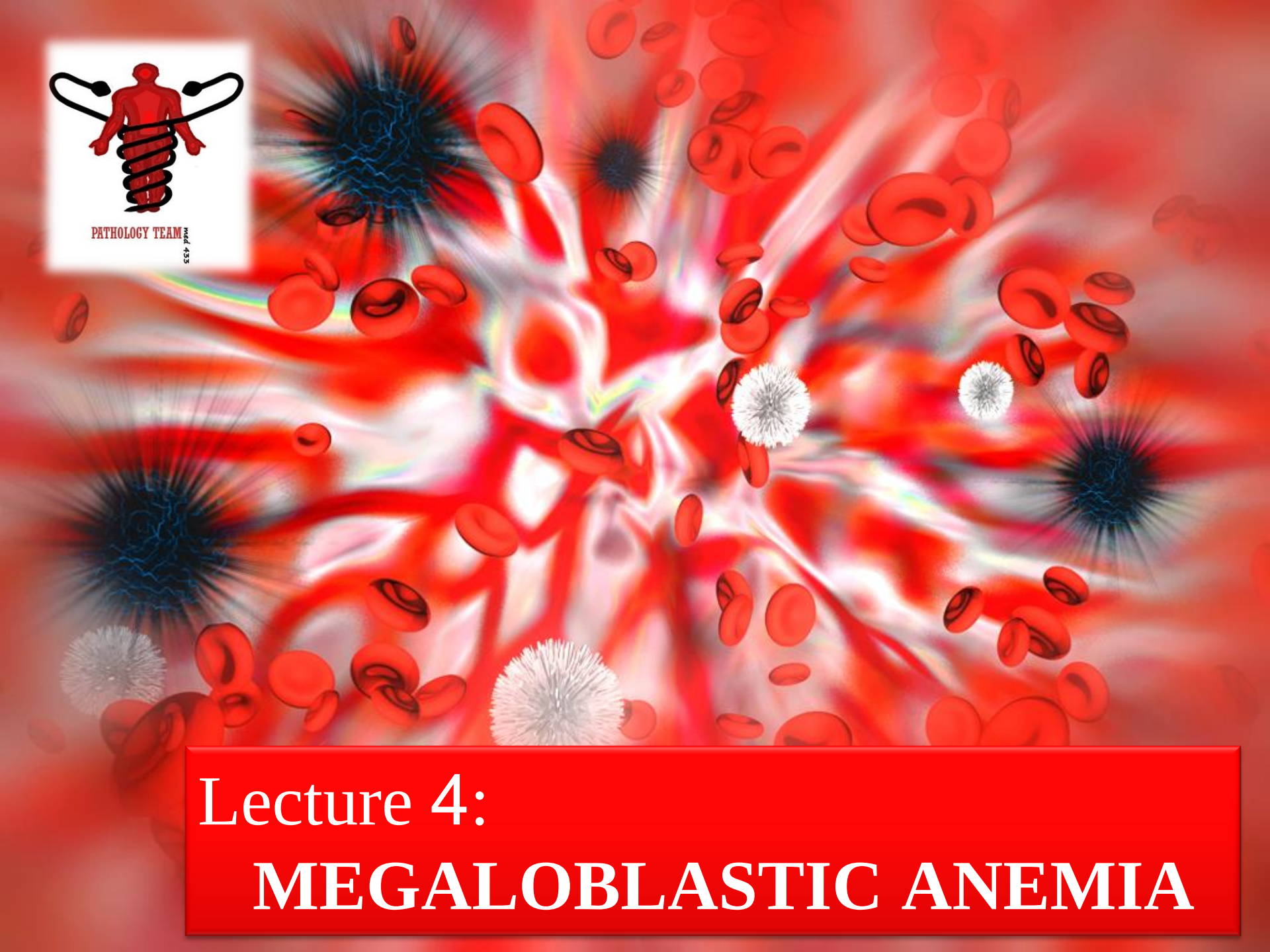


Lecture 4:

MEGALOBLASTIC ANEMIA

Normal adult RBC values

	MALE	FEMALE	Unit
Haemoglobin	13.5 – 17.5	11.5 – 15.5	g/dL
Haematocrit (PCV)	40 – 52	36 – 48	%
Red cell count	4.5 – 6.5	3.9 – 5.6	$x10^{12}/L$
MCH	27 – 34		Pg (picogram)
MCV	80 – 95		FL (femtolitres)
MCHC	30 – 35		g/dL
Reticulocyte count	25 – 125		$x10^{9}/L$

- **Notice : children has less values in the tests above than adult.**

Extra information

Test	Definition
Haemoglobin	The amount of Hb in the blood
packed cell volume	Fraction of whole blood volume that consists of red cells
MCH	the average hemoglobin per red cell
MCV	the average volume of the red cells+
MCHC	the average concentration of Hb/cell
Reticulocyte count	An early, immature form of a red blood cell (خلايا الدم الحمراء اللي عمرها أقل من 72ساعه لأنها تحويRNA)

- **dL (deciliter) = 0.1 L**

Megaloblastic Anaemia

Definition: is an anemia (of macrocytic classification) that results from inhibition of DNA synthesis during red blood cell production

The two principal causes of megaloblastic anemia are folate deficiency and vitamin B_{12} deficiency. Both vitamins are required for DNA synthesis and the effects of their deficiency on hematopoiesis are essentially identical

***We will get enlarged erythroid precursors (macrocytes)**

Causes:

Table 5.1 Causes of megaloblastic anaemia.

Vitamin B_{12} deficiency Folate deficiency — Most important
Abnormalities of vitamin B_{12} or folate metabolism (e.g. transcobalamin deficiency, nitrous oxide, antifolate drugs)
Other defects of DNA synthesis Congenital enzyme deficiencies (e.g. orotic aciduria) Acquired enzyme deficiencies (e.g. alcohol, therapy with hydroxyurea, cytosine arabinoside)

Table 5.2 Vitamin B_{12} and folate: nutritional aspects.

	Vitamin B_{12}	**Folate**
Normal daily dietary intake	7–30 µg	200–250 µg
Main foods	Animal produce only	Most, especially liver, greens and yeast
Cooking	Little effect	Easily destroyed
Minimal adult daily requirement	1–2 µg	100–150 µg*
Body stores	2–3 mg (sufficient for 2–4 years)	10–12 mg (sufficient for 4 months)
Absorption		
Site	Ileum	Duodenum and jejunum
Mechanism	Intrinsic factor	Conversion to methyltetrahydrofolate
Limit	2–3 µg/day	50–80% of dietary content

* Higher during pregnancy and lactation.

Mechanism of absorption

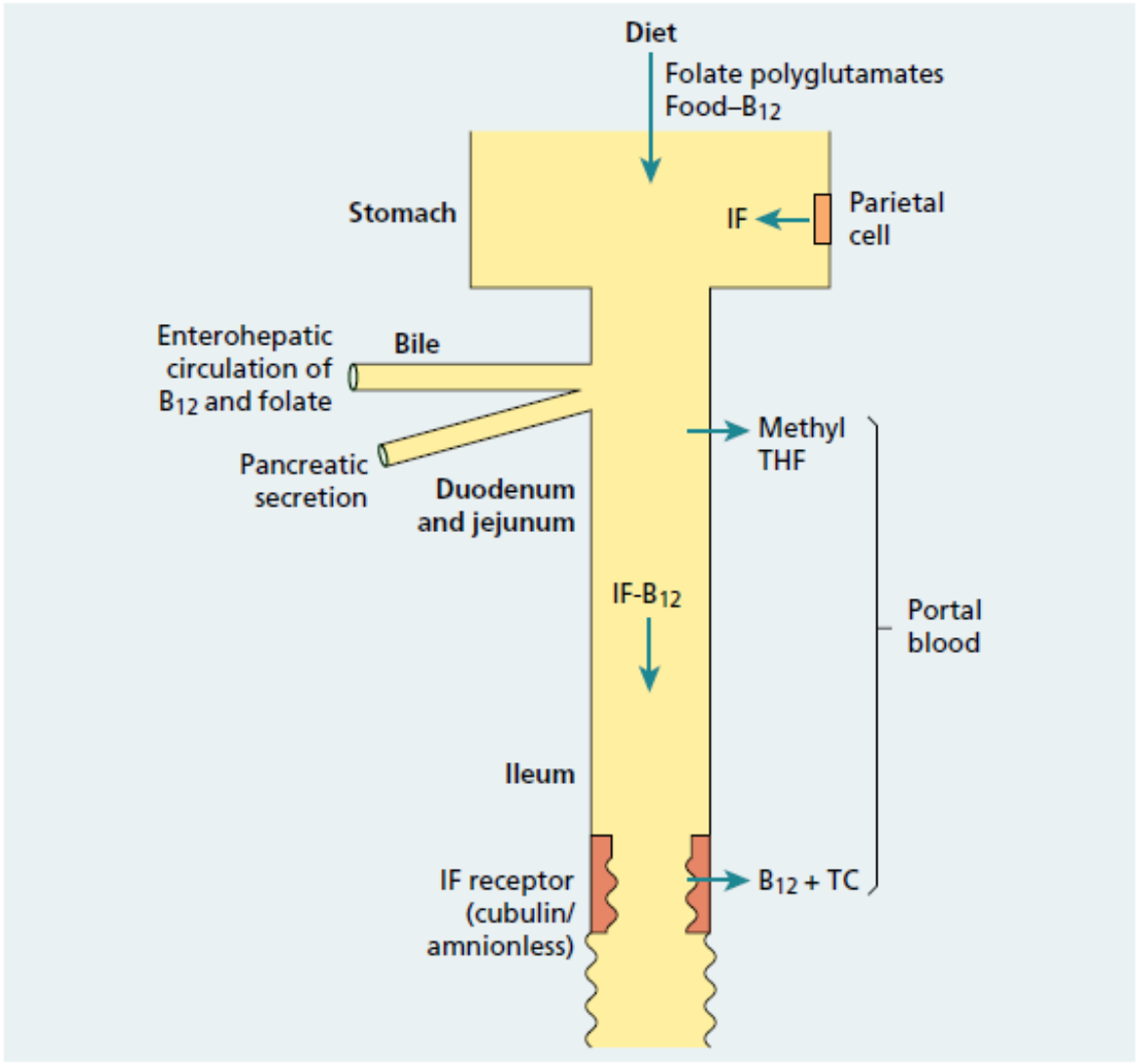


Figure 5.2 The absorption of dietary vitamin B_{12} after combination with intrinsic factor (IF), through the ileum. Folate absorption occurs through the duodenum and jejunum after conversion of all dietary forms to methyl-tetrahydrofolate (methyl THF). TC, transcobalamin.

Causes of Vitamin B_{12} Deficiency

Inadequate intake

- **Veganism (strict vegetarian), lactovegetarianism (can eat milk products)**

Inadequate secretion of intrinsic factor

- **Pernicious anaemia* , Total or partial gastrectomy , Congenital intrinsic factor deficiency**

Inadequate release of B_{12} from food

- **Partial gastrectomy, vagotomy, gastritis, acid-suppressing drugs, alcohol abuse**

Malabsorption

- **Crohn's disease, ileal resection, chronic tropical sprue, congenital selective B_{12} malabsorption with proteinuria (Imerslund-Grasbeck syndrome)**

Diversion of dietary B_{12}

- **Abnormal intestinal bacterial flora ,multiple jejunal diverticula, small intestinal strictures**

Causes of folate deficiency

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***

* Auto immune disease develop antibody against parietal or intrinsic factor leads to atrophied stomach

*Sprue occurring in the tropics, associated with enteric infection and nutritional deficiency, and often complicated by anemia due to folic acid deficiency. Also called *tropical diarrhea*

Pathogenesis

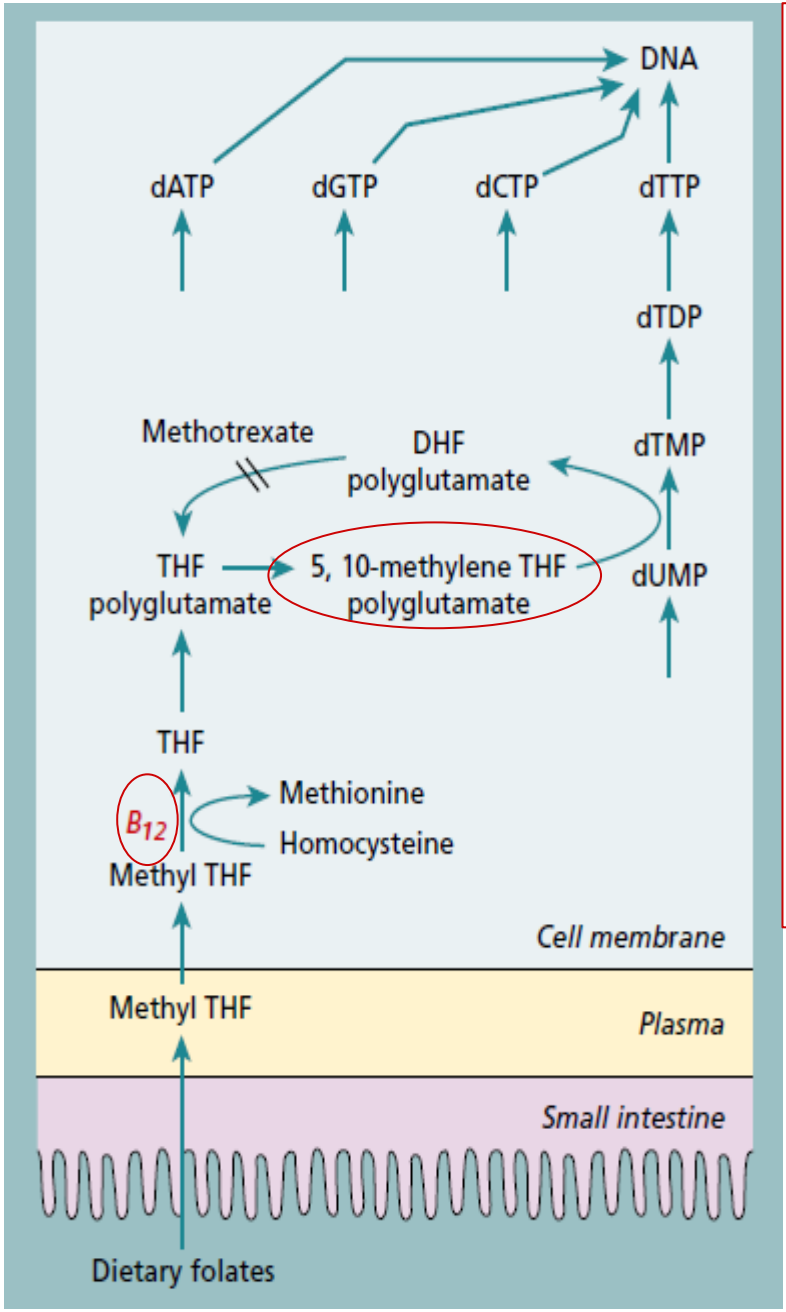


Figure: The biochemical basis of megaloblastic anemia caused by vitamin B12 or folate defi- ciency.

Folate: is required in one of its coenzyme forms, 5,10 - methylene tetrahydrofolate (THF) polyglutamate, in the synthesis of thymidine monophosphate from its precursor deoxyuridine monophosphate.

Vitamin B12: 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.

A, adenine; C, cytosine; d, deoxyribose;
DHF, dihydrofolate; DP, diphosphate;
G, guanine; MP, monophosphate; T, thymine;
TP, triphosphate; U, uracil.

* If we have Vit B12 deficiency , the level of homocysteine will be increase (we can use it as a laboratory findings)
* So folate and Vitamin B1 are important in DNA replication.

Clinical Features of Megaloblastic Anaemia

Symptoms due to megaloblastic anemia
Weakness
Anorexia
Weight loss
Diarrhoea or constipation
Tiredness
Shortness of breath
angina of effort
heart failure in last stages
Mild jaundice, glossitis, stomatitis, angular cheilosis (Pic)
Purpura*

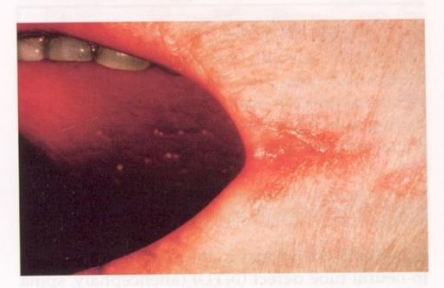


Table 5.6 Effects of vitamin B_{12} or folate deficiency.
Megaloblastic anaemia
Macrocytosis of epithelial cell surfaces
Neuropathy (for vitamin B_{12} only)*
Sterility
Rarely, reversible melanin skin pigmentation
Decreased osteoblast activity
Neural tube defects in the fetus are related to folate or B_{12} deficiency
Cardiovascular disease, e.g. stroke

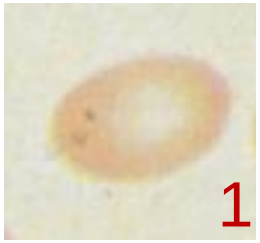
*Such as Psychiatric symptoms, Anencephaly, encephalocoele, degeneration of the columns of the spinal cord, or Cleft lip and palate

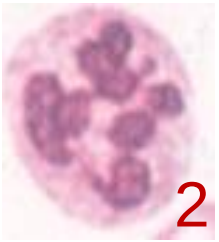
* بقع نزيفيه في الجلد due to ↓ platelet

Haematological findings in Megaloblastic Anaemia

Peripheral Blood

- Macrocytic anaemia = high MCV
- Oval macrocytes (in picture 1)
- Anisocytosis
- Poikilocytosis





- Dimorphic anemia when it is associated with iron deficiency or with thalassemia trait

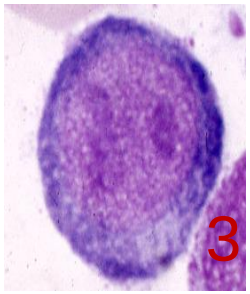
- Hypersegmented neutrophils (in the picture2)*
- Leucopenia and thrombocytopenia

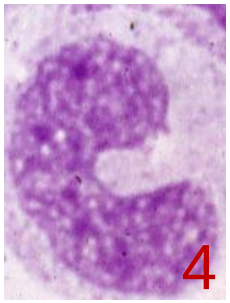
Bone Marrow

- Megaloblast (large erythroblast which has a nucleus of open, fine, lacy chromatin).
Picture 3

- Giant and abnormally shaped, metamyelocytes**
picture 4

- Polypoid megakaryocytes (origin of platelets)





- Increased stainable iron in the macrophage and in the erythroblasts

*if more than 5 lobes it consider abnormal

**a stage in the development of the granulocyte series of leukocytes.

laboratory abnormalities:

- ↑ **LDH (lactate-de-hydrogenase)**
- ↑ **serum iron** Due to breakdown on RBC **as a result of this the execration of iron in urine will increase (Positive urine hemosiderin).**
- **Chromosomal abnormalities**
- **Schumm's test positive (blood test)**

Extra information
Treatment of megaloblatic anaemia

Vitamin B_{12} deficiency	Folate deficiency
Hydroxocobalamin	Folic acid
Intramuscular	Oral
6 days (for each weak) 2- 3 weeks Then once every 3 months	Daily for 4 months
In some cases we give treatment as <u>prophylactic</u> 1. Total gastrectomy 2. Ileal resection	In some cases we give treatment as <u>prophylactic</u> 1. Pregnancy 2. severe hemolytic anemia 3. dialysis 4. prematurity

Causes of macrocytosis and hypersegmented neutrophils other than megaloblastic anemia:

Table 5.10 Causes of macrocytosis other than megaloblastic anaemia.
Alcohol
Liver disease
Myxoedema
Myelodysplastic syndromes
Cytotoxic drugs
Aplastic anaemia
Pregnancy
Smoking
Reticulocytosis
Myeloma and paraproteinaemia
Neonatal

Stem cells disorder leads to defective in cell maturation

Hypersegmented Neutrophils

-Renal failure

-Congenital (familial) abnormality .

Done by

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Good luck …