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Pathology HLS

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PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM – LECTURE 2

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ANEMIA OF DECREASED PRODUCTION

General causes:

- Nutritional deficiency The most common
- Chronic inflammation
- Bone marrow failure

IRON DEFICIENCY ANEMIA

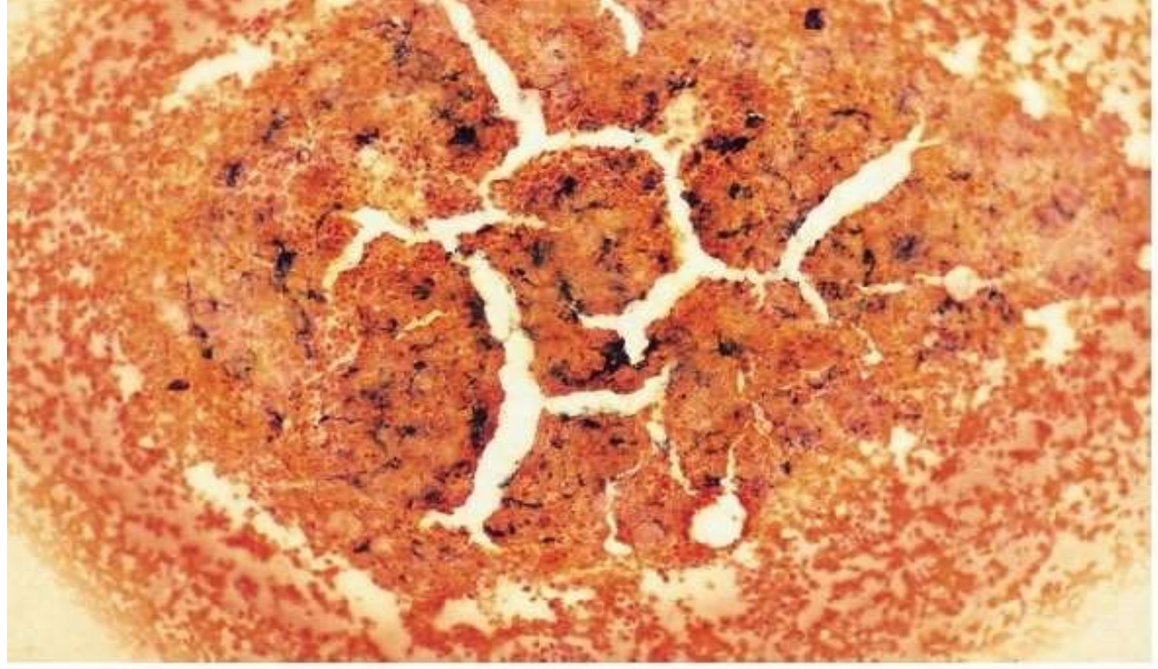
- Most common type of anemia (worldwide and in all age groups, this is based on the community, so you will find it the most common type of anemia between normal people in the community not in the hospitals)
- Affects 10% of people in developed countries and 25-50% of people in developing countries
- Iron storage pool: iron is stored in ferritin (soluble) (small molecule dissolved in the cytoplasm can't be visualized) and hemosiderin (insoluble) (large) in bone marrow, liver and spleen, forming 15-20% of total iron (most of the iron is present inside the RBCs in the blood then the storage and the remaining few precents are present in the serum as transferrin and also we have some iron in the enzymes in skeletal muscles and brain)
- Hemosiderin consists of large iron particles, granular in shape, intracellular(inside the cytoplasm of macrophages in the reticuloendothelial system(BM , liver ,spleen), visible by light microscope
- Hemosiderin is a large ferritin with some different characteristics and additional minerals
- Serum ferritin is derived from stored ferritin (ferritin in the BM detaches and goes into the serum)

INDICATORS OF IRON STATUS

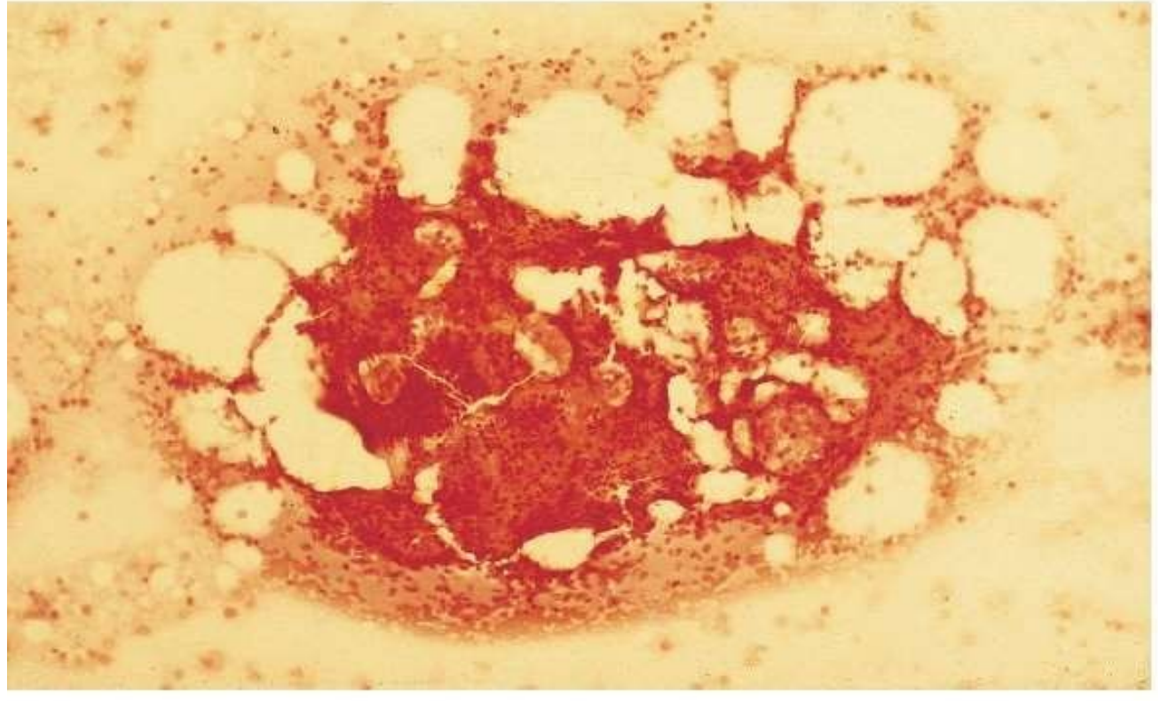
- Bone marrow aspirate: earliest changes, invasive procedure (we use a needle and introduce it inside the bone, not comfortable, painful and expensive), Perl's Prussian blue stain (↓ in IDA) [the most accurate one, iron normally doesn't stain with Giza or Lishman stain so we use Perl's Prussian blue stain , any decrease in the iron storage in the BM means that the patient has decreasing iron status in the body)
- Serum (the venous system) ferritin level (↓ in IDA)* (while it's decreased there's decrease in the iron storage in the BM)

* *Affected by inflammation, fasting, vitamin C status and pregnancy* (ferritin is an acute phase reactant so inflammation increases its level as well as fasting while vitamin c deficiency decreases its level as well as pregnancy especially in the first trimesters due to dilution)

- Serum iron level (↓ in IDA) (iron is bound to another protein is called transferrin , this decrease takes a long time so if you measure the Perl's serum iron alone and it's normal it could be a false normal reading)
- Total iron binding capacity (↑ in IDA) (this test is an old one and is reliable most of the time, we take the patient's serum and artificially add iron to it. And see how many of this iron can bind to the transferrin, if the iron level is low then there is more binding capacity)
- Reticulocyte hemoglobin content (CHr): (↓ in IDA) (Reticulocytes are less than 2% of the normal RBCs in the blood , if the iron or hemoglobin in the Reticulocytes is decreased this indicates iron deficiency)
- Mean reticulocyte volume (MRV): (↓ in IDA) (if the patient has iron deficiency, the Reticulocytes will be smaller)



Aspirate of normal bone marrow (BM): bluish-black iron (haemosiderin) in macrophages in a fragment. Perls' stain ×40.



Iron deficiency

Aspirate of normal BM: a fragment with no stainable iron. Perls' stain ×40.

IRON HOMEOSTASIS

- Normal loss of body iron: shedding skin and mucosal epithelium (no excretion with urine or sweat or bile) so if there is excess iron in BM it's difficult to excrete it outside the body
- Dietary iron is either hem (red meat, liver) or non-hem (inorganic, vegetarian(spinach, lentils, beans))
- 20% of heme and 1% of non-heme iron are absorbed in duodenum

IRON HOMEOSTASIS

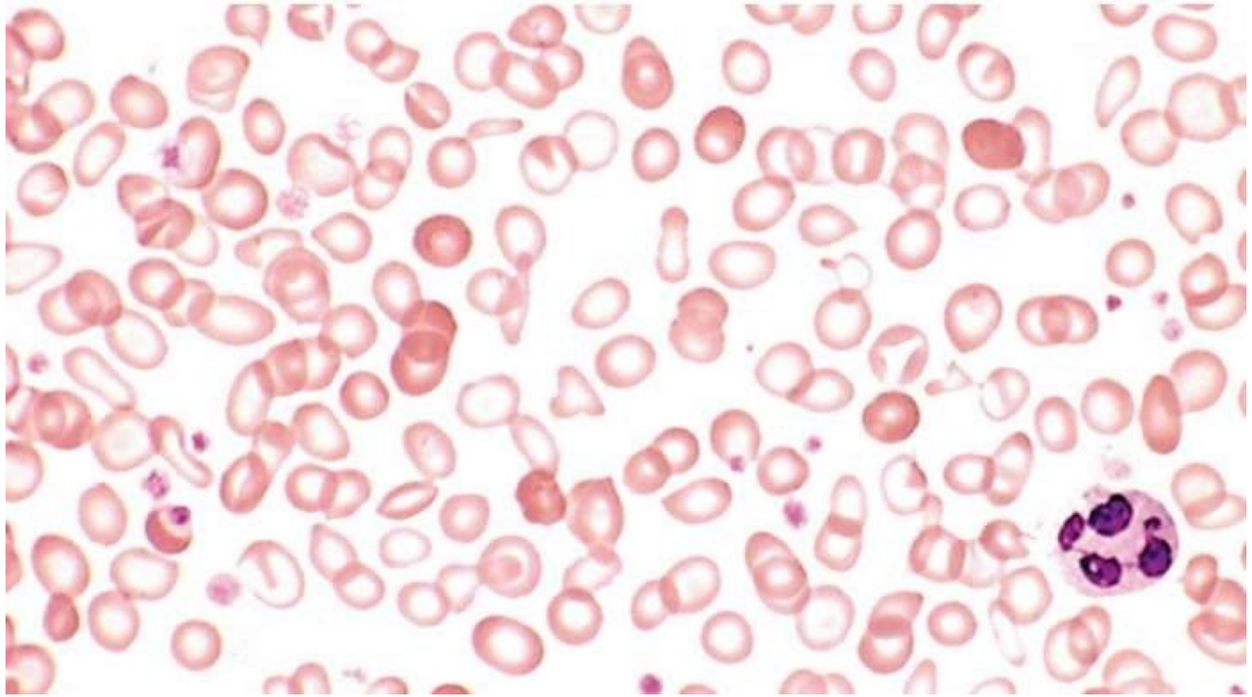
- Hepcidin: hormone secreted from liver, inhibits iron absorption (degrade ferroportin on enterocytes)
- Hepcidin increases in situations of high serum iron and inflammation (effect of IL-6)
- Low hepcidin: iron deficiency. Very low: thalassemia major, primary hemaochromatosis

CAUSES OF IRON DEFICIENCY

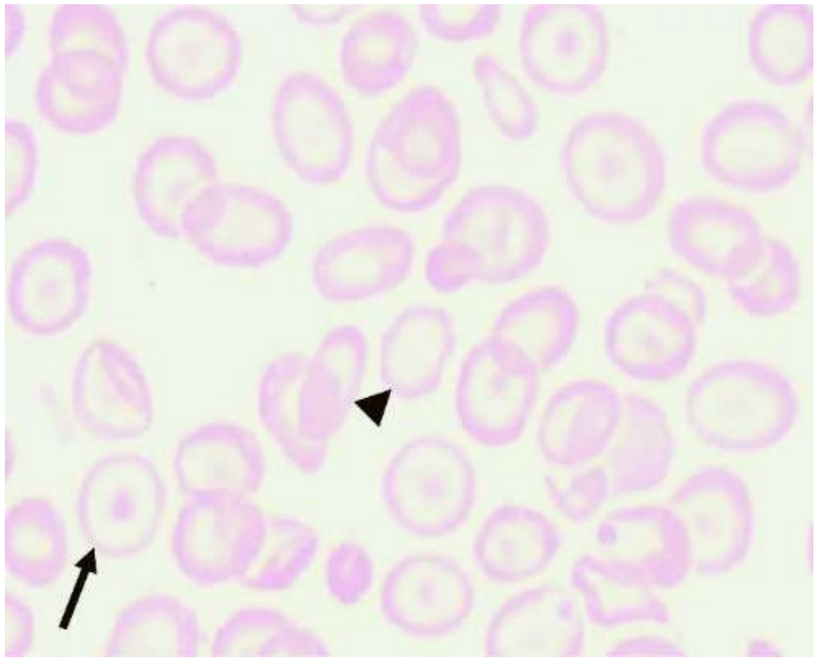
- Chronic blood loss (because it's difficult to regain this loss)
- Dietary: vegetarians, infants (human milk has low amount of iron) , teenagers (because of bad habits of eating)
- Decreased absorption: gastrectomy (like in case of cancer or obesity, there is less amounts of acids which are important for iron absorption), hypochlorhydria (acquired disease where there is destruction of the parietal cells so no enough acid in the stomach), intestinal diseases(like celiac disease), elderly (with aging the function of the stomach and GIS decreases, also they have comorbidities which result in chronic blood loss)
- Increased demands: growing children, pregnancy, myeloproliferative neoplasms
- Hypotransferritinemia: decreased synthesis of transferritin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in urine (nephrotic syndrome)
- Enzymatic deficiency (enzymes that are responsible of iron absorption in GIS and transport are rare and appear early and can't be corrected by oral iron)

MORPHOLOGY

- RBCs appear small and empty (hypochromic microcytic)
- Different shapes of RBCs appear (poikelocytosis) (measured by the RBC distribution width and it's increased in IDA which means there is a variation in the size and shape of the RBCs)
- Target cells (it is a RBC with a red dot in the center so it's looks like the target that we shoot)
- Low reticulocytes (Erythropoietin is high, but ineffective) (we have erythropoietin but no iron so no RBC production)
- Thrombocytosis (increase in Platelets)is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid)



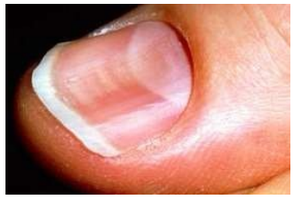
- IDA: note the hypochromia and poikelocytosis (in thalassemia major the blood film is very similar to iron deficiency)



- IDA: note the target cells (arrow)

SYMPTOMS

- IDA is a chronic anemia (iron takes a long time to be depleted and RBCs become hypochromic and microcytic)
- General symptoms of anemia
- Pica (patient likes to eat abnormal things like ice, paints, dirts)
- Glossitis (inflammation of tongue) , stomatitis (inflammation of lips) (for unknown reason but it's thought that the iron is important for the stability of epithelial cells)
- Spooning of fingernails (fingernails become brittle and thin with depression in the middle)
- Restless leg syndrome
- Hair loss
- Blue sclera (the sclera becomes very thin so it gives the shadow behind it)
- Weakened immunity (iron is important for the immune system, macrophages store iron and utilize it)
- Cognitive impairment (iron is present in the brain)



ANEMIA OF CHRONIC INFLAMMATION

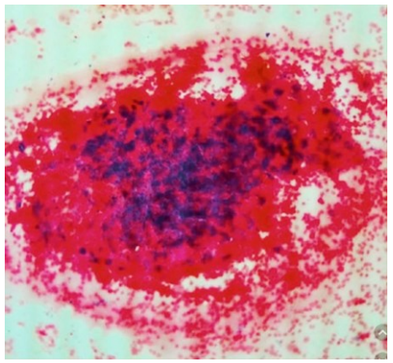
- Also called anemia of chronic disease
- Seen in chronic infections (tuberculosis, brucella, HIV) , cancer, chronic immune diseases (rheumatoid arthritis, systemic lupus erythematosus)
- Common in inpatients (patients in hospitals)
- Chronic inflammation inhibits synthesis of erythropoietin from kidneys
- High IL-6 —> high hepcidin —> blocks iron transfer from macrophages to RBC precursors in bone marrow (degrade ferroportin on macrophages) (hepcidin antagonizes erythropoietin and blocks iron absorption from the gut)

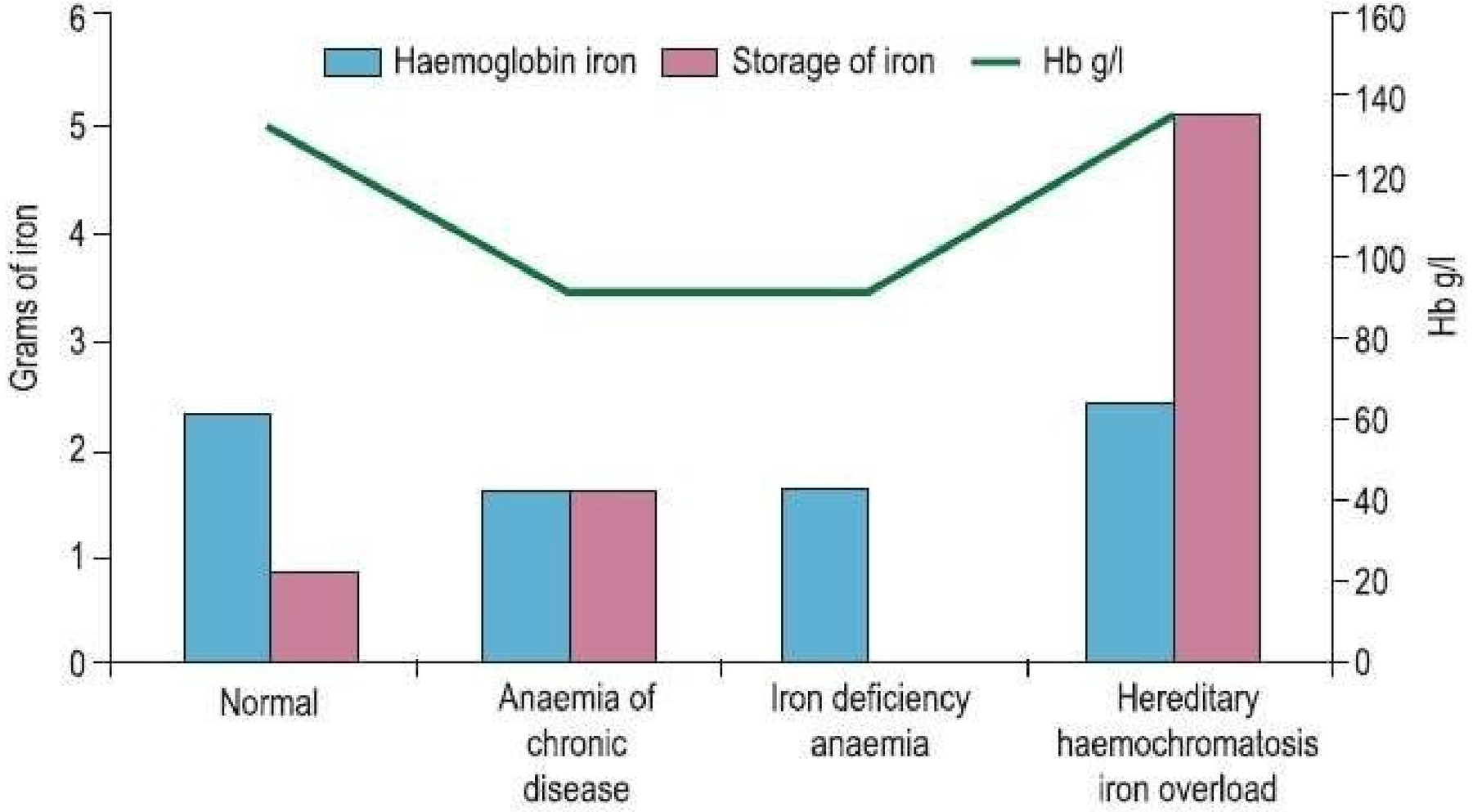
LABORATORY FINDINGS

- Similar to IDA: serum iron is low (because it's retained in BM)
- RBCs: normal morphology, then hypochromic microcytic
- Reticulocytes ↓ (no enough erythropoietin)

In contrast:

- Bone marrow iron stores ↑
- Serum ferritin ↑ (in inflammation it increases)





Body iron content and distribution in different conditions.

MEGALOBLASTIC ANEMIA

- Caused by deficiency in vitamin B12 or folate or both
- Both are required for synthesis of thymidine (nucleic acid) , thus DNA replication is impaired
- Abnormalities occur in all rapidly dividing cells, but hematopoietic cells are most severely affected (because they are rapidly dividing and use these vitamins very often)
- Maturation of RBC progenitors is deranged, many undergo apoptosis inside bone marrow (ineffective erythropoiesis, mild hemolysis)
- Viable nucleated RBCs take a longer time to mature, resulting in typical morphology (megaloblastoid) (mega : large , blastoid: immature)

FOLATE DEFICIENCY

- Normally, minimal amount of folate is stored in human body (has high turnover, it's depleted quickly and can be replenished quickly)
- Folate is vastly present in food (green leaves), but it is destroyed by cooking

Causes of deficiency:

- Decreased dietary intake
- Increased demands (pregnancy (pregnant woman needs folate for the DNA of the baby) , chronic hemolytic anemia(when there's hemolysis, there's damage to RBCs so the BM is active to produce more RBCs and needs more folate)
- Intestinal diseases (the site of absorption of folate)
- Beans, legume, alcohol, phenytoin (inhibit absorption)
- Methotrexate: inhibits folate metabolism and cellular usage

VITAMIN B12

- Mainly present in animal products
- Resistant to cooking
- Synthesized by bacteria in bowel (in the past people didn't use to get enough amounts of meat but they took vitamin B12 from the bacteria in the bowel or even from the contaminated water because of poor sanitation so they didn't have vit B12 deficiency)
- Enormous stores in the liver (so it takes a long time to have vit B12 deficiency)
- Dietary deficiency occurs most commonly in vegetarians
- More commonly: deficiency results from defective absorption

PERNICIOUS ANEMIA

- Autoimmune gastritis
- Autoreactive T-lymphocytes, causing injury to parietal cells (T lymphocytes recognize parietal cells as abnormal and damage them so cause deficiency of intrinsic factors which are important for vit B12 absorption)
- Activates B-lymphocytes and plasma cells to synthesize and secrete auto antibodies that further damage parietal cells(or even intrinsic factors or the complex of vit B12 and intrinsic factor), and blocks binding of vitamin B12 to intrinsic factors

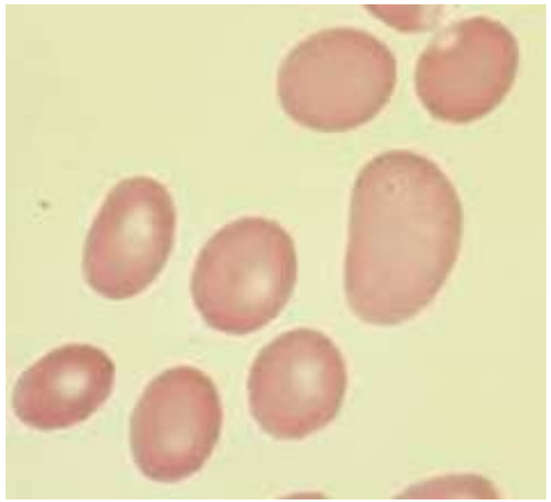
OTHER CAUSES OF VITAMIN B12 DEFICIENCY

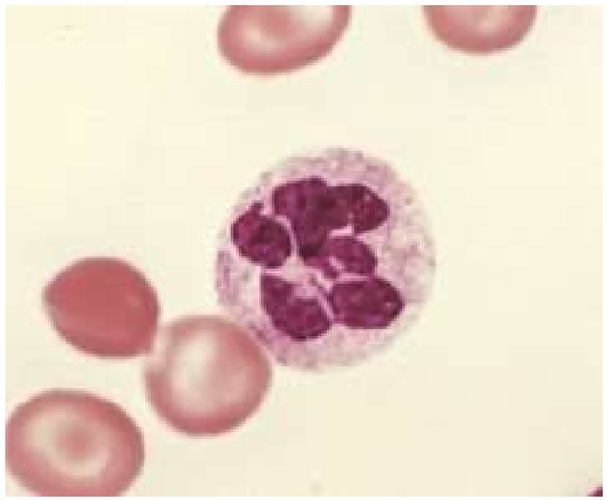
- Gastrectomy
- Small bowel diseases (malabsorption)
- Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
- Metformin (drug for DM and known in Jordan as Glucophage) (inhibits absorption)

OTHER FUNCTIONS OF VITAMIN B12

- Recycling of tetrahydrofolate
- Synthesis of myelin sheath (nerve becomes injured easily)
- Synthesis of neurotransmitters (dopamine, serotonin)
- Metabolism of homocysteine (toxic to neurons) (also it's important for the development of cardiac diseases)
- Degree of neuronal damage does not correlate with the degree of anemia

MORPHOLOGY OR MEGALOBLASTIC ANEMIA





More segments in the nucleus of neutrophils because the cell takes a longer time to mature and the cell is larger with big cytoplasm which can grow without thymidine

- Macroovalocyte: characteristic of megaloblastic anemia

SYMPTOMS

- Chronic, general symptoms of anemia
- Glossitis (beefy tongue)
- Mild jaundice (minor hemolysis)
- In severe cases: pancytopenia

In vitamin B12 deficiency:

- Posterior and lateral columns degeneration of spinal cord (paresthesia (numbness), loss of proprioception (loss of self position and balance))
- Peripheral neuropathy
- Neuropsychotic symptoms