Hematopoiesis,

- **200 billion new blood cells per day**

- **The hematopoietic machinery requires a constant supply iron, vitamin B_{12}, and folic acid.**

- **hematopoietic growth factors, proteins that regulate the proliferation and differentiation of hematopoietic cells.**

- **Inadequate supplies of either the essential nutrients or the growth factors result in deficiency of functional blood cells.**

  Anemia,

  a deficiency in oxygen-carrying erythrocytes, is the most common and several forms are easily treated

Iron Deficiency Anemia

- **Iron forms the nucleus of the iron-porphyrin heme ring, which together with globin chains forms hemoglobin.**

- **In the absence of adequate iron, small erythrocytes with insufficient hemoglobin are formed, giving rise to microcytic hypochromic anemia.**

- **Iron deficiency is the most common cause of chronic anemia.**

- **The cardiovascular adaptations to chronic anemia—tachycardia, increased cardiac output, vasodilation—can worsen the condition**

Iron Deficiency Anemia

- **Body has ~ 3.5 g total iron; 2.5 g is in hgb.**
- **Humans are poor at absorption- usually only 5-10% of intake is absorbed (this is increased to 20-30% in deficiency)**
- **Requirement:**

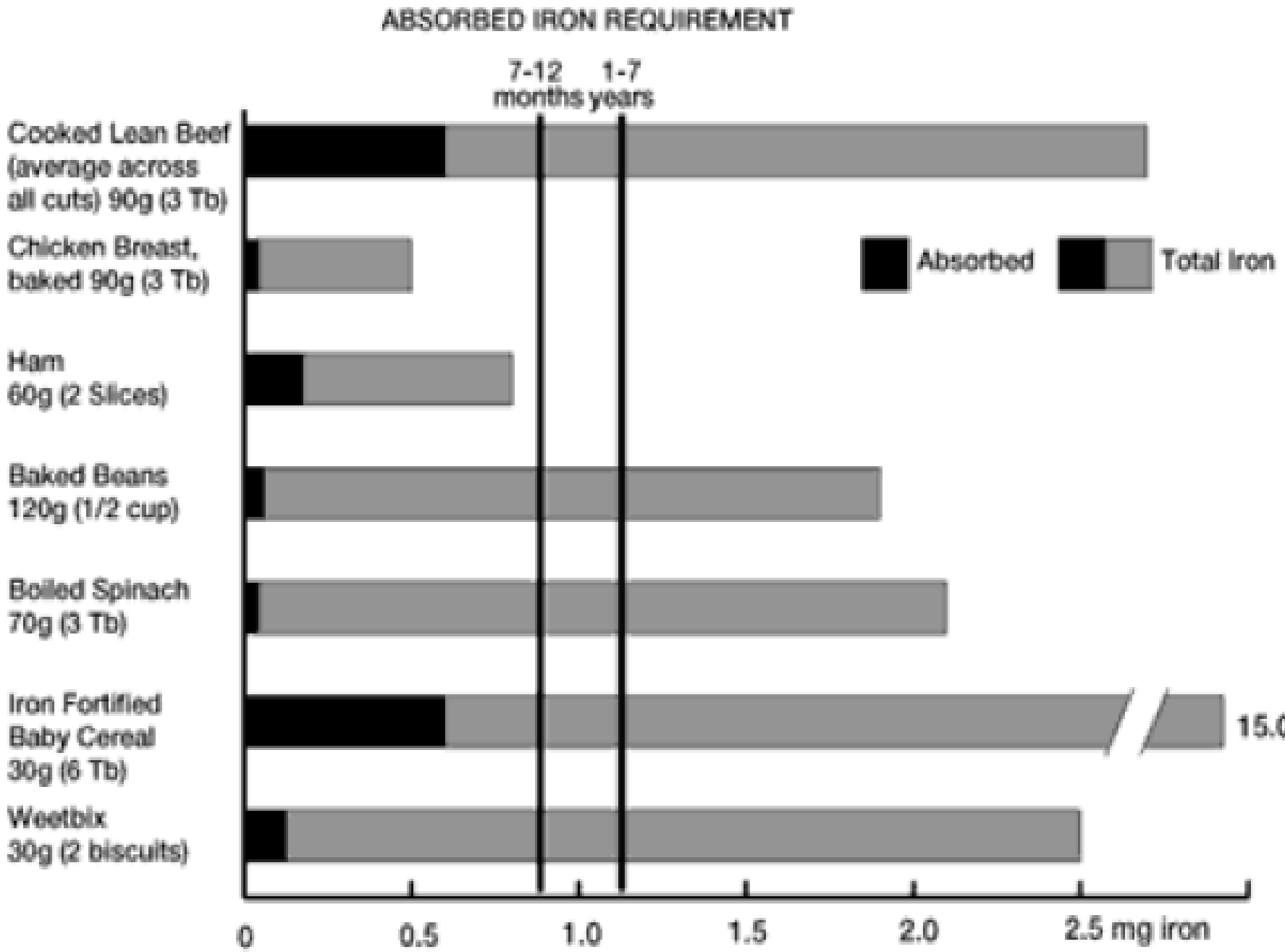
  Adult males 13 ug/kg.

  Female21 ug/kg,

  pregnant women and infants 80 ug/kg.

– dietary iron in form of heme (meat) can be absorbed intact

– Non-heme iron from vegetables, grains, therapeutic iron must be broken down to elemental iron for absorption



www.ironpanel.org.au/AIS/AISpics/IronGraph.gif

Indications for the Use of Iron

- **Treatment or prevention of iron deficiency anemia.**

- **Iron deficiency is commonly seen in populations with increased iron requirements.**

- ✓ **infants, especially premature infants; children during rapid growth periods;**
- ✓ **pregnant and lactating women;**
- ✓ **chronic kidney disease who lose erythrocytes at a relatively high rate during hemodialysis**

  and also form them at a high rate as a result of treatment with the erythrocyte growth factor erythropoietin.

Indications for the Use of Iron

- **Inadequate iron absorption can also cause iron deficiency.**

- **This is seen frequently after gastrectomy**
- **severe small bowel disease that results in generalized malabsorption.**

Oral Iron

- Preparations:

– **ferrous fumarate 33% elemental iron,**

– **ferrous gluconate 12% iron,**

– **ferrous sulfate 20%.**

Oral Iron

Adverse Effects: 20-25% have GI problems: nausea, epigastric pain, constipation, abd. cramps.

- **Food decreases absorption by 30 - 50%.**

- **– Drug interactions: tetracycline and antacids decrease iron absorption.**

Oral Iron

- **Treatment with oral iron should be continued for 3–6 months in order to replenishes iron stores.**

- **Patients taking oral iron develop black stools;**

Parenteral Iron

- **should be reserved for**

(1) patients with documented iron deficiency

(2) patients who are unable to tolerate or absorb oral iron

(3) patients with extensive chronic anemia who cannot be maintained with oral iron alone. This includes

patients with advanced chronic renal disease requiring hemodialysis and treatment with erythropoietin,

various post gastrectomy conditions and previous small bowel resection, inflammatory bowel disease involving the proximal small bowel, and malabsorption syndromes.

Parenteral Iron

- **It can be given by deep intramuscular injection or by intravenous infusion, although the intravenous route is used most commonly.**

Intravenous administration eliminates the local pain and tissue staining that often occur with the intramuscular route and allows delivery of the entire dose of iron necessary to correct the iron deficiency at one time.

- **Adverse effects of intravenous iron dextran therapy include**

1. **headache, light-headedness,**
2. **fever, arthralgias, back pain,**
3. **flushing, urticaria, bronchospasm, and, rarely, anaphylaxis and death.**

Acute iron toxicity

- exclusively in young children who accidentally ingest iron tablets.
- as few as 10 tablets can be lethal in young children.

- Children who are poisoned with oral iron experience necrotizing gastroenteritis, with vomiting, abdominal pain, and bloody diarrhea followed by shock, lethargy, and dyspnea.

- **Whole bowel irrigation** should be performed to flush out unabsorbed pills.

- **Deferoxamine,** a potent iron-chelating compound, can be given **systemically** to bind iron that has already been absorbed and to promote its excretion in urine and feces.

Chronic iron toxicity (iron overload) hemochromatosis

- excess iron is deposited in the heart, liver, pancreas, and other organs. It can lead to organ failure and death.
- It most commonly occurs in patients with inherited hemochromatosis, a disorder characterized by excessive iron absorption.
- and in patients who receive many red cell transfusions over a long period of time (eg, patients with thalassemia major).
- Chronic iron overload in the absence of anemia is most efficiently treated by intermittent phlebotomy. (One unit of blood can be removed every week)

Megaloblastic Anemias

Megalobastic Anemias:

Marrow disorder caused by defective DNA synthesis.

Vit. B_{12} Deficiency
Folic Acid Deficiency

- **Anemia may result from (1) deficiency (strict vegetarians)**

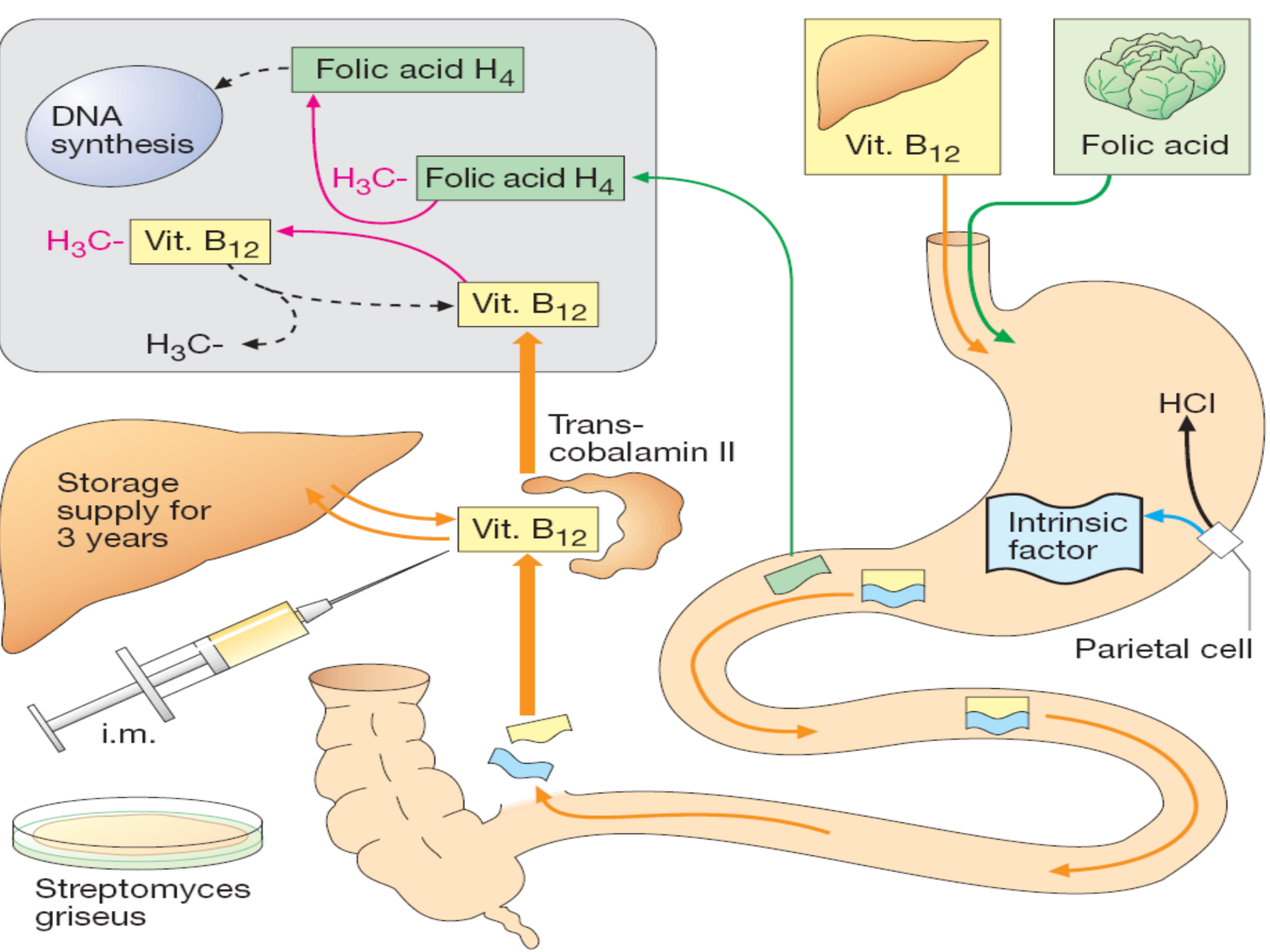
  (2) or impaired absorption (Pernicious anemia) from decreased intrinsic factor (protein secreted by stomach),

  (3) gastrectomy,

  (4) malnutrition, RA, thyroid conditions.

Vitamin B_{12} is used to treat or prevent deficiency.

Distinguished from other anemias by its Neurological Syndrome
Delirium, numbness, tingling of hand and feet, loss of fine learned movements, difficulty in walking, bladder and bowel dysfunction.


Folic acid H_4
DNA synthesis
H_3C- Folic acid H_4
H_3C- Vit. B_{12}
Vit. B_{12}
H_3C-
Vit. B_{12}
Folic acid
HCl
Trans-cobalamin II
Storage supply for 3 years
Vit. B_{12}
Intrinsic factor
Parietal cell
i.m.
Streptomyces griseus

-Vitamin B_{12} is used to treat or prevent deficiency.

- Injections only benefit if deficiency

– Neurologic symptoms (paresthesias occur first, then balance) in severe deficiency may be irreversible after several months

– May need lifelong injections if malabsorption; can not absorb B12/intrinsic factor complex

NOTE:

1. Folic acid alleviates anemic syndrome but the neurological disorder progresses.
2. Antagonism of Vit B_{12} by nitrous oxide (inactivates Vit B_{12} dependent enzymes) => megaloblastic response, neuropathies

Vitamin B_{12}

- Vitamin B_{12} for parenteral injection is available as cyanocobalamin or hydroxocobalamin. Hydroxocobalamin is preferred because it is more highly protein-bound and therefore remains longer in the circulation.

- Initial therapy should consist of 100–1000 mcg of vitamin B_{12} intramuscularly daily or every other day for 1–2 weeks to replenish body stores.

- Maintenance therapy consists of 100–1000 mcg intramuscularly once a month for life.

- If neurologic abnormalities are present, maintenance therapy injections should be given every 1–2 weeks for 6 months before switching to monthly injections.

- Oral vitamin B_{12}-intrinsic factor mixtures and liver extracts should not be used to treat vitamin B_{12} deficiency; however, oral doses of 1000 mcg of vitamin B_{12} daily are usually sufficient to treat patients with pernicious anemia who refuse or cannot tolerate the injections.

Megaloblastic Anemia- continued

- Folic Acid (folate, Vitamin B9) found in fresh green veggies, yeast, animal proteins but easily destroyed.

- Anemia may be indistinguishable from B12 deficiency but occurs rapidly.

- Must evaluate fully before treatment- folate therapy will correct hematological abnormalities but not neurological problems
- deficiency; B12 deficiency may be masked by folate supplementation

- because body stores of folates are relatively low and daily requirements high, folic acid deficiency and megaloblastic anemia can develop within 1–6 months after the intake of folic acid stops, depending on the patient's nutritional status and the rate of folate utilization.

- Patients with alcohol dependence and patients with liver disease can develop folic acid deficiency because of poor diet and diminished hepatic storage of folates.

- Patients who require renal dialysis develop folic acid deficiency because folates are removed from the plasma during the dialysis procedure.

FOLIC ACID

- Drug interactions:

In large doses may counteract the effects of anticonvulsants potentially leading to seizures.

- Adverse reactions:

Erythema, itching, and rash.

- Question
- he iron dextran formulations used clinically are distinguishable as high-molecular-weight and low-molecular-weight forms. In the USA, the InFeD preparation is a low-molecular-weight form while DexFerrum is a high-molecular-weight form. Clinical data—primarily from observational studies—indicate that the risk of anaphylaxis is largely associated with high-molecular-weight iron dextran formulations.

- Activated charcoal, a highly effective adsorbent for most toxins, **does not** bind iron and thus is ineffective. Appropriate supportive therapy for gastrointestinal bleeding, metabolic acidosis, and shock must also be provided.

- Question
- An exception is the high requirement for iron of patients with advanced chronic kidney disease who are undergoing hemodialysis and treatment with erythropoietin; for these patients, parenteral iron administration is preferred.

Absorption

- The average diet in the USA contains 10–15 mg of elemental iron daily. A normal individual absorbs 5–10% of this iron, or about 0.5–1 mg daily. Iron is absorbed in the duodenum and proximal jejunum, although the more distal small intestine can absorb iron if necessary. Iron absorption increases in response to low iron stores or increased iron requirements. Total iron absorption increases to 1–2 mg/d in menstruating women and may be as high as 3–4 mg/d in pregnant women.

- Treatment
- Iron deficiency anemia is treated with oral or parenteral iron preparations. Oral iron corrects the anemia just as rapidly and completely as parenteral iron in most cases if iron absorption from the gastrointestinal tract is normal. An exception is the high requirement for iron of patients with advanced chronic kidney disease who are undergoing hemodialysis and treatment with erythropoietin; for these patients, parenteral iron administration is preferred.

- Different iron salts provide different amounts of elemental iron, as shown in Table 33–3. In an iron-deficient individual, about 50–100 mg of iron can be incorporated into hemoglobin daily, and about 25% of oral iron given as ferrous salt can be absorbed. Therefore, 200–400 mg of elemental iron should be given daily to correct iron deficiency most rapidly. Patients unable to tolerate such large doses of iron can be given lower daily doses of iron, which results in slower but still complete correction of iron deficiency. Treatment with oral iron should be continued for 3–6 months after correction of the cause of the iron loss. This corrects the anemia and replenishes iron stores.

Kmn

- Vitamin B_{12}
- Vitamin B_{12} (cobalamin) serves as a cofactor for several essential biochemical reactions in humans. Deficiency of vitamin B_{12} leads to megaloblastic anemia (Table 33–2), gastrointestinal symptoms, and neurologic abnormalities. Although deficiency of vitamin B_{12} due to an inadequate supply in the diet is unusual, deficiency of B_{12} in adults—especially older adults—due to inadequate absorption of dietary vitamin B_{12} is a relatively common and easily treated disorder.

Nutritional Deficiency	Type of Anemia	Laboratory Abnormalities
Iron	Microcytic, hypochromic with MCV < 80 fL and MCHC < 30%	Low SI < 30 mcg/dL with increased TIBC, resulting in a % transferrin saturation (SI/TIBC) of < 10%; low serum ferritin level (< 20 mcg/L)
Folic acid	Macrocytic, normochromic with MCV > 100 fL and normal or elevated MCHC	Low serum folic acid (< 4 ng/mL)
Vitamin B_{12}		Low serum cobalamin (< 150 pmol/L) accompanied by increased serum homocysteine (> 13 mol/L), and increased serum (> 0.4 mol/L) and urine (> 3.6 mmol/mol creatinine) methylmalonic acid