Megaloblastic anemia

GNT Block

COLOR INDEX:

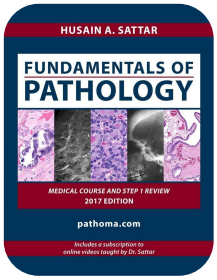
- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

Editing file:

Objectives

- To understand the mechanisms by which macrocytic anaemia may arise
- To appreciate the signs and symptoms of macrocytic anaemia
- To understand how macrocytic anaemia can be classified
- To be able to know the causes of macrocytic anaemia
- To understand the normal metabolism of vitamin B12 and folic acid, and to appreciate how megaloblastic anaemia may arise
- To suggest some normoblastic causes of macrocytosis

Click on PATHOMA for a revision and more info!



Our YouTube's playlist for this lecture!

This lecture was given by: Dr.Osama khojah and prof. Fatma Al Qahtani

*No objectives was found in new male slides

EXTRA

Overview

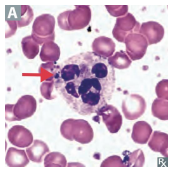
Definition

In **macrocytic anaemia** the red cells are **abnormally large** (MCV >100 fL). There are several causes but they can be broadly subdivided into megaloblastic and non-megaloblastic, based on the appearance of developing erythroblasts in the bone marrow.x

Macrocytosis — term used to describe red blood cells that are larger than normal

Hypersegmented neutrophils

- Neutrophils with more than 5 (normal is 3 - 5 lobes)
- The presence of hypersegmented neutrophils is an important diagnostic feature of megaloblastic anemias.



Macrocytic Anemia

Type	Megaloblastic Macrocytic	Non-Megaloblastic (Normoblastic) Macrocytic
DNA synthesis	Large RBC's as a result of **impaired DNA synthesis** Which causes inability of cell replication. **RNA and protein synthesis is not affected**, so the cell will continue to grow and increase in size.	Large RBC's with **no impairment of DNA synthesis.** The exact mechanisms creating large red cells in each of these conditions **is not clear.**
Etiology	Most commonly as a result of **Folate and Vitamin B12 deficiency**	Many possible causes like **alcoholism, liver disease, and aplastic anemia**
hypersegmented neutrophils	present	absent
Information	Not only RBC's are affected but also **leukocytes, megakaryocytes**, and the **intestinal epithelium**	**Table 5.10** Causes of macrocytosis other than megaloblastic anaemia. Alcohol Liver disease Myxoedema Myelodysplastic syndromes Antimetabolite drugs, e.g. hydroxycarbamide Aplastic anaemia Pregnancy Smoking Reticulocytosis Myeloma and paraproteinaemia Neonatal

EXTRA

Normoblastic macrocytic

Suggested mechanism of how normoblastic macrocytic anemia is caused:

Liver disease

- Chronic liver disease, such as cirrhosis, can lead to impaired synthesis of proteins, including those involved in the production and maintenance of red blood cells.
- The liver plays a role in processing and storing vitamin B12 and folate, essential for normal red blood cell production. Liver dysfunction can disrupt these processes, contributing to macrocytic anemia.

Alcoholism

- Chronic alcohol use can have multiple effects on the hematologic system, including macrocytosis.
- Alcohol can directly suppress the bone marrow, affecting the normal production of red blood cells.
- Additionally, alcohol can lead to nutritional deficiencies, particularly of vitamin B12 and folate, which are essential for proper red blood cell formation.

Aplastic anemia

- Aplastic anemia is characterized by a reduction in the number of blood cells produced in the bone marrow. In some cases, this can lead to macrocytic anemia.
- The bone marrow failure in aplastic anemia affects the normal production of red blood cells, leading to larger and fewer red blood cells (macrocytosis).
- remember aplastic anemia is mainly one of the causes of normocytic-normochromic anemia with some macrocytosis of remaining RBC.

Introduction

-Values are not important, you just have to know that:
The the first three are different in male than female And the last four are same in both
-WBC values are not important as well

Normal Adult Red Cell Values		
	Male	**Female**
Haemoglobin (g/L)	135-175	115-155
Haematocrit (PCV) (%)	40-52	36-48
Red cell count (x10 ^{12}/L)	4.5-6.5	3.9-5.6
Mean cell haemoglobin(pg)	27-34	
Mean cell volume (FL)	80-95	
Mean cell haemoglobin concentration (g/L)	300-350	
Reticulocyte count (x10^9/L)	25-125(1.0-2%)	

In children normal haemoglobin values (g/L) are:

- Newborn: 150 – 210
- 3 months: 95 – 125
- 1 year to puberty: 110 – 135

* PCV, Packed cell volume.

Normal WBC Count in Adults	
Characteristic	Value X 10^9/L
Total	4.0 - 11.0
Neutrophils	2.5 - 7.5
Lymphocytes	1.5 - 3.5
Monocytes	0.2 - 0.8
Eosinophiles	0.04 - 0.44
Basophiles	0.01 - 0.1
Platelets	150-450

Children normally have higher lymphocytes count

Classification of Anemia

Chick here for the original diagram from male slides

	Microcytic Hypochromic Anemia	Normocytic Normochromic Anemia	Macrocytic Anemia Characterized by: increased MCV
MCV	<80 fL	80-(95-100) fL	Increased MCV: >100 fL
MCH	< 27 pg	>26 pg	>34 pg
Etiology	1. **Iron def. Anemia** 2. Thalassemia 3. Anemia of chronic disease(some cases) 4. Lead poisoning 5. Sideroblastic anemia (some cases)	1. Many haemolytic anaemias 2. **Anemia of chronic disease (some cases)** 1. After acute blood loss 2. Renal disease(insufficiency) 3. Mixed deficiencies 4. Bone marrow failure, e.g. post-chemotherapy, infiltration by carcinoma, etc. 5. Chronic disease 6. infection 7. inflammation 8. malignancy 9. sickle cell disease	If serum B12 and folate normal: 1. alcoholism 2. bone marrow disorders 3. hypothyroidism 4. liver disease 5. medication (chemotherapy, antivirals) **If** 1-serum B12 and folate is low 2- elevated homocysteine : A-with **Elevated methylmalonic acid : Vit B12 deficiency** B-with **normal methylmalonic acid: Folate deficiency** Important points Will be discussed in next slide

Male Slides

Microcytic Anemia

Test blood levels:	1. Serum iron decreased 2. Serum ferritin decreased 3. TIBC elevated	1. Serum iron normal or elevated 2. Serum ferritin normal or elevated 3. TIBC normal 4. Hgb Electrophoresis: A-normal in α B-abnormal in β	1. Serum iron normal or decreased 2. Serum ferritin normal or elevated 3. TIBC normal or decreased 4. Hgb electrophoresis normal
Etiology	iron deficiency anemia	thalassemias	chronic disease

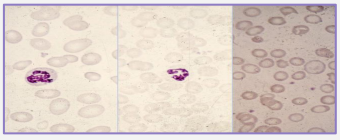
Macrocytic anemia

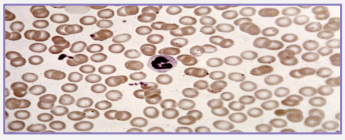
Macrocytic anemias can be divided into those showing:

Pictures are not important

Megaloblastic erythropoiesis

- Describes abnormal red cell development characterized by a lack of synchrony between the maturation of the red cell nucleus and its cytoplasm.
- It arises as a consequence of disordered DNA synthesis and results in a macrocytic anemia.

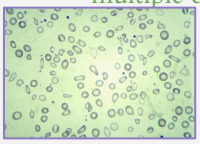


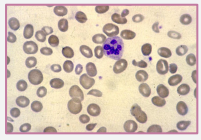


Normoblastic erythropoiesis

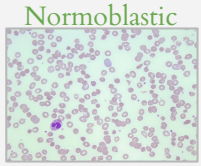
- Describes the normal appearance of red cell maturation, but may still be associated with macrocytosis in the peripheral blood.

multiple deficiencies





Normoblastic



Conditions in which **Macrocytosis or hypersegmented neutrophils** may occur in the **absence of megaloblastic anemia**

Macrocytosis

Female dr: focus on the bold and the rest is for reading

Female Slides

- Alcohol
- Liver disease (especially alcoholic)
- Reticulocytosis (hemolysis or haemorrhage)
- Aplastic anaemia or red cell aplasia*
- Hypothyroidism
- Myelodysplasia including acquired Sideroblastic anaemia
- Myeloma and macroglobulinaemia
- Leukoerythroblastic anemia
- Myeloproliferative disease
- Chronic respiratory failure
- Pregnancy
- Newborn

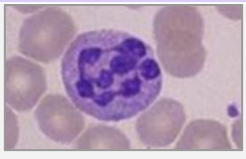
Macrocytosis with Normoblastic

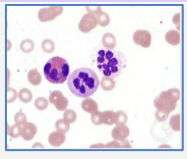
Female dr: focus on the bold and the rest is for reading

- **Normal neonates (Physiological)**
- **Chronic alcoholism**
- **Myelodysplastic syndromes**
- **Chronic liver disease**
- Hypothyroidism
- Normal pregnancy
- **Therapy with anticonvulsant drugs**
- Haemolytic anaemia
- Chronic lung disease (with hypoxia)
- Hypoplastic and aplastic anaemia
- Myeloma

Hypersegmented neutrophils

- Congenital (familial) abnormality
- **Iron deficiency**
- Renal failure



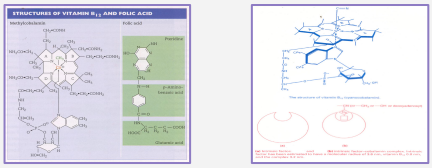
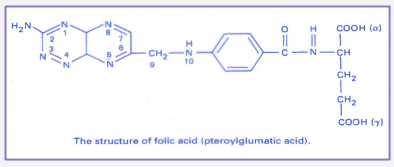
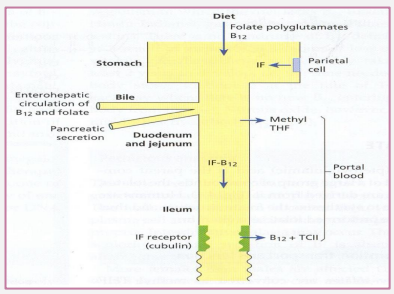


Note:- High MCV recorded when cold agglutinins or paraproteins are present.

Causes of Megaloblastic Anemia

The Cause	Details
B12 related Female dr: important	Cobalamin (B12) deficiency or abnormalities of cobalamin metabolism
Folate related Female dr: important	Folate deficiency or abnormalities of folate metabolism
Therapy with antifolate drugs Female dr: for reading	e.g. methotrexate
Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy. Female dr: for reading	a. Some cases of acute myeloid leukaemia, myelodysplasia. b. Orotic aciduria (responds to uridine) c. Therapy with drugs interfering with synthesis of DNA (e.g. cytosine arabinoside, hydroxyurea, 6-mercaptopurine, azidothymidine (AZT). d. Thiamine responsive
Suggested but poorly documented causes of megaloblastic anaemia not due to cobalamin or folate deficiency or metabolic abnormality: (Rare) Female dr: for reading	a. Vitamin E deficiency b. Lesch-Nyhan syndrome (?responds to adenine)
Other causes of megaloblasts Female dr: for reading	a. Abnormalities of nucleic acid synthesis b. Orotic aciduria c. Drug therapy : 1-Antipurines (mercaptopurine,azathioprine), 2-Antipyrimidines (fluorouracil, zidovudine (AZT)), 3-Others (hydroxyurea) d. Myelodysplastic syndromes, erythroleukaemia e. Some congenital dyserythropoietic anaemias f. Uncertain aetiology

Vitamin B12 & folate

	Vitamin B12	Folate
Dietary source	Only food of **animal** origin, especially **liver**	**Most foods**, especially **liver**, **green vegetable** and **yeast**; **destroyed by cooking**
Average daily intake In adults Team442: dr's notes: you won't be asked the exact numbers so just understand the concept	7 - 30 µg	200-250 µg
Minimum daily requirement In adults Team442: dr's notes: you won't be asked the exact numbers so just understand the concept	1-3 µg	100-200 µg Higher during pregnancy and lactation
Body stores In adults	3-5 mg, mainly in the liver	8-20 mg, mainly in the liver
Time to develop deficiency in the absence of intake or absorption In adults	Anemia in **2-10 years** (It takes time) (years)	Macrocytosis in 5 months (Months)
Requirements for absorption	Intrinsic factor secreted by gastric parietal cells Team442: due to large hepatic stores of Vit B12	Conversion of polyglutamates to monoglutamate by intestinal folate conjugase (this enzyme should be normal for the ability to absorb) Team442: because body stores are minimal
Site of absorption	Terminal **ileum**	**Duodenum** and **jejunum**
Structure (Not important)		
Forms	• **Methylcobalamin:** mostly found in blood circulation • **Adenosylcobalamin:** main form in tissue • **Hydroxocobalamin:** supplement, main form of treatment • **cyanocobalamin:** supplement	• **Tetrahydrofolic acid (THF):** active form • **Methyl THF:** primary form found in blood This pictures will be explained later 

Causes Vitamin B12 & folate deficiency

Vitamin B12 deficiency Female's dr: focus on red	Folate deficiency Female's dr: focus on red
Malabsorption	**Malabsorption**

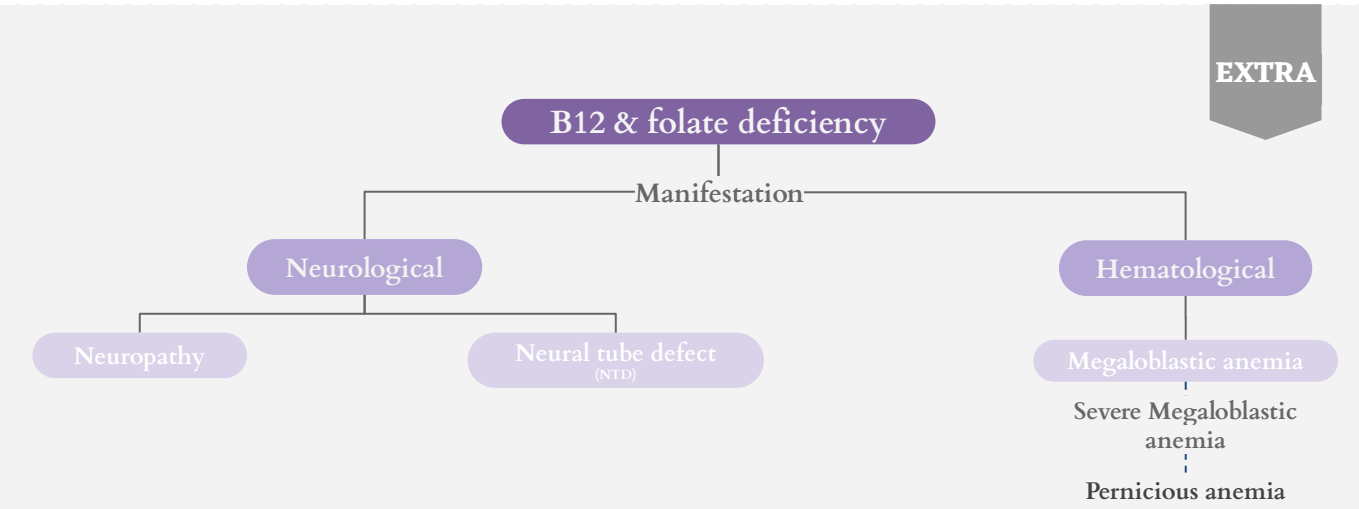
• Intestinal causes:
  ○ Crohn's disease
  ○ Ileal resection
  ○ Chronic tropical sprue
  ○ Multiple jejunal diverticula
  ○ Abnormal intestinal bacterial flora
  ○ Small intestinal strictures
• Gastric causes:
  ○ Total or partial gastrectomy
  ○ Gastritis
• Vagotomy
• Pernicious anaemia
• Inadequate secretion of intrinsic factor
	• Coeliac disease
	• Jejunal resection
	• Tropical sprue

	Increased requirement: (People who need more folate)
	• Pregnancy • Premature infants • Chronic haemolytic anaemias • Myelofibrosis • Various malignant diseases
	Increased loss
	• Long-term dialysis • congestive heart failure • acute liver disease
Nutritional	**Nutritional**
• Inadequate intake of meat • Veganism (vegans)	• Inadequate dietary intake
Others	**Complex mechanisms**
• Diphyllobothrium latum • acid-suppressing drugs • alcohol abuse • Congenital intrinsic factor deficiency (rare)	• Anticonvulsant therapy • ethanol abuse (only some cases with macrocytosis are folate deficient)

Certain anticonvulsant medications, specifically some older generation drugs, have been associated with causing folate deficiency by the following mechanisms:

1. Impaired Absorption: Some anticonvulsants, such as phenytoin and phenobarbital, can interfere with the absorption of folate in the gastrointestinal tract. This may result in reduced levels of folate available for the body to use.
2. Increased Metabolism: Anticonvulsants can induce hepatic enzymes, which may accelerate the breakdown of folate in the liver. This increased metabolism can lead to a decrease in the circulating levels of folate.
3. Altered Folate Metabolism: Anticonvulsants may affect the metabolism of folate within cells. For example, they can interfere with the conversion of folate to its active forms that are essential for various cellular processes.

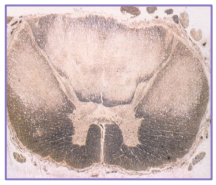
B12 & folate deficiency



Neuropathy due to Vit B_{12} and folate deficiency

Neuropathy is mostly due vit B12 deficiency, causes:

- **Progressive neuropathy, affecting:**
  - The peripheral sensory nerves.
  - **Posterior and lateral columns of the spinal cord (subacute combined degeneration of the cord).**
  - Optic atrophy.
- **Psychiatric symptoms**
- Cause:
  - The neuropathy is likely **due to accumulation of S-adenosyl homocysteine* and reduced level of S-adenosyl methionine in nervous tissue** resulting in defective methylation of myelin and other substrates.



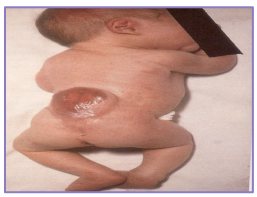
Also caused by ↑ **Methylmalonic acid, How?**

- Vitamin B12 a cofactor for the conversion of methylmalonic acid to succinyl CoA (important in fatty resulting in defective acid metabolism).
- Vitamin B12 deficiency results in increased levels of methylmalonic acid, which impairs spinal cord myelinization.
- Damage results in a condition known as **subacute combined degeneration of spinal cord**

Neural tube defect (NTD)

Female's dr: you just have to know that folate and vitamin B12 deficiency leads to spina bifida, the rest is for reading only

Folate or Vit B12 deficiency in the mother predisposes the fetus to neural tube defect (anencephaly, **spina bifida** or encephalocoele) .



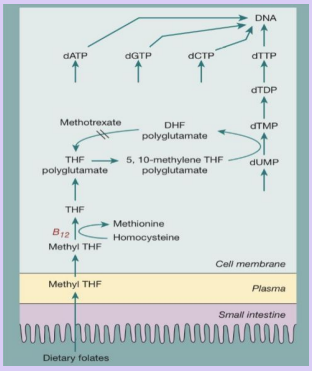
- This result in build-up of homocysteine and S-adenosyl homocysteine in the fetus which impair methylation of various proteins and lipids.
- Polymorphism in the enzyme 5,10 methylene tetrahydrofolate reductase (5,10-MTHFR). This mutation (677 C→T) in the MTHFR gene results in low serum and red cell folate and high serum homocysteine in the parents and fetus with NTD.
- Cleft palate in children and hair lip

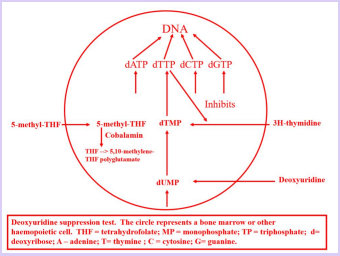
B12 & folate absorption

Explanation is **EXTRA**

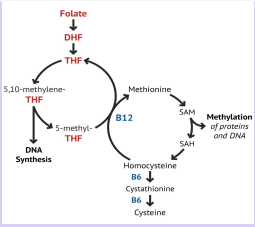
Pictures are from the main slides, but skipped by female's doctor

Absorption and metabolism of Folic acid



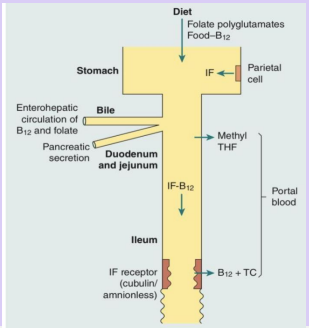


- **Dietary folate** is converted to **methyl tetrahydrofolate** form which circulates in plasma.
- After entering cells vitamin B12 is needed to convert:
  - Methyl THF to **THF** (the **active form** of folate)
  - **Homocysteine** to **methionine** (by transferring a methyl group).
- THF becomes **THF polyglutamate**, then becomes **5,10- methylene THF polyglutamate** which is essential for the formation of DNA building blocks (dTMP: dThymine-Monophospate).
- Once it forms DNA precursor, **5,10- methylene THF polyglutamate** becomes **DHF polyglutamate**
  - which can be reconverted to THF polyglutamate again though the enzyme: **dihydrofolate reductase** (**inhibited by methotrexate** which is useful in the treatment of malignant diseases)

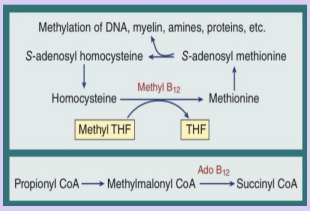


Summary:
Dietary folate → **methyl** tetrahydrofolate "circulates in plasma" → **THF** "in cell by help of B12" → THF **polyglutamate** → **5,10- methylene** THF polyglutamate " essential for DNA synthesis" → **DHF** polyglutamate

Absorption and metabolism of B12



- **B12** from the food is combined with the **intrinsic factor** (IF) which is secreted from the stomach by the parietal cells.
- IF–B12 complex reaches **terminal ileum** [1+2],
- Vitamin B12 is absorbed into portal blood where it becomes attached to the plasma-binding protein **transcobalamin** (TC, also called transcobalamin II)[3]



Vitamin B12 is a coenzyme for these biochemical reactions:

1. Conversion of **methyl THF** to the **active form THF** (By taking the **methyl group**), forming the main form of circulating B12 which is (methylcobalamin)
2. Conversion of **Homocysteine** (harmful) to **methionine** (By giving the **methyl group**).
3. Conversion of **methylmalonyl coA** to **succinyl coA** (By acting as a coenzyme (in the form Adenosylcobalamin, which is the main form in tissues)

EXTRA Vitamin B12

This summary was done by Rafan Alhazzani

Reaction	Substrate	Form of B12	Enzyme	Final product
Conversation of propionyl-CoA to succinyl-CoA	propionyl-CoA	Deoxy-adenosyl-cobalamine	Methylmalonyl CoA Mutase	Succinyl-CoA
Conversion of homocysteine to methionine	homocysteine	Methylcobalamin	Methionine Synthase	Methionine, N5-methyl-TH4 → TH4

Pernicious anemia

Pernicious Anemia (PA)

Definition	Severe megaloblastic anemia	

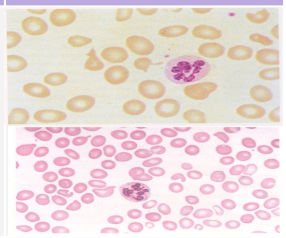
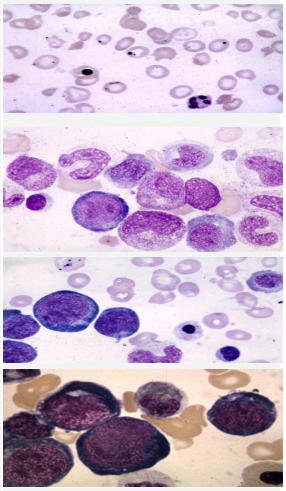
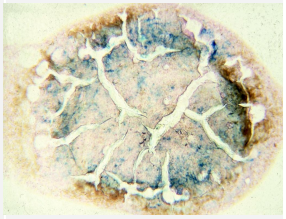
Etiology	**Due Autoimmune attack of the gastric mucosa leading to atrophy.**
	• **Helicobacter pylori infection** may be the cause which present in:
	  ○ Younger age as iron deficiency anaemia
	  ○ Elderly as pernicious anaemia	

Epidemiology	**Genetic**	Tends to be in **families**
	Age & Gender	More common in **elderly female** patients than males (1.6:1) at the age of 60 and above (rare in children)
	Location	More common in **Northern Europeans** (Denmark, Sweden, Norway etc)
Pathophysiology	• The mucosa become thin with plasma cells and lymphoid infiltration of the lamina propria. • Intestinal metaplasia may occur, **Increased** incidence of **gastric carcinoma** in (2-3% of pernicious anaemia patients). (Very common as a complication) • It may be associated with autoimmune diseases including the autoimmune polyendocrine syndrome. • Achlorhydria is present and absent secretion of intrinsic factor (IF)	
	Pernicious anemia is not caused by a problem in the uptake (not a cubilin receptor problem) of vitamin B12, **it's caused by a problem in the secretion of Intrinsic factor.** **Q:** Is pernicious anemia caused by a defective problem in the uptake of vitamin b12? **A:** no. It's a problem in secretion of intrinsic factor	
Findings	1. **Absent serum vitamin B12** level or almost absent level (main finding) 2. **Raised serum gastrin** levels* 3. Progressive neuropathy is common feature	

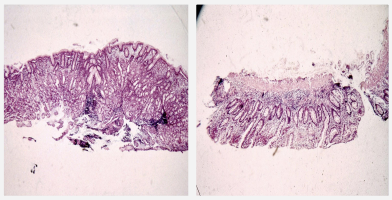
*How is the gastrin levels is elevated in pernicious anemia?
The autoimmune response in pernicious anemia often targets the gastric parietal cells, leading to their destruction. As a result:
1.Intrinsic Factor Decrease: With the loss of parietal cells, there is a reduction in the production of intrinsic factor, a protein required for the absorption of vitamin B12 in the small intestine.
2.Decreased B12 Absorption: The diminished intrinsic factor results in impaired absorption of vitamin B12, leading to the characteristic B12 deficiency seen in pernicious anemia.
3.Feedback Loop with Gastrin: Gastrin is a hormone that stimulates the secretion of gastric acid. In response to the decreased gastric acid production due to the loss of parietal cells, there is a feedback mechanism that increases the secretion of gastrin.
4.Elevated Gastrin Levels: The increased gastrin levels aim to stimulate the remaining parietal cells, promoting the production of gastric acid. However, since the primary defect is the destruction of parietal cells, this feedback loop results in persistently elevated gastrin levels.
The elevated gastrin levels can be observed in blood tests and may contribute to other symptoms or conditions, such as an increased risk of gastric carcinoid tumors or gastric cancer.
Monitoring and managing gastrin levels are important aspects of the overall care for individuals with pernicious anemia

Megaloblastic Anaemia

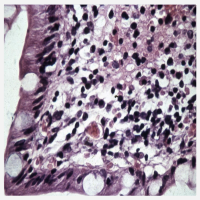
Hematological findings

Tissue	Findings	Microscope
Peripheral blood	1. **Macrocytic anaemia, oval macrocytes, anisocytosis, poikilocytosis, high MCV.** 2. Dimorphic anemia when it is associated with iron deficiency or with thalassaemia trait. 3. **Hypersegmented neutrophils** 4. Leukopenia and thrombocytopenia	
Bone marrow	1. **Hypercellular marrow with M:E ratio in normal or reduced** 2. Accumulation of primitive cells due to selective death of more mature cells. 3. **Megaloblast** (large erythroblast which has a nucleus of open, fine,lacy chromatin). 4. Dissociation between the nuclear and cytoplasmic development in the erythroblasts. 5. Mitosis and dying cells are more frequent than normal (due to ineffective hematopoiesis) 1. **Giant and abnormally shaped, metamyelocytes, polypoid megakaryocytes.** 2. Increased stainable iron in the macrophage and in the erythroblasts.	
Other laboratory abnormalities	1. Chromosomal abnormalities 2. Ineffective hematopoiesis (intramedullary cell death by apoptosis) associated with increased serum indirect bilirubin. 1. ↑urobillinogen and faecal stercobillinogen 2. ↑LDH, ↑serum iron, ↑blood carbon monoxide (↑LDH,= lactate dehydrogenase is an abundant enzyme is in red blood cells and functions as a marker for hemolysis (or turn-over of cells)) 1. ↑serum lysozyme 2. ↓ haptoglobins (large amounts bind to free hemoglobin causing reduced serum level (marker of hemolysis)) 3. **Positive schumm's test** 4. Positive urine hemosiderin	

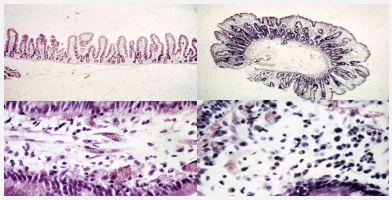
Histopathological findings



Left: Normal Gastric mucosa
Right: Gastric atrophy in patients with pernicious Anemia



Heavy infiltration of lamina propria with plasma cells and lymphocytes in patients with pernicious Anemia

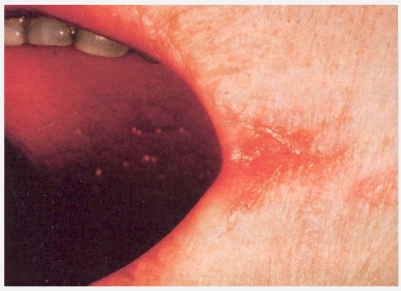


Left: Normal small intestinal mucosa
Right: Histopathology of small intestinal mucosa in malabsorption syndrome

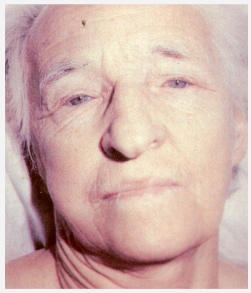
Megaloblastic Anaemia

Clinical Features
Progressive symptoms and signs of anaemia

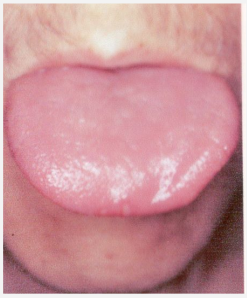
- **Weakness**, anorexia, weight loss, diarrhoea or constipation, tiredness, shortness of breath, angina of effort, heart failure
- Mild **jaundice**, **glossitis**, **stomatitis**, **angular cheilitis.**
- Purpura, melanin pigmentations.
- Infections



angular cheilitis
(Fissures)



Pallor



Glossitis
(Tongue swelling)

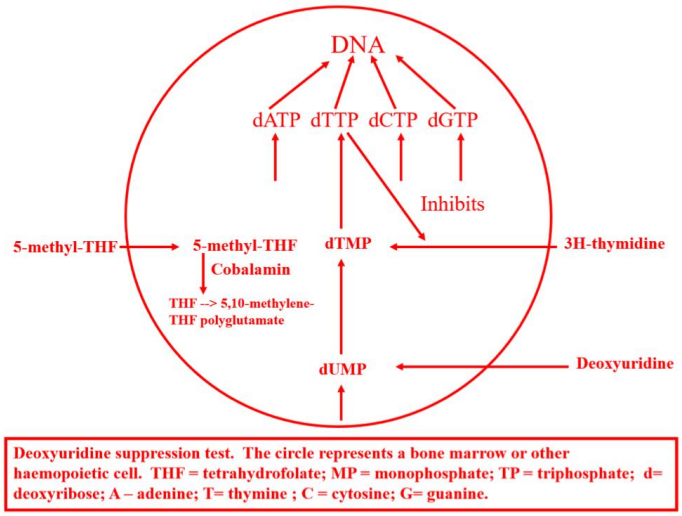
Treatment

In case of	Vitamin B12 deficiency	Folate deficiency
Compound	Hydroxocobalamin	Folic acid
Route	Intramuscular	Oral
Dose	1000µg	5 mg
Initial dose	6X1000 µg over 2-3 weeks	Daily for 4 months
Maintenance	1000µg every 3 months	Depends on underlying disease; life-long therapy may be needed in chronic inherited hemolytic anemia, renal dialysis, myelofibrosis
Prophylactic	- Total gastrectomy - Ileal resection	- Pregnancy - severe hemolytic anemias - dialysis - prematurity

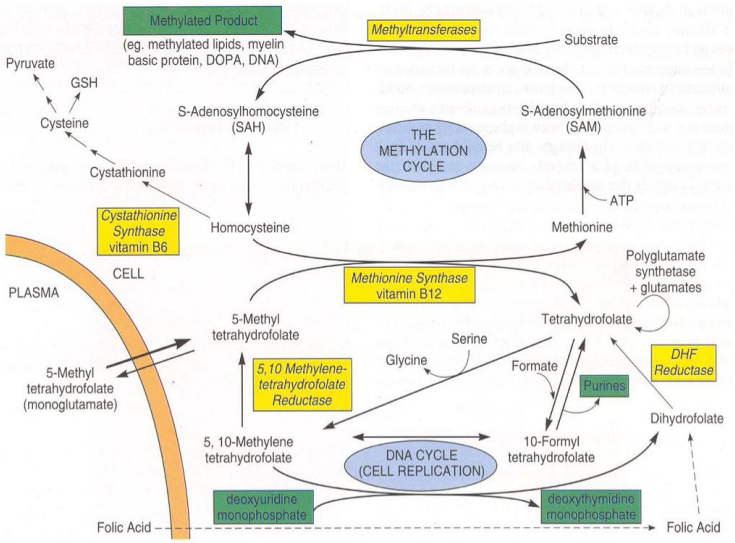
Pictures of the Lecture

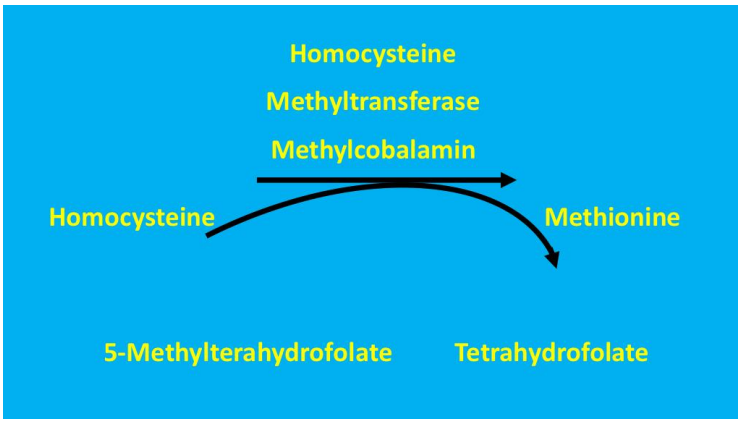
EXTRA
Pics are from the slides

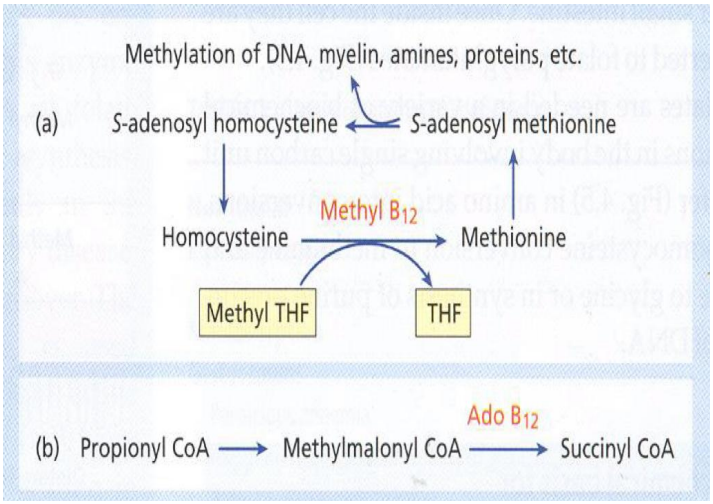
Dr. Fatma didn't mention or explain these pics, so we are adding them here if you want to take a look ;)



Deoxyuridine suppression test. The circle represents a bone marrow or other haemopoietic cell. THF = tetrahydrofolate; MP = monophosphate; TP = triphosphate; d= deoxyribose; A – adenine; T= thymine ; C = cytosine; G= guanine.







Summary

Thanks to hematology team 439

- Megaloblastic erythropoiesis describes abnormal red cell development characterized by a lack of synchrony between the maturation of the red cell nucleus and its cytoplasm. It arises as a consequence of disordered DNA synthesis and results in a macrocytic megaloblastic anemia.
- It can be caused by vitamin B12 or folate deficiency or antifolate drugs (ex. methotrexate)
- Clinical features include: jaundice, **glottitis**, **angular cheilosis**, purpura

	Vitamin B12 Deficiency	Folate Deficiency
Found in	Only food of **animal** origin	green **vegetable** and **yeast**
Time to develop deficiency in the absence of intake or absorption	Anemia in 2-10 **years**	Macrocytosis in 5 **months.**
Absorption	Requires **intrinsic factor** secreted by gastric parietal cells, Cubilin, transcobalamin II	Conversion of polyglutamates to monoglutamates by intestinal folate conjugase
Site of absorption	**Terminal ileum**	**Duodenum and jejunum**
Cause of deficiency	(Malabsorption) • Total or partial gastrectomy • Inadequate secretion of intrinsic factor • **Pernicious anaemia** (Nutritional) • Veganism (Others) • Alcohol abuse	• Pregnancy • Infants • Inadequate dietary intake • Malabsorption • Increased requirement
Manifestation of deficiency	**Neuropathy** can manifest due to vit B12 or folate deficiency. Cause of the neuropathy as a result of **B12 deficiency** is likely to be related to **Accumulation of S-adenosyl homocysteine and reduced levels of S-adenosyl methionine in nervous tissue.**	
Hematological findings in peripheral blood	• **Macrocytic** anemia, oval macrocytes, anisocytosis,Poikilocytosis • Hypersegmented neutrophils, leukopenia, and thrombocytopenia	
Hematological findings in bone marrow	• Giant and abnormally shaped, metamyelocytes, polyploid megakaryocytes • **Megaloblast** (large erythroblast which has a nucleus of open, fine, lacy chromatin). • Increased stainable iron in the macrophage and in the erythroblasts. • **Hypercellular marrow** with M:E ratio in normal or reduced. • **Accumulation of primitive cells** due to selective death of more mature cells.	
Treatment	Hydroxocobalamin, IM	Folic acid, oral
Pernicious Anemia	• **It's a problem in secretion of intrinsic factor** • Severe megaloblastic anaemia due to **autoimmune attack** on the gastric mucosa leading to atrophy and **absence of intrinsic factor (IF) secretion** • **Absent serum vitamin B12** • Raised serum Gastrin	

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- **Reuf Alahmari**
- **Deema almadi**
- **huda bin jadaan**
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Special thanks to 442 team

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