

Nutritional Anemias

NUTR 207 Module 8 Chap 7 and 8

Oct. 29 2020

Fe, Folate, B12

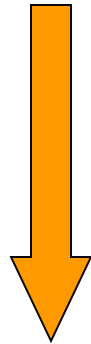
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Nutritional Anemias

Iron Deficiency



Hypochromic
Microcytic Anemia

Folate or Vitamin B12
Deficiency



Megaloblastic or
Pernicious Anemia

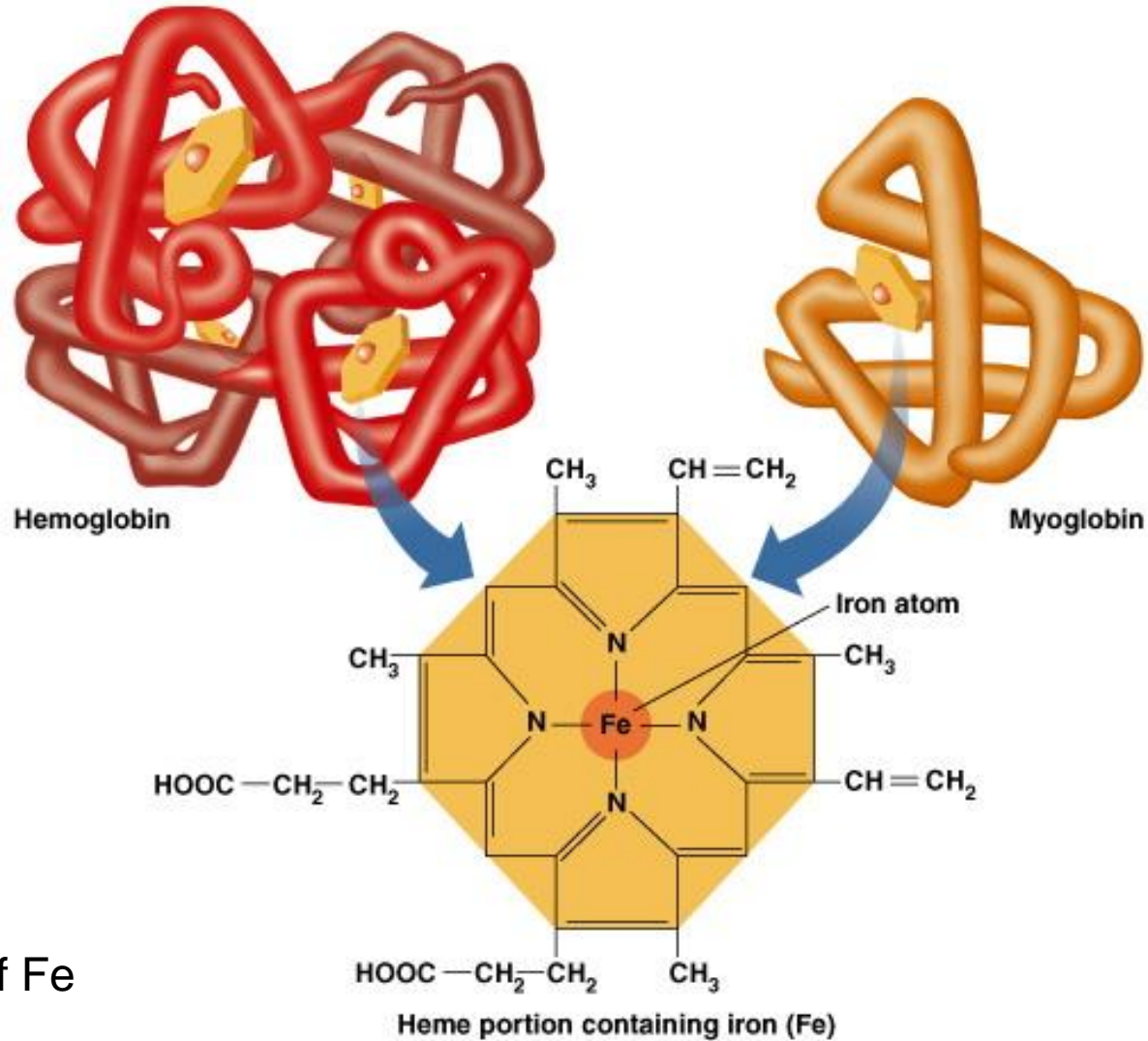


Iron Functions

- To transfer oxygen:
- As part of a Heme group in a protein
 - ▢ Hemoglobin for transport of oxygen to tissues
 - ▢ Myoglobin for muscle storage of oxygen
 - ▢ Part of electron transport chain to make ATP
 - ▢ Many enzymes such as peroxidase, myeloperoxidase, catalase



Iron

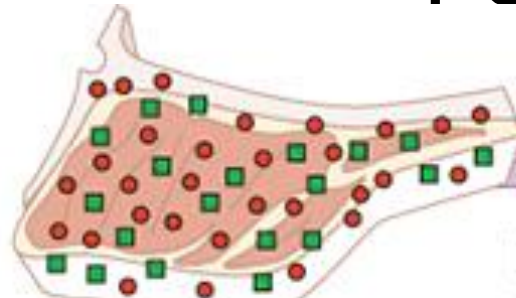


Heme and Nonheme Iron in Foods

About 40% of the iron in meat, fish, and poultry is bound into heme; the other 60% is nonheme iron.



Fe 2+ ferrous-
Heme animal
sources



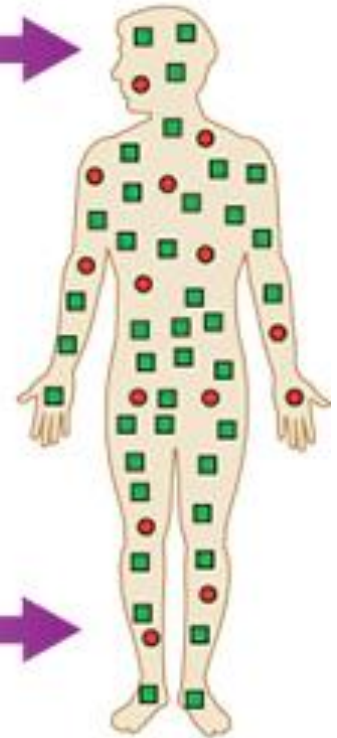
Heme accounts for about 10% of the average daily iron intake, but it is well absorbed (about 25%).

Nonheme iron accounts for the remaining 90%, but it is less well absorbed (about 17%).

All of the iron in foods derived from plants is nonheme iron.



Fe 3+ Ferric-
nonheme plant
sources



Dietary Iron Sources



Heme iron:

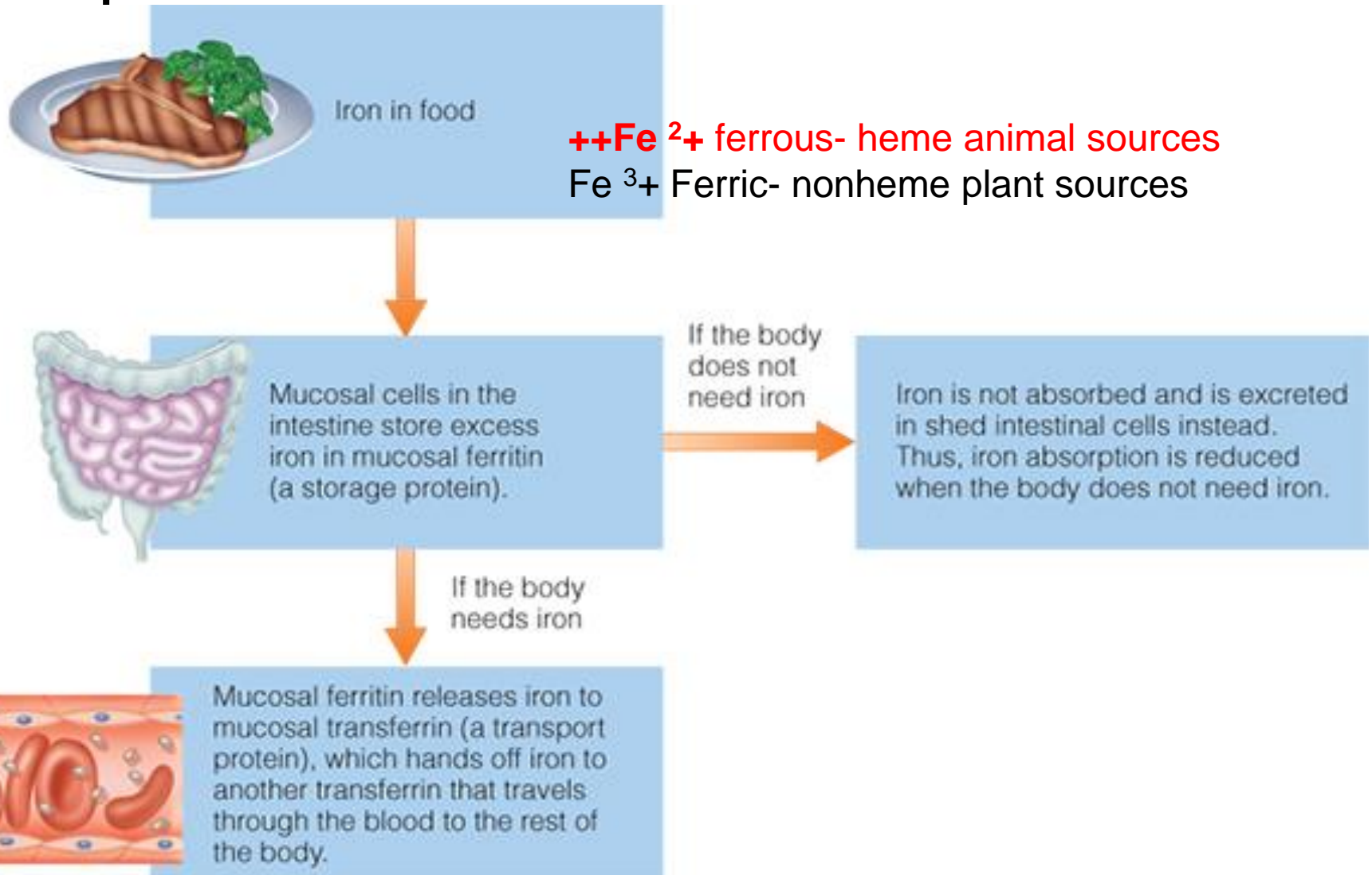
- 10% of dietary iron
- from hemoglobin and myoglobin, primarily in meat, fish and poultry (MFP factor)
- ~25% absorbed
- Absorbed as heme

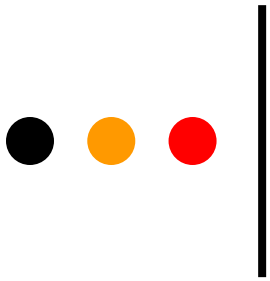


Nonheme: Elemental iron:

- 90% of dietary iron
- primarily plant foods (nuts, fruits, vegetables and enriched grains)
- 1-50% absorbed, mostly <17%
- **increased** by Vit C, sugars, acids including amino acids
- **decreased** by Ca, P, phytates, oxalates, polyphenols, tannins, EDTA
- Vegetarians..

Iron Absorption Process

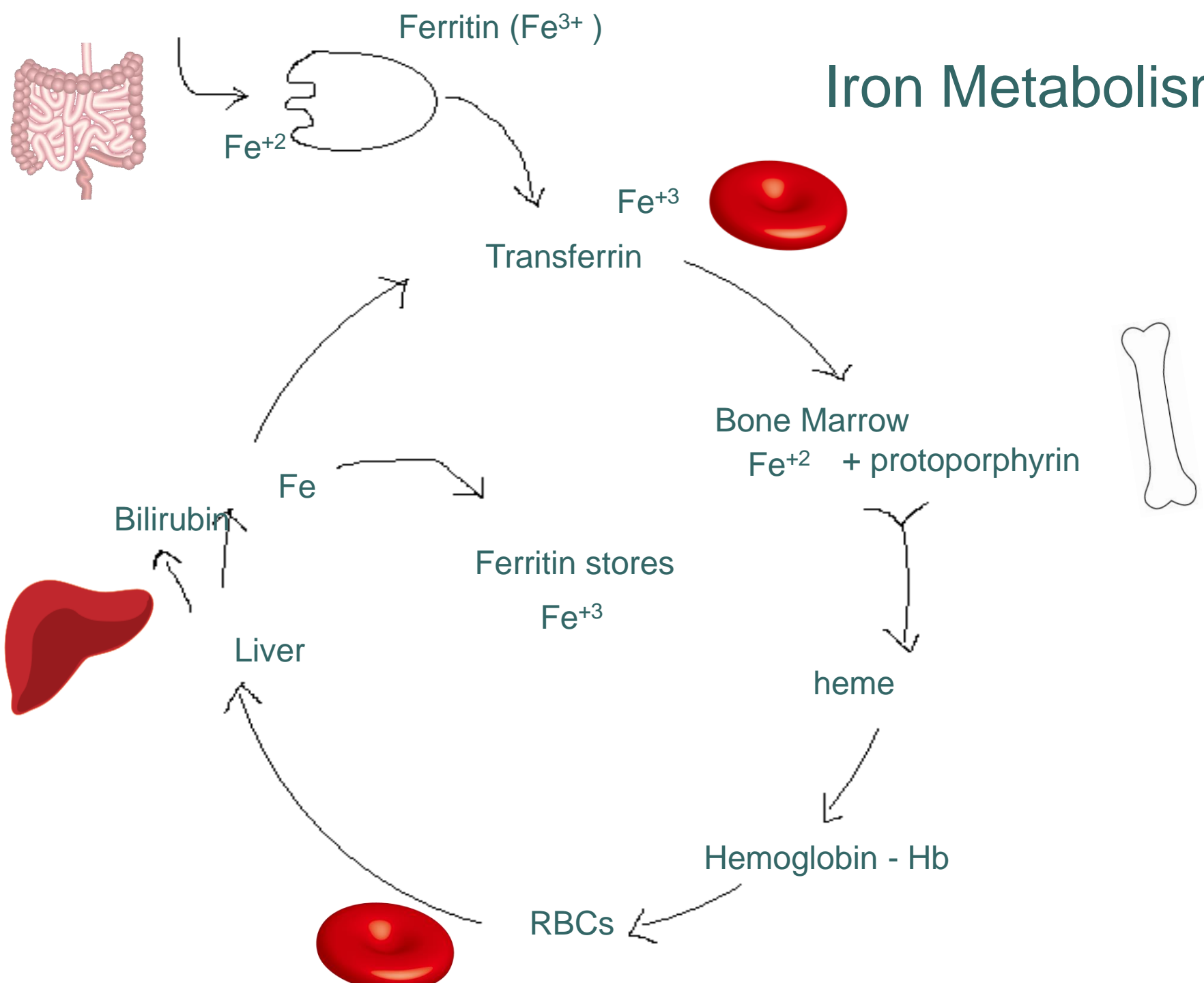




Iron Transport and Storage

- Blood: Transferrin delivers iron to bone marrow and other tissues
- Storage proteins
 - Ferritin: bone marrow, liver, spleen
 - Hemosiderin: Liver
- Recycling
- Balance

Iron Metabolism





Transferrin saturation

- Usually 1/3 saturated i.e. 1/3 of iron binding sites on the protein are occupied by Fe^{3+}
- Low saturation indicates deficiency of iron
- High saturation indicates over-supply of iron
- The number of transferrin receptors is highly regulated (increase in adequate iron environment and decrease in iron rich environment)



Iron Storage:

Ferritin and Hemosiderin

- Primarily in liver, bone marrow and spleen

Plasma ferritin is a window on iron stores:

- 1 ug ferritin/L plasma equivalent to 10 mg storage iron
- Total body iron 2.5 to 3.8 g most in circulating RBCs

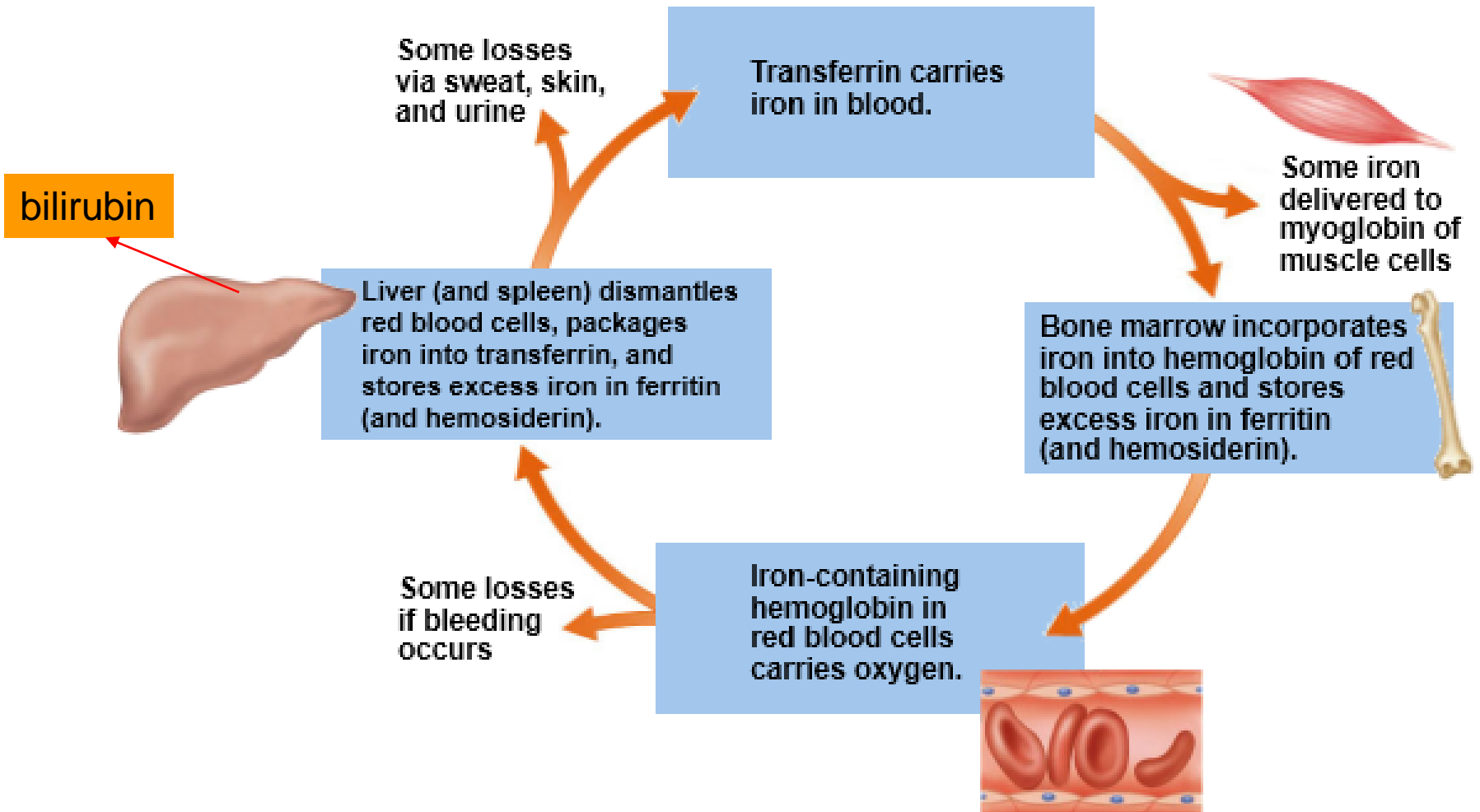


Basal daily iron losses

- Total: 1.0 mg (men)
1.4 mg (premenopausal women)
- GI losses:
 - GI blood (Hgb 0.35 mg)
 - GI mucosal (ferritin 0.10 mg)
 - Bile (0.20 mg)
- Desquamated skin cells and sweat (0.2-0.3 mg)
- Urinary losses (<0.1 mg)
- Menstrual losses (0.5 mg)



Iron Recycled in the Body





Iron Balance

- Iron intake: dietary iron and its bioavailability
- Absorption
- Regulating hormone **hepcidin** from liver inhibits Fe absorption in mucosa if too much Fe
- Amount of iron in storage
- Rate of erythrocyte production
- Iron Losses

Assessment of Iron Status

**Here is what is happening
inside the body:**

**Primary deficiency caused by
inadequate diet
or
Secondary deficiency caused
by problem inside the body**



Declining nutrient stores



**Abnormal functions
inside the body**



**Physical (outward) signs
and symptoms**

**How can the health
care provider tell?**

Diet history

Health history

Laboratory tests

Laboratory tests

**Physical examination and
anthropometric measures**



Adaptations to increase iron availability in **deficiency**

- Increase efficiency of absorption and release from intestinal epithelial cells
- Increase transferrin synthesis and transferrin receptors
- Decrease ferritin synthesis

Normal Blood Cells and Blood Cells in Iron Deficiency Anemia Compared

Normal red blood cell production

DNA synthesis and cell division begins



Hemoglobin synthesis begins



Hemoglobin synthesis intensifies, slowing DNA synthesis and cell division



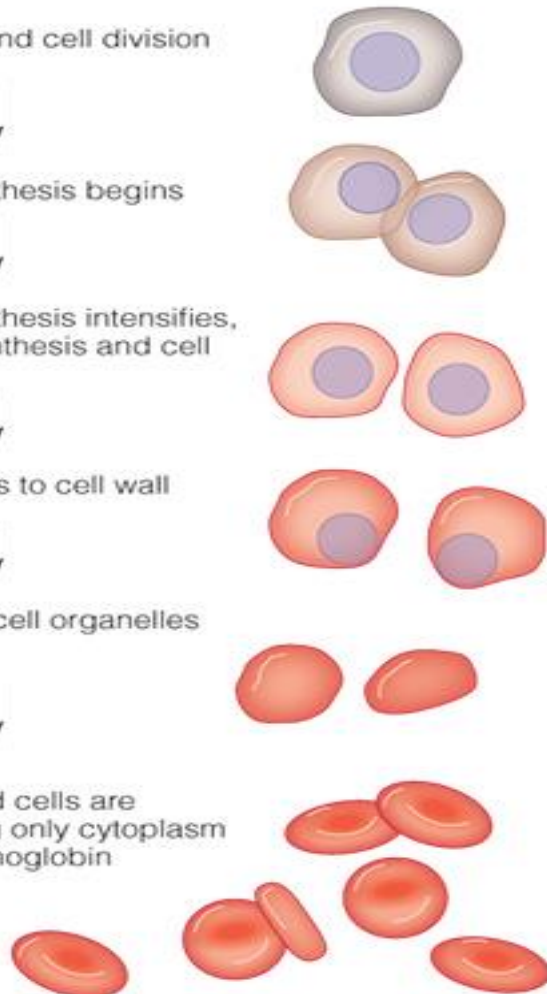
Nucleus migrates to cell wall



Nucleus and all cell organelles leave the cell



Mature red blood cells are small, containing only cytoplasm packed with hemoglobin



In iron deficiency



Without iron, hemoglobin synthesis is impaired



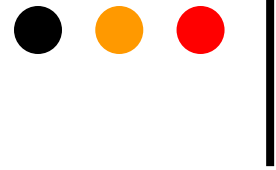
Red blood cells in iron-deficiency anemia are relatively smaller (microcytic) and pale (hypochromic)



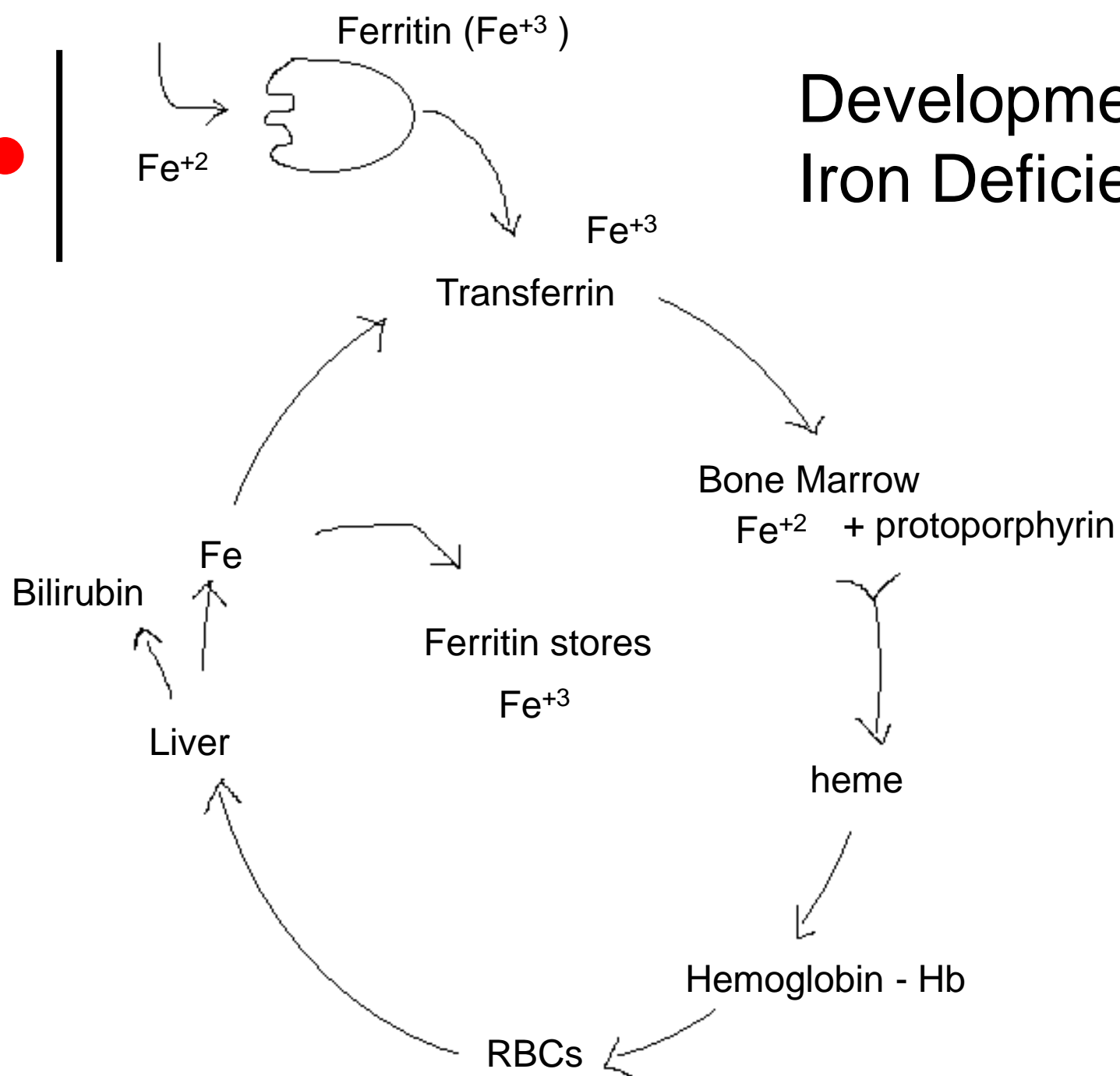
Sequential changes with development of iron deficiency

1. Stage 1: Depletion of iron stores
 - ↓ plasma ferritin
2. Stage 2: Changes in iron transport
 - ↑ absorption efficiency
 - ↑ transferrin iron binding capacity
 - ↓ transferrin saturation %
 - ↑ transferrin receptors
3. Stage 3: Defective erythropoiesis
 - ↓ serum iron
 - Erythrocyte protoporphyrin
4. Iron Deficiency Anemia
 - Microcytic hypochromic erythrocytes
 - Associated behavioural signs get worse

↓Hgb/Hct, MCV



Development of Iron Deficiency





Iron Deficiency Anemia:

Signs and Symptoms

- Tired and pale
- ↓ work performance & mental productivity
- ↓ childhood development-psychomotor and intellectual
- Pica
- ↑ lead poisoning susceptibility

- Men: Hgb < 140 g/L
- Women: Hgb < 120 g/L



Causes of iron deficiency

1. Decreased dietary iron
 - Less iron absorbed
 - Vegetarian diets lack heme
2. Inhibition of absorption
 - Mineral Interactions: Calcium, zinc supplements can ↓ iron absorption
 - Absorption inhibitors
3. Increased red cell mass
 - Pregnancy, growth
4. Increased losses
 - Hemolysis
 - GI bleeding (occult)
 - Heavy menstrual losses



Prevalence of IDA

- Developing Countries
 - 50% of women and children, 25% of men
- Developed Countries
 - 7-12% of women and children
 - 25% of low income infants in Montreal
 - Tip of the iceberg
 - 4 to 5 billion people are deficient in iron
 - Why are women and children at increased risk?



Iron DRIs

Use the % Daily Value (% DV) in the Nutrition Facts table.

Remember: 5% DV or less is a little and 15% DV or more is a lot for all nutrients. Iron is a nutrient you may want more of.

RDA

- Men: 19+:
 - 8 mg/d
 - 14 mg if vegan
- Women: 19-50:
 - 18 mg/d
 - 11 mg if on OCs
 - 33 mg if vegan
 - 27 mg if pregnant
 - Woman >50: 8 mg

○ UL

- 45 mg/d

- Only 25% of women meet their RDA

Vegetarians need 1.8 times as much iron RDA

IDA: Treatment/Prevention

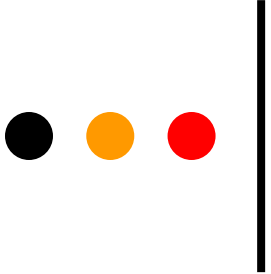
o Treatment

- diet
- supplement
 - ferrous sulphate or gluconate
- retest

o Prevention

- fortify food supply
- pros/cons





24 hr recall- 19 yo woman

- Breakfast:

- Oatmeal (1c), 1 c milk, 1 banana, coffee

- Lunch:

- PBJ sandwich, cookie, apple, water

- Dinner:

- mac and cheese (2c), spinach salad with 2 Tb ranch, tea

- Snacks: nuts, granola bar, tea and coffee



Iron overload and toxicity

- Acute iron toxicity or poisoning....
 - Keep supplements away from kids
- Iron overload from repeated transfusions:
Hemosiderosis... cirrhosis
- Megadoses of Vitamin C – Pro-oxidant
 - can reduce ferric iron bound to transferrin to free ferrous iron
 - free iron is a powerful oxidant: Fenton reaction



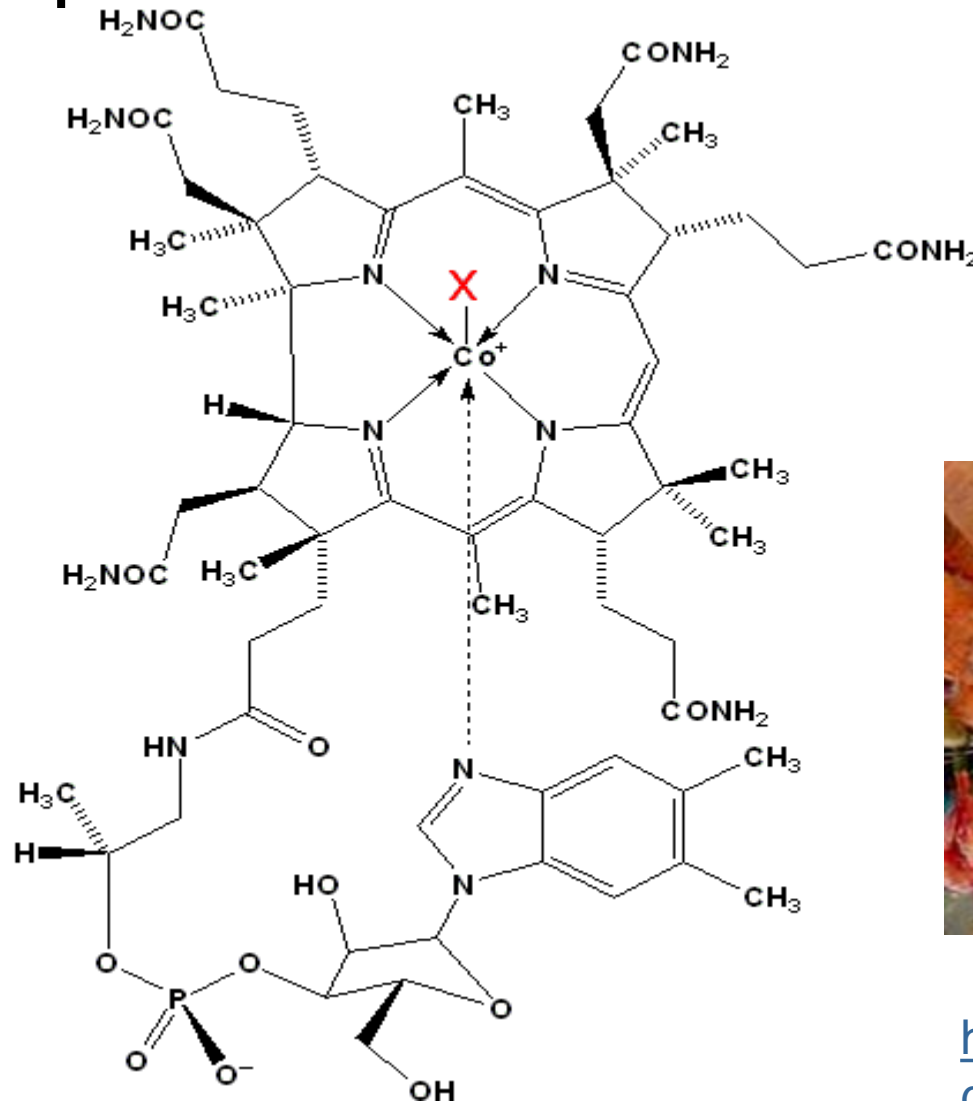
Hemochromatosis:

Chronic iron overload with potential tissue damage d/t accumulation of iron in organs, joints... Can be fatal

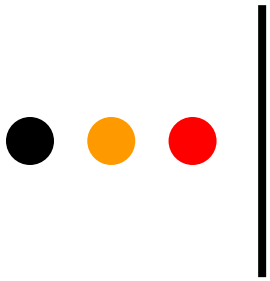
- Autosomal recessive, most common **genetic** disorder in US (1.5 million people)
- More common in men than iron deficiency
- Very efficient iron absorption due to defective hepcidin production (hormone that inhibits iron release from IECs)
- TX: phlebotomy, desferroxamine, low iron diet...Vit. C...

Cobalamin-B12

STRUCTURE AND FUNCTION



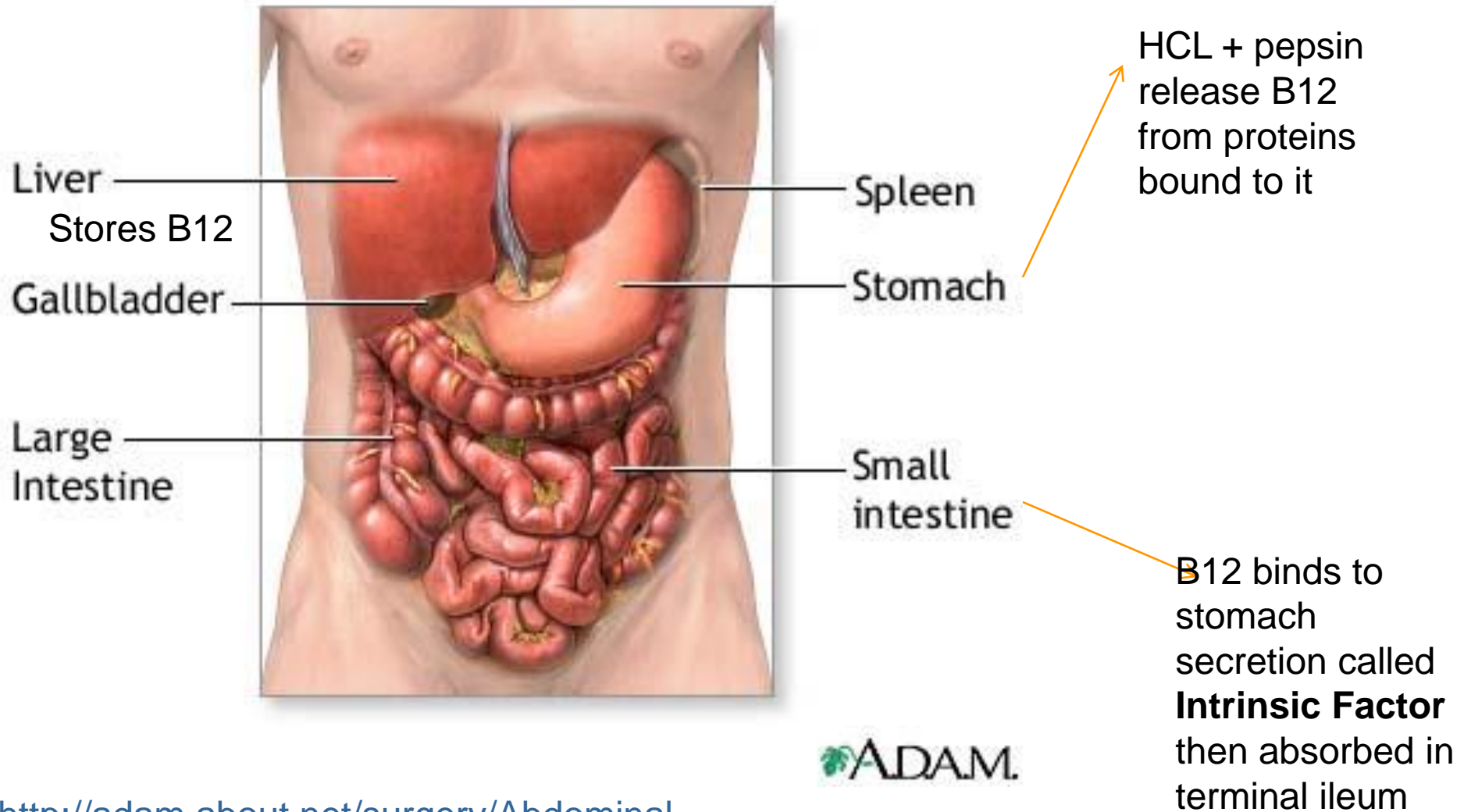
<http://www.brasch-group.com/research/vitamin-b12/>

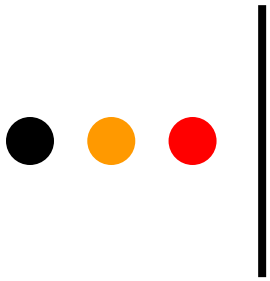


Vitamin B₁₂

- Vitamin B₁₂ and folate depend on each other for activation
 - Regeneration of methionine
 - Synthesis of DNA and RNA
- Individual roles of vitamin B₁₂
 - Protect nerve fibers, and bone cell activity
- Digestion and absorption
 - Stomach → hydrochloric acid and intrinsic factor
 - Absorption in small intestine
 - Enteropathic circulation for both folate and B12 - bile

● B12 | Digestion, Absorption and Transport

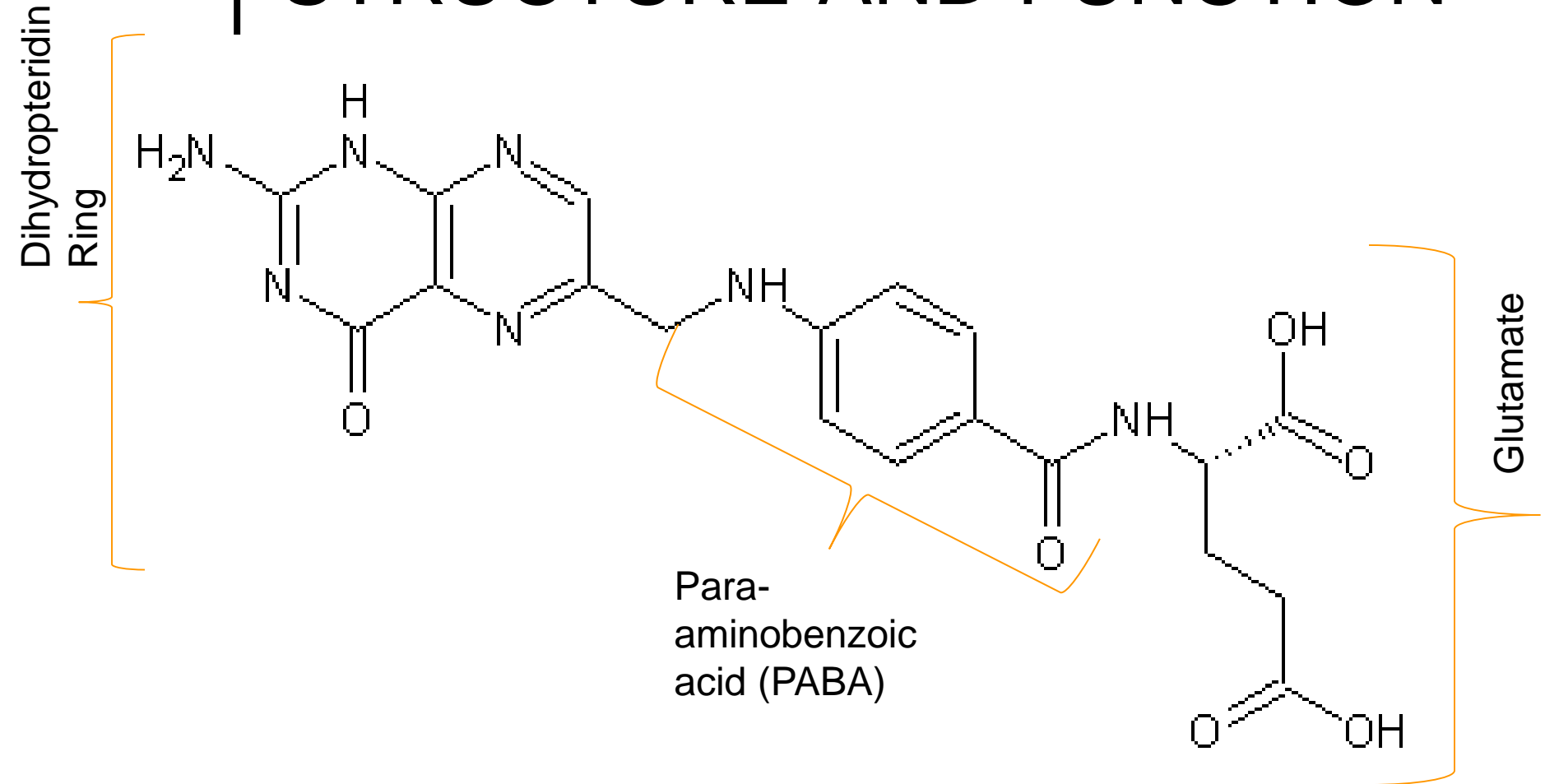


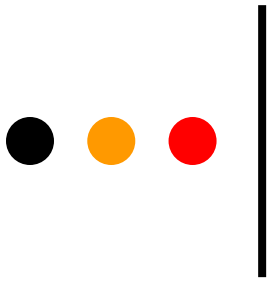


Vitamin B₁₂

- Food sources: animal
 - Best bioavail: Fish, meat and milk, eggs
 - Vegan: fortified plant beverages and cereals, B12 fortified nutritional yeast
 - RDA: 2.4 micrograms
- Deficiency sx: fatigue, dementia, peripheral nerve degeneration – paralysis
- Rx interactions: PPI's
- Toxicity
 - No adverse effectsNo UL

FOLATE (folic acid) STRUCTURE AND FUNCTION



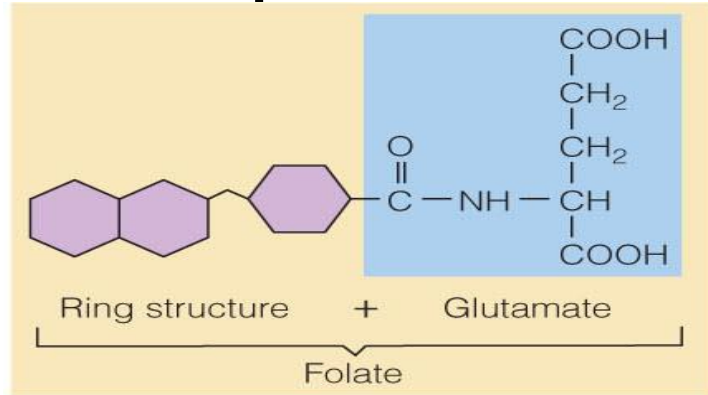


Folate

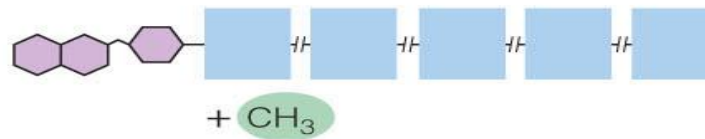
- Also known as folacin or folic acid
- Primary coenzyme form—THF (tetrahydrofolate)
 - Transfers 1-carbon compounds during metabolism
 - Converts vitamin B₁₂ to coenzyme form
 - Synthesizes DNA
 - Regenerates methionine from homocysteine



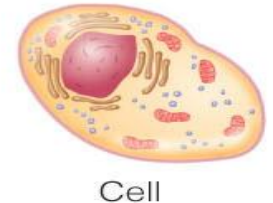
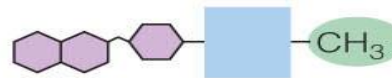
Folate absorption and metabolism



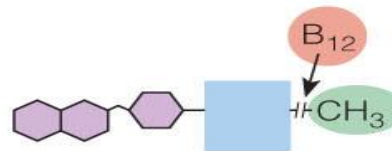
In foods, folate naturally occurs as polyglutamate. (Folate occurs as monoglutamate in fortified foods and supplements.)



In the intestine, digestion breaks glutamates off . . . and adds a methyl group. Folate is absorbed and delivered to cells.



In the cells, folate is trapped in its inactive form.



To activate folate, vitamin B_{12} removes and keeps the methyl group, which activates vitamin B_{12} .

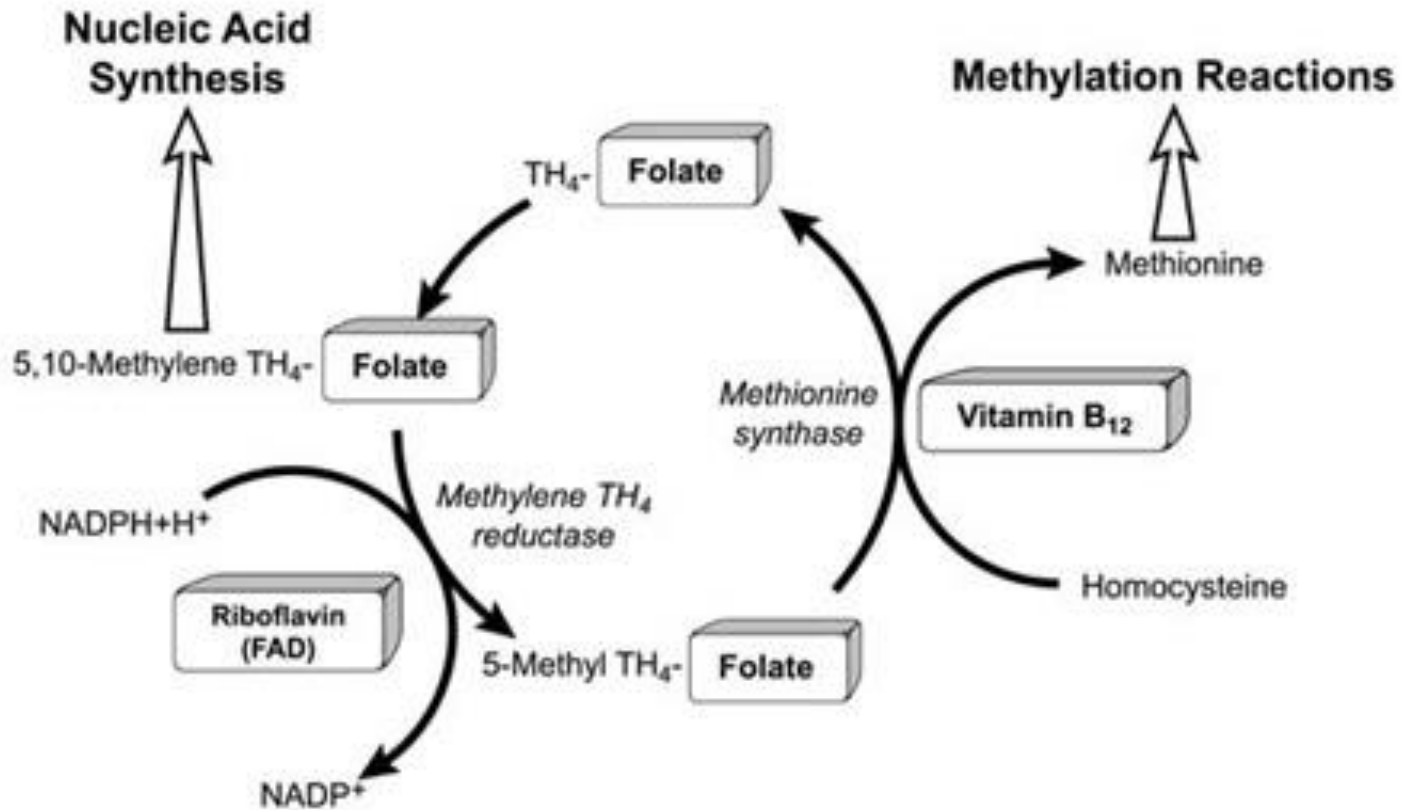


Both the folate coenzyme and the vitamin B_{12} coenzyme are now active and available for DNA synthesis.

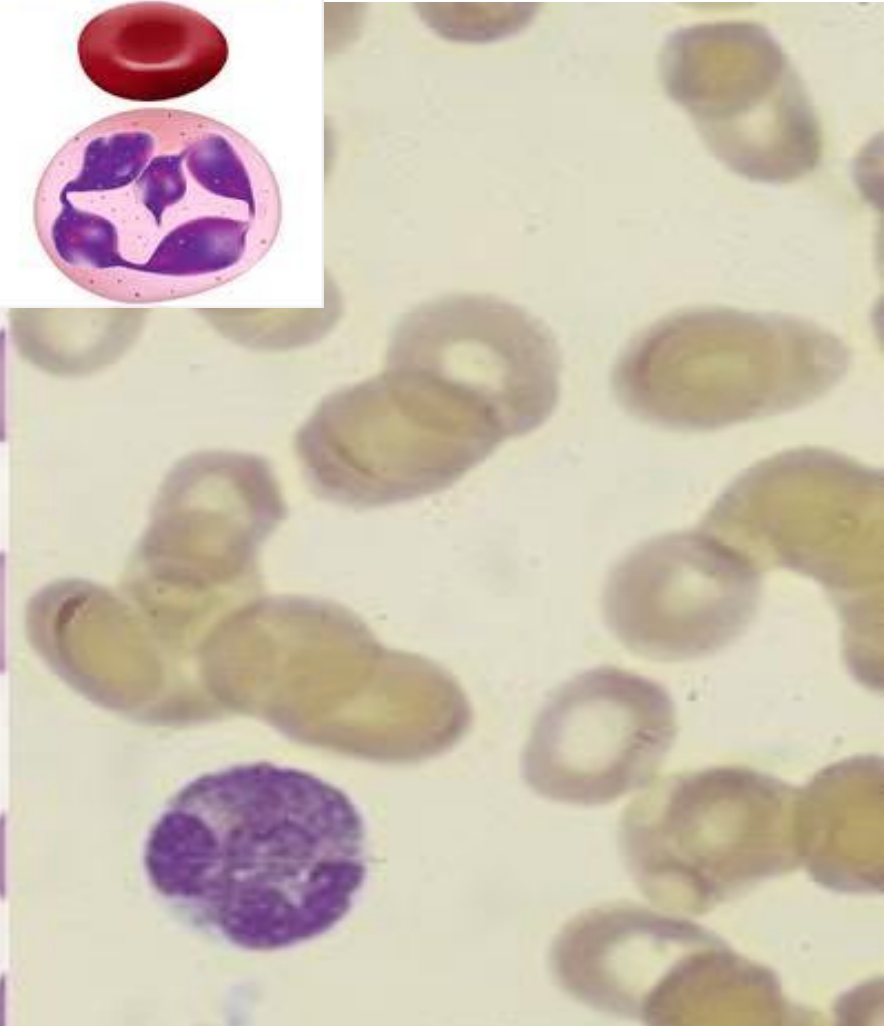
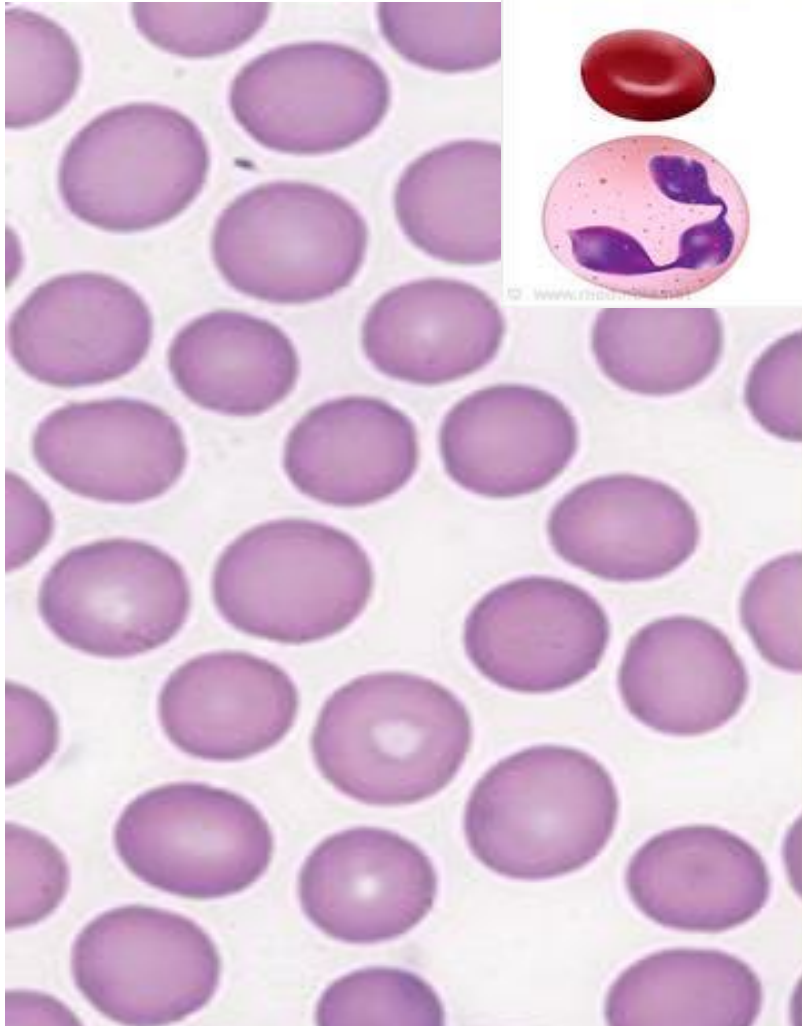
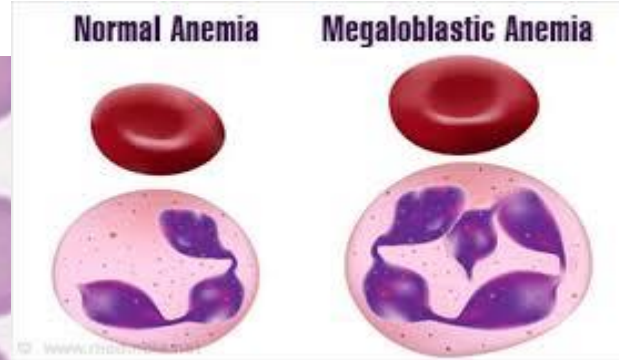


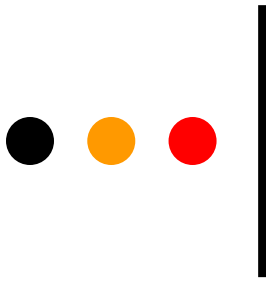
Natural vs
Synthetic folate monoglutamate

Folate activation and relationship with B12

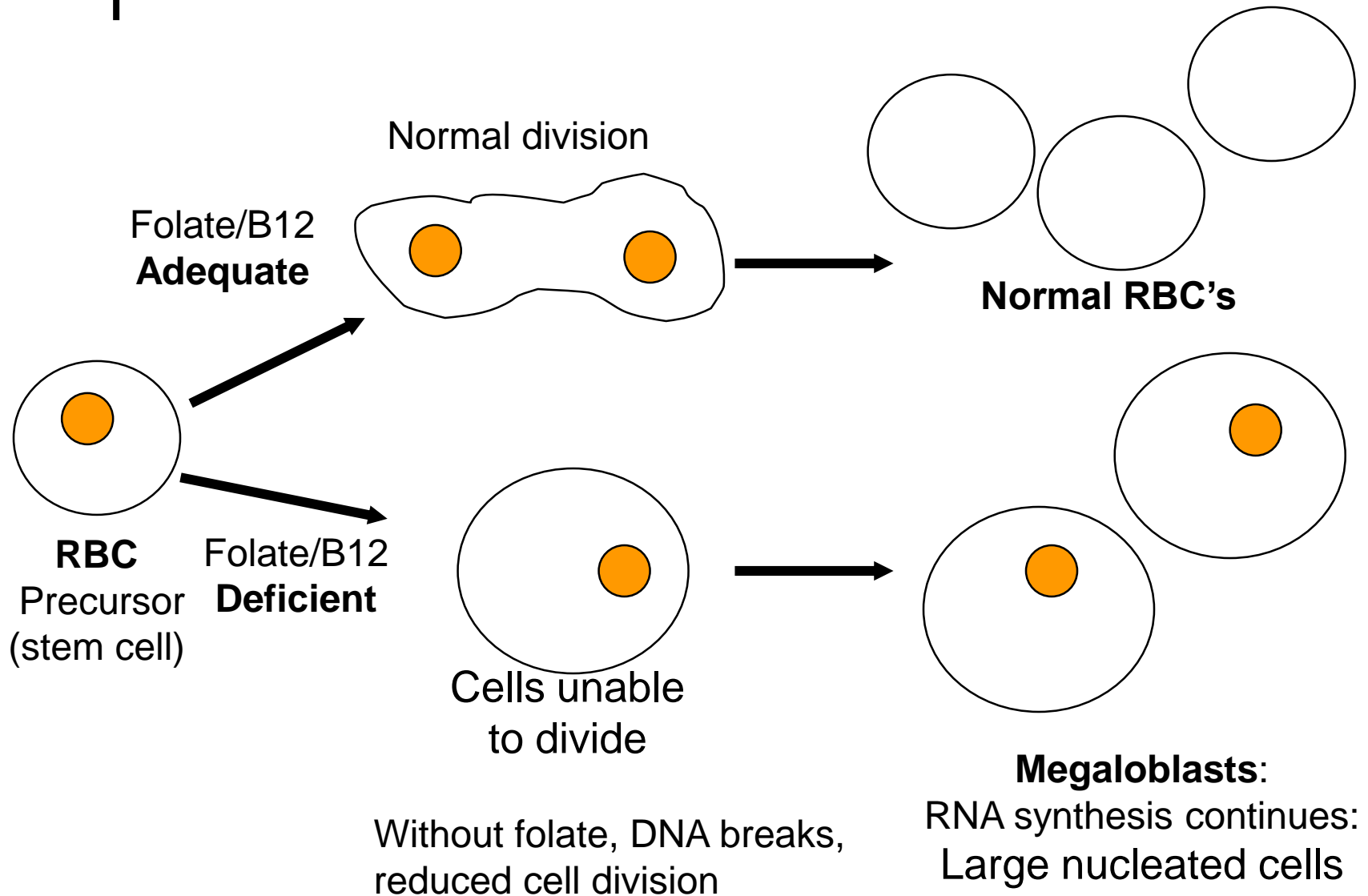


What is Megaloblastic Anemia?

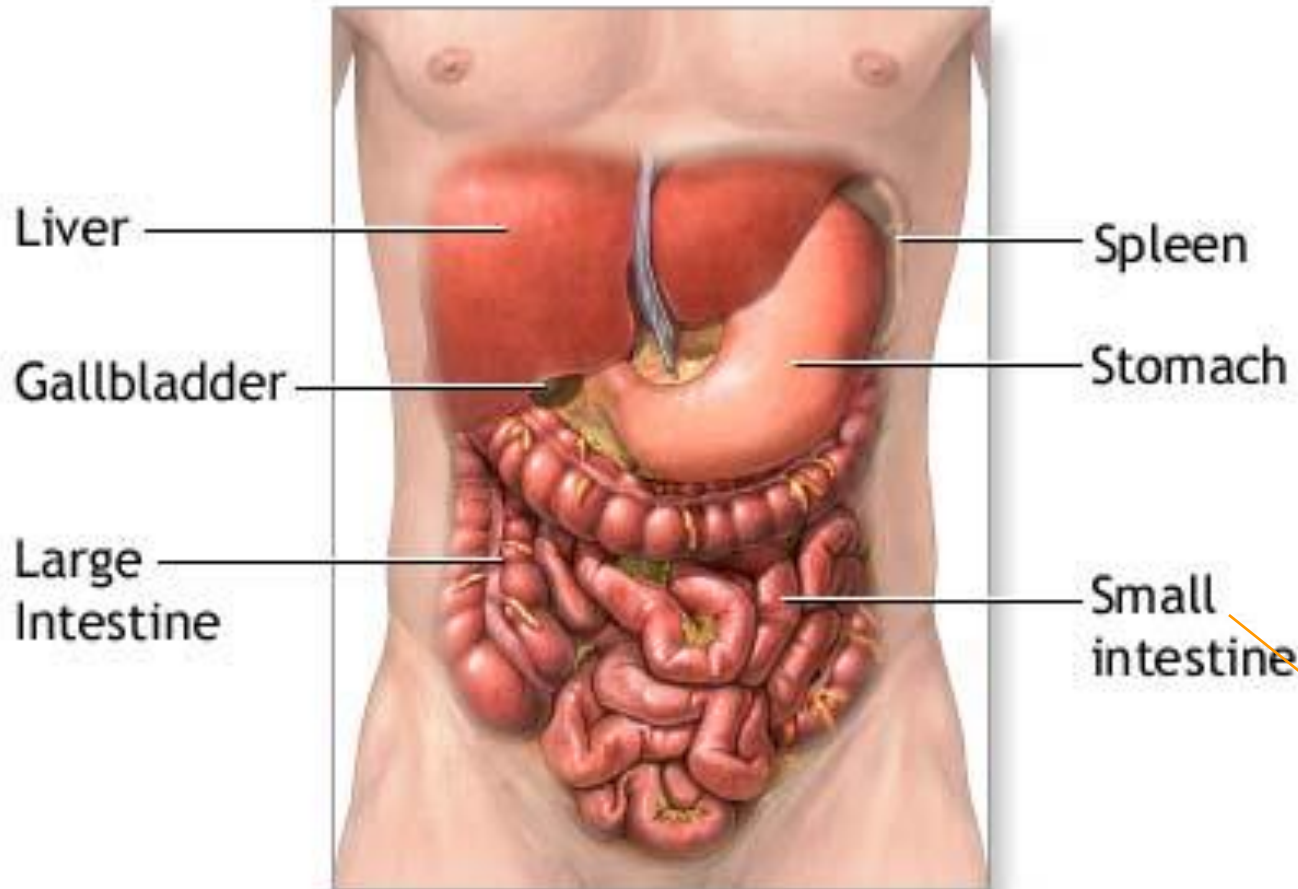




Megaloblastic Anemia



DO not confuse Pernicious Anemia with other Megaloblastic Anemias



HCL + pepsin
release B12
from proteins

**-NO PRODUCTION
OF INTRINSIC
FACTOR**
-B12 is left unbound
and is not recognized
by intestinal surface
receptor cells, for
absorption.
-Secondary B12
deficiency



Anemias

- Megaloblastic Anemia

- Primary Deficiency

- Lack of dietary Folate **or** B12
 - Large immature RBCs
 - Vegans
 - (B12 only found in animal foods, fortified plant milks, fortified foods)
 - But not common, slow to develop

- Pernicious Anemia

- Secondary Deficiency

- Also large immature RBCs
 - Neurological component
 - Intrinsic factor deficiency
 - Does not respond to B12 supplement – why?
 - Elderly at risk
 - Given B12 injections or nasal spray

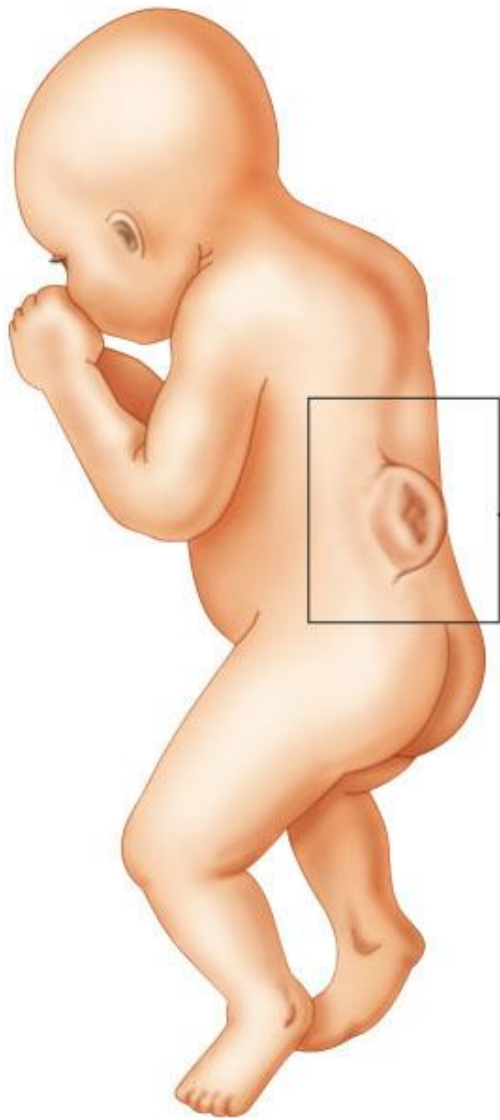
FOLATE DEFICIENCY

Impairs cell division and protein synthesis

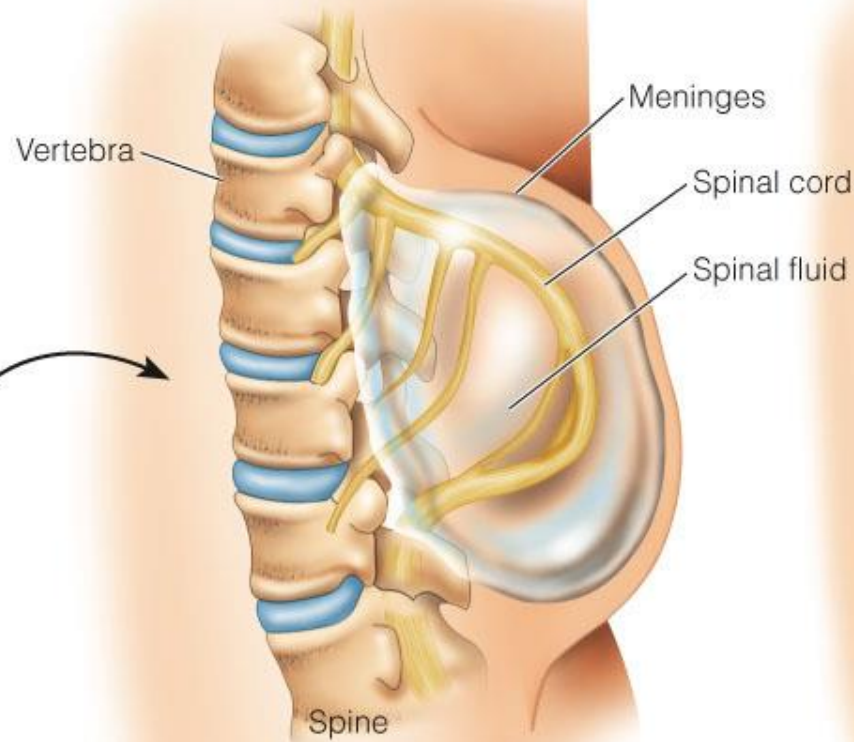
- Megaloblastic anemia
- GI tract deterioration, smooth red tongue
- Neural tube defects
- Mental confusion, irritability, fatigue
- Elevated Homocysteine/CVD Risk
- Drug interactions



I



Spina Bifida



Normal Spine





Risk Factors

Incidence - any pregnancy is at risk

- 3/1000 live births (+ miscarriages and abortions)
- 400 infants/year in Canada
- 95% have no previous history
- 20 X more likely recurrence risk

Diet – Preconceptional Folate Status

Genetic Link

- Family history of NTD on either side

Ethnic Background

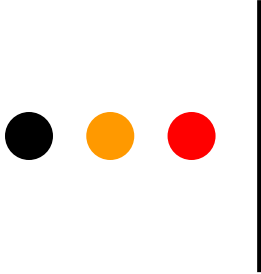
- Northern European and Hungarian ancestry

60-75% of NTD's can be **prevented** by 400ug/d adding folic acid to diet before conception



Health Canada Recommendations Women who can become pregnant

- Take a 400 ug folate supplement to reduce risk of FIRST time NTD occurrence
 - Folate RDA 14+: 400ug
 - RDA pregnancy: 600 ug
 - Total folate=folic acid (suppl) + dietary folate (foods plus fortified foods)
 - Starting 3 months prior to conception
 - Many pregnancies unplanned (50%)...



Fortification has cut NTD births by 50% -
see Fig10-12

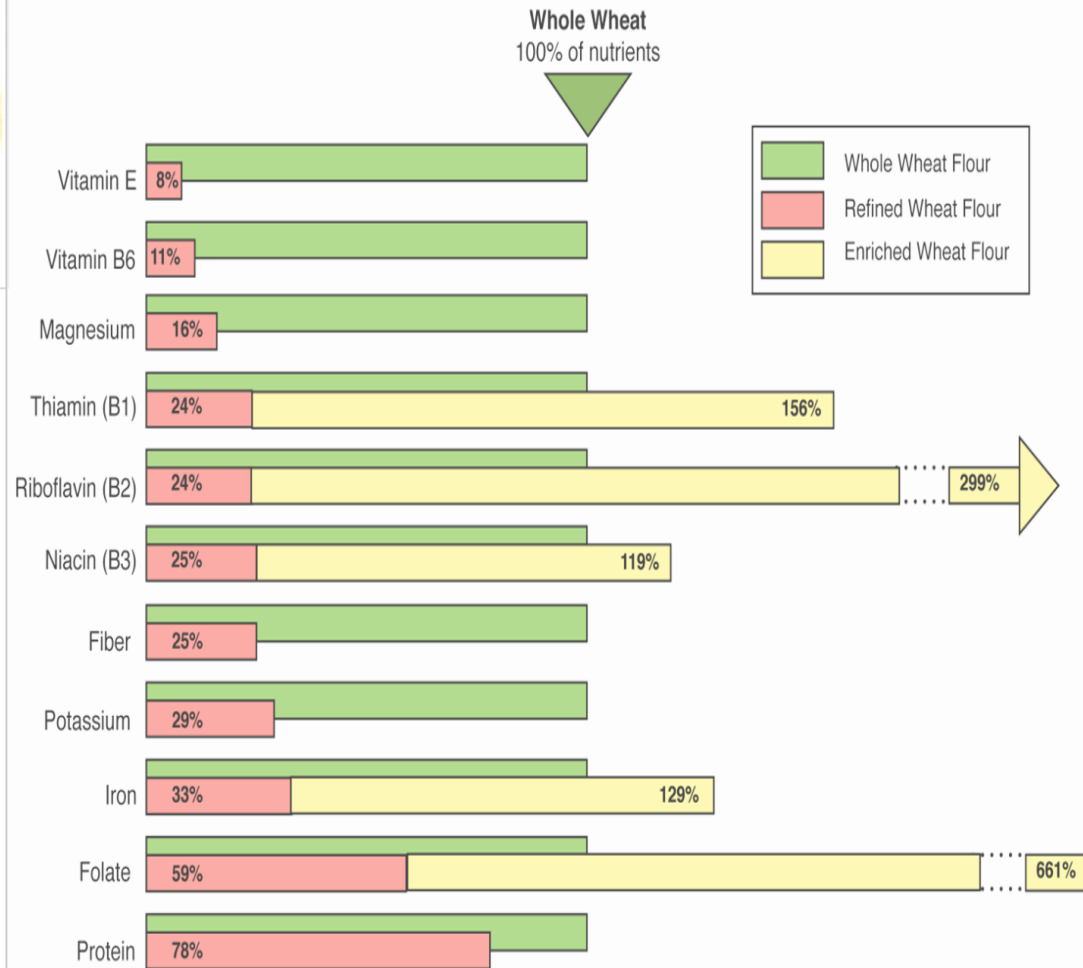
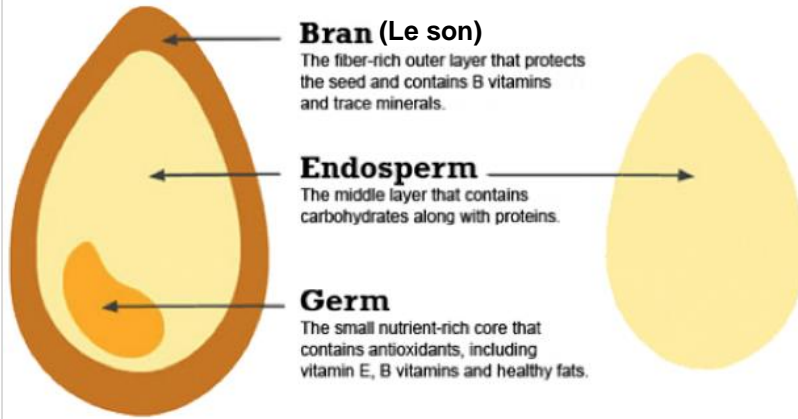
Current levels in 100 grams of flour, white flour, enriched flour, or enriched white flour

Nutrient	Level
Thiamin (mg)	0.64
Riboflavin (mg)	0.40
Niacin (mg)	5.30
Folic acid (mg)	0.15
Iron (mg)	4.4

SOURCE: Justice Canada, Food and Drug Regulations, Part B, Division 13, 13.001.[S], Grain and bakery products.

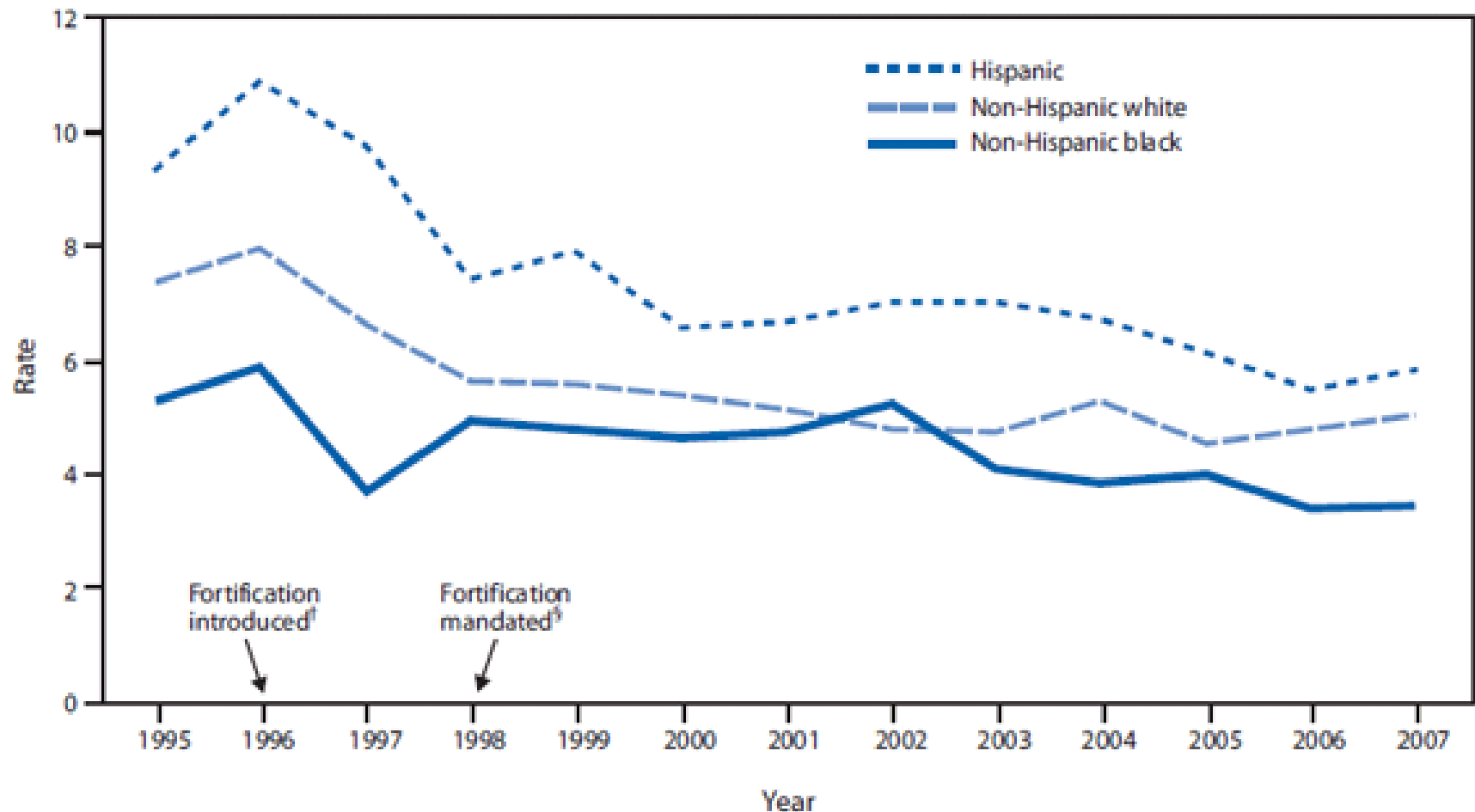
Grains

Whole Grain vs. "White" Grain



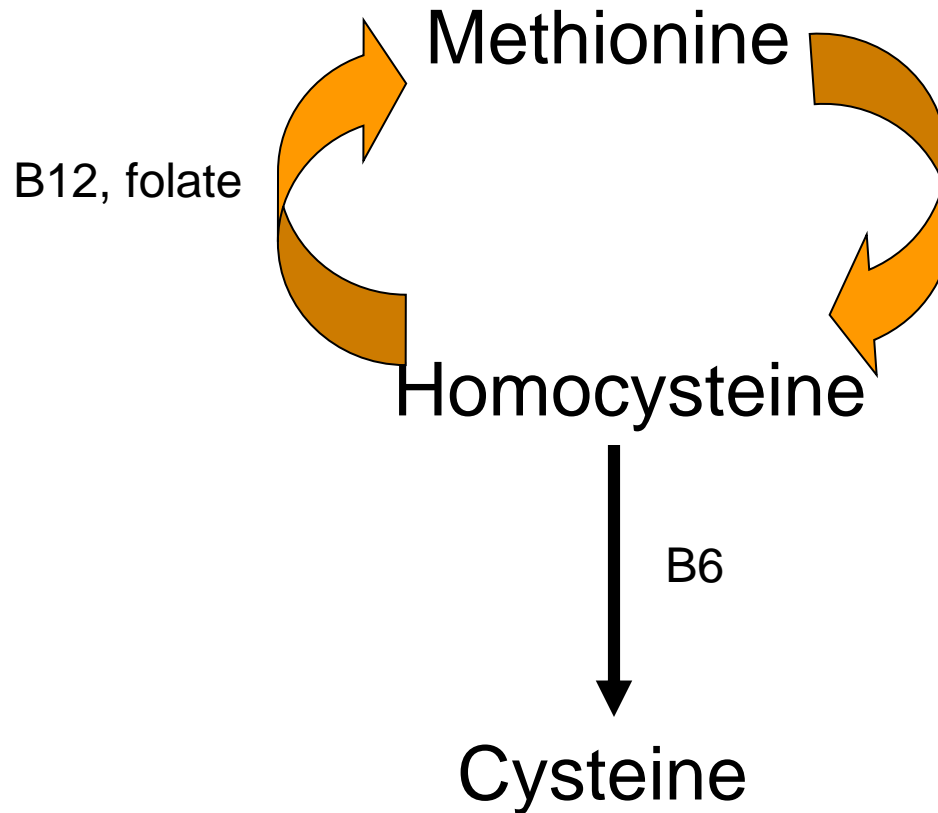
● ● ●

FIGURE 2. Neural tube defect rates per 10,000 population, by race/ethnicity and fortification period status --- National Birth Defects Prevention Network,* 1995--2007



<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a2.htm>

Vitamins affect Homocysteine



Vitamin deficiency causes a bottleneck in homocysteine removal – build up and



Homocysteine and CVD

- ... the homocysteine damages arteries
- patients with CVD and strokes have high levels
- **independent** risk factor for CVD
 - independent of smoking, cholesterol
 - ... Folate /Vit B supplementation does not seem to prevent CVD risk or mortality

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4169527/>



Increase Folate Status

o Dietary Strategies

- Increase Fruits and Veg
- Increase Grains, Seeds and Legumes

o Folate Supplements

- Needed pre-conception

o Fortify the food supply...

- - flour, cereals

Folate in Selected Foods

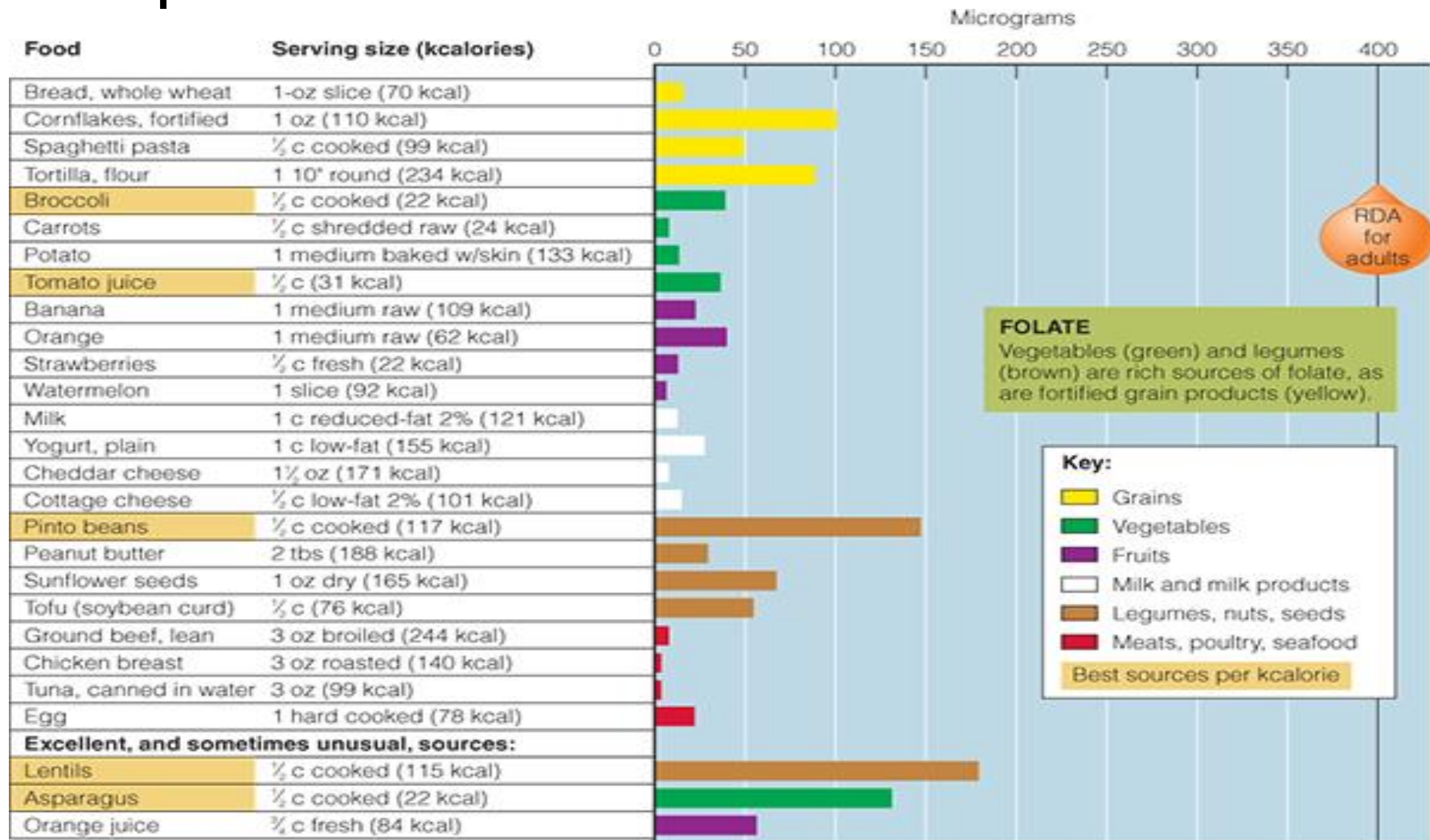


Figure 10-13 Cengage 2019



Fortification of the Food Supply

- Add nutrients to a food
 - to correct or prevent a widespread nutrient deficiency
 - to restore nutrients lost in processing
 - to add nutrients normally supplied in the food the product replaces

Health Canada



Fortification Controversy

- Targetting the at-risk population
 - Can you reach the population who need it?
- Optimal intake
 - Can you provide enough to fix the problem in those who need it without endangering others



But folate supplements can mask
B12 deficiency....

Additional folate will fix megaloblastic anemia
regardless whether anemia was due to B12 or
folate deficiency

But **does not** fix the irreversible neurological
problems of B12 deficiency

The fundamental neurological problem is masked
(and therefore not treated) because the visible
blood problem is fixed

Folate Toxicity: UL= 1000 micrograms/d



Folate Fortification

○ Beneficial effects?

- ↓Anemia
- ↓Neural tube defects
- ↑Mental function
- ↓Homocysteine
- May reduce cancer, heart disease risk

○ Adverse Effects?

- Mask Vit B12 deficiency in elderly
- May promote cancer growth once started



Fortification controversy - iron

- o Beneficial effects?
- o Adverse Effects?