ANEMIA
Lois E. Brenneman, MSN, ANP, FNP, C

GENERAL PRINCIPLES

DEFINITION: Definition: reduction in Hgb or Hct (Hct is volume of RBC as %)

HEMATOPOIETIC PHYSIOLOGY

Conditions Needed for Blood Formation
- Intact marrow microenvironment
- Functional erythropoietin mechanism
- Uncompromised DNA synthesis
- Hemoglobin (Hgb) synthesis unimpaired by lack of iron or globin production

Life Cycle of Red Blood Cell
- 120 days with 0.8% being replaced every day
- Reticulocytes mature in about 24 hours in circulation
- 85% of aged RBCs engulfed by macrocyte-macrophage system
- 15% undergo hemolysis in circulation

Hemoglobin (main component of RBC)
- Vehicle for O2 and CO2 transport: combines readily with oxygen
- Red color from combination of heme (iron) and porphyrins (red pigment)
- Globulin, amino acids
- Normal adult Hg (Hgb A) comprised of alpha and beta polypeptide chains
- Hemoglobinopathies with variation of alpha and beta chains -> anemias
  - Sickle cell
  - Thalassemia,
  - Fetal Hg present by 8th week of gestation
    - Predominates in fetus
    - 70% by birth; trace by 6-12 months

ETIOLOGY OF ANEMIA

1. Decreased RBC production: deficiency of hematonic agents; bone marrow failure
2. Increase RBC destruction: hemolysis, hemorrhage

ERYTHROPOIESIS

Top (L->R): rubriblast, prorubricyte, rubricyte
Bottom: metarubricyte, diffusely basophilic erythrocyte, erythrocyte

© 2002 Lois E. Brenneman, MSN, CS, ANP, FNP
all rights reserved  —  www.npceu.com
PATHOPHYSIOLOGY OF ANEMIA

ANEMIAS SECONDARY TO REDUCED RED CELL PRODUCTION

HGB SYNTHESIS:
• Fe deficiency
• Thalassemia
• Anemia of chronic disease

DNA SYNTHESIS (Megaloblastic anemia):
• B12 deficiency
• Folate deficiency anemia

STEM CELL:
• Aplastic anemia
• Myeloproliferative leukemia

BONE CELL INFILTRATION
• Carcinoma
• Lymphoma

PURE RED CELL APLASIA

ANEMIAS SECONDARY TO PREMATURE DESTRUCTION

HEMOLYSIS INTRINSIC
• Membrane: hereditary spherocytosis, elliptocytosis
• Hgb: sickle cell, unstable hemoglobin
• Glycolysis: pyruvate kinase deficiency, etc.
• Oxygenation: G6PD deficiency

HEMOLYSIS EXTRINSIC
• Immune: warm antibody, cold antibody
• Microangiopathic:
  Thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, mechanical cardiac valve, paravalvular leak
• Infection: Clostridia
• Hypersplenism

BLOOD LOSS
• Acute blood loss
• Chronic blood loss

Aplastic anemia: thrombocytopenia responsible for widespread purpura and ecchymoses

Hepatosplenomegaly and characteristic facies of beta-thalassemia

Pallor with jaundice characteristic of pernicious anemia - premature greying and blue eyes is common

© 2002 Lois E. Brenneman, MSN, CS, ANP, FNP
all rights reserved — www.npceu.com 2
CLINICAL PRESENTATION

DIAGNOSIS:

HISTORY

- Family/ethnic history: thalassemia, sickle cell, splenectomy, cholelithiasis at early age
- Drug and toxic exposure:
  - chloramphenicol, methyldopa, quinidine, benzene, alkylating agents
- External blood loss: GI, GU (melena, hematochezia, hematuria)
- Dietary habits: poor habits and ETOH intake -> folic acid
- Rapidity of onset:
  - Gradual suggests BM failure or chronic blood loss
  - Sudden: hemolysis or acute hemorrhage
- History of infection: sepsis, AIDS, malaria

PHYSICAL EXAM

- General appearance, evaluation nutritional status
- Vital signs: hypotension, tachycardia (acute blood loss)
- Skin
  - Pallor: conjunctiva, lips, oral mucosa, nail beds, palmar creases
  - Jaundice (hemolysis)
  - Petechiae, purpura (thrombocytopenia)
- Mouth: glossitis (pernicious anemia, Fe deficiency anemia)
- Heart: flow murmurs, prosthetic valves (inc RBC destruct)
- Abdomen: splenomegaly (hemolysis, neoplasm, infiltrative disorders)
- Rectum: stool or occult blood
- Lymph noes: infiltrative lesions, infections

CLINICAL CONSIDERATIONS

Two types of erythrocyte disorders
- Anemia - deficit of red cells
- Polycythemia - excess of red cells

Relative anemia and relative polycythemia
- Normal total red cell mass with disturbances in regulation of plasma volume
- Pregnancy "dilutional anemia" - plasma volume is 43% greater in pregnancy

Absolute anemia: absolute decrease in numbers of RBC
CLINICAL PARAMETERS RELEVANT TO ANEMIA

HGB AND HCT: guide to severity of anemia
- Adult male: (norm: 13.6-17.7 g/dl; anemia: hct < 41%; hgb < 13.5 g/dL)
- Adult female: (norm: 12.0-15.0 g/dl; anemia: hct < 37%; hgb < 12g/dL)

RBC COUNT
- Norm male: 4.3-5.9 million/uL
- Norm female: 3.5-5.5 million/uL

RETICULOCYTE COUNT (young RBCs) normal: 0.5% to 1.5%
- Performed before any therapeutic maneuvers
- Less than 1%: inadequate BM productions
- Greater than 4% RBC destruction or acute blood loss
  must consider in light of degree of anemia and shift of reticulocytes in peripheral blood
- Further lab studies determined by reticulocyte count

RBC INDICES

MCH: index of amount of Hgb contained in RBC (norm: 27-31)
  Measure of hypochromia, hyperchromia, normochromic

MCV: measure of size of RBC (norm: 80-100); e.g. microcytic, macrocytic, normocytic

Normocytic
  Reticulocyte count: to distinguish
    - Excess destruction (high reticulocyte)
    - Decreased production (low reticulocyte)

Bone marrow: to distinguish
  - Marrow hypoplasia (toxic drugs, radiation)
  - RBC aplasia
    - marrow infiltration (myeloma, lymphoma, leukemia)
    - myelofibrosis; renal insufficiency

Microcytic anemia
  - Fe deficiency is most common cause
  - Thalassemia, lead poisoning
  - Anemia of chronic disease (ACD), sideroblastic anemia
  - Peripheral smear and RBC count to distinguish

Iron-deficiency vs thalassemia minor
  - Thalassemia minor: high RBC count
  - Fe deficiency: basophilic stippling

Serum ferritin - measure of iron stores
  - Low ferritin: establishes diagnosis Fe-deficiency
  - Normal or elevated ferritin:
    - R/O thalassemia (hgb electrophoresis)
    - Sideroblastic anemia
    - Anemia of chronic disease
      - Low Fe, low TIBC, increased ferritin, decreased reticulocytes
Macrocytic anemia:
- Elevated reticulocyte count (large diameter) r/o elevated MCV
- If elevated reticulocyte, do hemolytic studies
  Haptoglobin, LDH, indirect bilirubin
- If hemolysis is confirmed, determine cause eg Coombs
- Normal reticulocyte with macrocytic anemia: B12 or folate anemia
  RBC folate, serum B12, serum folate
- Bone marrow
  - Megaloblastic suggest B12/folate
  - Abnormal erythropoiesis/WBC - myelodysplastic

MCHC: measure of concentration of Hgb in gms/100 mg (norm 32-36)
- Not used much clinically

RDW: mathematical coefficient of width variation in RBC size measures anisocytosis
- As RDW increases there is greater variation in cell size
- Norm: 11.5-14.5
  - Normal RDW and
  - With elevated MCV: aplastic anemia, preleukemia
  - With normal MCV:
    - Normal, anemia of chronic disease (ACD)
    - Acute blood loss/hemolysis
    - Chronic lymphocytic leukemia (CLL)
    - Chronic myelocytic leukemia (CML)
    - Nonanemic enzymopathy or hemoglobinopathy
  - With decreased MCV: ACD, heterozygous thalassemia

- Elevated RDW
  - With elevated MCV:
    Vitamin B12 deficiency, folate deficiency, immune hemolytic anemia, cold agglutinins, chronic lymphocytic leukemia with high count, liver disease
  - With normal MCV:
    Early Fe-deficiency, early B12 deficiency, early folate deficiency, anemic hemoglobinopathy
  - With decreased MCV:
    Fe deficiency, RBC fragmentation, H.H. disease, thalassemia intermedia
RBC MORPHOLOGY

Anisocytosis - variation in size

Normal RBC: diameter equal to that of nucleus of mature lymphocyte
Macrocyte (macrocytosis): large RBC (high MCV)
   indicates megaloblastic anemia, liver disease or refractor anemia
Microcyte (microcytosis): small RBC (low MCV)
   iron deficiency anemia, hemoglobinopathies, sideroblastic anemias

NOTE: microcytes and macrocytes may coexist resulting in a normal MCV (but abnormal RDW)
resulting in marked anisocytosis (seen in hemolytic anemias)

Poikilocytosis - variation in shape - poikilocytes

- Spherocytes: hereditary spherocytosis, immune or other hemolytic states
- Tear drop cells: myeloproliferative diseases, pernicious anemia, thalassemia
- Helmet cells: microangiopathic hemolysis, severe iron deficiency
- Sickle cell: (HbSS)
- Target cells:
  - erythrocytes with distinct peripheral and central zone of hgb and annular area of pallor
  - aka "Mexican hat cells"
  - Anemias:
    Hemoglobinopathies, iron deficiencies, liver disease, thalassemias, hemoglobin C, hereditary stomatocytosis
- Nucleated RBCs: extramedullary hematopoiesis, hypoxia, hemolysis

© 2002 Lois E. Brenneman, MSN, CS, ANP, FNP
all rights reserved - www.npceu.com
Color

**Hypochromasia - pale** - cells lack hgb
Examples: Fe deficiency, sideroblastic anemia
Individual blood cell is pale in appearance due to too little hgb

**Polychromasia - bluish coloring** - sign of an immature cell (reticulocyte)
Cells stain light to moderate blue
Cells are larger than normal erythrocytes and correspond to reticulocytes

**Hyperchromasia - darkly stained without normal pale center**
Examples: megaloblastic anemia, spherocytosis
Cells appear to contain too much hgb

**Reticulocytes: young erythrocytes** recently released into blood
Requires supravital (stain while alive) staining with brilliant cresyl blue which reveals chromatin remnants of nucleus

**Basophilic stippling:** lead poisoning, thalassemia, hemolytic states

NOTE: do not confuse w basophilic stippling (heavy metal poisoning) where basophilic granules appear in cytoplasm of RBC. Due to a vascular degeneration of polychromatic substance of cytoplasm. Visualized w Romanowsky-type staining vs supravital staining (reticulocytes). Distinguish between fine physiologic and coarse pathologic stippling
Other Erythrocyte Abnormalities

**Basophilic stippling:** lead poisoning, thalassemia, hemolytic states

**Heinz bodies:** (denatured Hb: requires supravital stain)
- unstable hemoglobinopathies, some hemolytic anemias

**Howell-jolly bodies** (nuclear fragments): hemolytic, megaloblastic anemias, splenectomy
**Cabot ring** (nuclear remnants): megaloblastic anemias
**Pappenheimer bodies:** post splenectomy, hemolytic sideroblastic and megaloblastic anemias
**Rouleaux formation:** multiple myeloma, Waldenström’s macroglobulinemia
**Presence of parasites:** Plasmodium (malaria), Babesia (babesiosis)

**Nucleated RBCs:** extramedullary hematopoiesis, hypoxia, hemolysis
**Target cells:** see shape
**Tear drop:** myeloproliferative disease, pernicious anemia, thalassemia
**Acanthocytes or spur cells:** spur-cell anemia

**Spherocytes:** (special form of microcytes approx 6 um in diameter and spheroid shaped)
- hereditary spherocytosis, immunohemolytic disease

**Schistocytes:** greatly changed, shrunk and poorly stained
- Traumatic and microangiopathic hemolysis
- Hemolytic anemias and pernicious anemia

**Burr cells or echinocytes or acanthocytes:**
- Thorn-like processes
- May be artefacts in stained preps
  - best seen in fresh wet mount with phase contrast microscopy
- Normal cells easily converted in drying process
- Uremia
  - Congenital acanthocytoses (rare disease), advanced liver diseases
  - Sometimes in atrophy of spleen and possibly in various hemolytic processes

**Bite cells:** anemia associated w Heinz body formation
**Ovalocytes:** oval shaped erythrocytes of normal size (congenital hemolytic anemias)
**Stomatocytes:** mouth shaped central slit (stoma = mouth)
- alcoholism, chronic liver disease, rarely in congenital hemolytic anemias
**Elliptocytes:** elliptical form (seen most frequency in sickle cell)
MEASURES OF IRON

**Serum iron:** norm - 50-150
- Fe necessary for heme and other enzymes
- Majority of total Fe is present in hgb (70-95%)

**Serum ferritin:** form in which iron is stored in tissues
- Aside from RBC, major location of Fe in body is in storage pool.
- Fe deposited as either ferritin or hemosiderin and located largely in macrophages
- Norm: 30-250
  - range for storage of iron is wide
  - 25% of US women have no Fe stores

**Total Iron Binding Capacity (TIBC)**
- Normal 250-460 ug/dl
- Elevated: Fe deficiency anemia, pregnancy, polycythemia, wt loss
- Decreased:
  - Anemia of chronic disease, hemochromatosis, chronic liver disease, hemolytic anemias, malnutrition (protein depletion)

CLINICAL EFFECTS OF ANEMIA

- Pathophysiology
  - **Reduction in oxygen carrying capacity**
  - Tissue hypoxia

Compensatory mechanisms to restore tissue oxygenation
- **Increased O2 extraction**
  - Increased pulmonary and cardiac function -> increases O2 consumption and increase in O2 extraction to protect tissues

- **Selective tissue perfusion** (short term compensation) - shunting to vital organs
- **Increased erythropoietic activity** (long term compensation)

Common symptoms

Vasoconstriction, **pallor, tachypnea, dyspnea, tachycardia**, angina pectoris, high-output failure, intermittent claudication, night cramps in muscles, headache, **light-headedness**, tinnitus, roaring in ears, faintness, GI and GU symptoms
LABORATORY DIAGNOSIS OF ANEMIA

NORMAL VALUES

- **Hgb** (g/100 ml): men 14-16, women 12-15, newborn 14-20, infant 11-14, toddler 11.5-15
- **HCT** (%): men 40-50, women 37-47, Infants 33-42, toddlers 33-45
- **RBC** count (millions per mm3)
  - Male 4.6-6
  - Female 4.0-5.2
  - Newborn 4.0-6.6, infant 2.7-4.9, toddler 3.9-4.5

BLOOD COMPONENTS

HEMATOCRIT

WBC: 6-9,000/mm3
Platelets 200-

RBC: 4-5 mil/mm3

Plasma 400,000/mm3

Buffy Coat

**MCV**
- Microcytic: below 82 (60-80)
- Normocytic 83-100
- Macrocytic: greater than 100 (100-160)

* Adult levels by age 17
  < 2 yrs 77; 2-4 yrs 79; 5-7 yrs 81, 8-11 yrs 83

**MCHC**
- Hypochromic: below 32%
- Normochromic: 32-36%
- Hyperchromic: above 36%

RBC INDICES

**MCV:** Mean corpuscular volume (reflects size of cell)
**MCH:** Mean corpuscular hemoglobin (measures average wt of RBC Hg)
**MCHC:** Mean corpuscular hemoglobin concentration (measures avg concentration of Hg in RBC)
**RDW:** Red blood cell distribution width (degree of variation in RBC width)

**Ferritin:** major iron storage protein
  - Good indicator of iron stores in body
  - Decreased with fe-deficiency anemia

**Total Iron Binding Capacity (TIBC):**
  - Measurement of all proteins available for binding mobile iron
  - Increased in 70% of patients with iron deficiency anemia

**Hemoglobin electrophoresis:** identifies abnormal forms of hemoglobin (hemoglobinopathies)
**B12 and Folate levels:** differentiates various macrocytic anemias
CLASSES OF ANEMIAS

HEMOGLOBINOPATHIES
- Sickle cell disease, sickle cell trait
- Thalassemia major, thalassemia minor
- Hemoglobin C disease, hemoglobin H disease

HEMOLYTIC ANEMIAS
- Membrane defects
  - Hereditary spherocytosis
  - Hereditary elliptocytosis, paroxysmal nocturnal hemoglobinuria
- Glycolytic defects
  - Pyruvate kinase deficiency
  - Severe hypophosphatemia
- Oxygenation vulnerability:
  - G6PD deficiency
  - Methemoglobinemia
- Hemoglobinopathies
  - Sickle syndromes
  - Unstable hemoglobins, methemoglobinemas
- Extrinsic
  - Immune, autoimmune
    - Lymphoproliferative disease, drug toxicity
- Microangiopathic
  - Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
  - Disseminated intravascular coagulation (DIC)
  - Valve hemolysis, metastatic adenocarcinoma, vasculitis
- Infection: Plasmodium, Clostridium, Borrelia
- Hypersplenism
- Burns

MICROCYTIC ANEMIAS
- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease

MACROCYTIC
- Megaloblastic
  - B12
  - Folate deficiency
- Non-megaloblastic
  - Myelodysplasia, chemotherapy
  - Liver disease
  - Increased reticulocytosis
  - Myxedema

NORMOCYTIC: MANY CAUSES
- Aplastic anemia
- Others
COMMON ANEMIAS

IRON DEFICIENCY ANEMIA

ESSENTIALS OF DIAGNOSIS:

- Both pathognomonic: absent bone marrow Fe stores or serum ferritin < 12 uG/L
- Nearly always caused by bleeding in adults
- Responds to iron therapy

GENERAL CONSIDERATIONS

- Most common cause of anemia worldwide
- Usually mild but can be moderate or severe
- **Diagnosis is important so underlying cause can be treated** (eg GI blood loss)
- Aside from RBC, major location of Fe in body is in storage pool as ferritin or hemosiderin.
  - Fe deposited as either ferritin or hemosiderin and located largely in macrophages
  - Range for storage of iron is wide (0.5-2.0) and 25% of US women have none
- Average diet 10-15 mg Fe/day: 10% is absorbed: stomach, duodenum and upper jejunum
- Dietary intake as heme is efficiently absorbed (10-20%)
- Non-heme Fe is less absorbed (1-5%) - interference of PO4, tannins, other food components
- Small amounts (1 mg/day) lost thru exfoliation (skin, mucosal cells)
- **Menstrual blood** loss in women is major role in Fe metabolism
  - Average monthly blood loss is 50mL or about 0.7 mg/d
  - Loss may be 5 times the average flow
  - Women with **menorrhagia** of this degree almost always become Fe-deficient
- **Pregnancy** may upset Fe balance
  - Requirements increase to 2-5 mg/day during pregnancy and lactation
  - **Normal dietary Fe cannot supply** these requirements
  - Supplemental Fe needed during pregnancy and lactation
  - **Repeated pregnancy** is common cause of Fe deficiency
- Fe deficiency due to diet possible but rare
- Decreased Fe absorption can cause deficiency and usually due to gastric surgery
- **Blood loss** is most important cause of Fe deficiency esp GI
- Look for *GI source* unless another causes is ID
- Other sources: menorrhagia, uterine bleeding, repeated blood donation, abnormal valve function

SYMPTOMS

- Only symptoms are those of anemia (**fatigability, tachycardia, palpitations, tachypnea**)
- Severe causes progressive skin/mucosal changes (**smooth tongue, brittle nails, cheilosis**)
- Dysphagia with severe from esophageal webs (Lummer-Vinson syndrome)
- May develop **pica** for items that may not contain Fe (ice-cubes, etc.)
- ‘Spoon nails’ is common - koilonychia

**Koilonychia**: concave, deformed nails with Fe-deficiency anemia
LABORATORY FINDINGS

- Develops slowly and in stages
- Depletion of iron stores occurs first then depletion of FE in RBC
  
  **Anemia and no change in RBC size**
  
  Serum ferritin becomes abnormally low (highly reliable indicator)
  TIBC rises

- **MCV falls** - blood smears show **hypochromic microcytic anemia**
- **Anisocytosis** (size) followed by **poikilocytosis** (shape) develops
- Severe Fe deficiency:
  
  Bizarre peripheral smear with severely hypochromia cells, target cells, hypochromic
  penicillin-shaped cells and occasionally nucleated RBCs

- Elevated platelets in severe cases (normal in mild)

TREATMENT:

- Fe deficient state or response to Fe replacement confirms diagnosis
- Rarely life-threatening therefore **ID cause is important** (GI loss etc)
- **Cannot be treated with dietary Fe** - requires medicinal Fe

**ORAL FE:** Ferrous SO₄ is best
- Compliance is enhanced if introduced slowly; optimal is tid on empty stomach
- Dosing: Ferrous So₄ 325 tid
- Provides 180 mg Fe daily of which 10-20 mg is absorbed
- Even greater absorption in severe deficiency
- Take w food if not tolerate empty stomach

- HCT halfway towards normal in 3 weeks is appropriate response
- Should return to normal in 2 months
- **Treat for 3-6 months after restoration of normal to replenish Fe stores**
- Failure of treatment is usually due to non-compliance
- Other reasons for failure: incorrect dx, GI loss which exceeds rate of new erythropoiesis

**PARENTERAL FE**
- Indications: intolerance to oral Fe (poor absorption)
- GI disease (IBD)
- Continued uncorrectable blood loss
  
  **Severe even fatal hypersensitivity reaction :**
  
  Use parenteral Fe only with clinically documented cases of Fe-deficiency after reasonable attempt made to use oral therapy
MACROCYTIC ANEMIAS

B12 DEFICIENCY - Pernicious anemia

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia
  - Macro-ovalocytes and hypersegmented neutrophils on smear
  - Serum B12 less than 100 ug/ml

ETIOLOGY AND PATHOGENESIS

- After being ingested B12 bound to intrinsic factor - protein secreted by gastric parietal cells
- B12 present in all foods of animal origin
  - Dietary B12 rare and seen only in vegans *
  - * strict vegetarians who eat no animal products including dairy, eggs
- Abdominal surgery may lead to B12 deficiency
  - Gastrectomy: eliminate site of intrinsic factor production
  - Blind loop cause bacterial overgrowth in lumen thus competition of B12
  - Surgery resection of ilium will eliminate site of B12 absorption
- Rare causes B12 deficiency: fish tapeworm, pancreatic insufficiency, Crohn's disease

- Pernicious anemia: classic anemia in this classification
  - Lack of intrinsic factor: is the fundamental defect causing PA
  - B12 not absorbed -> vitamin B12 deficiency *
  - Hereditary autoimmune disorder historically
    - Traditionally seen in pts of Scandinavian or northern European ancestry
    - Now seen in young black and Hispanic women
  - Rarely manifests before age 35
  - Additional clinical findings
    - Atrophic gastritis invariably present -> histamine-fast achlorhydria
    - Autoimmune diseases (incl IgA deficiency)
    - Polyglandular endocrine insufficiency
    - Increased risk gastric carcinoma from atrophic gastritis

* Dietary deficiency e.g. vegans do NOT require IM administration (PO is sufficient) vs pernicious anemia wherein the lack of intrinsic factor requires IM administration

- Pathophysiology of macrocytic anemias
  - Anemia resulting from deficiency of B12 or folic acid
  - Caused by disruption of DNA synthesis of blast cells in bone marrow
  - Disruption produces
    - Megaloblasts: large abnormal bone marrow cells
    - Macrocytic RBCs in peripheral blood
    - Granulocytes hypersegmented
  - Decreased: RBC, WBC, platelets
  - Megaloblastic dyspepsia:
    - Results from disordered nucleic acid metabolism
    - Abnormal production and maturation of RBCs WBC and platelet systems
    - Evidence that PA develops due to genetically determined autoimmune disease
    - Manifested by serum/gastric juice antibodies vs intrinsic factor and parietal cells
- **Neurologic lesions occur with pernicious anemia** (not with folic acid deficiency anemia)
  - Biochemistry basis not known
  - Peripheral nerve degeneration
  - Degeneration of posterior columns of spinal cord
  - Possibly etiology
    - Abnormal fatty acid metabolism in peripheral nerves
    - Degeneration of white matter of spinal cord

**CLINICAL MANIFESTATIONS:**

- Hallmark is **megaloblastic anemia** - severe w HCT as low as 10-15%
- Megaloblastic state -> changes in mucosal cells -> **glossitis** and vague **GI complaints** (anorexia, diarrhea)
- **Achlorhydria**
- **Complex neurologic syndrome**
  - peripheral nerves affected first -> pt c/o of paraphasias
  - posterior columns next affected -> difficulty in balance
  - more advanced stages: cerebral function affected
  - sometimes dementia/ neuropsychiatric changes may precede hematologic changes

- **Physical Exam**
  - Pallor, possibly mildly icteric
  - **Neuro** deficits: **decreased vibration and position sense**

- B12 is non specific:
  - **Megaloblastic anemia**
  - Nonspecific **glossitis**
  - Elevated LDH
  - Weight loss
  - **Neurologic abnormalities**
  - **Decreased serum B12**
  - Methylmalonic acidemia
  - **Response to B12 therapy** vs folic acid (no response)

- Neurologic manifestations B12
  - **Symmetric paresthesias of feet and hands**
  - **Vibratory** sense and proprioception disturbances
  - Progresses to **spastic ataxia**
    - Degenerative changes in dorsal and lateral columns of spinal cord
  - **Cerebral signs**
    - Irritability, somnolence, memory impairment/perversion of taste, smell, vision
    - Psychologic and mental derangement a.k.a. "**megaloblastic madness**"

- Normal neutrophils
- Blue eyes and premature greying and northern European descent are associated with pernicious anemia

© 2002  Lois E. Brenneman, MSN, CS, ANP, FNP
all rights reserved  —  www.npceu.com
LABORATORY FEATURES:

- **Megaloblastic anemia** of variable severity which may be severe
- MCV usually strikingly elevated **110-140**
- Occasional normal MCV with folate deficiency due to coexistent thalassemia or Fe deficiency
- Evaluate pt with normal MCV and absence of anemia if suggestive neurologic symptoms

- Peripheral blood smear strikingly abnormal
  - Anisocytosis and poikilocytosis
  - Macro-ovalocyte is characteristic
  - Numerous other abnormal shapes
- Frequently mistaken for hemolytic due to striking abnormal RBC

- **Neutrophils are hypersegmented**: mean lobe count > 4 or finding 6-lobed cells
- **Reticulocyte count is reduced**
  - WBC and platelets decreased in severe cases and pancytopenia present
  - B12 affects all hematopoietic cells
- **Hypersegmented neutrophils** is characteristic
  - Bone marrow is characteristically abnormal
    - Marked erythroid hyperplasia
    - Defective RBC production
    - Ineffective erythropoiesis
    - Characteristic megaloblastic erythroid changes
    - Abnormally large cell size
    - Asynchronous maturation: nucleus/cytoplasm *
    - Myeloid series, giant metamyelocytes

* Cytoplasmic maturation continues while impaired DNA synthesis causes nuclear development

- Other laboratory abnormalities
  - Elevated serum LDH
  - Modest increase in indirect bilirubin
    - Both due to intramedullary destruction of developing abnormal erythroid cells
  - Abnormally low B12 serum level: key to diagnosis
    - Norm: 150-350 pg/ml; B12 def: < 100

- **Schillings test** used to document the decreased absorption of oral B12
  - Large IM dose B12 to saturate plasma transport proteins
  - Radiolabeled B12 given orally
  - 24 hr urine collection determines how much B12 absorbed and excreted
  - Normally less than 7% of administered dose is present in urine
  - With impaired absorption less than 3% will be present in urine
  - **Second stage**: administer radiolabeled B12 with intrinsic factor
    - Should correct normally low absorption where problem is pernicious anemia
  - Treatment of other causes of B12 deficiency will reverse abnormal 2nd stage of test
    - Antibiotics for bacterial overgrowth
    - Pancreatic enzymes for pancreatic def
    - Antibiotics for tapeworm

Note: where full-blown megaloblastic state causes abnormalities in intestinal epithelium -> generalized malabsorption. Here second stage will remain abnormal until intestinal mucosal defect is corrected by B12 replacement (2 months).
TREATMENT

- **Parenteral B12**: 100 ug per dose
  - Daily x 1 week; Weekly x 1 month
  - Monthly for life
- Lifelong disorder - if d/c treatment -> pernicious anemia will recur
- **Oral cobalamin** in high doses (1000 ug/d)
  - Can replace in some cases
  - Must be continuous and daily
- Patients respond immediately - improvement in well-being
- Hypokalemia may complicate first several days of therapy esp if anemia is severe
- Brisk reticulocytosis in 5-7 days
- Normal hematologic picture in 2 months
- **CNS s/s reversible if short duration** (< 6 mo) otherwise may be permanent

FOLIC ACID DEFICIENCY ANEMIA

ESSENTIALS OF DIAGNOSIS

- Macrocytic anemia
- Macro-ovalocytes and hypersegmented neutrophils
- Normal serum B12 levels
- Reduced folate levels in RBC or serum

PATHOPHYSIOLOGY

- **Folic acid** is common term for pteroylmonoglutamic acid
- Present in most **fruits and vegetables** - esp citrus and green leafy vegetables
- Daily requirement: 50-100 ug/d usually met in diet
- Total body stores approx 5000 ug (enough for 2-3 months)
- **Inadequate dietary intake** most common cause of deficiency
- Candidates
  - **Alcoholics**, elderly who do **not eat fresh fruits and vegetables**
  - Anorectic patients, persons who overcook food
  - **Reduced folate absorption** rare absorbed via entire GI tract
- Certain **drugs** may interfere: **phenytoin, Bactrim, sulfasalazine**
- Increased need (5-10X normal): require 1 mg/d supplements
- **Pregnancy**, hemolytic anemia, exfoliative skin disease

CLINICAL FINDINGS

**Signs and Symptoms**
- similar to B12 deficiency
- **Megaloblastic anemia**, megaloblastic changes in mucosa
- **None of the neurologic abnormalities**

**Laboratory Findings**
- ID to B12 deficiency, however B12 is normal
- Folic acid is low (less than 3 ug/ml)
- RBC folate more reliable:
  - Replaced serum folate as appropriate test (level less than 150 ug is dx)
TREATMENT

- Treat with **folic acid 1 mg/d PO**
- Response is **rapid improvement** in sense of well being
- **Reticulocytosis in 5-7 days**; total correction within 2 months
- **B12 deficiency:**
  - Large doses of folate may produce hematologic improvement but will not prevent progressive neurologic damage

SICKLE CELL ANEMIA

ESSENTIALS OF DIAGNOSIS

- Irreversibly **sickled cells** on peripheral blood smear
- Positive family history and lifelong history of hemolytic anemia
- Recurrent painful episodes
- **Hgb S** is the major hgb on electrophoresis

GENERAL CONSIDERATIONS

- **Autosomal recessive disorder** - single gene (valine substitutes for glutamine on B chain)
- **Hemolytic anemia with severe clinical consequences**
  - **Hgb S** forms polymers in the deoxy form which damage RBC membrane
    - Polymer formation and early membrane damage are reversible
    - Repeated sickling results in irreversible damage and **sickle configuration of RBC**
  - Rate of sickling
    - Concentration of hgb S in RBC
    - RBC dehydration renders cell very vulnerable
    - Factors which increase: **acidosis, hypoxemia** (systemic or local)
    - Influenced by other hgb in cell:
      - HgbF cannot participate in polymer formation thus reduces sickling
  - Prenatal diagnosis is available; **genetic counseling** available

CLINICAL SIGNS AND SYMPTOMS

- Carried in **8% of American blacks**; 1 in 400 births of American blacks produce disease
- Onset during first year of life when Hgb F falls
- Chronic **hemolytic anemia**: jaundice, gallstones, splenomegaly, poorly healing tibial ulcers
- Chronic anemia may be **life threatening** (hemolytic or aplastic crisis)
- **Spleen** may actually sequester sickle cells in childhood before it infarcts predisposing to crisis
- Coexisting abnormalities can exist: Hgb S-C disease, G6PD deficiencies
- Acute painful episodes due to **vaso-occlusion**
  - Etiology: Spontaneous or induced (infection, dehydration, hypoxia)
  - Clusters of **sickled cells occlude microvasculature of organs**
  - Last hours to days
  - Sites: **bones** (esp long bone and back) and chest
  - Episodes not associated with increased hemolysis
- **Organ dysfunction** occurs with repeated episodes esp heart and liver
  - **Ischemic necrosis**: bone predisposed to **osteomyelitis**
  - **Renal tubular** concentrating deficits and gross hematuria (more common w trait)
  - **Retinopathy** similar to diabetic retinopathy
- Delayed puberty
- Increased susceptibility to infection (hyposplenism and defects in complement pathways)
- Patients appear chronically ill and jaundice
- Hepatomegaly but spleen is not palpable in adults
- Heart enlarged with hyperdynamic precordium and systolic murmur
- Non-healing tibial ulcers; retinopathy
- Develops into chronic multisystem disease with death from organ failure
- Life expectancy 40-50 with supportive care

LABORATORY FINDINGS

- **Chronic hemolytic anemia:** HCT 20-30%
- Peripheral smear shows 5-50% **sickled cells**
- **Reticulocytoses** (10-25%), nucleated RBCs
- Hallmarks of **hyposplenism:** Howell-Jolly bodies and target cells
- WBC elevated: 12,000-15,000/uL; thrombocytosis
- Elevated indirect **bilirubin**
- Testing: screening tests with **hemoglobin electrophoresis** for confirmation
  - Homozygous disease: no Hgb A is present
  - Increased Hgb F (high Hgb F associated with more benign course)

TREATMENT

- No specific treatment available
- Folic acid supplementation; **transfusions** for aplastic or hemolytic crisis
- Pneumococcal vaccination
- Treat precipitating factors with crisis: hydration, oxygenation
- Exchange transfusion for **acute vaso-occlusive crisis:** intractable pain, priapism and CVA
- Cytotoxic agents (hydroxyurea) increases hgb F levels
- **Hydroxyurea** (500-750 mg/d) reduces painful crisis
  - Indicated for quality-of-life issues with intractable pain
  - Long-term safety not established; concerns re: secondary malignancy
- Allogenic bone marrow transplantation under investigation

SICKLE CELl TRAIT

- **Heterozygous genotype** (AS)
- Clinically normal; acute painful episodes only under extreme conditions
  - Vigorous exercise under high altitude
  - Unpressurized aircraft
- Hematologically normal: no anemia or sickle cells on smear
- Predisposed to renal tubular function defect: dilute urine and gross hematuria
- Screening test will be positive; electrophoresis reveals approximately 40% hgb S
- No treatment indicated; genetic counseling encouraged
SICKLE THALASSEMIA

- Homozygous sickle cell anemia and alpha thalassemia
  - Milder form of hemolysis
  - Slower sickling rate results from reduced RBC hgb concentration (MCHC)
- Heterozygous sickle cell and heterozygous beta thalassemia
  - Clinically affected with sickle cell syndrome; very similar to homozygous SS
  - Less severe vaso-occlusive crisis; spleen usually not infarcted
  - MCV low vs normal MCV with SS
  - Electrophoresis: no Hgb A but increase Hgb A2 (not present in SS)
- Sickle B+ thalassemia: milder disorder vs SS w fewer crisis
  - Splenomegaly; less severe hemolytic anemia; HCT 30-38% w 5-10% reticulocytes
  - Electrophoresis shows some hgb A