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OBJECTIVES

1. Define anemia, including signs and symptoms.
2. Discuss various causes of anemia.
3. Utilize lab results to distinguish different types of anemia.

2

INTRODUCTION

- Red blood cells (RBCs) are vital because they deliver oxygen (O_2) to organs and tissues.
- Hemoglobin (HGB) within the RBCs picks up O_2 in the lungs and the releases it where needed.
- HGB concentration tends to reflect the capability of RBCs to deliver O_2.
- Decrease in HGB or RBCs (not always both) results *tissue hypoxia*.

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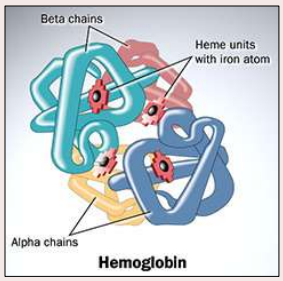

HGB STRUCTURE & COMPOSITION

- 1 hemoglobin protein = 4 heme rings + 4 globin chains + 4 iron atoms
- One O_2 molecule binds to each iron atom.
- **1 hemoglobin carries 4 O_2 molecules**

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ANEMIA

- From the Greek word ***anaimia*** meaning "without blood."
- Functional definition: a decrease in the oxygen-carrying capacity of the blood
  - Insufficient [HGB]
  - Impaired HGB function
  - Not always accompanied by a decrease in RBC count
- One of the most common problems encountered in clinical medicine
- Can have various causes
- IS NOT A DISEASE

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CAUSES OF ANEMIA

- **Blood loss**
  - Acute vs. chronic
- **Nutritional deficiencies**
  - Iron vs. B_{12} vs folate
- **Chronic inflammation**
- **Bone marrow disorders**
  - Damage vs. infiltration
- **Accelerated RBC destruction** (hemolysis)
  - Intrinsic vs. extrinsic defects
- **Hereditary defects in HGB structure or production**
  - Sickle cell anemia vs. thalassemia

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GENERAL CLINICAL FINDINGS

- Classic symptoms: fatigue and dyspnea
- Tachycardia, vertigo, headache
- Muscle weakness, and lethargy
- Pallor of conjunctiva and nail beds

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SPECIFIC CLINICAL FINDINGS

- Bleeding (acute or chronic)
- Hypotension, syncope
- Jaundice
- Heart abnormalities
- Organomegaly of the spleen and/or liver
- Bone deformities

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SIGNS AND SYMPTOMS

- May range from slight fatigue or barely noticeable physiologic changes to life-threatening circumstances
- Depend on:
  - Rate of onset
  - Severity of underlying cause
  - Ability of body to adapt

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ADAPTATIONS TO ANEMIA

- Different patients respond differently to similar changes in HGB based on:
  - Duration and severity of anemia
  - Competency of the cardiovascular and respiratory systems
  - O_2 requirements of the individual (physical and metabolic activity)
  - Disease or condition that caused the anemia
  - Presence and severity of coexisting disease(s)

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ADAPTATIONS TO ANEMIA, CONT.

- Increasing oxygenated blood flow
  - Cardiac output and circulation rate
  - Blood flow to vital organs (heart and brain)
  - Oxygen intake
    - Deepening the amount of inspiration
    - Increase respiration rate
- Increasing oxygen utilization by tissue
- Increasing erythropoietin (EPO) production

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ADAPTATIONS, CONT.

- If capable, bone marrow increases production to meet demands of anemia and compensates for decreased RBC survival to some degree.
- Anemia develops if:
  - RBC loss or destruction exceeds the maximum capacity of the bone marrow RBC production.
  - The bone marrow RBC production is impaired.

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ANEMIA DUE TO ACUTE HEMORRHAGE

- Rapidly developing, most often due to traumatic injury
- Clinical manifestations are related to degree of blood loss.
  - Loss of up to 20% of blood volume in a healthy person: no clinical symptoms at rest and tachycardia with mild exertion
  - 30-40% loss: circulatory collapse and shock
  - ≥50%: death

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ANEMIA DUE TO CHRONIC HEMORRHAGE

- Slowly developing
- Can show an equally severe drop in HGB, but threat of shock or death is not usually a concern
- Most common causes of chronic anemia
  - In men and non-menstruating females: **gastrointestinal bleed**
  - In menstruating females: **menstruation**

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LABORATORY INVESTIGATION

- Comprehensive assessment for anemia determination:
  - **Compete Blood Count (CBC)**
    - RBC count
    - HGB
    - HCT
    - RBC indices
    - WBC count
    - PLT count
  - **Reticulocyte count** to assess functionality of the bone marrow and evaluate RBC production and destruction or loss
  - **Microscopic review of blood smear** for morphological abnormalities

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CLASSIFYING ANEMIAS IN 6 EASY STEPS

Classifying the anemia based on routine lab values usually aids in narrowing down the cause(s).

1. HGB
2. HCT
3. MCV
4. MCHC
5. Reticulocyte count
6. Blood smear evaluation

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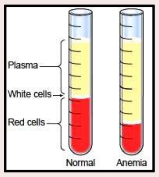
USUAL LABORATORY CRITERIA FOR ANEMIA

- **Decreased RBC count***
- **Decreased hemoglobin (HGB)**
- **Decreased hematocrit (HCT)**



Hematocrit (HCT) – packed cell volume

*Note: RBC count may be normal, but cells are so small that the patient is still anemic. Must look at other lab values to completely assess.

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RBC INDICES – FURTHER CLASSIFICATION

- Help classify the RBCs by morphology/appearance
  - Size and HGB content
- HGB, HCT, and RBC count used to calculate indices
- Indices
  - **Mean cell volume (MCV) – average size**
  - **Mean cell hemoglobin concentration (MCHC) – average concentration of HGB**
  - Mean cell hemoglobin (MCH) – average dry weight of HGB
  - Red cell distribution width (RDW) – variation in RBC size

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CLASSIFICATION OF ANEMIAS BY MORPHOLOGY

- Normocytic, normochromic
  - Normal MCV, normal MCHC
- Macrocytic, normochromic
  - Increased MCV, normal MCHC
- Microcytic, hypochromic
  - Decreased MCV, decreased MCHC

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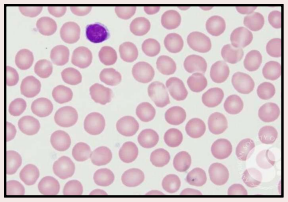
CAUSES OF NORMOCYTIC, NORMOCHROMIC ANEMIA



- **Leukemia** – infiltration with abnormal WBCs
- **Hypoproliferative bone marrow disorders** – decreased production
- **Anemia of chronic renal disease** – decreased erythropoietin (EPO)
- **Chronic hemolytic anemia** – mild-to-moderate, ongoing hemolysis

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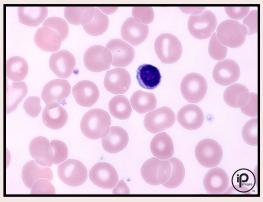
CAUSES OF MACROCYTIC, NORMOCHROMIC ANEMIA

- **Megaloblastic** – defective DNA synthesis
  - B_{12} or folate deficiencies
  - Pernicious anemia
- **Non-megaloblastic** – abnormal RBC membrane
  - Liver disease
  - Chronic alcohol use
- **Marked reticulocytosis** – acute hemolysis or blood loss



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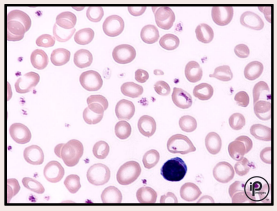
CAUSES OF MICROCYTIC, HYPOCHROMIC ANEMIA



- Diminished or defective hemoglobin synthesis
  - **Iron deficiency anemia** – lack of iron
  - **Chronic inflammation** – iron stuck in storage
  - **Lead poisoning** – heme ring synthesis disrupted
  - **Thalassemias** – decreased globin chain production
  - **Hemoglobinopathies** (e.g. Sickle cell anemia) – defective globin chain production

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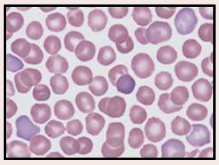
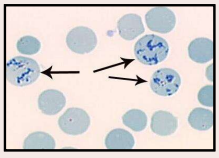
RETICULOCYTE COUNT – FURTHER CLASSIFICATION

- Immature RBCs that still contain residual RNA – "polychromasia"
- One of the most useful and cost-effective lab tests in monitoring anemia
- Helpful assessing marrow's ability to increase RBC production in response to anemia
- Expressed as % of total RBC count
  - Adult RR: ~0.5-2.5%
  - ↑ in acute hemolytic anemia
  - ↓ bone marrow failure



Polychromasia – Wright's stain



Residual RNA – Supravital stain

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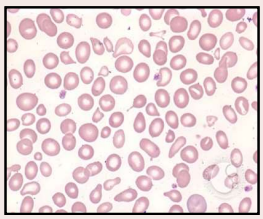
PERIPHERAL SMEAR EXAMINATION – FURTHER CLASSIFICATION

- Anisocytosis – variation in RBC size
- Poikilocytosis – variation in RBC shape
- Chromasia – RBC coloration
- RBC inclusions – cytoplasmic bodies
  - Iron
  - DNA
  - RNA
  - Pathogens
- Cell estimates & morphology:
  - WBC
  - PLT



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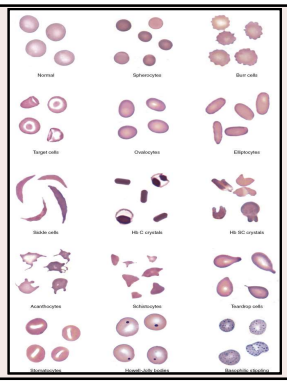
VARIOUS RBC MORPHOLOGIES



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FURTHER INVESTIGATION

- Additional tests
  - **B_{12} and folate levels**
  - **Iron studies**
  - **Hgb electrophoresis** – detection of abnormal hemoglobins
  - **Haptoglobin, lactate dehydrogenase (LDH), bilirubin** – indicators of RBC destruction/hemolysis
  - **Osmotic fragility** – RBC membrane integrity
  - **Erythropoietin levels** – hormone that controls marrow production of RBCs
  - **Bone marrow smear/biopsy** – marrow cellularity

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LET'S SOLVE A CASE!

- A 39-year-old woman was referred for evaluation of anemia. She had undergone extensive evaluation elsewhere as an outpatient, but results failed to yield an explanation. She was known to have multiple comorbidities and had a baseline HGB of ~10.5 g/dL (RR: 12-16g/dL). About 6 months before her referral, the patient began having recurrent episodes of severe anemia, with HGB values as low as 3.5 g/dL.

- She had become transfusion-dependent and had received ~30 units of pRBCs in the preceding 3 months. She denied any history of easy bruisability, menorrhagia, or overt bleeding from any site. She also denied any change in the appearance or color of her urine or feces, and she had no history of jaundice. There was no family history of anemia or any other hematologic disorder.

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CASE STUDY, CONT. #1

- The patient's medical history was remarkable for severe asthma, and she had a surgically placed central venous catheter for self-administration of IV corticosteroids at the earliest sign of an asthmatic exacerbation. Her other medications included bronchodilators, weekly erythropoietin injections, IV iron therapy, an antidepressant, and an anxiolytic.
- On the day of admission, the patient's vital signs were normal. Physical examination was unremarkable except for mild generalized pallor. A CBC revealed the following:

HGB, 4.9 g/dL (12.0-16 g/dL)
WBC count, 6.0 × 10^3/µL (3.5-10.5 × 10^3/µL)
HCT, 13.4% (35-45%)
PLT count, 203 × 10^3/µL (150-450 × 10^3/µL)
MCV, 94.4 fL (80-100 fL)

- Routine coagulation tests were normal. These results were obtained within 24 hours of her last transfusion.

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CASE STUDY, CONT. #2

1. Which ONE of the following is the LEAST LIKELY in the differential diagnosis of this patient's anemia?
   a. Acute hemolysis
   b. Bone marrow disorder
   c. Chronic blood loss
   d. Nutrient deficiency
   e. Renal failure

2. Which of the following would be the next BEST test to narrow the list of differential diagnoses?
   a. Blood smear review
   b. Bone marrow aspirate
   c. Erythropoietin level
   d. Iron studies
   e. Reticulocyte count

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CASE STUDY, CONT. #3

- The patient's reticulocyte count was **13.3%** (0.5-2.5%), revealing significant reticulocytosis.

3. At this time, which ONE of the following tests would be MOST helpful in further narrowing the differential diagnosis?
   a. Blood smear review
   b. Further coagulation testing
   c. Total and direct bilirubin, haptoglobin, LDH
   d. Tests for antibodies to RBCs

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CASE STUDY, CONT. #4

- Results were as follows:
  - **Haptoglobin, 32 mg/dL (30-200 mg/dL)**
  - **LDH, 205 U/L (122-222 U/L)**
  - **Total bilirubin, 0.4 mg/dL (0.1-1.0 mg/dL)**
  - **Direct bilirubin, 0.1 mg/dL (0.0-0.3 mg/dL)**
- A peripheral blood smear evaluation was then performed and showed **no RBC abnormalities.**
- Fecal occult blood testing was **negative.**

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CASE STUDY, CONT. #5

- On the first day of her evaluation, prior to being referred, the patient's HGB was 11.1 g/dL. By Day 2 of her outpatient work-up, it had decreased to 5.6 g/ dL, and she received 4 units of packed RBCs. Despite the transfusions, her HGB decreased further within 24 hours to 4.9 g/dL, at which point she was referred for further evaluation, where she was admitted and received 3 more units of packed RBCs. During this time, she was asymptomatic, and her vital signs remained stable.

4. At this point, which of the following would be the BEST step in the management of this patient?
   a. CT scan for abdominal bleeding
   b. Colonoscopy
   c. Transfer to ICU
   d. Upper GI endoscopy

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CASE STUDY, CONT. #6

- **Non-contrast CT of the patient's abdomen and pelvis revealed normal findings.**
- **What else could it be??**

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IN CONCLUSION

- "Anemia" is far from a final diagnosis.
- To prevent unnecessary testing, it is important to utilize lab testing and results effectively.
- Using a standardized approach (here, MCV, MCHC, and reticulocyte count), the vast number of causes of anemia can be easily narrowed down.
- Once one of several diagnoses are deemed likely, more specialized testing can be used to arrive at a final diagnosis.
- Despite the absolute necessity of lab testing, sometimes factors contributing to the diagnosis cannot be assessed in the lab.

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- Palmer, S. (2010). 39-Year-Old Woman With an Obscure Case of Anemia. *Mayo Clinic Proceedings*, 85(1): e1-e4. https://doi:10.4065/mcp.2008.0721

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THANK YOU!
ANY QUESTIONS?

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