS
- 1 500cc bag 0.9 NS
- 1 IMED cassette tubing
- 1 10cc syringe with needle
- 1 1cc syringe with needle
- Fe Dextrin in 2ml or 5ml ampoules
- Alcohol wipes
- 1 Buretrol

PROCEDURE

1. Obtain MD orders and ensure her/his ability to be in attendance, to administer test dose, and to be available during the infusion of full dose. Dose

calculation: Mg iron = [0.3 x wt (lbs) x 100 (14.8 - Hb)]/14.8

Note: in this calculation, 14.8 is the desired final hemoglobin value. The "Hb" in the equation is the patient's current hemoglobin value.

NOTE: Potential for anaphylactic reaction requires the administration of test dose.

2. Prepare full dose of Fe Dextran as ordered in 10cc syringe - use single-dose ampoules.

NOTE: Multi-dose vials of Fe dextran should not be used for IV administration due to their phenol content.

3. Transfer 25 mg of dose into 1cc syringe and inject into the 50cc bag of 0.9 NS (or as ordered by M.D.)

Administration of intravenous iron dextrin

NOTE: The use of 5% dextrose as diluent is associated with increased incidence of local pain and phlebitis. 250 to 1000 ml of 0.9 NS diluent is recommended for the full dose of iron dextran.

4. Place IV access, hang bag 500cc 0.9 NS using an IMED cassette tubing and regulate IV to KVO.
5. With the M.D. present, hook the 50 ml bag with Fe dextran 25mg test dose into a side-port of the main IV tubing set, and run the test dose in over

10-15 minutes, carefully observing the patient's vital signs.

NOTE: M.D. to stay in attendance.

6. Monitor patient for 15-20 minutes for signs of adverse reaction.
7. Only after the completion of the IV test dose should the remainder of the iron dextran be added to the 500 cc 0.9 NS bag. Administer full dose of

Fe dextrin via IMED pump over 2-6 hours as ordered by M.D.

NOTE: M.D. should be available during the infusion, but not necessarily at bedside. Administration rate should not exceed 500 mg/hr.

Administration of intravenous iron dextran

8. Flush medication through tubing, using 0.9 NS 50cc bag.
9. D/C IV per institutional procedure.
10. Document on appropriate patient forms.

Large IV does of iron dextrin can produce delayed adverse reactions (1-2 days) which usually subside within 3-4 days. These include: arthralgias,

myalgias, moderate to high fever, backache, chills, dizziness, headache, malaise, nausea and/or vomiting. Nonsteroidal anti-inflammatory agents

usually give good relief of these symptoms.

To provide prophylaxis against these problems, physicians can premedicate patients with 60 mg of methylprednisolone. Premedication is

particularly helpful to patients with inflammatory conditions, such as rheumatoid arthritis. These flairs may be caused by the inflammatory cytokines

from reticuloendothelial cells, which are "activated" when they engulf the circulating iron dextran complexes in the circulation

High MCV

- MCV >100
- Hints:
  - Sore or smooth tongue
  - Peripheral munopathy
  - ETOH
  - Dilantin
  - Malabsorption
  - Inanition
  - Liver Disease

Differential Diagnosis of an MCV Greater than 100 fl

1. Spurious
2. Reticulocytosis (marked)
3. Liver Disease
4. Alcoholism
5. No Associated Disease
6. Refractory Anemia (preleukemia, sideroblastic anemia)
7. Drugs
8. Megaloblastic anemia’s

Causes of Vitamin B-12 and Folic Acid Megaloblastosis B-12

- Pernicious anemia (acquired and congenital)
- Gastrectomy
- Illeal resection
- Crohn's disease
- Fish tapeworm infestation
- Blind loop syndrome
- Nutritional deficiency (vegan's diet, rare)
- Familial selective malabsorption (Imerslund's syndrome)
- Dietary (old age, alcoholic, chronic disease)
- Malabsorption (sprue)
- Hemodialysis
- Severe exfoliative skin disease (e.g. psoriasis)
- Drugs:
  - Interference with absorption or metabolism (dilantin, alcohol)
  - Dihydrofolate reductase inhibitors (methotrexate, trimethoprim)

Increased requirements: Pregnancy, Infancy, Hemolysis (e.g., Sickle Cell Anemia)

Serum B-12 Assay

1. Spuriously low in some patients with folate deficiency.
2. Spuriously low in some pregnant patients.
3. May be elevated for weeks after one shot of B-12.
4. Increased in myeloproliferative syndromes.

RBC Folate Assay

1. Reflects chronic folate deficiency.
2. Falsely low in some patients with B-12 deficiency.
3. Falsely high in reticulocytes.

Serum Folate Assay

1. A measure of recent dietary intake of folate.
2. Usually normal or elevated in B-12 deficiency.

- Pernicious anemia is thought to be the true and most common cause of B12 deficiency. However, dietary B12 is rare. B12 stores are usually plentiful and take years to deplete. Shillings test no longer used to diagnose Pernicious Anemia. Measuring homocysteine and methylmalonic acid levels are used...and increased in B12 deficiency.

- Remember hyperhomocysteinemia may lead to atherosclerosis. If pernicious anemia is suspected, then measure parietal cell antibodies and intrinsic factor antibodies. With the ubiquitous use of gastric acid blocking agents (H2 and proton pump inhibitors) B12 and folate levels may be reduced.

Differentiating Between Folate and B-12 Megaloblastosis

Etiology by History	RBC Folate	Serum B-12	Interpretation	Further Testing
Suggests Folate	Decreased	Nl or elevated	Folate deficiency	None
Suggests Folate	Decreased	Sl or decreased	Folate deficiency	Recheck B-12 after folate Rx for 1 week
Suggests B-12	Nl or elevated	Decreased	B-12 deficiency	None
Suggests B-12	Decreased (serum folate usually elevated)	Decreased	B-12 deficiency	May confirm with schilling test
All other combinations → Schilling test.				

Laboratory Features in Three Conditions Associated with an Elevated MCV

	Liver Disease	Megaloblastic Anemia	Preleukemia
MCV	Usually < 110 fl	Maybe >110 fl	Usually <110 fl
WBC's	Variable	Frequently decreased	Frequently decreased
Platelets	Variable	Frequently decreased	Frequently decreased
RBC Morphology	Targets No A and P	Marked A and P, Macro-ovalocytes, Tear drop cells	Marked A and P, May mimic megaloblastic anemia
NRB's	Not common	Common	Common
WBC Morphology	Normal	Hyper segmented	Abnormal mononuclear cells, no hyper segmentation
Platelet morphology	Normal	Normal	Frequently large and degranulated
Serum Folate	Depends on diet	Decreased in folate deficiency; elevated in B-12 deficiency	Normal or elevated
Serum B-12	Normal	Decreased in B-12 deficiency; may be slightly decreased in folate deficiency	Normal or elevated

- Hemolysis and Bleeding Anemia with a normal or slightly elevated MCV and an appropriate Reticulocyte Index. Increase in reticulocyte count in absence of bleeding suggests HEMOLYSIS.
- Approach to suspected hemolysis :

Clinical States Associated with Intravascular Hemolysis

1. Acute hemolytic transfusion reactions.
2. Severe and extensive burns.
3. Physical trauma (e.g., March hemoglobinuria).
4. Severe microangiopathic hemolysis (e.g., aortic valve prosthesis).
5. Acute G-6-PD hemolysis.
6. Paroxysmal nocturnal hemoglobinuria.
7. Clostridial sepsis.

Common Clinical States Associated with Extravascular Hemolysis

1. Autoimmune hemolysis.
2. Delayed hemolytic transfusion reactions.
3. Hemoglobinopathies.
4. Heredity spherocytosis.
5. Hypersplenism.
6. Hemolysis with liver disease.

Alloantibody Versus Autoantibody

	Alloantibody	Autoantibody
Direct Coombs'	Frequently negative. May be positive if sensitized foreign red cells are still circulating.	Positive
Indirect Coombs'	Positive	Positive or Negative
Antibody Screen (Panel)	Specificity is seen	Pan agglutination, no specificity seen

Anemia with a Normal MCV and Low Reticulocyte Index

Differential Diagnosis

- Renal Failure
- Anemia of Inflamatory Disease (anemia of malignancy)
- Anemia of hypoendocrine states (hypothyroidism etc…)
- Mild (early) Iron Deficiency
- Combined iron deficiency and megaloblastic anemia
- Sideroblastic Anemia
- Bone Marrow inflatration (myelophthisis)
- Bleeding or hemolysis plus one of the above

Inappropriately Normal or Elevated Serum Ferritin Levels

- Acute Liver Disease
- Cirrhosis
- Hodgkin's Disease
- Acute Leukemia
- Solid Tumors (occasional)
- Fever
- Acute Inflammation
- Renal Dialysis Patients
- Recent Treatment with Iron

- Anemia of Renal Failure....decreased marrow erythropoiesis secondary to decreased erythropoietin (EPO). EPO and ESA are a whole 'nother topic !!! Interference by uremic toxins. Excess PTH (secondary PTH). Hemolytic component. Patients on hemodialysis...iron deficiency (bleeding into the coil, phlebotomy, GI bleed). Folate deficiency (folate is hemodialyzable). Measure GFR ! Don't always depend upon the serum creatinine. Measure ferritin. Inflammation elevates the ferritin level in iron deficient patients...so, a ferritin level less than 55 u g/l is highly suggestive of iron deficiency...whereas a level greater than 100 usually means iron stores are present.

- Anemia of Chronic Inflammation Very common ! Serum iron is low and TIBC is low, so % iron saturation may be low or normal, and serum ferritin is normal or elevated and bone marrow iron stores are normal or increased. Malignancies and acute and chronic infections. Not the best idea to measure iron parameters during acute febrile illness. Look at peripheral blood smear (PBS...I call it "the po man's bone marrow".

- Anemia of Hypoendocrine States Hypothyroidism, hypoadrenalism, hypopituitarism,androgen lack/deprivation. Don't forget andropause and testosterone. Lessened peripheral oxygen requirements. Mention BEPO and PEPO.
- Don't or Do Shotgun the Patient !!! New anemia w/u by shotgun...you might hit sumpin :CBC with diff, iron, transferrin, ferritin, % iron saturation, hgb electrophoresis, reticulocyte count, LDH, SPEP, UPEP, B12, folate, T4, TSH, haptoglobin.
- What is left out ?
- Myelodysplasia(MDS) and Myeloproliferative Disorders(MPD) MDS...elevated MCV, other cell lines involved besides red blood cells. MPD...MCV variable and other cell lines involved.

Sideroblastic Anemia: Differential Diagnosis

- Congenital

  Acquired

  Primary Idiopathic

  Secondary

  Drugs (alcohol, lead, antituberculosis drugs, chloramphenicol)

  Collagen vascular disease

  Multiple myeloma

  Marked hemolysis

  Thalassemia

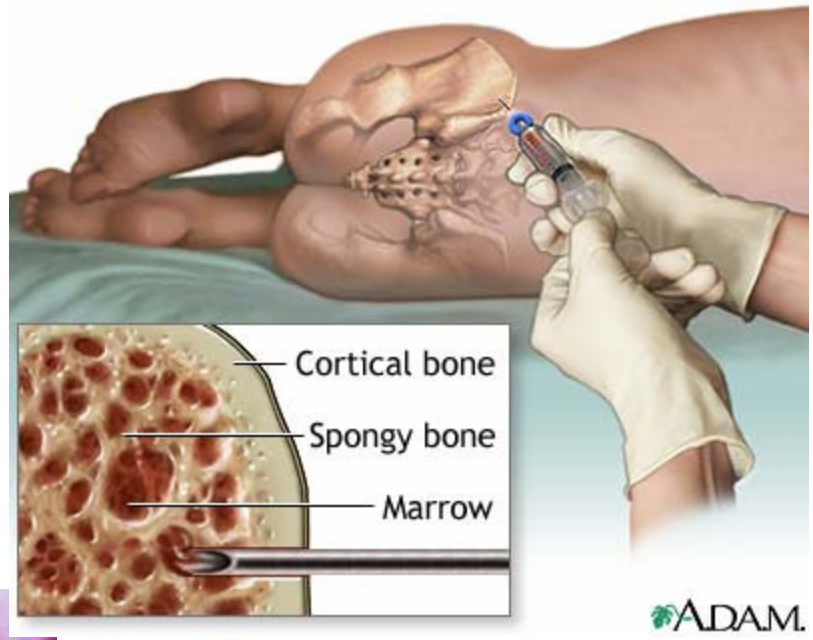
  Megaloblastic anemia

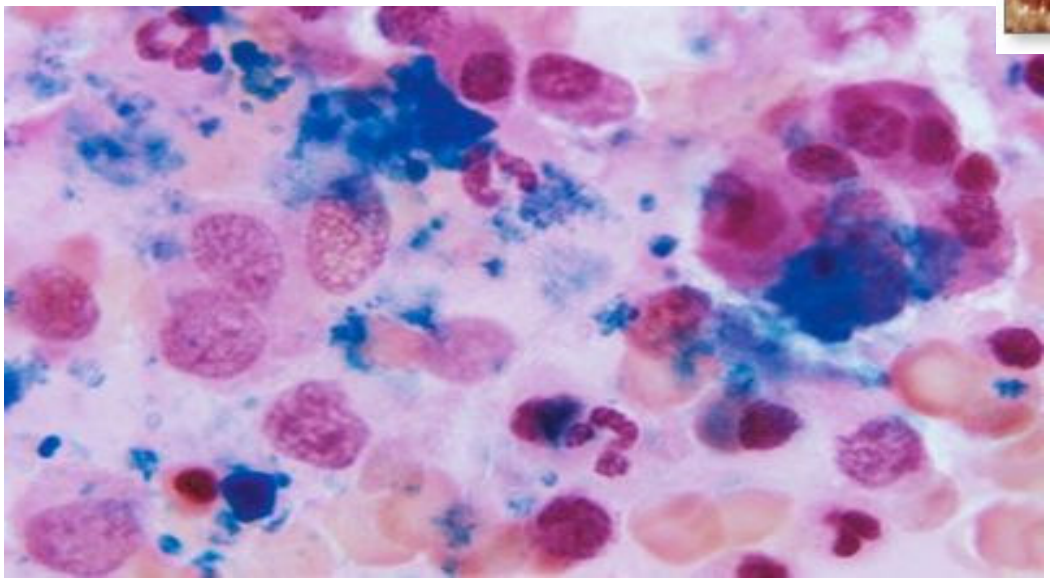
  Preleukemia and the non lymphocytic acute leukemia

Leukoerythroblastosis (Common Etiologies)

- Primary myelofibrosis (Agnogenic myeloid metaplasia)
- End-stage polycythemia vera
- Metastatic Cancer
  - Breast
  - Prostate
  - Oat cell carcinoma of the lung
- Acute leukemia (occasionally)
- Other hematologic malignancies on occasion (CLL, multiple myeloma, lymphosarcoma)

Bone Marrow





Help from the Bone Marrow

- Bone Marrow NOT Helpful
  - Anemia of chronic disease
  - Chronic renal failure
  - Hypoendocrine states

- Bone Marrow Helpful
  - Myelophthisis (need a marrow biopsy)
  - Iron deficiency (serum ferritin is cheaper and less uncomfortable)
  - Combined iron deficiency and megaloblastic anemia
  - Sideroblastic anemia
  - Aplastic anemia
  - Primary marrow malignancy (leukemia, myeloma, etc.)

Why do a Bone Marrow?

- Q. Will a bone marrow (aspirate and biopsy) find something I did not already suspect by the patients' history, physical examination, lab, peripheral blood smear (PBS) and xrays ? A. Chances of finding something in the bone marrow that I did not already suspect are low.
- Q. What about the time involved, cost and discomfort of a bone marrow ? A. Discomfort is variable (sedation, anesthetic). The procedure usually takes less than 20 minutes (dependent on patient's body habitus).

Why do a Bone Marrow?

- Q. Costs?
  A. Interpretation of the bone marrow by the pathologist...maturity of the cells (red, white, platelet), number of cells vs. amount of fat , fibrosis, iron content. Blood (aspirate) from the bone marrow (sometimes also peripheral blood) can be sent for special studies like flow cytometry and cytogenetics. To make a diagnosis of 'refractory anemia' a bone marrow exam may be needed. 'Refractory' has variable interpretation...clinical or pathological ? When to give Erythrocyte Stimulating Agents (ESA) ? Empiric treatment for anemia ? Do you 'just give' iron, B12 or folate just to see if it will work ?

Anemia with Normal MCV and low Reticulocyte Index

- EPO (Erythropoietin)
- RBC Morphology
- Ferritin, serum iron, TIBC, Iron saturation
- Hormone
- Inflammation
- Thyroid
- Combined
- Bone marrow failure
- Peripheral blood smear