Macrocytic Anaemia (Megaloblastic and Non-Megaloblastic)

In macrocytic anaemia the red cells are abnormally large (mean corpuscular volume, MCV >100fL).

— There are several causes of marocytosis but they can be broadly subdivided into megaloblastic and non megaloblastic based on the appearance of developing erythroblasts in the bone marrow and red cells morphology in the peripheral blood

Causes of macrocytosis (MCV>100Fimto liter)

Megaloblastic: **Impaired DNA formation due to lack of,** B12 or folic acid	**Non megaloblastic** **Not related to B12/folate deficiency**
Vitamin B12 deficiency, Folale deficiency Defective Vitamin B12 or folate metabolism Transcobalamin II deficiency Defects of DNA synthesis ***Ovale red cells shape*** ***Megaloblastic maturation of bone marrow hemopoietic precursors***	Physiological: Pregnancy and Infants Pathological: Alcohol**,** Liver disease, MDS, Myxodema Reticulocytosis (Acute haemolytic anaemia) Neonates ***Round red cells shape*** ***Normal bone marrow***

Megaloblastic anaemias (MGBA)

Are anaemia with large RBC (ovalocytes,MCV>100fl) in the peripheral, and large erythroid cells (megaloblast) in the bone marrow. Usually associated with leukopenia with *hyper segmented neutrophils* and thrombocytopenia

Megaloblastic anemias result from conditions in which nucleic acid synthesis is abnormal, due to vitamin B12 and Folate deficiency result in failure or delayed of mitotic division

Biochemichal basis of megaloblastic anaemia:

Vitamin B12 and Folic acid play role as cofactors in the conversion of deoxy—uridine monophosphate (dUMP) to deoxy—thymidine (dTMP), an essential step in the synthesis of DNA

Folate is required in one of its coenzyme forms, 5,IO-methylene tetrahydrofolate (THF) polyglutamate, in the synthesis of thymidine monophosphate from its precursor deoxyuridine monophosphate.
Vitamin BI2 is needed to convert methyl THF, which enters the cells from plasma, to THF, from which polyglutamate forms of folate are synthesized.
Dietary folates are all converted to methyl THF (a monoglutamate) by the small intestine.

Dietary folates (In the small intestine) → MTHF in the plasma → in the cells cytoplasm reduced to THF by B12 as Co—enzyme

THF→5, 10-methylene THF →dUMP→DTMP→DTDP→DTTP→DNA Synthesis

When DNA synthesis is delayed causing delayed nuclear maturation and decrease number of mitotic division result in decrease of red cells production, and erythropoiesis changes from normoblastic to megaloblastic .

Also Megaloblast late erythroid precursors cells undergo intramedullary (in the bone marrow) death or hemolysis and this will aggravate the anaemia and producing mild elevation in serum indirect bilirubin (jaundice) and lactate dehydrogenase.

Causes of vitamin B12 deficiency	Causes of folate deficiency.
Nutritional (vegans) Malabsorption *A. Gastric causes* 1.Pernicious anaemia 2,Total or partial gash'ectomy *B. Intestinal causes* diverticulosis, blind-loop, Ileal resection and Crohn's disease Congenital selective malabsorption with proteinuria Fish tapeworm	A. Nutritional: old age, poverty, goat's milk B. Malabsorption: gluten-induced enteropathy extensive jejunal resection or Crolm's disease C. Excess utilization *1,Physiological:* Pregnancy and lactation. *2. Patilological* Haematological diseases: chronic haemolytic anaemias, Leukaemia. Inflammatory diseases , psoriasis, exfoliative dermatitis, Drugs, Anticonvulsants, alcoholism,

B12 and folic Acid nutritional aspects

	B12	**Folic acid**
Normal daily dietary intake	7-30µg/day	200-250 µg/day
Main foods	Vegetable diet ,Animal	liver, greens and yeast
Effect of Cooking	Little effect	Easily destroyed
Minimal daily requirement	1-2 µg/day	100-150 µg/day
Body stores	2-3 mg (sufficient for 2-4 years)	10-12 mg (sufficient for 4 months)
Absorption Site	Ileum	Duodenum and jejlUlum
Mechanism	Intrinsic factor	Conversion to methyltetrahydrofolate

Laboratory feature of megaloblastic anaemia:

A. Hematologial:

1; low Hct, low Hb, Low red cells count, High MCV>100
low WBC (neutrophils), low platelets

2. Peripheral blood show: . Macrocytes with ovale shape red cells, hypersegmented neutrophils (>5lobes), low platelets count

Low reticulocytes count which is also seen in IRON deficiency anaemia, aplastic anaemia , anaemia of chronic disorders and pernicious anaemia.

3. **B**one marrow hypercellular with hemopoietic precursors show:
   a. Erythroid precursors macroerythroblast show open stippled chromatin and mature hemoglobin in the cytoplasm. (nuclear cytoplasmic asynchrony).
   b. Myeloid precursors show giant meatamyelocytes and band cells,
   c. megakaryocytes show hypepolyploidy (increase number of nuclear lobes >16 lobe)

B. Biochemichal investigations

1. increase indirect bilirubin and LDH (lactate dehydrogenase)
2. Increase homocystein in blood and urine
3. Assay of serum B12/folate, and red cells folate
   a. In B12 deficiency result low serum B12 and normal serum folate, low red cells folate
   b. In folate deficiency result normal serum B12 and low serum folate , low red cells folate

Investigation of B12 and folic acid

Test	**In B12 deficiency**	**In Folate deficiency**
Serum vitamin BI2	Low	Normal
Serum folate	Normal or raised	Low
Red cell folate	low	Low

Pernicious anemia: failure of B12 binding from diet or failure of it absorption

This is caused by autoimmune antibodies attack the gastric mucosa leading to atrophy of the stomach. The wall of the stomach becomes thin, with chronic inflammatory cells infiltration, a plasma cell and lymphocytes There is achlorhydria and absent secretion of IF (B12—binding factor)

More females than males are affected (1.6 : 1), with a peak occurrence at 60 years, and there may be associated other autoimmune disease including the autoimmune polyendocrine syndrome (Table 4.4).

The disease is common in northern Europeans and tends to occur in families

Antibodies (investigated in the serum of the patient)

1. 95% of patients show parietal cell antibody however it is not specific only for Pernicious .anemia
2. 50% type I or blocking antibody to IF which inhibits IF binding to B12 – (it is the most specific for pernicious anaemia)
3. 35% show a second (type II or precipitating) antibody to IF receptors which inhibits its ileal binding site.

Diagnosis of pernicious anemia:

1. Megaloblastic anemia on peripheral blood and bone marrow with positive biochemical investigations
2. Investigation of Antibody in the serum of the patients
3. Gastric endoscopy and biopsy show chronic atrophic gastritis
4. history of chronic dyspepsia and indigestion