بسم الله الرحمن الرحيم

Pharmacology

FINAL | Lecture 7

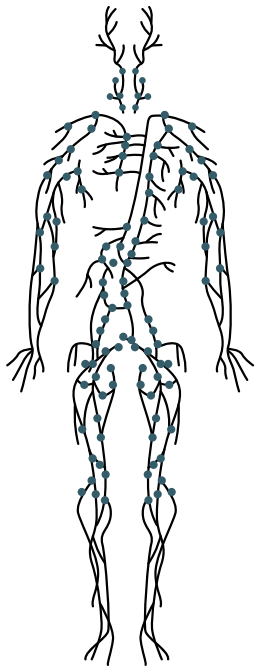
Anemia

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

Written by: Almothana Khalil
Omar Ibrahim

Reviewed by: Almothana Khalil



Hematopoiesis

- 200 billion new red blood cells per day

- The hematopoietic machinery requires a constant supply of **iron, vitamin B_{12}, and folic acid** (all 3 cases are discussed in this lecture).

- Hematopoietic growth factors are 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.

- Anemia:
  a deficiency in oxygen-carrying erythrocytes, is the most common hematological disorder, and several forms are easily treated.

Iron Deficiency Anemia

More common in females
- Menstruation
- Pregnancy/Breastfeeding

- 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.

  Less iron → less/smaller RBCs → oxygen-carrying capacity is diminished.

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

  Cardiovascular compensation can overload the heart, raising the risk of heart failure.

Iron Deficiency Anemia

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

The body adapts to increase absorption in cases of deficiency.

Requirement:

- Adult males 13 ug/kg,
- Adult females 21 ug/kg,

  pregnant women and infants 80 ug/kg.

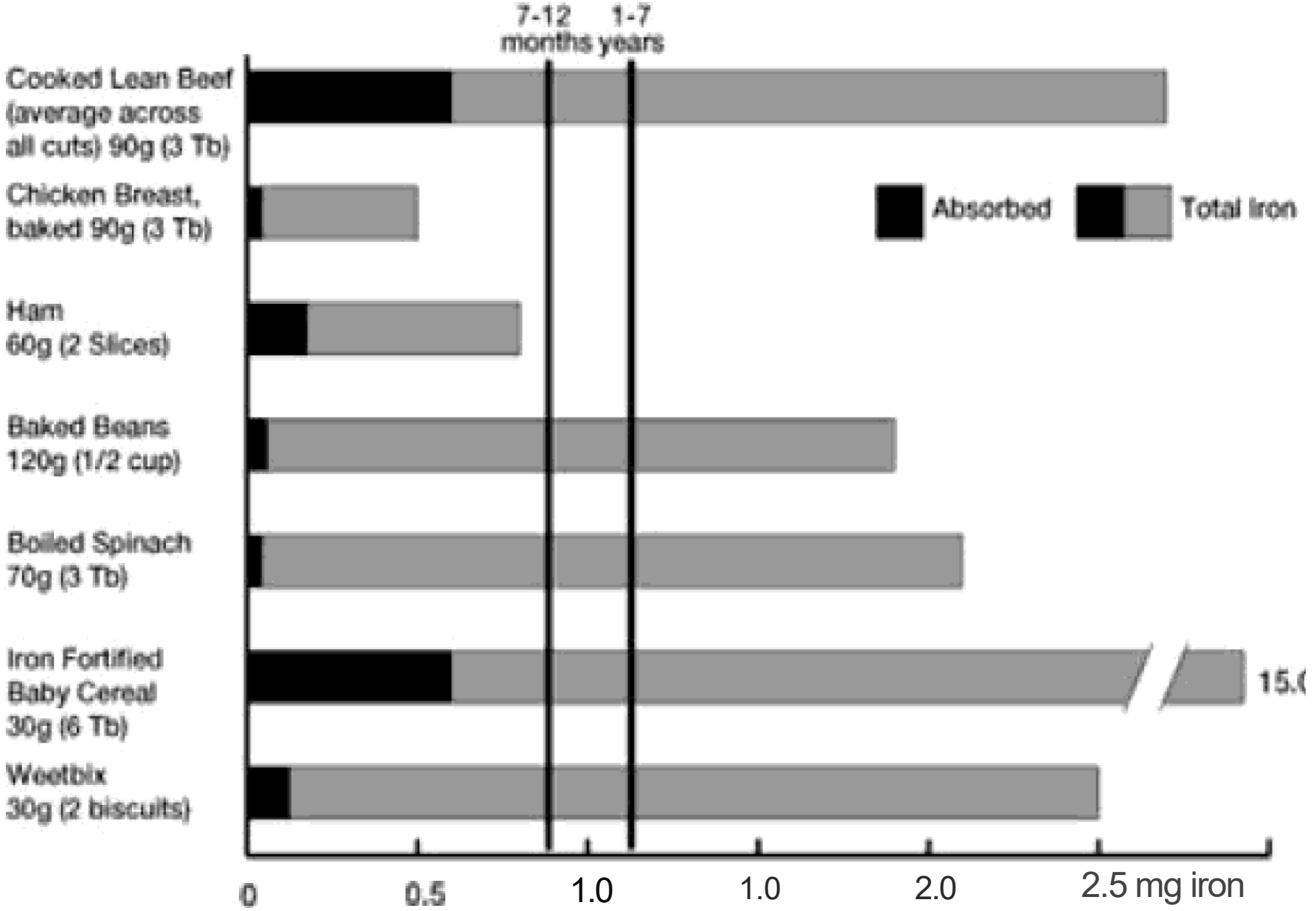
– Dietary iron in form of heme (meat) can be absorbed intact.

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

Heme iron is better absorbed (20:1) vs non-heme.

ABSORBED IRON REQUIREMENT

Beef, chicken, ham, and cereals were mentioned, but take a look at all the list.



Indications for the Use of Iron

- Treatment or prevention of iron deficiency anemia.
- Iron deficiency is commonly seen in populations with

1) 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.

2) Inadequate iron absorption:

✓ this is seen frequently after gastrectomy

✓ severe small bowel disease that results in generalized malabsorption.

Oral Iron

- Preparations:

BEST ONE ➔ **ferrous fumarate 33% elemental iron,**

– **ferrous gluconate 12% elemental iron,**

– **ferrous sulfate 20% elemental iron.**

Oral Iron

- Adverse Effects: 20-25% (very high number) have GI problems, especially females: nausea, epigastric pain, constipation, abdominal cramps.

- Food decreases oral iron absorption by 30 - 50%.

  Ideally, taking oral iron on empty stomach is better, but some adverse effects can be dealt with by taking oral iron with food, which compromises the absorption efficiency (but it's OK).

- Drug interactions:

✓ tetracyclines (iron-chelating agents);

✓ antacids (reduce stomach acidity, so less soluble ferrous iron (Fe^{2+}))

both decrease iron absorption.

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

- Patients taking oral iron develop black stools (another side effect).

Parenteral Iron

Less commonly used compared to oral iron.

Should be reserved for

(1) patients with **documented iron deficiency**

(2) patients who are **unable to tolerate or absorb oral iron;** intolerance is probably due to the severity of the adverse effects mentioned previously

(3) patients with extensive chronic anemia who cannot be maintained with oral iron alone, so larger amounts (depot) are injected to correct severe anemia, such as

- ✓ 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 (most common; need-to-know), 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, probably because iron tablets are usually appealing, in appearance, for little children.
- 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 (antidote for iron toxicity),** 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**.

1. It most commonly occurs in patients with **inherited hemochromatosis**, a disorder characterized by **excessive iron absorption**.

2. and in patients who **receive** many red cell **transfusions** over a long period of time (e.g., 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

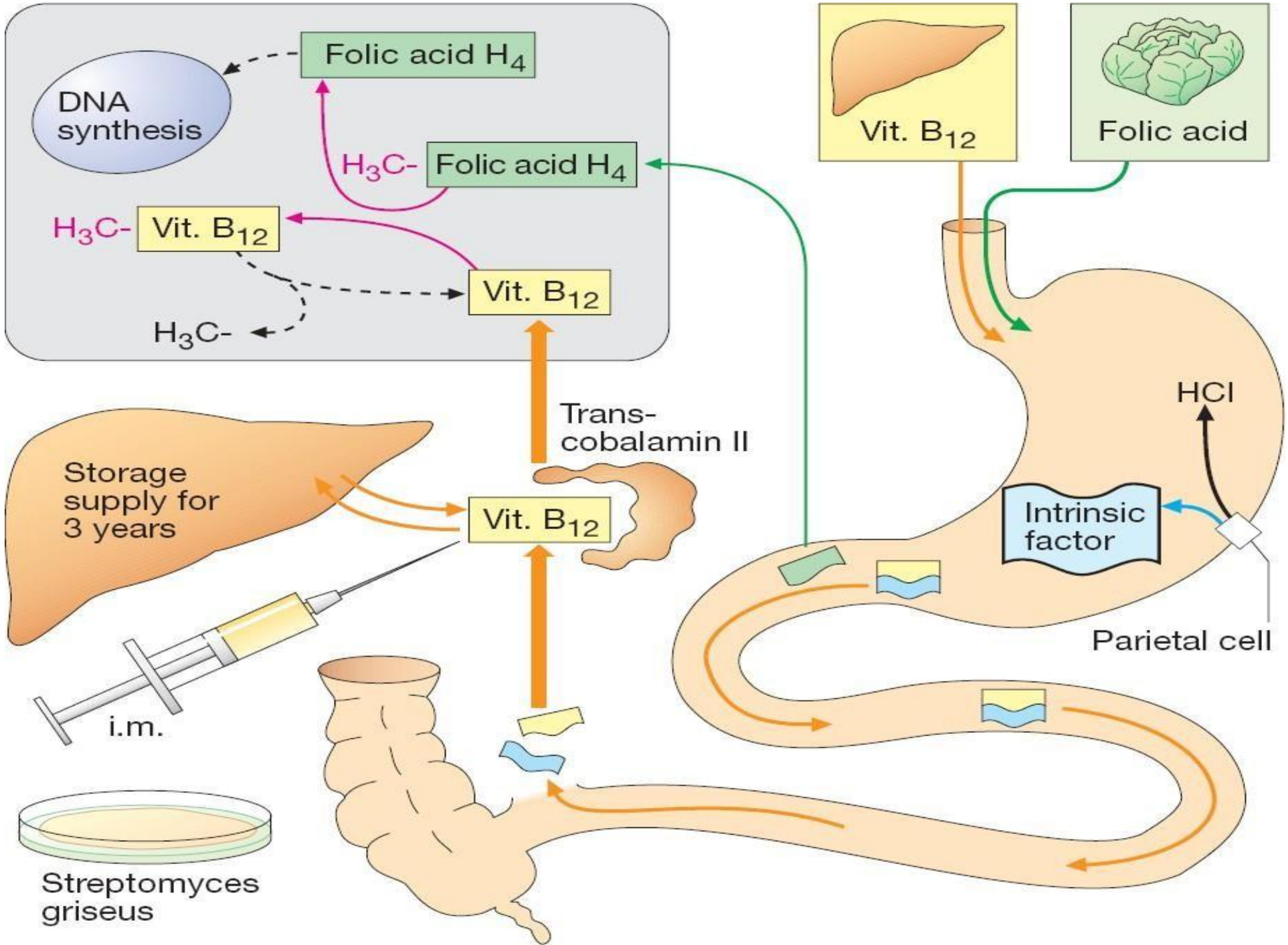
Marrow disorder caused by defective DNA synthesis, causes include:

- Vitamin B_{12} deficiency (Mainly found in Meat)
- Folic acid deficiency (Mainly found in green vegetables)

Anemia may result from: (Causes of Vitamin B12 and Folate difficiency)

1. **Dietary deficiency** – e.g., strict vegetarians (lack of Vitamin B_{12}).
2. **Impaired absorption** – e.g., **pernicious anemia**
3. **Gastrectomy** – loss of intrinsic factor secretion.
4. **Malnutrition**, **rheumatoid arthritis**, or **thyroid conditions**.

Vitamin B12 Anemia particularly is 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.



Notes on this picture in the next slide.

Doctor's Notes on the previous slide

- **Vitamin B12** acts as an **essential cofactor** in the conversion of **methylmalonyl-CoA → succinyl-CoA**.

- **Deficiency** of vitamin B12 leads to **accumulation of methylmalonic acid**, which **disrupts myelin synthesis** and causes **neurological symptoms** (e.g., paresthesia, ataxia, loss of position and vibration sense).

- Most of folate in our bodies exist in the methylated form (Methyl-THF). Vitamin B12 is required to transfer that **methyl group from methyl-THF to homocysteine**, forming **methionine,** yielding two points:
  - **Methionine** is further turned into **SAM** (S-Adenosyl Methionine), a **Methyl Group Donor** that is **essential for DNA synthesis.**
  - Methyl-THF is demethylated into **THF**, which also can act as a methyl group donor **in DNA synthesis.**

- **Folic acid supplementation** can **partially correct the anemia** (by flooding the body with folate, leading to the restoration of THF) but **does not prevent neurological damage**, since methylmalonic acid remains elevated in B12 deficiency.

- Vitamin B_{12} is used to treat or prevent deficiency.
- Injections only benefit if deficiency (In case of severe deficiency, oral administration is not sufficient)
- Neurologic symptoms (paresthesias occur first, then balance and fine movement loss) in severe deficiency may be irreversible after several months
- May need lifelong injections if malabsorption is present; can not absorb B12/intrinsic factor complex

- NOTE:

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

Vitamin B_{12}

- Vitamin B12 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. (Binds more to proteins = Lower renal clearance rate = would stay in the circulation longer and act as a reservoir)
- **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 (insufficient to cover 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
- 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. Megaloblastic anemia develops relatively faster upon dietary folic acid cessation when compared to Vitamin B12, as folic acid reserves are much smaller than vitamin B12 reserves.

- 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. *-To be discussed in the CNS 🧠-*

Adverse reactions:

- Erythema, itching, and rash.

QUIZ

PHARMACOLOGY

LECTURE 7

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			