

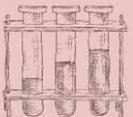
Sheet No.



# H PATHOLOGY S



W r i t e r : DR 018



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## *Anemia of decreased production:*

Erythropoiesis occurs normally in the bone marrow. So, anemia due to decreased erythropoiesis starts from the bone marrow.

They are classified according to the cause:

- a) Nutritional deficiency (**most common**)  
*Includes iron deficiency, vitamin B12 deficiency, and folic acid deficiency*
- b) Chronic inflammation
- c) Bone marrow failure

## Iron deficiency anemia (IDA)

### a) Epidemiology

- Most common type of anemia worldwide and in all age groups (*most common in the community in general*)
- It affects 10% of individuals in developed countries and 25-50% of individuals in developing countries (because it's related to nutrition).

### b) Where is iron normally found in the body?

- The majority of iron in the body is found in the red blood cells (in **hemoglobin**).
- Iron storage pool, which consists of 1-**ferritin** (soluble and found in the cytoplasm) and 2-**hemosiderin** (insoluble)(storage protein for iron) , is found in the bone marrow, liver, and spleen. It Forms around 15-20% of total body iron.
- Iron might also be found in certain **enzymes**.
- The remaining iron is found in the serum attached to **transferrin**. (around 1% of total body iron)

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**Hemosiderin** is basically a large ferritin , consisting of **large iron particles, granular** in shape,**intracellular** in the cytoplasm of **macrophages** of the reticuloendothelial system (in **bone marrow**), and is visible by **light microscope** using a special stain.

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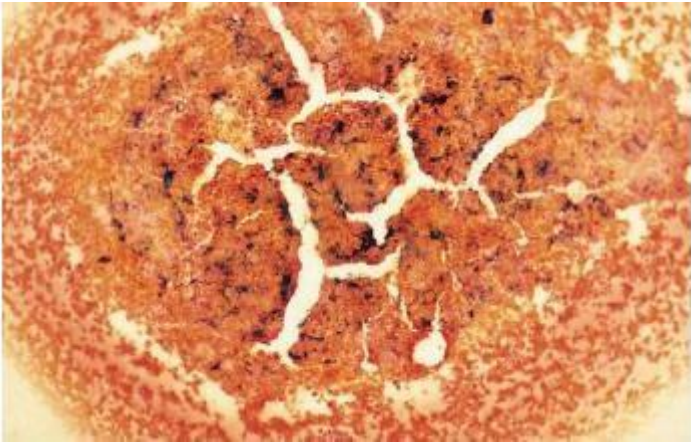
### c) Indicators of iron status (lab tests)

#### 1) Bone marrow aspirate (**most accurate**)

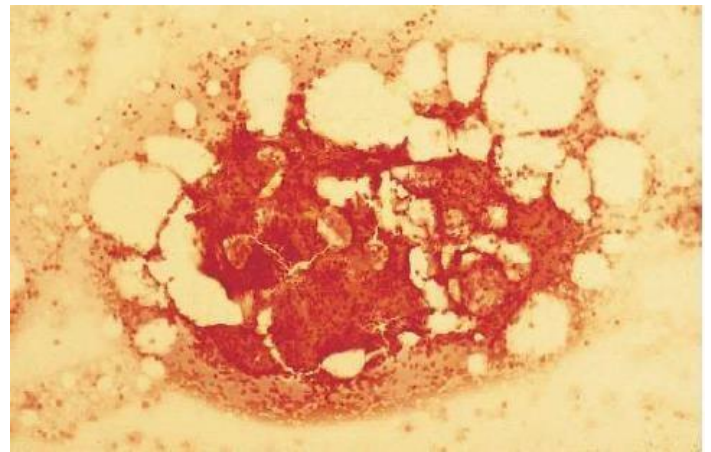
It is an invasive procedure and detects the earliest changes.

The aspirate is stained using **Perl's Prussian blue stain** and the iron will stain blue. However, this test is uncomfortable (because it's invasive) and expensive.

Therefore, we do not start with it. **Iron status is low in Iron deficiency anemia.**



Aspirate of **normal** bone marrow. Bluish-black iron (hemosiderin) in macrophages found.



Aspirate of **iron deficiency anemia**. No stainable iron found.

## 2) Serum ferritin level

- We measure the serum ferritin level in the venous system. The serum ferritin will reflect the ferritin in the bone marrow, therefore, it is the second to be affected by decreasing iron level, after the bone marrow iron storage pool. (when there`s iron def. the no. of ferritin (and iron storage pool in BM decreases so serum ferritin levels will be decreased as well – serum ferritin is derived from stored ferritin).
- However, there are other factors that affect the serum ferritin level (other than iron). These include:
  - a) Inflammation (serum ferritin **increases**)
  - b) Fasting (serum ferritin **increases**)
  - c) Vitamin C deficiency (serum ferritin **decreases**)
  - d) Pregnancy (serum ferritin **decreases**), especially during the first trimester due to dilution (because of the increase of the fluids in pregnancy)

**Serum ferritin is low in Iron deficiency anemia using this test.**

## 3) Serum iron level

- Iron is transported in the plasma bound to the protein transferrin.
- Measuring serum iron level is **not** always accurate as it takes time for the serum iron level to decrease in cases of iron deficiency.

**Serum iron is low in Iron deficiency anemia using this test.**

## 4) Transferrin saturation

- In normal persons, 30% of transferrin is saturated with iron

**Transferrin saturation is low in Iron deficiency anemia using this test.**

### 5) Total iron binding capacity (TIBC)

- Old and reliable test (indirect test)
- Mechanism: a sample of the patient serum is taken, and iron is added to the sample artificially. Depending on the **saturation** of transferrin, the added iron will bind to transferrin if there was a deficiency in iron in the sample. And we say that the total iron binding capacity for the sample is high. If the serum sample already had enough iron, then the artificially added iron will not be able to bind to the transferrin, and the total iron binding capacity for the sample is low. (the idea of this test: it measures the deficiency by how much the sample absorbs iron and bind it to transferrin).

**Total iron binding capacity is high in iron deficiency anemia.**

### 5) Serum transferrin and transferrin receptors \*not mentioned\*

- Both are synthesized in the liver and secreted into the serum
- In cases of iron deficiency, the synthesis of transferrin and transferrin receptors by the liver increases, in order to compensate. *(The liver thinks that there's not enough transferrin to meet the body's need of iron. So it starts to make more. However, the problem isn't the transferrin, rather, it is the decreased iron in the body)*

**Serum transferrin and transferrin receptors are high in iron deficiency anemia.**

### 6) Reticulocyte hemoglobin content (CHr) ~same concept as MCH

**Reticulocyte hemoglobin content is low in iron deficiency anemia.**

### 7) Mean reticulocyte volume (MRV) ~same concept as MCV

- Both erythrocytes and reticulocytes will have a smaller mean volume.

**Mean reticulocyte volume is low in iron deficiency anemia.**

## D) Iron homeostasis

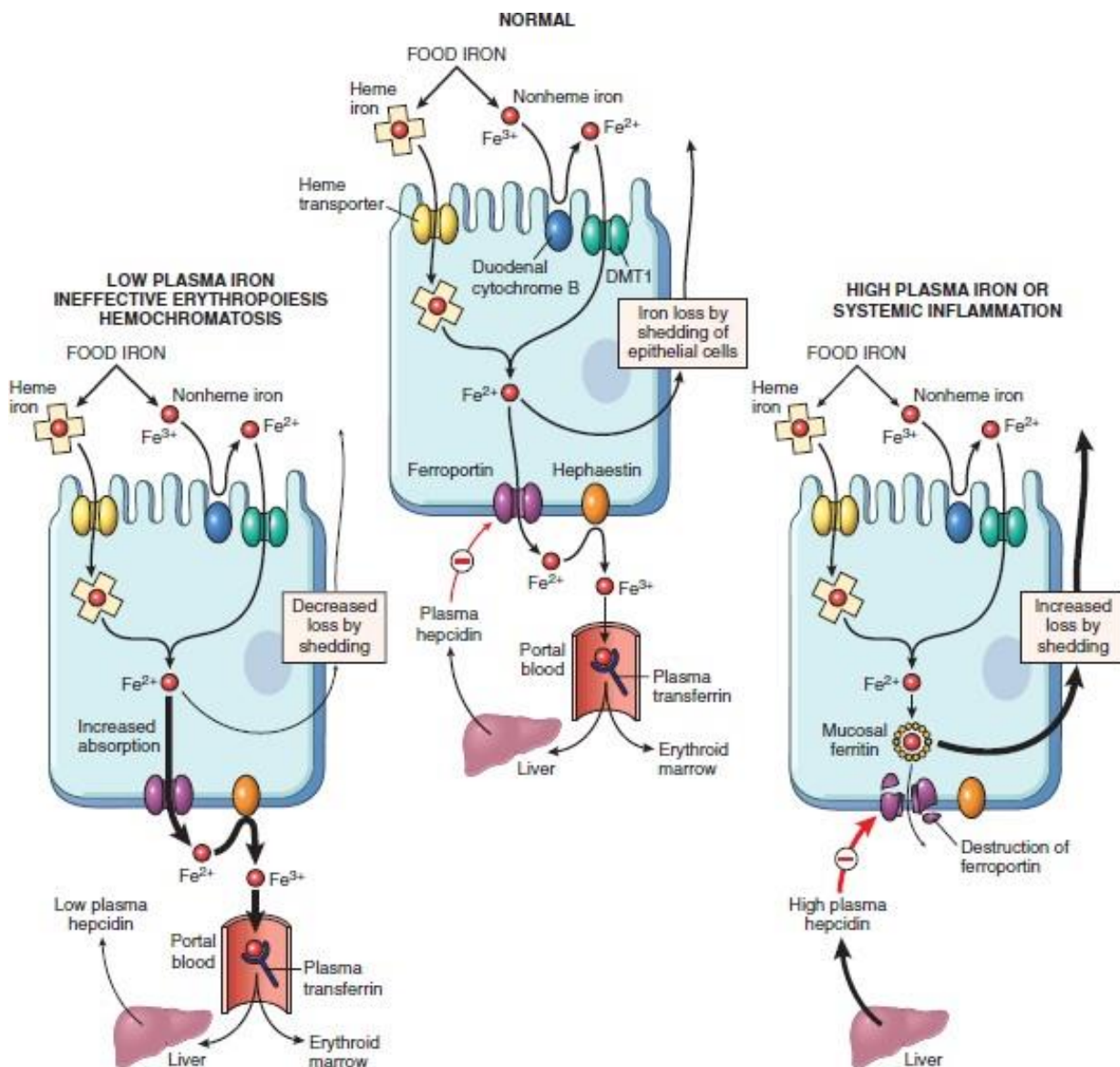
- Iron cannot be excreted through bile, sweat, or urine. With the exception of menstruation, the removal of body iron occurs through shedding of the mucosal and skin epithelial cells. These cells contain small amounts of iron, and they have a rapid turnover (3-5 days) and then they die and shed outside the body with the iron.

Dietary iron is either **heme**, which is found in red meat (has 20% bioavailability), or **nonheme**, which is inorganic and found in vegetables (1% bioavailability only!). And they are absorbed in the duodenum.

- Once the fraction of dietary iron is absorbed, it is regulated by hepcidin.  
Hepcidin is a hormone secreted from the liver, it inhibits the absorption of iron from the duodenum. It works by degrading ferroportin on enterocytes. Note that ferroportin is required for the transportation of iron to the circulation.
- Hepcidin increases in situations of high serum iron and inflammation (IL-6 stimulates the liver to produce hepcidin)
- Low hepcidin indicates iron deficiency, whereas very low hepcidin could be caused by thalassemia major, or primary hemochromatosis.

This picture is from the book and wasn't mentioned by the doctor.

it's just meant to give you a visual idea of what's happening.



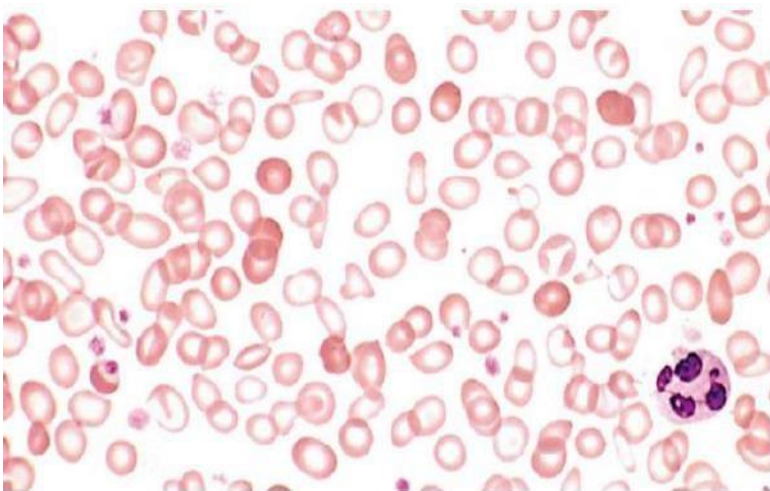
## E) Causes of iron deficiency

- Chronic blood loss (RBCs contain Hb which contains iron)
- Vegetarian diets because of low bioavailability of the nonheme iron, infants drinking human milk (low iron), and teenagers not eating properly.
- Decreased absorption in the GIT (gastrectomy, hypochlorhydria, intestinal diseases, aging)
- Increased demands for iron, such as in growing children, pregnancy, and chronic bone marrow neoplasms (AKA myeloproliferative neoplasms)
- Hypotransferritinemia (less common): decreased synthesis of transferrin, secondary to liver disease, protein deficiency (poor diet or malabsorption), or loss in urine (nephrotic syndrome)
- Enzymatic deficiency of enzymes responsible for absorption in the GIT (very rare and appear in infants (from birth) and cannot be corrected through oral iron supplements)

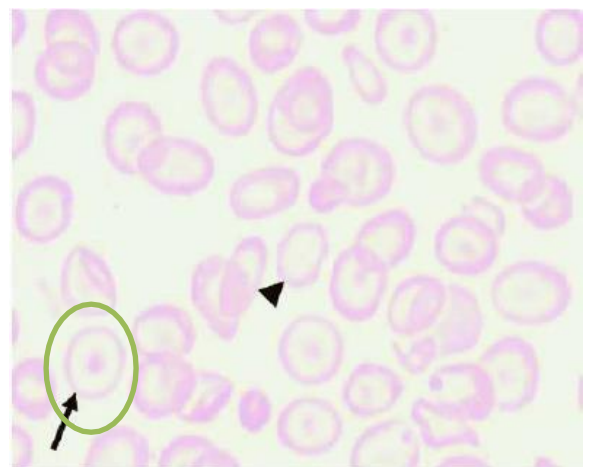
## F) Morphology of IDA

- Red blood cells appear small and empty (hypochromic microcytic)
- Poikilocytosis (different shapes of RBCs)
- Target cell appearance (caused by abnormal hemoglobinization in cells)
- Low reticulocytes (*although erythropoietin is high, but there's no iron so it's ineffective*)
- Thrombocytosis is common (low iron levels in bone marrow stimulates (shifts) progenitor cells to form megakaryocytic lineage instead of erythroid).

↓ IRON → ABNORMAL HEMOGLOBIN SYNTHESIS → ↓ HB → ↓ RED PIGMENTATION (HYPOCHROMIC) AND SIZE (MICROCYTIC)

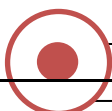


Note the poikilocytosis and hypochromia



Target cell appearance (green circle)

**\*\*Hypochromic mean that the pale center is more than 1/3 the RBC diameter.**



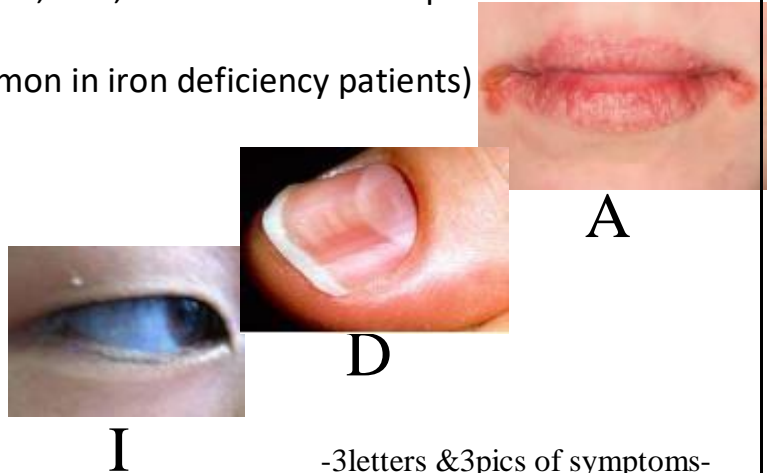
## H) Symptoms of IDA

- General symptoms of anemia (pallor, headache, dizziness, fatigue etc...)
- Pica (patient eats abnormal things e.g. ice, dirt, paint)
- Glossitis (inflammation of the tongue), stomatitis (inflammation of the lips) usually at the angle of the lip. Unknown reason.
- Spooning of fingernails (fragile, thin, brittle nails with depression in the middle like a spoon)
- Restless leg syndrome (common in iron deficiency patients)
- Hair loss
- Blue sclera
- Weakened immunity
- Cognitive impairment

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*IDA is a chronic type of anemia*

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## Anemia of chronic inflammation

- Also known as anemia of chronic disease.
- Seen in chronic infections (e.g. brucella, HIV, TB infections etc..), cancers, immune diseases (SLE, Rheumatoid arthritis etc.)
- Most common type in inpatients (hospitalized patients)

How can chronic inflammation cause anemia?

- 1) Chronic inflammation inhibits synthesis of erythropoietin from kidneys, lowering RBCs production from the bone marrow
- 2) High levels of IL-6 released during inflammation by inflammatory cells will stimulate the liver to produce high amounts of hepcidin, which will block iron transfer from macrophages to RBC precursors in the bone marrow, by degrading ferroportin on macrophages.

1-inhibits EPO so decreases RBCs      2-↑IL-6 ->↑hepcidin -> inhibits iron absorption by degrading ferroportin

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*Why does all this happen? [extra info]*

*The functional advantages of these adaptations in the face of systemic inflammation are unclear; They may serve to inhibit the growth of iron-dependent microorganisms or to augment certain aspects of host immunity.*

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## Laboratory findings: decreased serum Fe and increased stored Fe in BM

Similar to Iron deficiency anemia in that both **serum iron level** and **transferrin saturation** are **low**.

The morphology of red blood cells appears to be normal in the beginning of the anemia, but with time, they become hypochromic microcytic (like IDA).

Reticulocytes are low (due to low erythropoietin)

Bone marrow iron stores **increase**, and so does the **serum ferritin**.

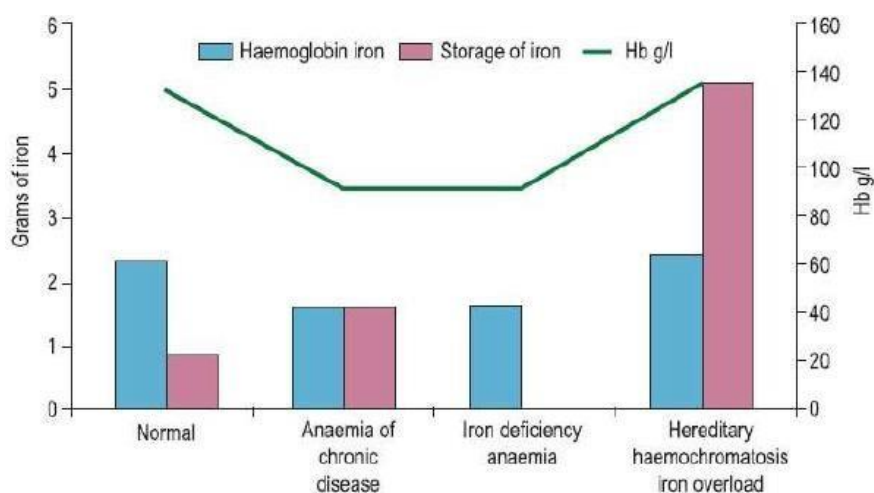
Transferrin saturation is normal to low due to lack of serum iron levels. However, the more important factor is the TIBC and transferrin receptor, which distinguishes it from IDA.

Transferrin receptors are **normal** in anemia of chronic inflammation. BUT the TIBC is **low**.

**Table 5.1:** Laboratory Findings in Microcytic Anemia

STATE	FERRITIN	TIBC	SERUM IRON	% SATURATION
Normal	-	300 µg/dL	100 µg/dL	33%
Iron Deficiency Anemia	<u>Low</u>	<u>High</u>	Low	Low
Anemia of Chronic Disease	<u>High</u>	<u>Low</u>	Low	Normal to low

*This table summarizes the main differences in the lab findings (not from the slides)*



**Body iron content and distribution in different conditions.**

*This graph also summarizes the lab findings (found in slides)*

\*just know that the transferrin saturation is normal in anemia of chronic inflammation



## Megaloblastic Anemia

- Caused by deficiency in vitamin B12 or folate or both
- Both vitamin B12 and folate are required for the synthesis of thymidine, thus DNA replication is impaired.

This abnormality will affect all rapidly dividing cells in the body. But hematopoietic cells are the most severely affected.

- Maturation of RBC progenitors becomes abnormal. Because the DNA is defective, many will undergo apoptosis inside the bone marrow, (ineffective erythropoiesis, mild hemolysis that occurs in the bone marrow as well)
- Viable nucleated RBCs progenitors take longer time to mature, resulting in typical morphology of megaloblastoid. (they appear larger in size and have immature nucleus)

### a) Folate

- Small amount of folate is stored in the human body normally. However, there is a high turnover rate for folate, meaning that it can be depleted rapidly.  
It is found vastly in food (mainly green leaves), but it is destroyed by cooking (so don't cook it or try to eat it fresh).
- Causes of folate deficiency:
  - 1) Decreased dietary intake.
  - 2) Increased demand in pregnancy and chronic hemolytic anemia (causes mixed anemia).
  - 3) Intestinal diseases.
  - 4) *Beans, legume, alcohol, and phenytoin* (antiepileptic drug) all inhibit absorption of folate
  - 5) *Methotrexate* inhibits folate metabolism and thus cannot be utilized by cells.

### b) Vitamin B12

- Mainly present in animal products and is resistant to cooking
  - Synthesized by bacteria in bowel
  - There are enormous stores in the liver. Therefore, it will take a long time for deficiency to occur.
  - Causes of vitamin B12 deficiency:
    - 1) Dietary deficiency most commonly in vegetarians
    - 2) More commonly deficiency secondary to defective absorption
- ### 3) Pernicious anemia

- Autoimmune gastritis
  - Mechanism: autoreactive T-lymphocytes causes injury to parietal cells in the stomach and activates B-lymphocytes and plasma cells to synthesize and secrete autoantibodies that further damages parietal cells, causing a deficiency of intrinsic factor.  
Autoantibodies also block binding of vitamin B12 to intrinsic factors. Sometimes, if vitamin B12 and intrinsic factor managed to bind and form a complex, autoantibodies binds the entire complex and inhibits vitamin B12 absorption.
  - 4) Gastrectomy (low intrinsic factors)
  - 5) Small bowel diseases (malabsorption)
  - 6) Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
  - 7) Metformin, which is used for diabetes, inhibits absorption of B12
- Other functions of vitamin B12
    - 1) Important for recycling of tetrahydrofolate
    - 2) Synthesis of myelin sheath
    - 3) Synthesis of neurotransmitters (such as dopamine and serotonin)
    - 4) Metabolism of homocysteine (In vitamin B12 deficiency, homocysteine levels rise, and they cause neuronal damage and cardiac diseases)

*Degree of neuronal damage does not correlate with the degree of anemia.*



**Macroovalocyte: characteristic of megaloblastic anemia**

**Notice in the right picture that the neutrophil nucleus is highly segmented. Normally the nucleus of neutrophils has 2-4 segments, whereas in megaloblastic anemia it becomes highly segmented because cells take longer time to mature (more time to segment even further)**

### Symptoms of megaloblastic anemia:

- General symptoms of anemia
- Glossitis (beefy tongue and very red due to inflammation)
- Mild jaundice (due to mild hemolysis)
- In severe cases, pancytopenia occurs when all bone marrow cells fail

#### In vitamin B12 deficiency:

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*Megaloblastic anemia is a chronic type of anemia*

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- Posterior and lateral columns degeneration of spinal cord (due to impaired myelin sheath), thus patients complain of paresthesia (numbness), and loss of proprioception (balance)
- Peripheral neuropathy
- Neuropsychotic symptoms in severe megaloblastic anemia

Note:

Regarding transferrin saturation in anemia of chronic inflammation, this is what the doctor said: "In anemia of chronic inflammation, there is a poor correlation with transferrin saturation alone. It can be normal or decreased. The more important one is the TIBC and transferrin receptor, which distinguish it from IDA."

**Summary** for the previous sheet from [HERE](#).

**Good Luck.**