HAEMATOLOGY 436

MEDICINE
KING SAUD UNIVERSITY

تمت المراجعة
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Megaloblastic Anemia

- 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 microcytosis.

Important
Extra.
Notes

References:
436 girls & boys' slides
435 teamwork slides

Editing file

Do you have any suggestions? Please contact us!

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or simply use this form

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 (1-2 %)	

*In children normal hemoglobin values are: newborn, 150 – 210g/L , 3 months, 95 – 125g/L , 1 year to puberty, 110 – 135g/L.
* PCV, packed cell volume.

Normal White Cells (WBC) Count In Adults	
TOTAL	4.0 - 11.0 X 10^9/L
Neutrophils	2.5 - 7.5 x 10^9/L
Lymphocytes	1.5 - 3.5 x 10^9/L
Monocytes	0.2 - 0.8 x 10^9/L
Eosinophils	0.04 - 0.44 x 10^9/L
Basophil	0.01 - 0.1 x 10^9/L
Platelets	150-450 x 10^9/L

* Children have higher lymphocytes count

Microcytic, Hypochromic Anaemia	Normocytic, Normochromic Anaemia
MCV< 80 fL	MCV 80 – 95 fL
MCH<27pg	MCH>26pg
Types: Iron deficiency Thalassaemia Anaemia of chronic disease (some cases) Lead poisoning Sideroblastic anaemia (some cases)	Types: Many haemolytic anaemias Anaemia of chronic disease (some cases) After acute blood loss Renal disease Mixed deficiencies Bone marrow failure, e.g. post-chemotherapy, infiltration by carcinoma, etc.

Macrocytic Anaemia:

Macrocytic anaemias can be divided into those showing

Megaloblastic erythropoiesis	Normoblastic 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 anaemia.	describes the normal appearance of red cell maturation - but may still be associated with a macrocytosis (enlargment of red blood cells) in the peripheral blood

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

1. Macrocytosis:

- Alcohol (affect the membrane by affecting the phosphate)
- Liver disease (especially alcoholic)
- Reticulocytosis (haemolysis or haemorrhage)
- Aplastic anaemia or red cell aplasia
- Hypothyroidism
- Myelodysplasia (bone marrow is not making enough blood cells) including acquired Sideroblastic anaemia
- myeloma and macroglobulinaemia
- Leucoerythroblastic anaemia (resulting from space occupying lesion in the bone marrow)
- Myeloproliferative disease
- Pregnancy (physiological)
- Newborn (physiological)
- Chronic respiratory failure

2. Hypersegmented Neutrophils

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

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

Macrocytosis with Normoblasts

- 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

Causes of megaloblastic anaemia : Important

- Cobalamin deficiency or abnormalities of cobalamin metabolism
- Folate deficiency or abnormalities of folate metabolism
- Therapy with anitfolate drugs (e.g. methotrexate)

Cont'd

- Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy.
  a. Some cases of acute myeloid leukaemia, myelodysplasia.
  b. Orotic aciduria (responds to uridine)
  c. Therapy with drugs interfering with synthemis 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:
  a. Vitamin E deficiency
  b. Lesch-Nyhan syndrome (responds to adenine)

Others causes

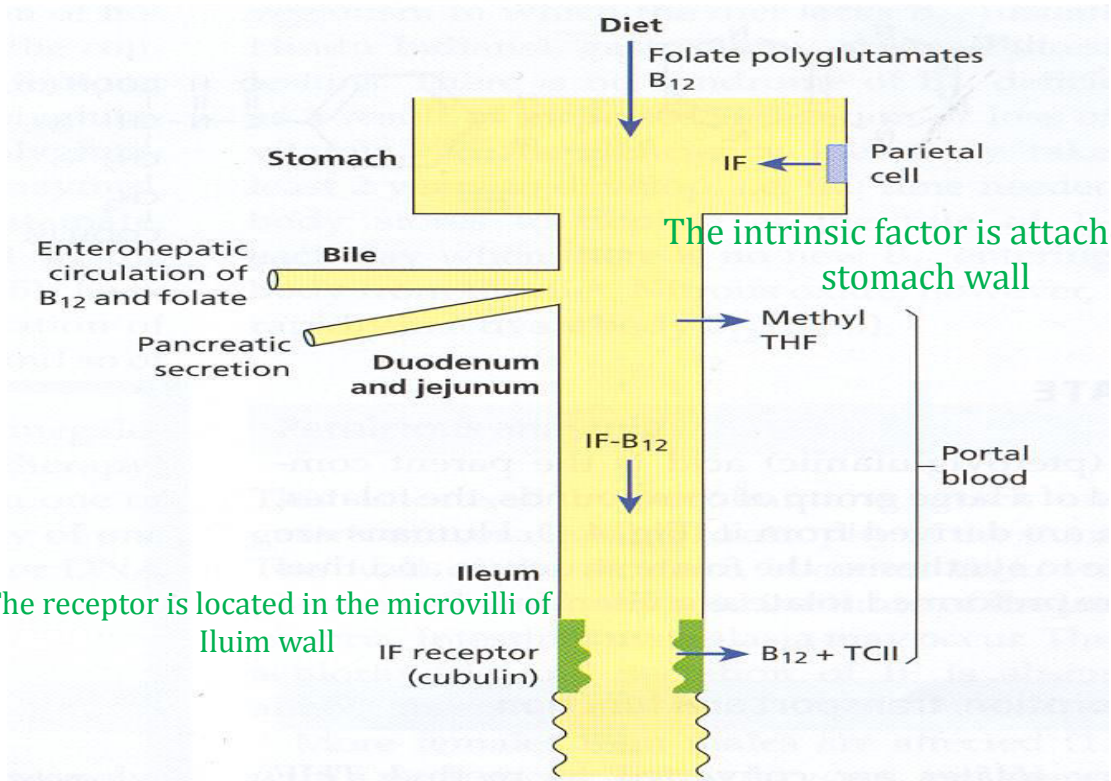
- Abnormalities of nucleic acid synthesis
- Drug therapy: Antipurines (mercaptopurine, azathioprine), Antipyrimidines (fluorouracil, zydovudine (AZT)), Others (hydrozyurea)
- Orotic aciduria
- Uncertain aetiology: Myelodysplastic syndromes, erythroleukaemia Some congenital dyserythropoietic anaemias

Vitamin B_{12} and folate nutrition and absorption: Important!

	Vitamin B12	Folate
Diterary sourse	Only food of animal origin, especially liver Our bodies are not able to synthesize it	Most foods, especially liver, green vegetable and yeast; destroyed by cooking
Average daily intake*	7 - 30 µg	200-250 µg
Minimum daily requirement*	1-3 µg	100-200 µg† This value and the previous one are higher comparing to vitamin B12
Body stores*	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*	Anaemia in 2-10 years	Macrocytosis in 5 months.
Requirements for absorption	Intrinsic factor (To modify the absorption) secreted by gastric parietal cells	Conversiion of polyglutamates to monoglutamates by intestinal folate conjugase
Site of absorption	Terminal ileum	Duodenum and jejunum

* In adults.

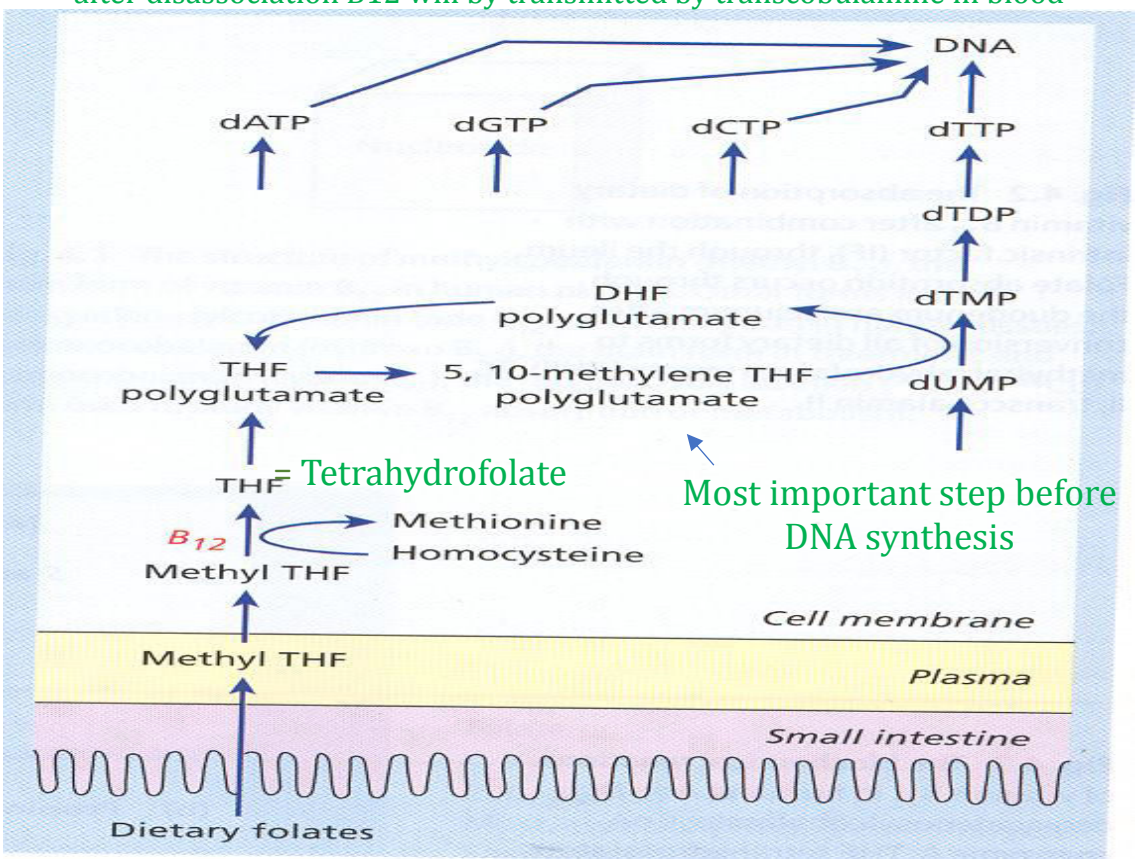
† Higher during pregnancy and lactation.



The intrinsic factor is attached to stomach wall

The receptor is located in the microvilli of Iluim wall

After attachment of IF and B12 its passage become facilitated to the circulation, after disassociation B12 will by transmitted by transcobulamine in blood



Most important step before DNA synthesis

This summaries the pathogenesis of megaloblastic anemia

Causes of vitamin B12 and folate deficiency:

Vitamin B_{12} Deficiency	folate deficiency
• Inadequate intake • Veganism but they have normal enterohepatic circulation so even a small amount of B12 maybe enough for them • Inadequate secretion of intrinsic factor • Pernicious anaemia • Total or partial gastrectomy • Congenital intrinsic factor deficiency (rare) • Partial gastrectomy, vagotomy, gastritis, acid-suppressing drugs, alcohol abuse • Abnormal intestinal bacterial flora, multiple jejunal diverticula, small intestinal strictures • Diphyllobothrium latum • Malabsorption • Crohn's disease, ileal resection, chronic tropical sprue	• Inadequate dietary intake • Malabsorption • Coeliac disease, jejunal resection, tropical sprue • Increased requirement • Pregnancy, premature infants, chronic haemolytic anaemias, myelofibrosis, various malignant diseases • Increased loss • Long-term dialysis, congestive heart failure, acute liver disease • Complex mechanism • Anticonvulsant therapy, * ethanol abuse* • * Only some cases with macrocytosis are folate deficient.

Pernicious Anaemia:

It is a severe megaloblastic anemia due to autoimmune attack on the gastric mucosa leading to atrophy. so there is lack of intrinsic factor

- More common in elderly female patients than males (1.6:1) at the age of 60 and above
- More common in Northern European and tends to be in families

Pathogenesis:

- The mucosa become thin with plasma cells and lymphoid infiltration of the lamina propria.
- Intestinal metaplasia may occur. gastric carcinoma
- It maybe associated with autoimmune diseases including the autoimmune poly-endocrine syndrome.

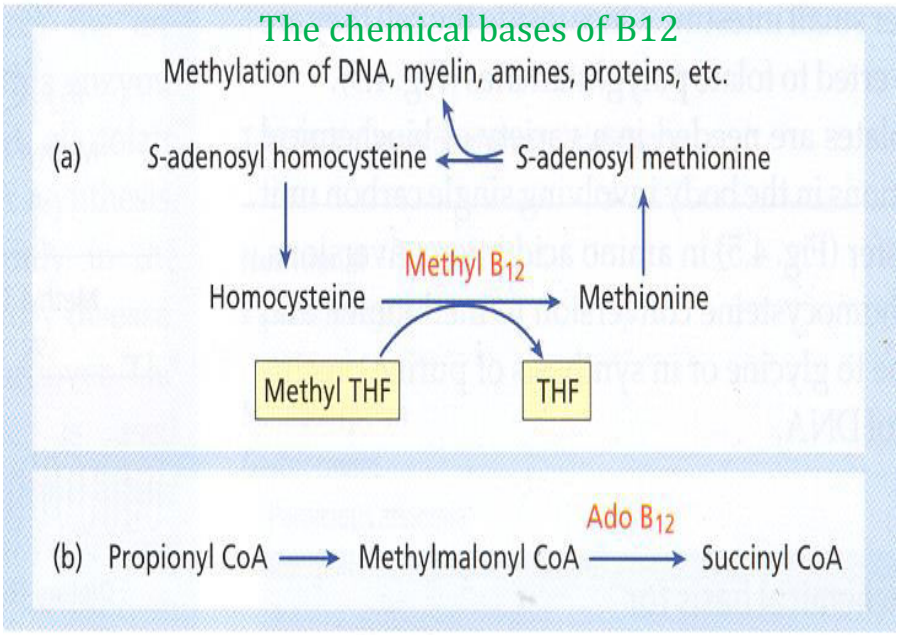
Findings:

- Achlorhydria* and absent secretion of intrinsic factor (IF).
- Progressive neuropathy is a common feature
- Absent serum vitamin B12 level or almost absent level
- Raised serum gastrin levels
- Helicobacter pylori infection may be the cause which present in younger age as iron deficiency anaemia and in the elderly as pernicious anaemia may occur at early stage of the anemia
- Increased incidence of gastric carcinoma in (2-3% of pernicious anaemia patients).

* Combination of Vit.b12 and IF need acidic environment

The integration between B12 and IF

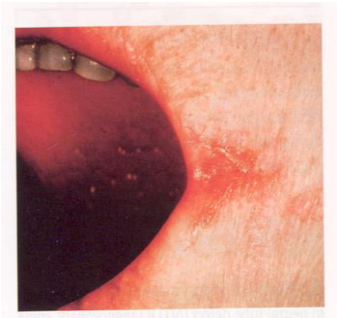
Homocysteine
Methyltransferase
Methylcobalamin



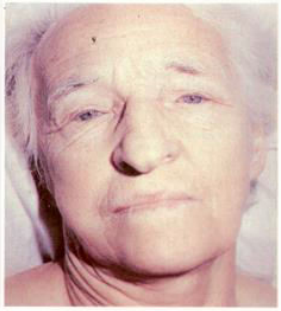
Clinical Features of Megaloblastic Anaemia:

-Progressive symptoms and signs of anaemia

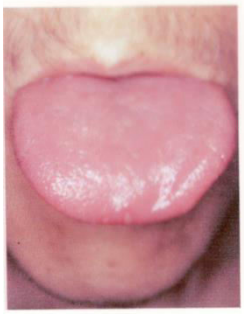
- Weakness, anorexia, weight loss, diarrhoea or constipation, tiredness, shortness of breath, angina of effort, heart failure
- Mild jaundice, glossitis, stomatitis, angular cheilosis
- Purpura, melanin pigmentations
- Infections



angular cheilosis



jaundice



red swollen painful tongue with beef like appearance angular somatitis

❖ Neuropathy due to Vit B_{12} and folate deficiency:

Progressive neuropathy affecting:

- The peripheral sensory nerves
- Posterior and lateral columns (sensory ataxia) of the spinal cord (subacute combined degeneration of the cord)
- Optic atrophy
- Psychiatric symptoms

Pathogenesis:

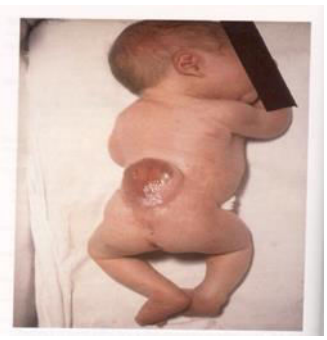
- The neuropathy is likely due to accumulation of S-adenosyl homocysteine and reduced level of S-adenosyl methionine in nervous tissue resulting in defective methylation of myelin and other substrates.
- Neuropathy is mostly due to vitamin B_{12} deficiency. In new born (encephalopathy)

❖Neural tube defect (NTD):

Anencephaly, spina bifida or encephalocoele in the fetus due to folate or Vit B_{12} deficiency in the mother

This results 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 and hair lip

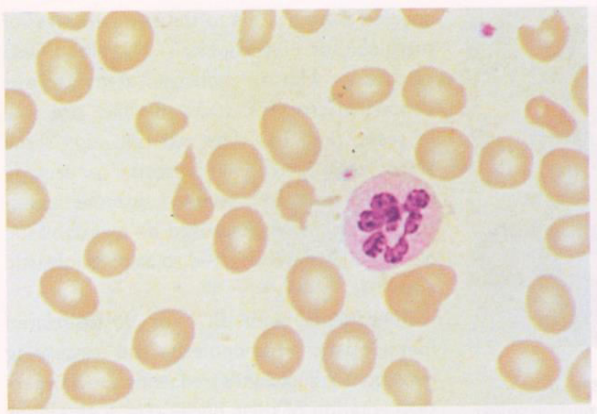


❖Haematological findings in Megaloblastic Anaemia:

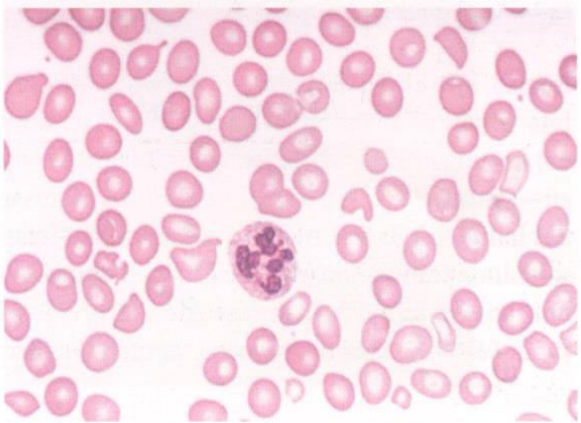
1- Peripheral Blood:

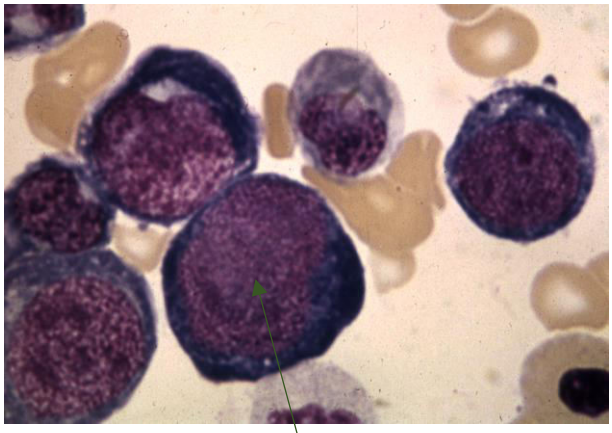
•Macrocytic anaemia, oval macrocytes, anisocytosis, poikilocytosis high MCV.
•Dimorphic anaemia when it is associated with iron deficiency or with thalassaemia trait.
•Hypersegmented neutrophils.
•Leucopenia and thrombocytopenia

- **2-Bone Marrow: important**
- Hypercellular (increased cell count.) marrow with M:E ratio in normal or reduced.
- Accumulation of primitive cells due to selective death of more mature cells.
- Megaloblast (large erythroblast which has a nucleus of open, fine, lacy chromatin).
- Dissociation between the nuclear and cytoplasmic development in the erythroblasts.
- Mitosis and dying cells are more frequent than normal.
- Giant and abnormally shaped, metamyelocytes, polypoid megakaryocytes.
- Increased stainable iron in the macrophage and in the erythroblasts.



Hypersegmented neutrophile (normal segments 3-5) but it is not charactristic for megaloplastic





Erythroblast (Early precursor) Nucleated

❖ Other laboratory abnormalities:

- Chromosomal abnormalities
- Ineffective haemopoiesis (erythrocytosis) . (Intramedullary cell death by apoptosis) associated with increased serum indirect bilirubin.
- ↑ urobillinogen and faecal stercobillinogen.
- ↑ LDH ↑ serum iron ↑ blood carbon monoxide.
- ↑ serum lysozyme
- ↓ reduced haptoglobins
- Positive schumm's test
- Positive urine haemosiderin.

All are symptoms of hemolysis (increased turnover of the cell)

❖ Treatment of megaloblatic anaemia: NOT IMPORTANT!

	Vitamin B_{12} deficiency	**Folate deficiency**
Compound	Hydroxocobalamin	Folic acid
Route	Intramuscular	Oral
Dose	1000 µg	5mg
Initial dose	6X1000 µg over 2-3 weeks	Daily for 4 months
Maintenance	1000 µg every 3 months	Depends on underlying disease; life-long therapy may be needed in chronic inherited haemolytic anaemia, myelofibrosis, renal dialysis
Prophylactic	Total gastrectomy Ileal resection	Pregnancy, severe haemolytic anaemias, dialysis, prematurity

Summery:

	TYPES	CAUSES:
Anemia	Microcytic, Hypochromic	Iron deficiency Thalassaemia Lead poisoning Sideroblastic anaemia
	Normocytic, Normochromic	Anemia of chronic disease After acute blood loss Renal disease Mixed deficiencies Bone marrow failure, e.g. post-chemotherapy
	MACROCYTIC Has 2 types : Megaloplastic & Normoblastic	Pregnancy Newborn Alcohol Liver disease Aplastic anemia
	A-megaloplastic	Cobalamin (B12) deficiency Folate deficiency Drugs, ex:(methotrexate, mercaptopurine) Myeloid leukemia Vitamin E deficiency Lesch-Nyhan syndrome
Vitamin B12 Deficiency		Inadequate intake Veganism Inadequate secretion of intrinsic factor Pernicious anaemia Total or partial gastrectomy Malabsorption Crohn's disease, ileal resection
Folate Deficiency		Inadequate dietary intake pregnancy Malabsorption Coeliac disease, jejunal resection Long-term dialysis, congestive heart failure acute liver disease

MCQs:

1-Pernicious anemia it's autoimmune disease against:
A- IF
B- parietal cell
C- chief cell
D- A&B

2- B12 absorbed in the:
A-duodenum
B-jejunum
C-ileum
D- A&b

3- which one of the following cause folate deficiency?
A- total gastrectomy
B- veganism
C- ileal resection
D- long term dialysis

4-bone marrow failure can cause:
A-microcytic, hypochromic anemia
B-normocytic, normochromic anemia
C- macrocytic anemia

Answers:
1-D
2-C
3-D
4-B

Good Luck!

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