

Red Blood Cells

Blood composition: 1) RBCs 2) WBCs 3) Megak. Reticulocytes (1-2% Total RBC) → RBC's

Symptoms: Weakness, Fatigue, dyspnea
Pale conjunctiva and skin
Headache (↓ O₂ to brain)
Angina (↓ O₂ to heart)

ANEMIA

MCV: mean corpuscular volume

measured: 1) HB 2) HCT 3) RBC COUNT
 <13.5: males
 <12.5: females

abnormal

normal

Microcytic <80 MCV

Hb = Heme (Iron + protoporphyrin) + globin

↓ serum Fe

Chronic disease

↑ Hepcidin due to inflammation (IL-6)
 Labs: ↑ Ferritin

↓ vit transferrin
 ↓ TIBC



mφ size increases
 ↓ vit iron absorption
 ↓ erythropoietin

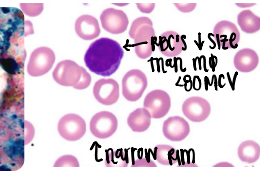
Iron deficiency

• most common anemia

• hypochromic RBC's

Labs: ↓ Ferritin

↓ % vit transferrin
 ↑ TIBC: # transferrin



Iron is stored in mφ as Ferritin in tissues

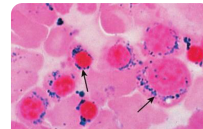
Sideroblastic

• defect in heme synthesis

• gene defect: ALAS, ALAD

and ↓ vitamin B₆

iron remains trapped in mitochondria, and sits around the nucleus



Toxic iron radicals will form due to free iron

Megaloblastic

α: cis: two deletion same 16

trans: two opposite 16

chromosome 16 deletion

clinical = infant CHF → edema

β: B/B+ = diminished B, asymp.

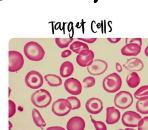
B0/B0 = severe form

erythroid hyperplasia
 hematopoiesis skull
 chimeric faces

Big infection

↑ risk of hemochromatosis

Labs: ↑ HbA, ↑ HbF/HbA₂



Differentials by MCV			
Microcytic (MCV < 80 fL)	"TAILS"		
	• Thalassemia • ACD (inflammation) • Iron deficiency • Lead poisoning • Sideroblastic anemia		
Normocytic (MCV 80-100 fL)	Non-hemolytic • ACD • Aplastic anemia • CKD	Hemolytic	
		Intrinsic	• H.Spherocytosis • J. G6PD, PK • HbC • HbSS • PNH
			Extrinsic
		Macrocytic (MCV > 100 fL)	Megaloblastic • Folate deficiency • B12 deficiency • Orotic aciduria • Drugs (e.g., hydroxyurea, antifolate)
• Liver disease • Alcoholism • Hypothyroidism • Reticulocytosis • MDS (especially if MCV > 110 fL)			
Helpful smear findings			
• Agglutination: cold AIHA, WM, MM • Basophilic stippling: thalassemia, heavy metal • Bite cells/Heinz bodies: G6PD • Burr cells: artifact, uremia • Elliptocytosis: hereditary, MDS, MF, IDA • Howell-Jolly: asplenia • Leukoerythroblastic: MPN, infiltration, sepsis • Megaloblastic: B12/folate deficiency • Pappenheimer bodies: alcohol, asplenia • Parasites: malaria, babesiosis (Maltese cross) • Peigler-Huet anomaly or dysplastic: MDS • Ringed sideroblasts: lead, isoniazid, alcohol, B6 def, MDS • Schistocytes: DIC, sepsis, MAHA • Spherocytes: AIHA, hereditary • Spur cells: liver disease • Stomatocytes: hereditary, liver disease • Target cells: HbC/SC, asplenia, liver disease, thalassemia, IDA			

check reticulocytes

DNA left in RBC

ret. ↑

ret. ↓

↑ hemolysis

large spleen

Extravascular hemolysis

Intravascular hemolysis

Hereditary spherocytosis

sickle cell

Hemoglobin C

PNH

G6PD

AIHA

microangiopathic

malaria

↓ production

BM failure

• Parvo B19

• aplastic anemia

• renal failure

• leukemia

Macrocytic anemia

>100 MCV

Pernicious anemia: most common cause B12 def.

deficiency of intrinsic factor

B12 deficiency

• needs methyl from Folate to convert Homocysteine to Methionine

• Required for TGA

Methylmalonic

Acid → Succinyl CoA

Labs: ↑ Homocysteine

↓ Methionine

↑ Methylmalonic A

which will ↓ Succinyl CoA affecting the brain (CNS)

neurological A's

Folate deficiency

essential for DNA synthesis

most common macro. anemia

Folate absorbed in jejunum

anemia develop in months

(B12 = years)

caused by: poor diet, drugs

- methotrexate (cancer or SLE)

Symptoms: red tongue - glossitis

Labs: ↓ serum Folate

↑ Homocysteine

↑ risk thrombosis & atherosclerosis

Normal Methylmalonic A.

IntraCELLular (intrinsic) RBC Defects/Abnormalities

Membrane Defects

- Hereditary Spherocytosis/Elliptocytosis

- PNH

Hemaglobinopathy (Hb defect)

- Sickle Cell Anemia

- Thalassemias (MCV < 80)

Deficient Enzymes

- G6PD

- Pyruvate Kinase deficiency

Extracellular (extrinsic)

Antibody Mediated

- Autoimmune hemolytic anemia

- HDN

Mechanical Trauma to RBCs

- Calcified/Prosthetic heart valve

- Microangiopathic hemolytic anemias

- DIC: disseminated intravascular coagulation

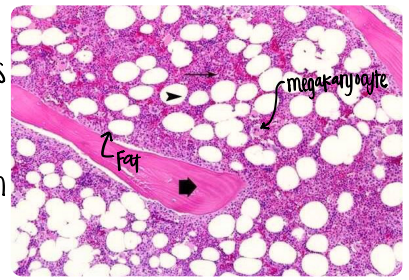
- TTP: Thrombotic thrombocytopenic purpura

- Malaria infection

Bone marrow

contains: 1) RBCs
2) WBCs
3) megakaryocytes
normal ratio: myeloid (white) 3:1 erythroid (red)

50/50
Fat to cells
mixed
maturation

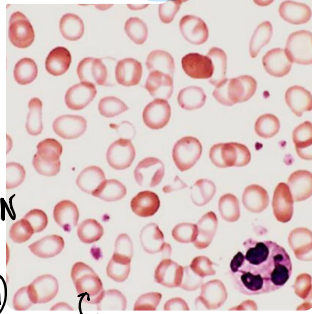


Heme (iron + protoporphyrin) + globin

microcytic <80 mcv

IRON DEFICIENCY ANEMIA (iron)

- Most common type of anemia
- absorption Fe^{2+} in duodenum which enters via **Ferroportin**
- enters blood stream bound to **Transferrin**
- stored in organs in macrophages as **Ferritin**



thin, hypochromic

causes: **Pika: eat dirt ect.**

children: diet adults: menstruation, ulcers (men)

elderly: colon, polyp, carcinoma, hookworm

Labs:

- ↓ Ferritin
- ↓ Serum Iron
- ↓ % saturation
- hypochromic (flat)

Hemochromin: poor quality iron

↑ TIBC, # transferrin

ANEMIA OF CHRONIC DISEASE (iron)

- associated with chronic inflammation/malignancy
- ↑ **Hepcidin** from liver limits iron and ↓ erythropoietin
- normocytic → microcytic



PRUSSIAN BLUE

causes

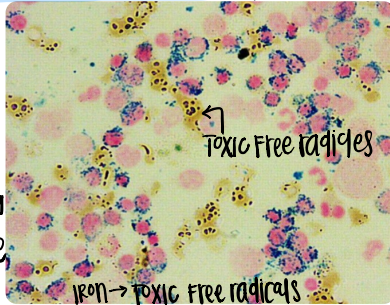
- chronic inflammatory disease/CA

Labs:

- ↑ Ferritin
- ↓ Serum Iron
- ↓ % sat transferrin
- ↓ TIBC: # transferrin
- ↑ PEF
- ↑ Hepcidin

SIDEROBLASTIC ANEMIA (proto) B.m. smear

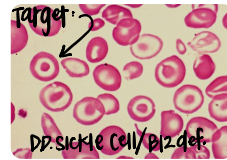
- defect in **protoporphyrin** enzyme: **ALAS, ALAD, VIT B6**



toxic free radicals

normal: iron transferred to erythroid precursors to enter mitochondria bind to protoporphyrin → Heme

defect in protoporphyrin leads to accumulation of iron in mitochondria of erythroid precursors



target cells

THALASSEMIA

HbA: ($\alpha_2\beta_2$) HbA₂: ($\alpha_2\delta_2$)
HbF: ($\alpha_2\gamma_2$)

decreased production of globulin chains of Hb.

Newborn erythropoiesis is by B.m.

alpha: deletion

- diseased infants ↑ CO → CHF → edema

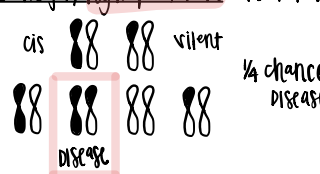
silent carrier: one deleted

trait: two deleted: cis (asian): rare

trans (afican): opp

Hemoglobin H: (diseased) 3 deleted

alpha major/hydrops fetalis: 4 deleted



Beta: B+ = diminished B0 = absent

B/B+: slight ↓ HbA, ↑ HbF/HbA₂: asymptomatic

B0/B0: **COLE FORM** few months after birth (due to protection of HbF)

- massive erythroid hyperplasia
- ineffective erythropoiesis due to unpaired α chain. Little HbA, ↑ HbF/HbA₂
- growth stull: hematology still
- chipmunk faces
- parvo B19 infection
- blood transfusion → hemochromatosis

>5 lobes

>100 mcv: hypersegmented neutrophils

target cell

macrocytic

impaired DNA synthesis → ineffective erythropoiesis
"marrow full, blood empty"

FOLATE DEFICIENCY ANEMIA

symptoms: glossitis (red tongue)

- most common cause of macrocytic anemia
- obtained from fruits/veggies absorbed in the duodenum takes months to cause

causes: alcoholism, cancer, pregnancy, **methotrexate**

which is a cancer/LE anti-inflammatory

homocysteine ↑: ↑ risk atherosclerosis & thrombosis

Labs:

- ↓ Serum Folate
- ↑ homocysteine
- Normal methylmalonic acid
- jaundice/splenomegaly

B12 DEFICIENCY ANEMIA

B12 constantly attached: B12-protein $\xrightarrow{\text{amylase}}$ B12-PE binder $\xrightarrow{\text{protease}}$ B12-IF (parietal)

B12 used in 2 reactions

1) methyl from folate → homocysteine → methionine

2) methylmalonic acid → succinyl CoA in TCA cycle

symptoms: glossitis

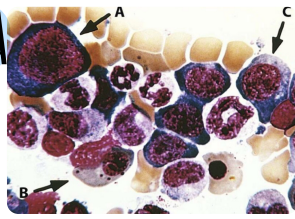
• neurological: subacute degeneration of spinal cord due to decrease succinyl CoA and ↑ MMA

Labs:

- ↓ Serum Folate
- ↑ homocysteine
- ↑ Methylmalonic acid
- jaundice/splenomegaly

MEGALOBlastic ANEMIA

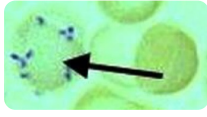
- megaloblasts in bone marrow in various stages
- Dark cytoplasm = erythroid precursor
- Light cytoplasm = WBC



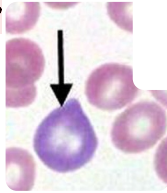
PERNICIOUS ANEMIA

- #1 cause of B12 deficiency: ↓ Intrinsic Factor (stomach)
- atrophic gastritis leads to autoimmune destruction of parietal cells leading ↓ IF

Reticulocytes: 1-2%, larger, purple



Light blue RNA



normocytic

80-100 MCV

Reticulocytes

< 3%
↓ Reticulocytes

↓ Production

Acute Blood Loss

Pure red cell aplasia:
MCC: immuno-compromised pts / after a transplant.
Platelets: N
WBC: N
Ret: Low

Parvo B19 / Thymoma

shuts off B.M. for 1-2 weeks. with pre-existing B.M. stress **sickle cell anemia** → significant anemia

myelophthisic process
replace B.M. w/ met. cancer/disease
pancytopenia

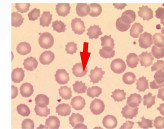
Aplastic anemia

Injury to stem cell → B.M. Failure
Hypocellular marrow, pancytopenia,
No abnormal cells in blood/marrow

Renal Disease

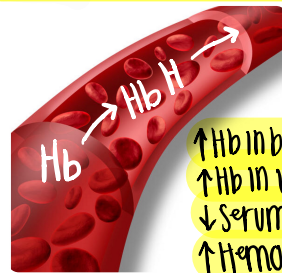
↓ erythropoietin

Treat w/ Recombinate erythropoietin



Seen in:
PK def
low erythropoietin in renal disease

Intravascular hemolysis



↑ Hb in blood
↑ Hb in urine
↓ Serum haptoglobin
↑ Hemociderin urine

Paroxysmal Nocturnal Hemoglobinuria (PNH)

defect myeloid stem cells in CD55/CD59 (DAF) which hold GPI protein to protect against complement.
At night, ↑ resp. distress → Hemoglobinuria (dark urine)
Complication: AML, Iron deficiency

GLPD XLR

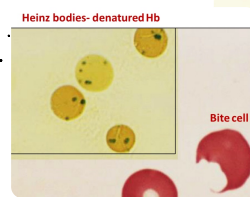
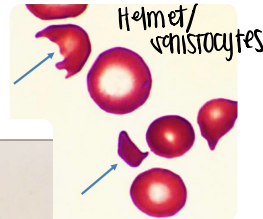
GLPD produces NADH which reduces glutathione to protect against H₂O₂ (oxidative stress)
Hemoglobinuria + back pain
Heinz bodies w/ bite cells

Immune Hemolytic anemia

Comb Test
Direct: RBC
Indirect: Ab
IgG = warm, extravascular, Central body, SLE/penicillin
IgM = cold, intravascular, umb

Microangiopathic hemolytic anemia

mechanical blood vessel damage due to microthrombi, prosthetic heart valve, and aortic stenosis
schistocytes and **helmet cells**



malaria

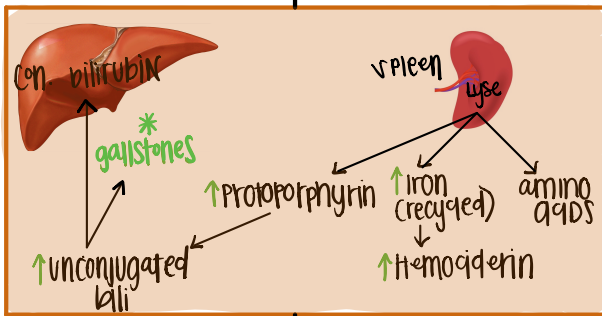
malaria multiply in RBC → hemolysis w/ Plasmodium
Spleen will also destroy RBC's

↑ Reticulocytes > 3%

↑ Hemolysis / destruction

Symptoms: anemia, jaundice, splenomegaly, B.M. hyperplasia

Extravascular hemolysis: in Spleen
REC: Liver & spleen L.N.



Hereditary spherocytosis

- AD disease
- RBC's cytoskeleton membrane protein defect
- Spheres (no dimple)

Diagnosis osmotic fragility test =

Hypotonic solution → lysis (+ test)

Lab: ↑ RDW, ↑ MCHC

Treat: Splenectomy

Howell jolly Bodies



Sickle cell

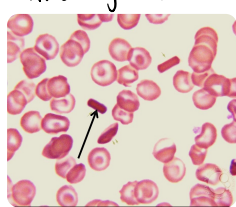
AR point mutation in Beta globin
glutamic acid → val
Disease: 2 abnormal
Trait: 1 abnormal
only sickle E. medulla

10% of African Am.
tremor, chills, fever, splenomegaly, infarction
chest pain, acidosis, hypoxia



Hemoglobin C

glutamic acid → lysine
Less common
HbC crystals



Banana shape

extracellular hemolysis ↑ R.C., Hemolysis

AD HEREDITARY SPHEROCYTOSIS

- Defect of RBC cytoskeleton membrane protein
- Membrane blebs are formed and lost w/ **sphere shape**
- Cells that are unable to maneuver in spleen → hemolysis and engulfed by macrophages **Ankyrin/Spectrin**

Diagnosis: **Osmotic fragility test:** hypotonic sol → lysis of RBCs

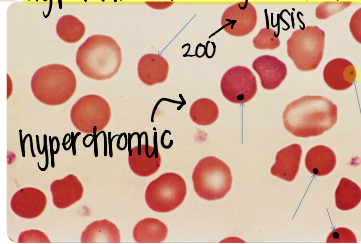
Lab: ↑ RDW, ↑ MCHC

Histology

Howell Jolly body: residual nuclear DNA normally cleared by spleen → splenic failure

Treatment

• **Splenectomy**

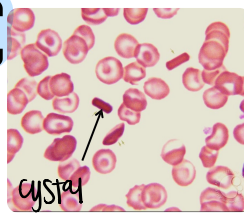


Symptoms:

- splenomegaly
 - Parvo B19
 - jaundice
- RBC structure issues Intracellular (intrinsic)*

HEMOGLOBIN C

glutamic acid → lysine
Less common
HbC crystals in RBC smear



Cause: malaria → replicate RBC's

intracellular ↑ R.C., hemolysis

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

clavred defect in myeloid stem cells in **CD55/CD59** attach to **GPI** protein leading to ↓ protection to complement:
At night, ↓ O₂ shallow breathing → **Hemolysis**
Hemolysis = iron storage complex with poor quality iron. only in damaged
GPI Mutation

Screening:

- 1) sucrose: activates complement → + lyse RBC
- 2) serum acidification **RBC issue → intracellular**
- 3) lack CD55/CD59

Complications: iron def. anemia / **acute myeloid leukemia**
Cause of death: Thrombosis: hepatic, portal, cerebral vein

IMMUNE HEMOLYTIC ANEMIA

Coomb Test = Direct - RBC, Indirect - Ab (plasma)

IgM = cold, intravascular hemolysis
binds to RBC fixing complement
Residual **C3b** serves as opsonin for spleen mφ result in
spherocytosis
extremities

IgG = warm, extravascular hemolysis
RBC's coated w/ ab. splenic mφ remove RBC membrane (+Ab). associated SLE/penicillin
Treatment: IVIG, splenectomy
Central

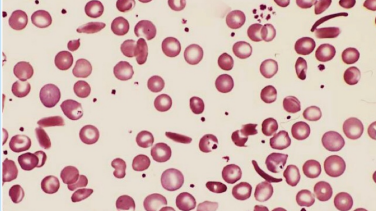
AR SICKLE CELL ANEMIA

HbS

- Point mutation (glutamic acid → val) in β-globin that promotes polymerization of degenerated hemoglobin → hemolytic anemia, microvascular obstruction, ischemia
- 10% of African Americans, likely protects against malaria falciparum

Sickle cell trait: 1 abnormal <50% HbS **asymptomatic** only sickle **renal medulla**

Sickle cell disease: 2 abnormal genes which results >90% HbS in RBCs
HbS = ↓ O₂ due to sickle
can sickle → desickle



Histology: banana = reversible

Howell Jolly Bodies = DNA RBC

Vaso-occlusive sickle cell: irreversible sickling: infants infarction in hands, **autosplenectomy**, MI, pain, renal papillary necrosis

Treatment: **hydroxyurea** (↑ HbF)

Screen: **metabisulfate**: cause sickling with any amount of HbS
electrophoresis: confirmation test

Symptoms

- Hip pain = femur ↓ blood
- renal papillary necrosis
- erythroid hyperplasia
- infarct hands (>6mm)

- BM infarct
- crepant

- **autosplenectomy**
- chipmunk faces

- pigmented gallstones
- chest pain

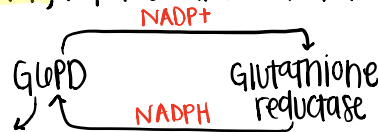
- **encapsulated** b₁₃ infection
- **Salmonella** osteomyelitis

intracellular

GLUCOSE-6-PHOSPHATE DEFICIENCY

XLR

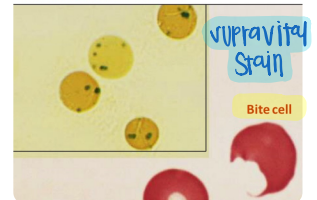
XLR, ↓ G6P t_{1/2} life → ↓ protection of RBC's to oxidative stress.



Deficiency in G6PD, unable to reduce glutathione with NADPH

← bite out **Heinz bodies**

Heinz bodies - denatured Hb



Symptoms: Hemoglobinuria + back pain

Variants: mild = african

severe = mediterranean

Causers: **Flava beans**, sulfa, primaquine

Histology: **Heinz bodies** = denatured hb

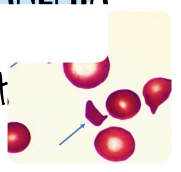
Bite cells: spleen bite inclusions

MICROANGIOPATHIC HEMOLYTIC ANEMIA

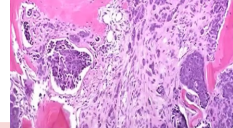
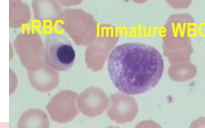
Damage or destruction of RBC's as they pass through circulation - microthrombi, prosthetic heart, valve, aortic stenosis, DIC

Histology = **schistocytes** and **helmet cells**

Hemolysis w/ Howell Jolly bodies



decreased reticulocytes



"Pure Red Cell Aplasia"
Absence of RBC pre-cursors in the marrow.

PARVO B19

Ex: THYMOMA

Self limiting viral infection which resolves 12 weeks in healthy individuals

vickle cell patients (or others w/ BM stress) can cause significant anemia

etiology = shut down B.M. for a few weeks

APLASTIC ANEMIA

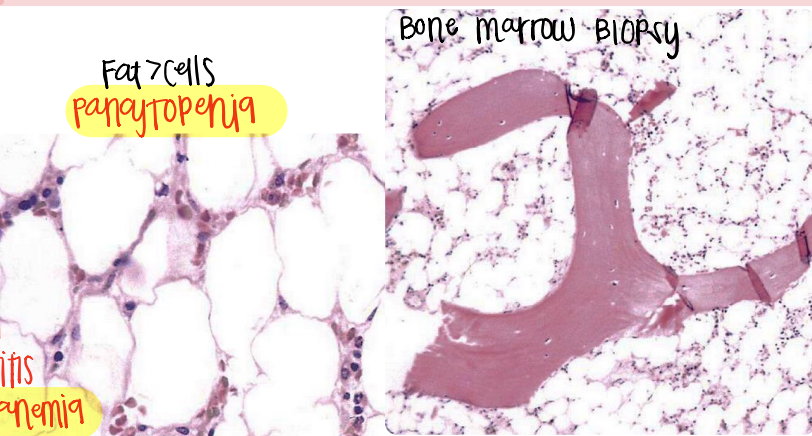
Rare and serious condition of bone marrow failure that arises from suppression/injury to hematopoietic stem cell.

characteristics: hypocellular marrow, pancytopenia with no abnormal cells in bone or marrow

causes: chemicals, viral infection, drugs, autoimmune → sickle cell

BIOPSY: empty bone marrow: Fat > cells

Treatment: treat underlying cause



Classification	Examples and discussion
Idiopathic	50-70% cases
Drugs	Most common known cause Alkylating agents (reversible) Chloramphenicol (irreversible)*
Chemical agents	Benzene**, insecticides, DDT, parathion
Infection	Hepatitis of unknown virus, EBV, CMV
Physical agents	Radiation* (therapeutic or accidental)
Inherited	Fanconi's Anemia; Telomerase defect
Miscellaneous	PNH* (Paroxysmal nocturnal hemoglobinuria)

* Parvovirus and thymoma: cause pure red cell aplasia.

MYELOPHTHISIC PROCESS

"tear drop"

Replacement of B.M. with nonhematopoietic tissue like cancer or other bone disease.

Bx to diagnose

Labs: pancytopenia: ↓ RBC, WBC, megakaryocyte, blast cells

Causes: Metastatic cancer, granulomas (TB), Marrow fibrosis

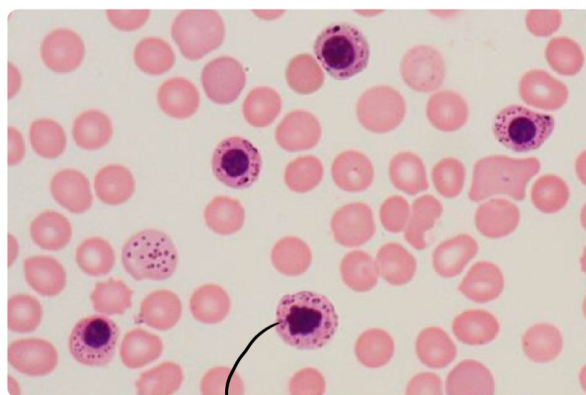
Summary of normocytic anemia with corrected reticulocyte count <3% (RBC Production Problem)

Anemia	Pathogenesis	Comments
Acute blood loss	Loss of whole blood	Initial Hb and Hct normal
Early stage IDA	Decreased iron stores	Normocytic anemia before microcytic. All Fe studies abnormal
Aplastic anemia	Suppression of trilineage Myeloid stem cell	Pancytopenia, hypocellular marrow
Renal disease	Deficiency of EPO	Rx with recombinant EPO

BASOPHILIC STIPPLING

A nonspecific histology finding with ribosomes in RBC's.

Found in: Thalassemia
vickle cell
lead poisoning
megaloblastic anemia
sideroblastic anemia



rna in cytoplasm