Macrocytic and Hypoproliferative Anemias

Macrocytic Anemias

Objectives

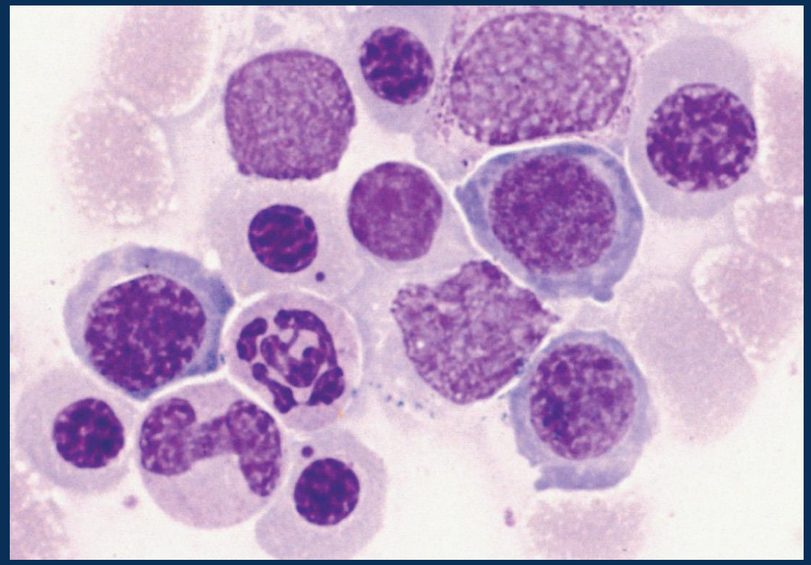
- Differentiate megaloblastic and nonmegaloblastic anemias
- Pathophysiology, clinical, and laboratory findings for:
  - Megaloblastic disorders
    - Folate Deficiency, Vitamin B12/Cobalamin Deficiency, Pernicious Anemia
  - Nonmegaloblastic disorders

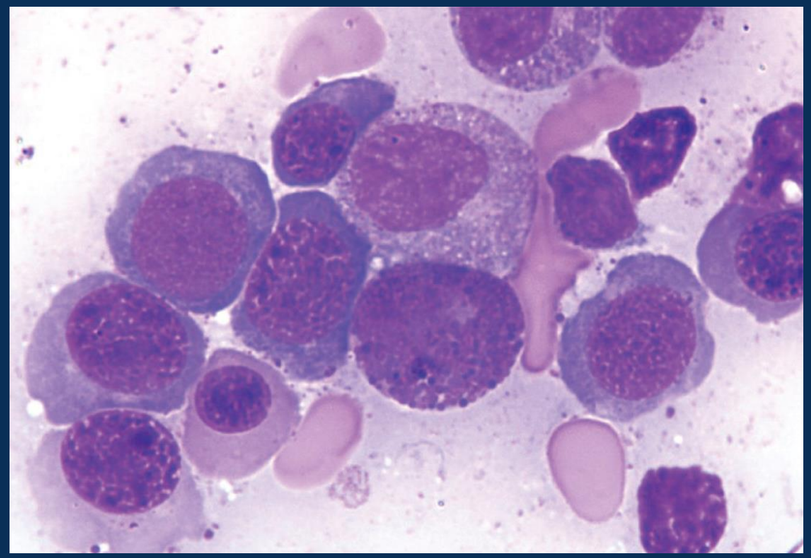
Macrocytic Anemia

- MCV > 100 fL, MCHC is normal, ↑ MCH
- Classification of macrocytic anemia
  - Megaloblastic
    - Abnormal DNA maturation
    - Delayed nuclear maturation impairs cell division
    - Nuclear cytoplasm asynchrony
  - Nonmegaloblastic
    - Normoblastic maturations

Megaloblastic

- Nuclear maturation defect
- Anemia
  - Due to ineffective erythropoiesis
  - Disrupted DNA synthesis
- BM
  - Megaloblasts
    - Giant, abnormal appearing erythroid precursors





Megaloblastic

- 95% of megaloblastic anemias
- Deficiency of vitamin B12 or folic acid/folate
  - Vitamin B12 deficiency
    - Deficiency of intrinsic factor (IF)
  - Folic acid/folate deficiency
    - Inadequate dietary uptake

Clinical Presentation

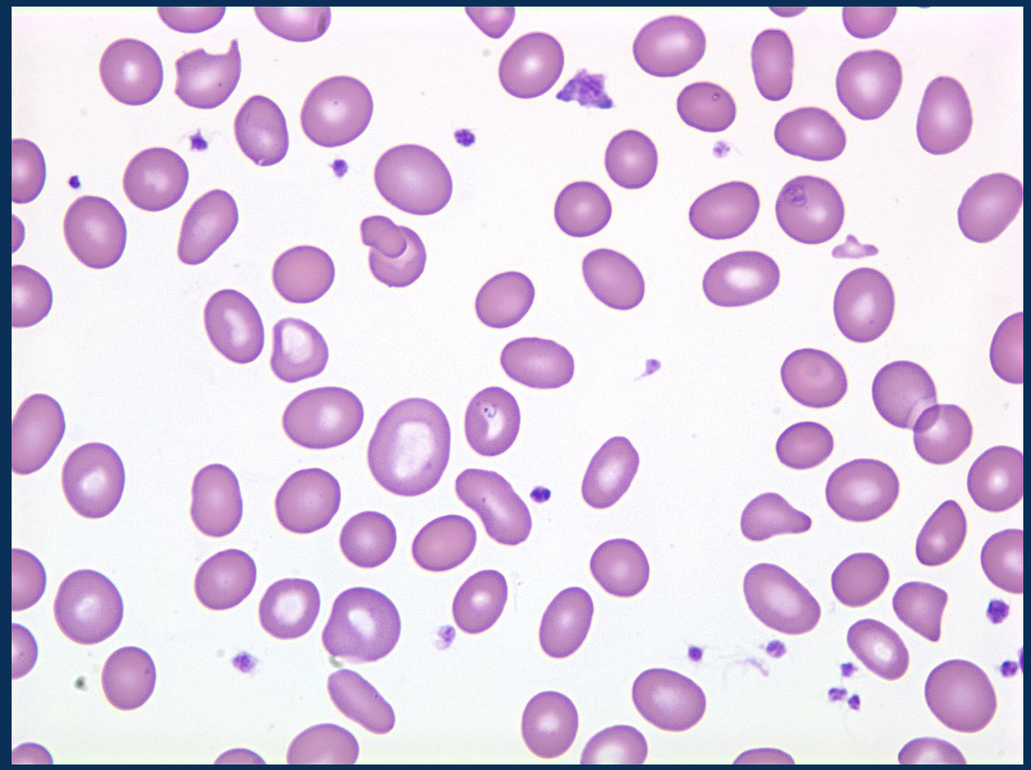
- Onset is insidious
- Anemia symptoms
  - Lethargy, weakness, yellow or waxy pallor
- Other symptoms
  - Dyspeptic symptoms
  - Glossitis with beefy red or smooth pale tongue
  - Loss of weight or appetite
  - Pernicious anemia
    - Atrophy of gastric parietal cells
    - Diarrhea

Clinical Presentation

- Vitamin B12 / Folate deficiency
  - Neurological disturbances
    - Tingling, numbness, weakness of the extremities
    - Abnormal gait and mental disturbances
      - Loss of memory, depression, irritability

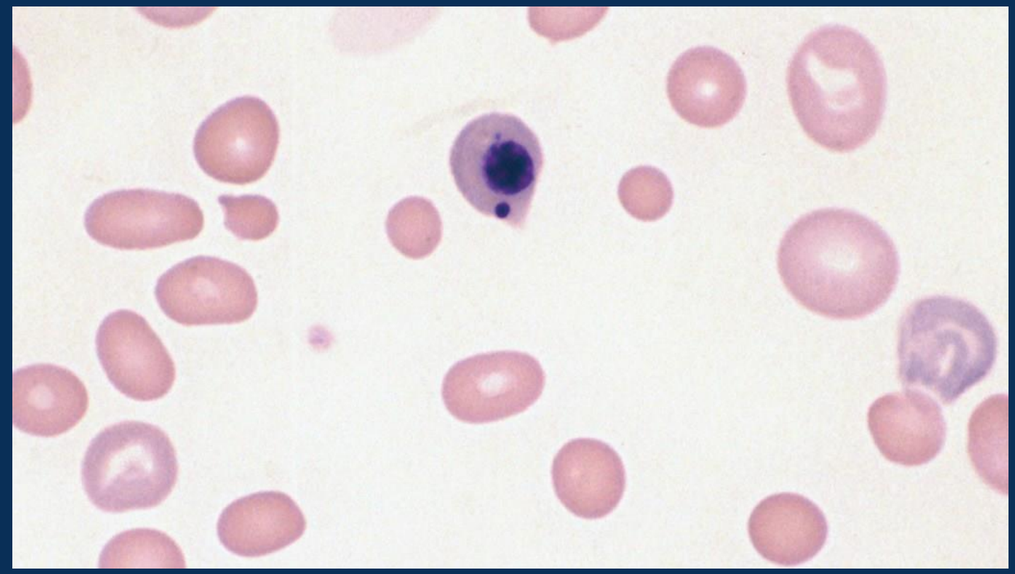
Laboratory Findings

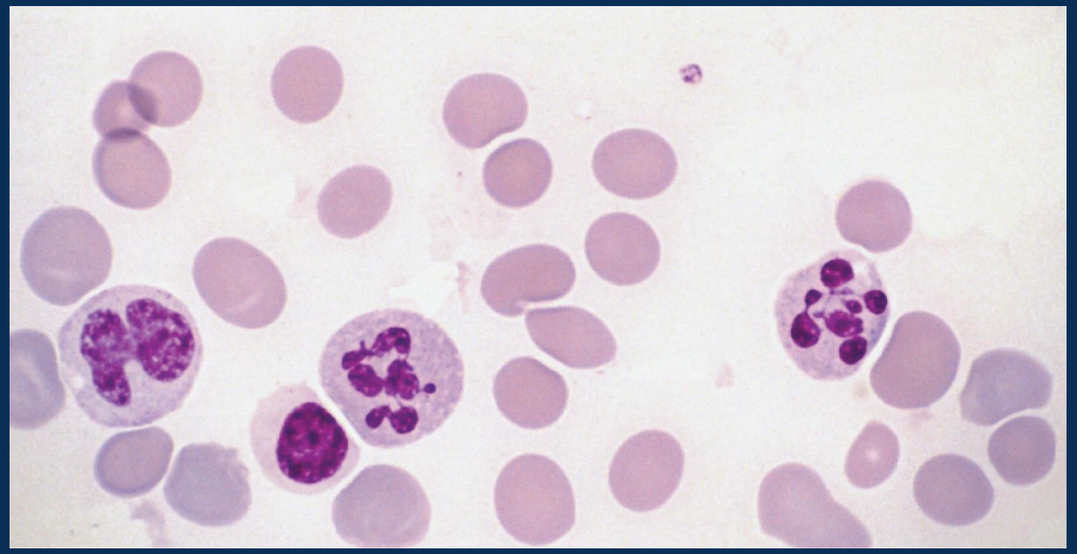
- CBC
  - MCV 100 to 140 fL (N or ↓ with coexisting IDA)
  - ↑ MCH, MCHC normal
  - RPI < 2
  - ↓ Platelets, >100 × 10^9/L
  - ↓ WBC's due to neutropenia

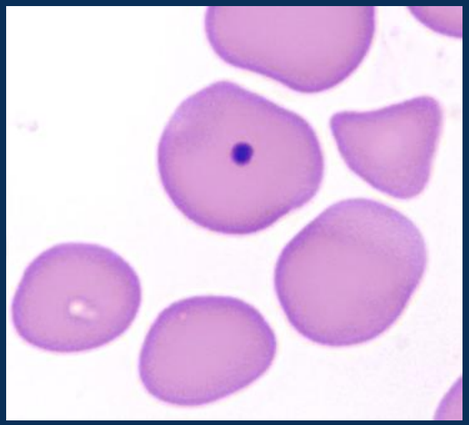


Laboratory Findings

- Smear evaluation
  - Macrocytic normochromic anemia
  - Macro ovalocytes
  - Howell-Jolly bodies
  - nRBC’s
  - ↑ Anisopoikilocytosis
  - Segs > 5 lobes

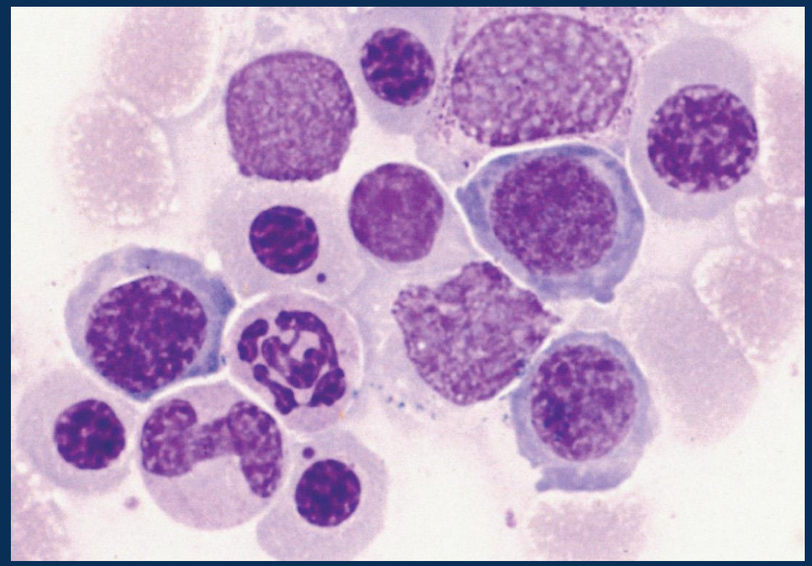


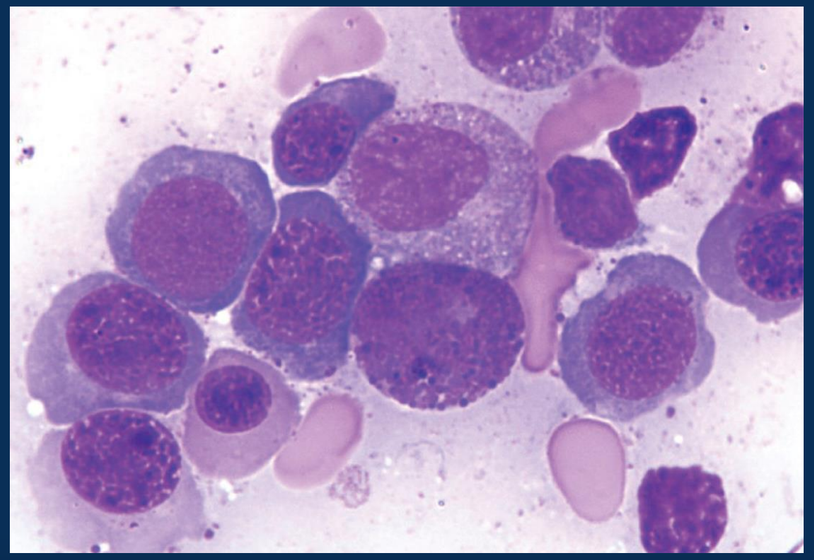




Laboratory Findings

- Bone Marrow
  - Hypercellular, ↓ M:E ratio, ineffective hematopoiesis
  - Large nRBC precursors (N-C asynchrony)
    - Nuclear maturation lags cytoplasmic maturation
    - Giant metamyelocytes and bands
    - Poor granulation
  - Megakaryocytes
    - Abnormal maturation



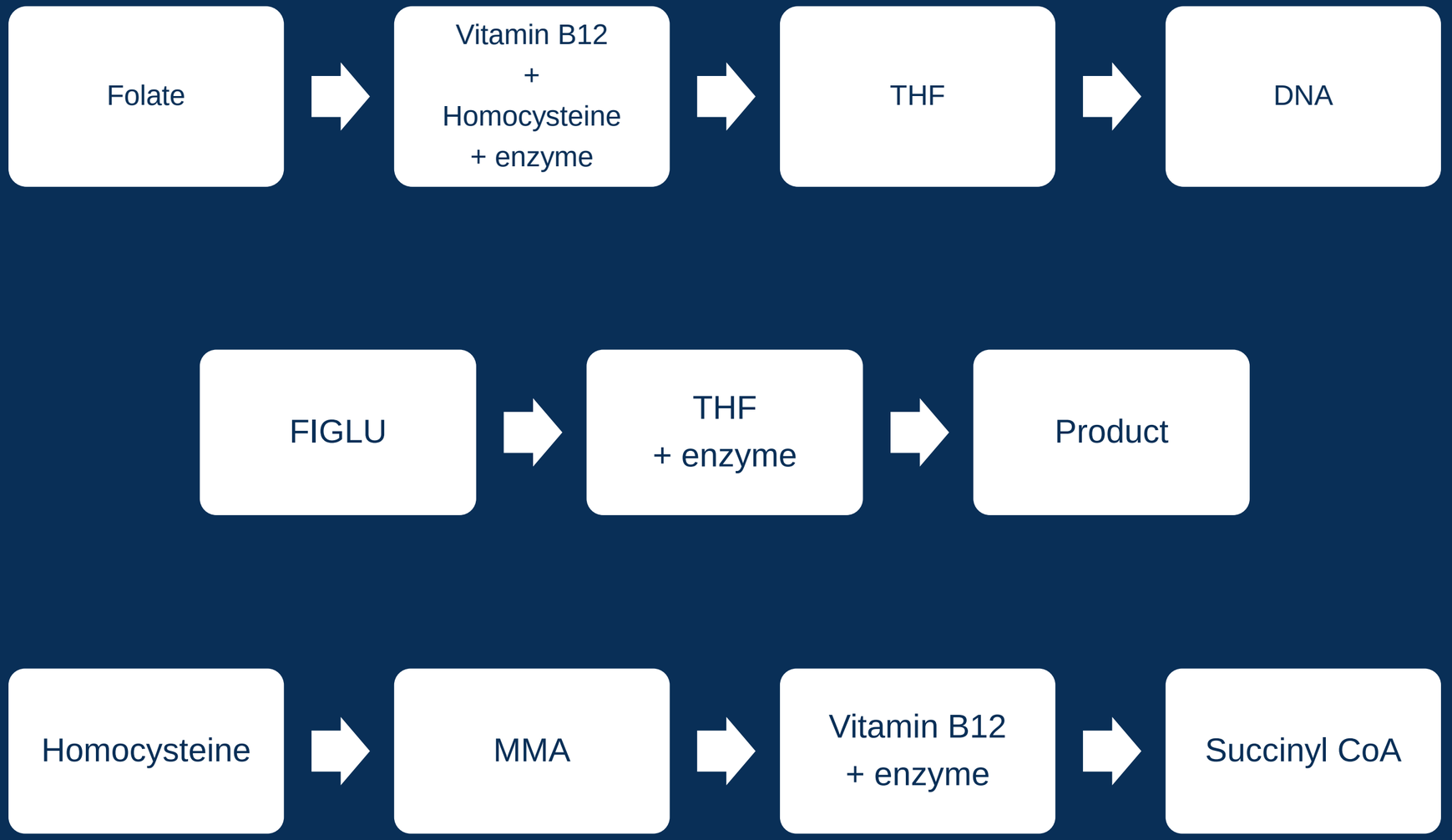


Laboratory Findings

- Chemistries
  - Vitamin B12 levels
    - 150–400 pg/mL (normal)
  - Serum folate
    - Used for initial testing (> 4 ng/mL normal)
  - Red cell folate
    - Estimate of deficiency
    - Measures folate over preceding several months

Laboratory Findings

- Chemistries
  - Intermediates in Folate and Vitamin B12 metabolism
    - Methylmalonic acid (MMA)
      - N in FD, ↑ in VB12D
    - Homocysteine levels
      - ↑ in VB12D and FD
    - Formiminoglutamic acid (FIGLU)
      - ↑ in FD


Folate
Vitamin B12
+
Homocysteine
+ enzyme
THF
DNA
FIGLU
THF
+ enzyme
Product
Homocysteine
MMA
Vitamin B12
+ enzyme
Succinyl CoA

Folate

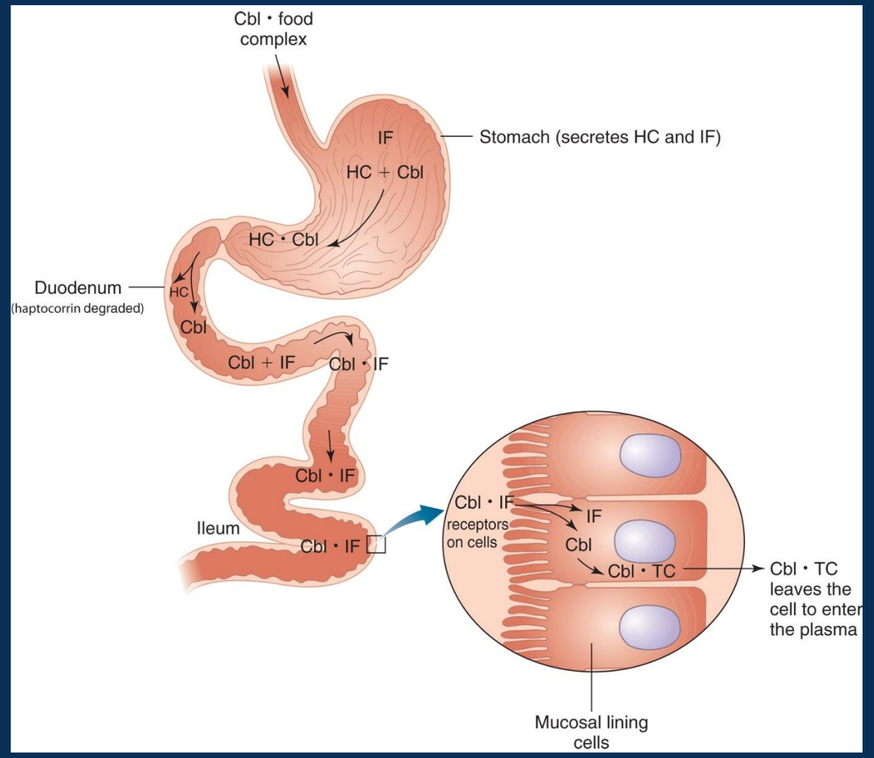
- Present in many foods
- Liver stores 3–6 month supply of folate
- Depleted quickly during
  - Rapid cell turnover, growth, pregnancy
- Produced from inert folic acid
- Active form is tetrahydrofolate (THF)
  - Vitamin B12 needed to maintain active form

Folate Deficiency

- Marked slowing of DNA synthesis
- Ineffective erythropoiesis (↓ RPI)
- ↑ heme catabolism and iron turnover
- Hemolysis, jaundice, pancytopenia
  - Circulating RBC survival ↓ by 30–50%
- ↑ in compounds requiring folic acid as a cofactor
  - ↑ Homocysteine, ↑ FIGLU
- Causes: inadequate diet, ↑ requirement, malabsorption, drug inhibition (medication effect)

Vitamin B12 / Cobalamin

- Vitamin B12
  - Therapeutic form of crystalline cobalamin
  - Required for DNA synthesis and neurologic function
- Metabolism
  - VB12 food ingested
  - Released during digestion
  - Binds to intrinsic factor (IF → VB12+IF)
  - VB12+IF complex captured by IF receptor on mucosal cells
  - Released to blood stream

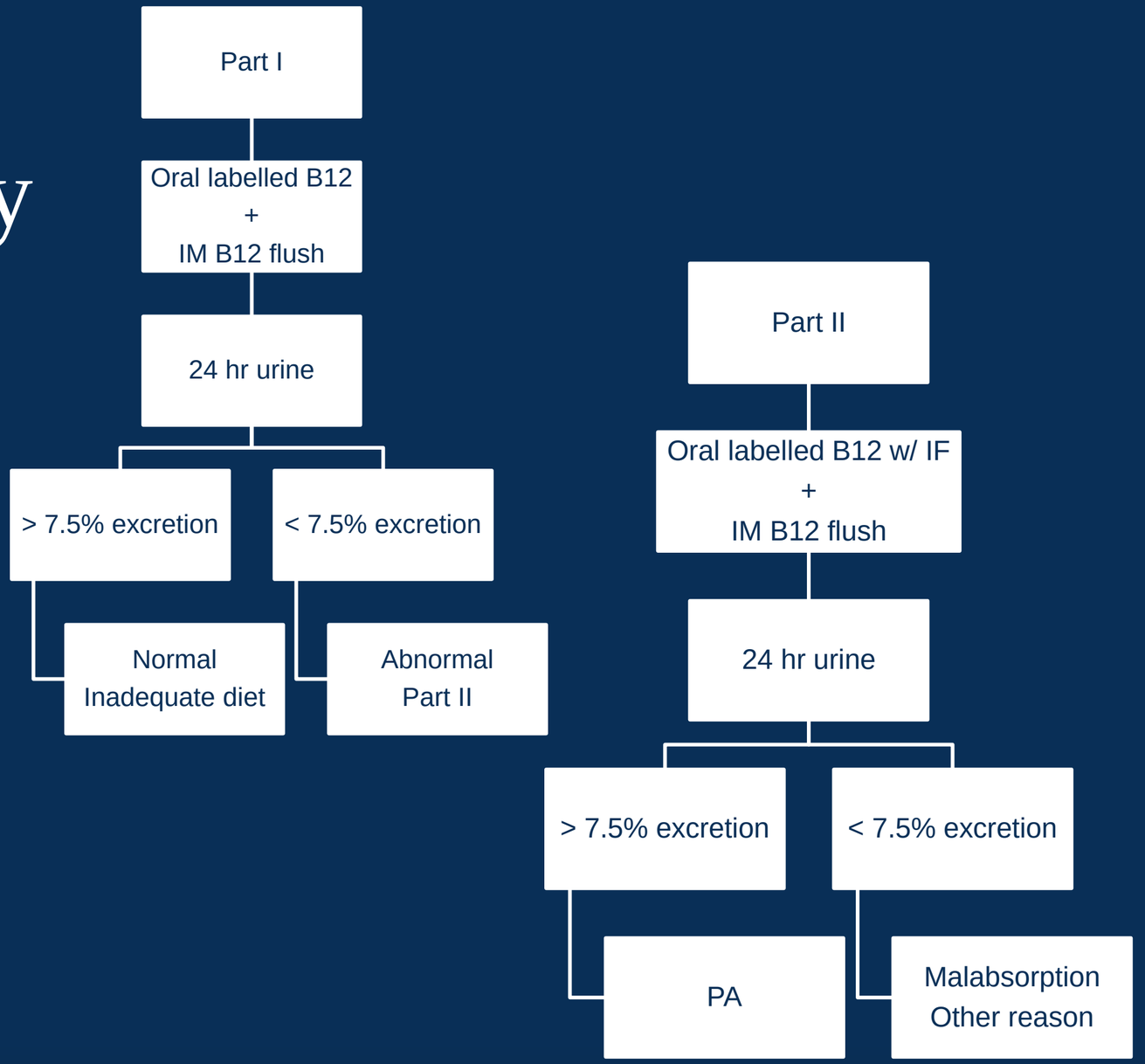


Vitamin B12 Deficiency

- Causes: lack of IF, malabsorption, inadequate diet, impaired tissue utilization
  - Pernicious anemia
    - Absence of IF secondary to gastric atrophy
    - Disease of older adults (> 40 years)
    - Seen with other autoimmune disorders

Vitamin B12 Deficiency

- Laboratory Analysis – Schilling test
  - Gold Standard
  - Distinguishes cobalamin deficiency due to
    - Dietary deficiency, absence of IF, malabsorption



Nonmegaloblastic

- Normal RBC, WBC, PLT with round macrocytes
- Megaloblastic symptoms absent
- Common causes:
  - Alcoholism (direct toxic effect on RBC precursors)
  - Reticulocytosis (hemolysis, GI bleed)
  - Liver disease (RBC membrane changes)

Hypoproliferative Anemias

Objectives

- Define hypoproliferative anemias
- Pathophysiology, clinical, and laboratory findings for:
  - Aplastic Anemia
  - Disorders mimicking hypoproliferative anemia:
    - Myelophthisic Anemia, Myelodysplastic Syndromes, Hypersplenism
- Erythroid aplasias:
  - Pure Red Cell Aplasia, Renal Disease

Hypoproliferative Anemias

- Heterogeneous group of acquired and inherited disorders
- Normocytic/normochromic or macrocytic/normochromic anemias
- Hypocellular bone marrow
- Hematopoietic tissue in BM replaced by fat
- Overall BM ↓ = Aplastic, aplasia, hypoplastic
- ↓ in only one cell lineage = erythroid, myeloid, or megakaryocytic hypoplasia

Aplastic Anemia

- Pancytopenia associated with a hypocellular BM
- Mature blood cells appear normal
- With disease progression, all cells become depleted
  - Impaired capacity of BM cells for renewal of cells
- BM cellularity < 25% plus two of:
  - Granulocyte < 0.5 $x10^9/L$
  - PLT < 20 $x10^9/L$
  - Corrected Retic < 1%

Aplastic Anemia

- Epidemiology
  - Rare
    - Most commonly seen in:
      - 2–5-year-olds (inherited forms)
      - 15–25-year-olds (inherited forms)
      - Adults > 60 (acquired forms)
        - » Acquired = immune-mediated diseases

Classification

- Two groups:
  - Acquired
    - Environmental exposures
      - Drugs, chemicals, radiation, infectious agents, and other factors
    - Idiopathic
      - No environmental link can be identified
  - Inherited

Classification

- Two groups:
  - Acquired
  - Inherited (Fanconi anemia)
    - Rare
    - Chronic failure of the BM
    - Due to an inherited abnormality
    - May or may not be present at birth
    - Can be associated with other congenital abnormalities

Clinical Findings

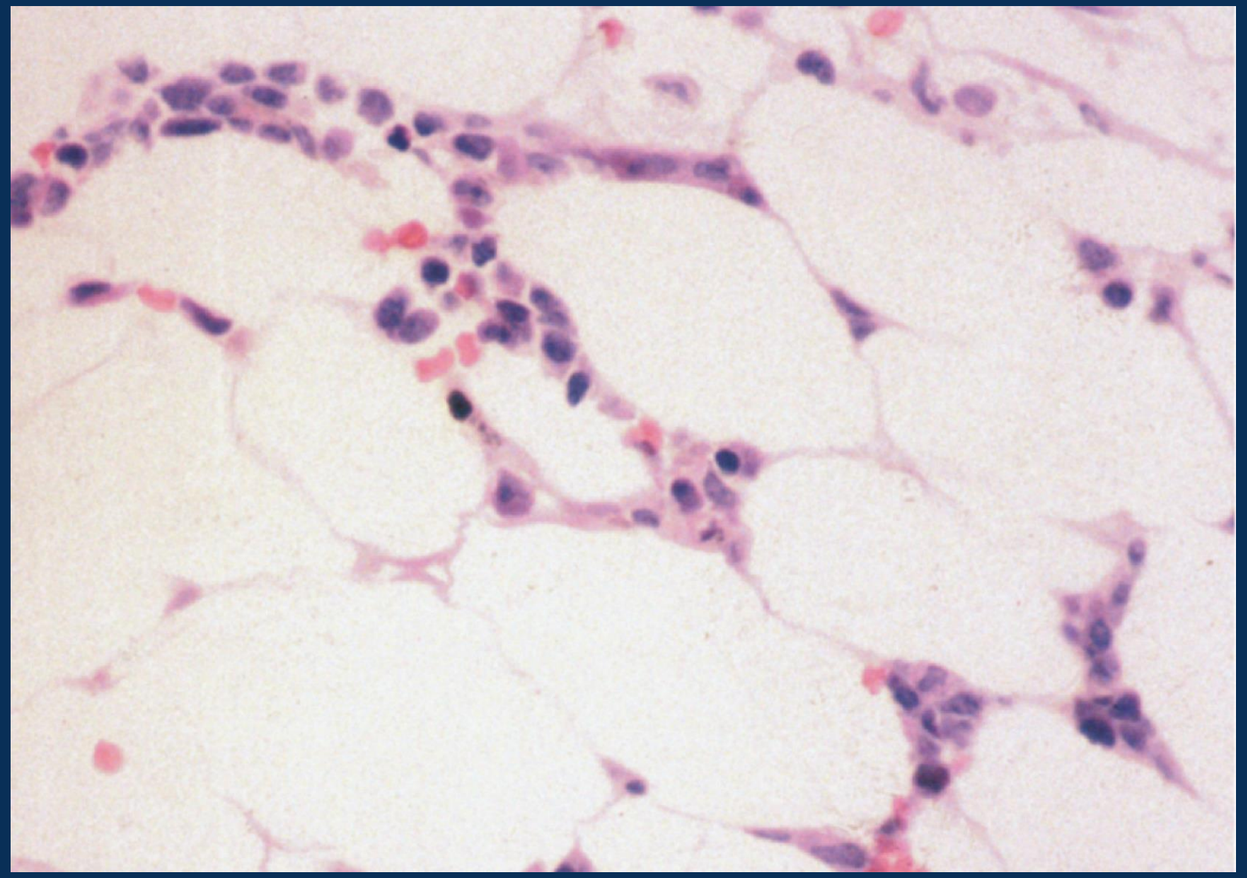
- Symptoms
  - Insidious
  - Related to cytopenias
  - Most common signs
    - Bleeding
    - Petechial and mucosal hemorrhages
  - Anemia (pallor, fatigue)
  - Infection

Laboratory Findings

- Peripheral blood
  - Pancytopenia
  - Hb < 7.0 g/dL
  - RBC’s normo-/macro-cytic, normochromic, cRetic < 1%
  - Thrombocytopenia
  - Relative lymphocytosis
  - Neutrophil granules
    - Frequently larger and stain dark red

Laboratory Findings

- Bone marrow
  - Necessary to diagnosis AA
  - Hypocellular, > 70% fat
  - "Dry tap" BM due to fat or infiltration of cancer cells leading to fibrosis



Laboratory Findings

- Other abnormal findings not specific:
  - HbF can be ↑
  - EPO is often ↑
  - ↑ serum iron, > 50% saturation of transferrin
  - Flow cytometry CD34+ cells < 0.3%

Differentiation of AA

- Myelophthisic Anemia
  - Marrow replacement or infiltration by fibrotic, granulomatous, or neoplastic cells
    - Reduce normal hematopoiesis
    - Disrupt normal BM architecture
    - Leukoerythroblastic reaction (characteristic finding)
    - Moderate or marked poikilocytosis
    - Dacryocytes, large bizarre platelets

Differentiation of AA

- Myelodysplastic Syndromes
  - Often terminate in acute leukemia
  - Peripheral blood findings
    - Pancytopenia, bicytopenia, or isolated cytopenia
    - Macrocytic anemia
  - BM normo- to hypo- cellular

Differentiation of AA

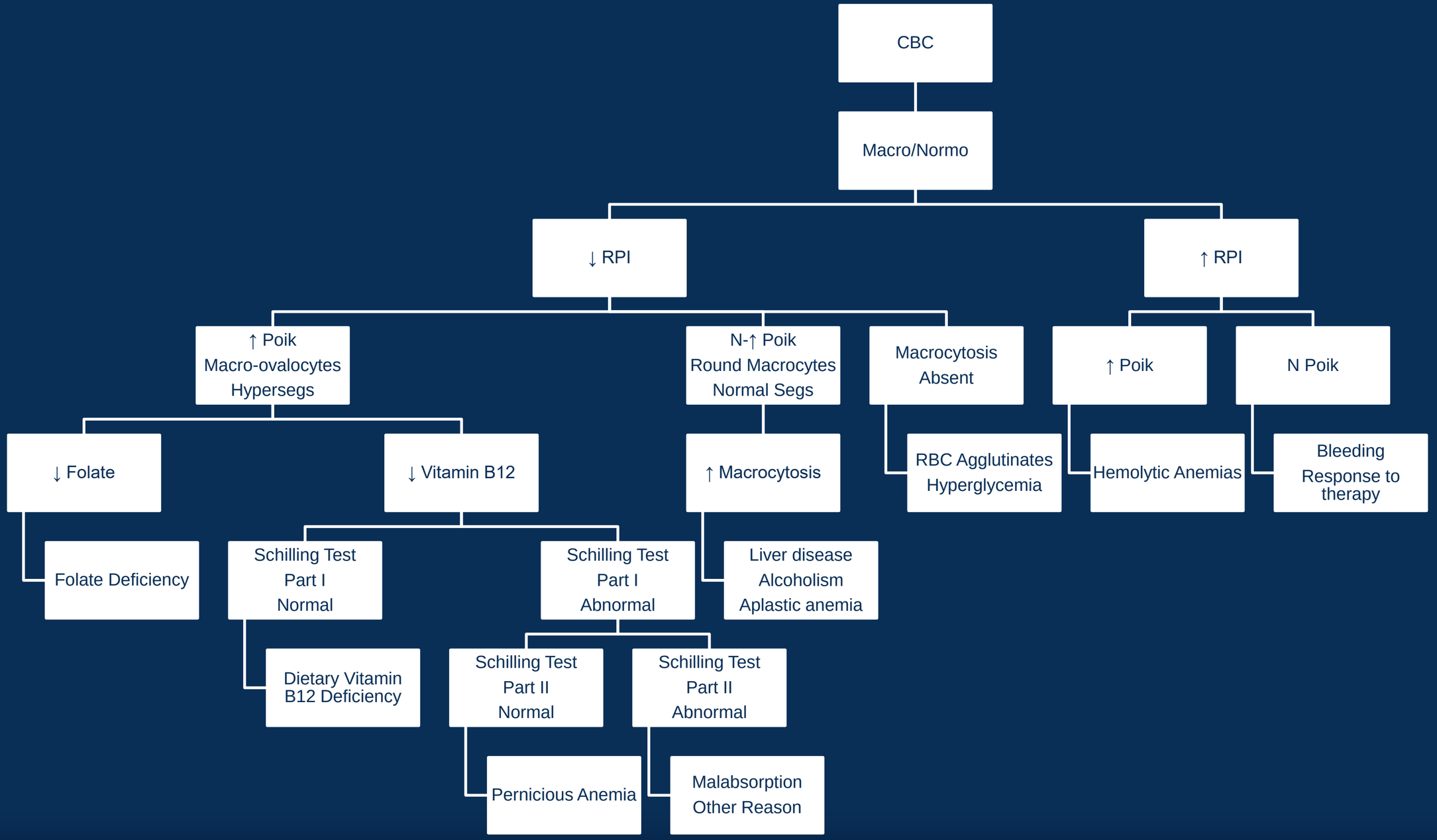
- Hypersplenism
  - Cells become pooled and sequestered in the spleen
  - BM is hyperplastic, corresponding to PB cytopenia
  - Anemia with reticulocytosis
  - Granulocytopenia, shift to the left
  - Splenectomy corrects cytopenias

Pure Red Cell Aplasia

- Selective aplasia of erythroid lineage
  - Hypoproliferation of the committed erythroid progenitor
- Normal leukocyte and platelet counts
- Corrected reticulocyte < 1%
- Cause
  - Acquired (acute or chronic)
    - Acute - Temporary depression of erythropoiesis (eg infections)
  - Inherited

Renal Disease

- BM erythroid hypoproliferation
  - ↓ in EPO by diseased kidney
- Normocytic normochromic anemia
- Hgb 5-8 g/dL, RPI ~ 1
- Moderate anisocytosis, some microcytosis
- Moderate to severe poikilocytosis
  - Echinocytes correlate roughly with severity of azotemia
  - Spherocytes, NRBCs
- WBC’s and PLT’s are normal


CBC
Macro/Normo
↓ RPI
↑ RPI
↑ Poik
Macro-ovalocytes
Hypersegs
N-↑ Poik
Round Macrocytes
Normal Segs
Macrocytosis
Absent
↑ Poik
N Poik
↓ Folate
↓ Vitamin B12
↑ Macrocytosis
RBC Agglutinates
Hyperglycemia
Hemolytic Anemias
Bleeding
Response to therapy
Folate Deficiency
Schilling Test
Part I
Normal
Schilling Test
Part I
Abnormal
Liver disease
Alcoholism
Aplastic anemia
Dietary Vitamin
B12 Deficiency
Schilling Test
Part II
Normal
Schilling Test
Part II
Abnormal
Pernicious Anemia
Malabsorption
Other Reason

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