Megalobalstic anaemia

8-12-2009

Introduction

- **Megalo** means abnormally large.
- **Megaloblastic anemias** are a heterogeneous group of disorders that share common morphologic characteristics.
- **Morphology:** large RBC, increased nuclear-to-cytoplasmic ratios, hypersegmented neutrophils, abnormal megakaryocytes.
- **Nucleus:** maturation of nucleus is delayed.
- **The most common causes** of megaloblastosis are cobalamin (vitamin B-12) and folate deficiencies.
- Both disease result in impaired DNA synthesis which causes megaloblastic anemia.
- Megaloblastic anemias show the same hematological picture whether they are caused by folic acid deficiency or by vitamin B12 deficiency.

Causes of megaloblastic anaemia

Table 4.1 Causes of megaloblastic anaemia.

Major causes	Vitamin B_{12} deficiency
	Folate deficiency
	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)

Causes of Vit-B12 and folate deficiency

Vitamin-B_{12} deficiency	Folic acid deficiency
Nutritional deficits, e. g. – Goat milk – Vegetarian diet – Alcoholism	**Nutritional deficits** – Chronic abuse of alcohol
Impaired absorption – Genuine pernicious anemia – Status after gastrectomy – Ileum resection – Crohn disease – Celiac disease, sprue (psilosis) – Intestinal diverticulosis – Insufficiency of the exocrine pancreas – Fish tapeworm	**Impaired absorption** – E. g., sprue (psilosis) **Increased requirement** – Pregnancy – Hemolytic anemia **Interference/antagonism** – Phenylhydantoin – Cytostatic antimetabolic drugs – Trimethoprim (antibacterial combination drug) – Oral contrazeptives – Antidepressants – Alcohol

Nutritional aspects of Vit B12 & folate

Table 4.2 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
Enterohepatic circulation	5–10 µg/day	90 µg/day
Transport in plasma	Most bound to haptocorrin; TC essential for cell uptake	Weakly bound to albumin
Major intracellular physiological forms	Methyl- and deoxyadenosylcobalamin	Reduced polyglutamate derivatives
Usual therapeutic form	Hydroxocobalamin	Folic (pteroylglutamic) acid

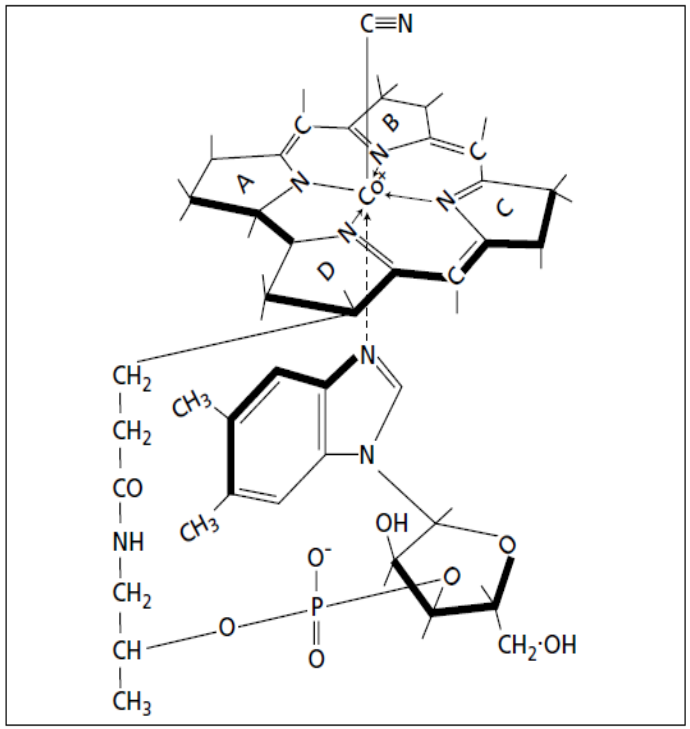
Vitamin B12

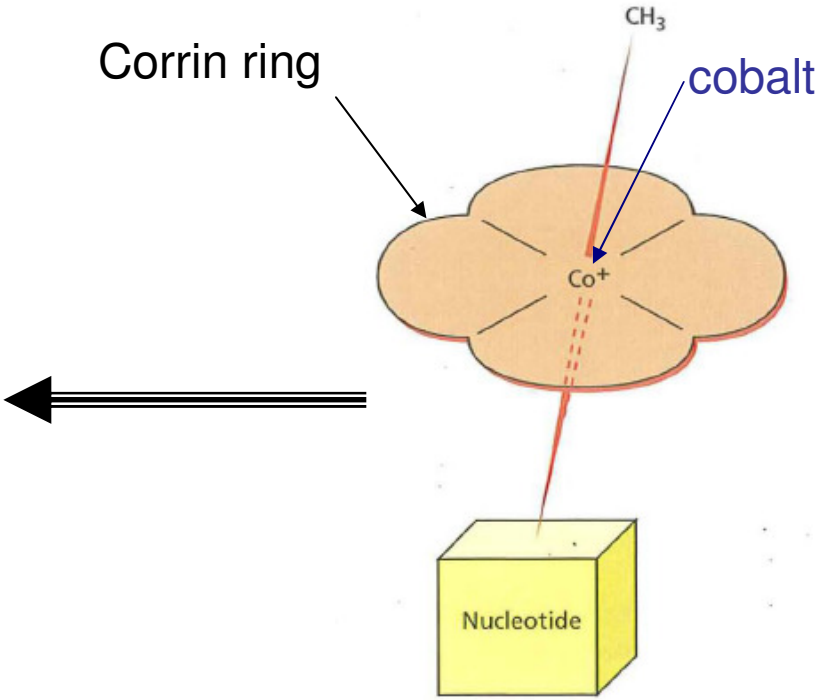
- Known as (B12 or cobalamin).
- Synthesised in nature by microorganisms outside or inside animal body.
- Found in foods of animal origin such as liver, meat, fish and

dairy produce but does not occur in fruit, cereals or vegetables.

- A normal diet contains a large excess of B12 compared with daily needs (1-2 µg).

Structure of Vitamin B12

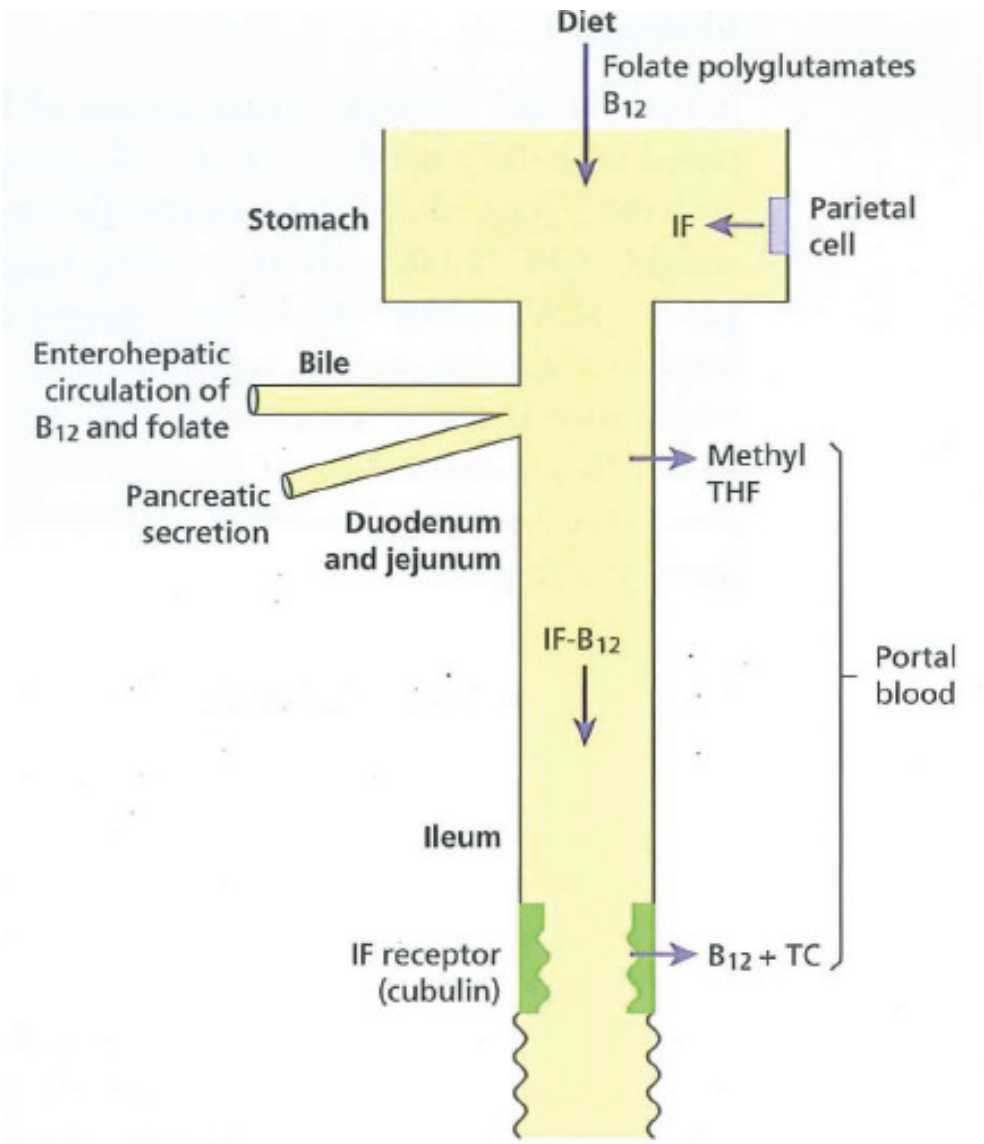




-Vitamin B12 consists of two halves: a ‘planar group’ and ‘nucleotide’ set at right angles to it.

- The planar group is a corrin ring and the nucleotide consists of the base, 5,6 dimethylbenziminazole, and a phosphorylated sugar, ribose-s-phosphate.

Absorption of B12



- Bl2 is combined with the intrinsic factor (IF) which is synthesized by the gastric parietal cells.

-The IF-B12 complex can then bind to a specific surface receptor for IF, cubilin.

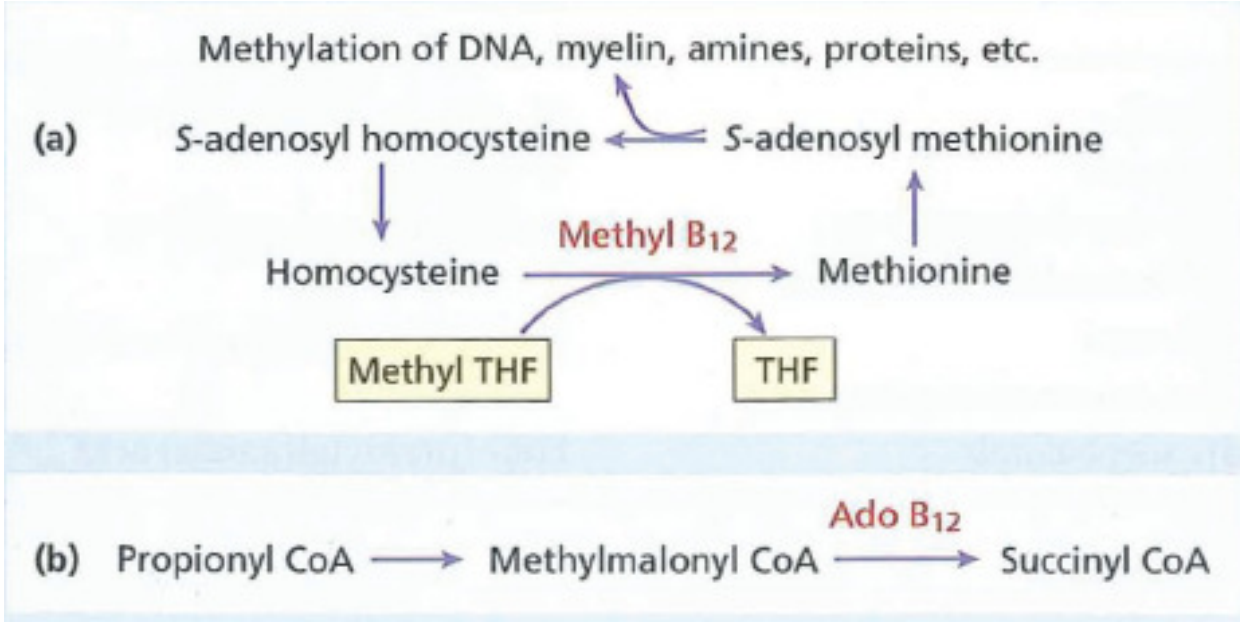
-Cubilin -IF-B12 complex bind to other protein called aminonless in the distal ileum where Bl2 is absorbed by endocytosis and IF Destroyed.

- Vitamin Bl2 is absorbed into portal blood where it becomes attached in the plasma to transcobalamin (TC) which delivers Bl2 to bone marrow and other tissues.

Table 4.3 Causes of severe vitamin B_{12} deficiency.

Nutritional
Especially vegans
Malabsorption
Gastric causes
Pernicious anaemia
Congenital lack or abnormality of intrinsic factor
Total or partial gastrectomy
Intestinal causes
Intestinal stagnant loop syndrome—jejunal diverticulosis, blind-loop, stricture, etc.
Chronic tropical sprue
Ileal resection and Crohn's disease
Congenital selective malabsorption with proteinuria (autosomal recessive megaloblastic anaemia)
Fish tapeworm

Biochemical function of B12

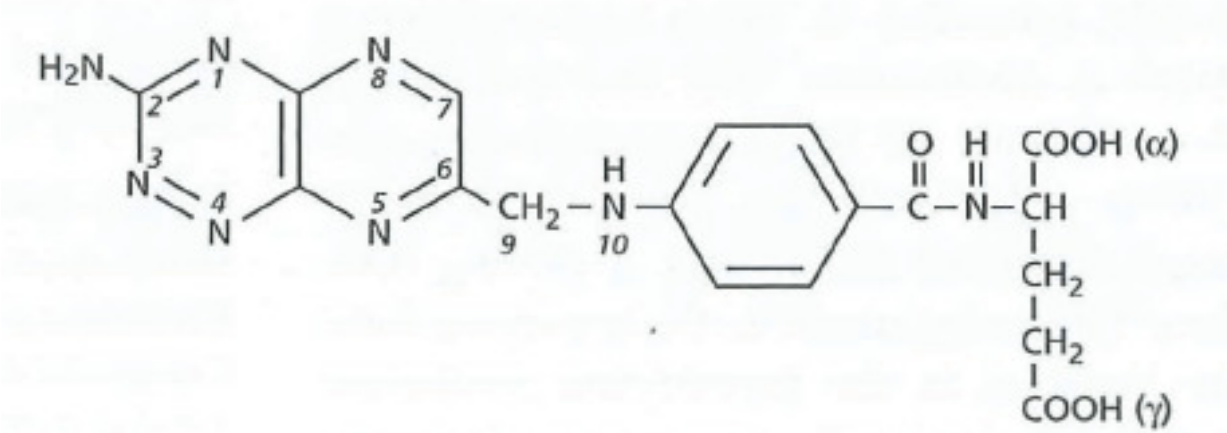


- Vitamin B12 is a coenzyme for two important biochemical reactions in the body.

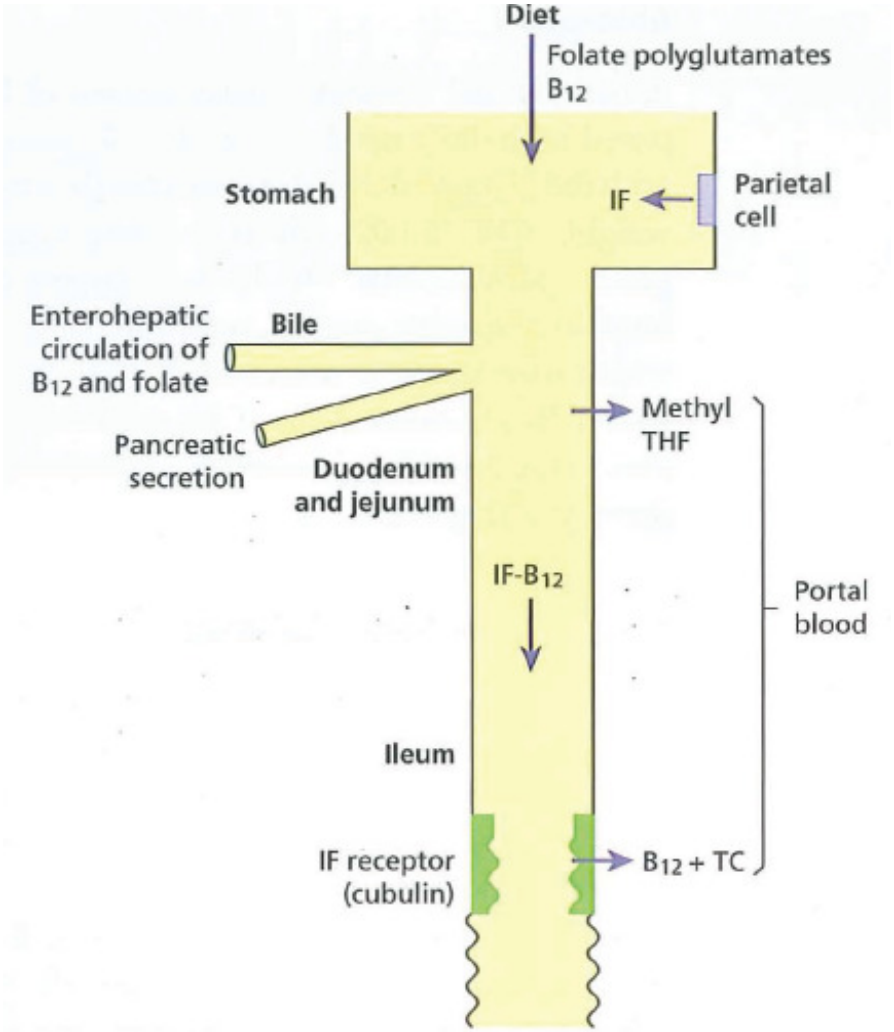
1- As Methyl B12 it acts as a co-enzyme for the convertion of homocysteine to mthionine.

2- As (ado B12) it assists in conversion of methylmalonyl coenzyme A (CoA) to succinyl CoA

Structure of folic acid

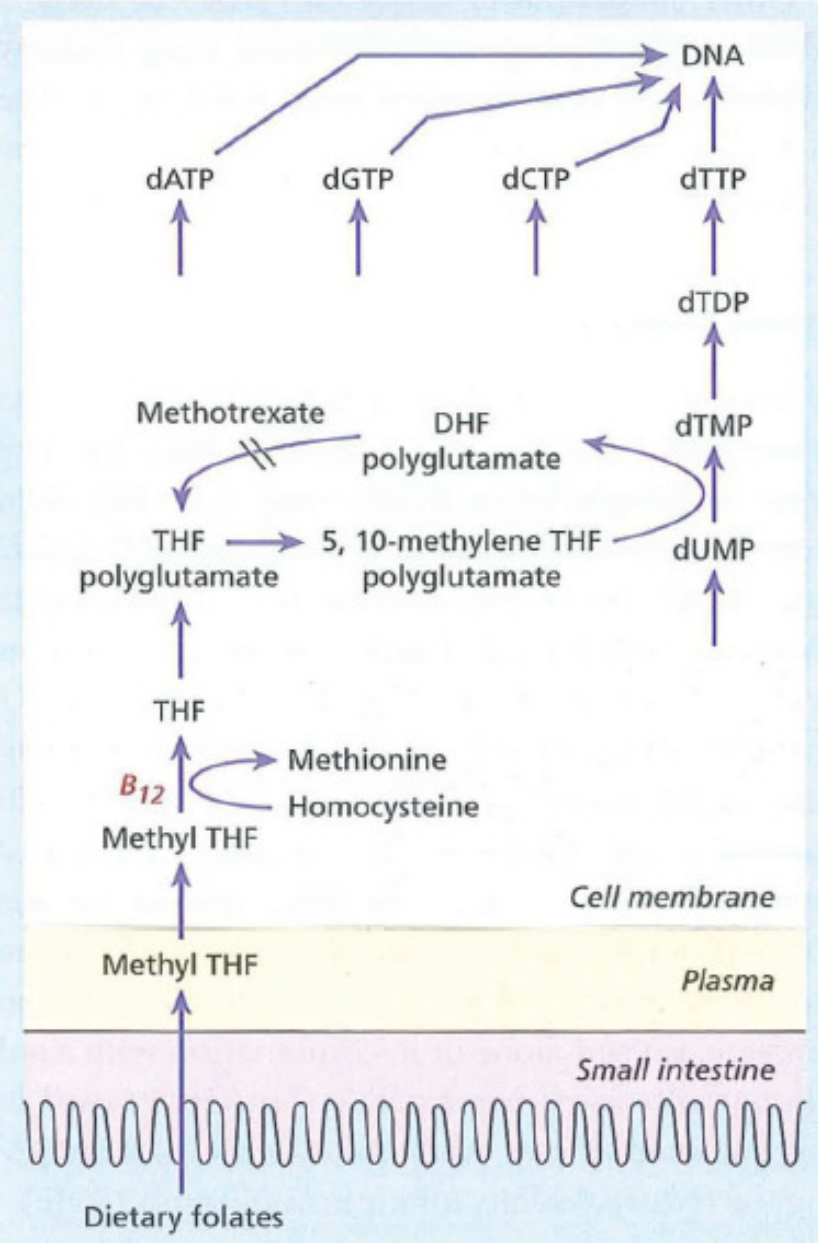


Absorption of folic acid



- Dietary folates are converted to methyl THF during absorption thorough the upper small intestine.
- inside the cell they are converted to folate polyglutamates.

Biochemical bases of B12 & folate deficiency



- DNA is formed by polymerization of the four deoxyribonucleoside triphosphates.

1- Folate is required in one of its coenzyme forms, 5,I0 methylene tetrahydrofolate (THF) polyglutamate, in the synthesis of thymidine monophosphate from its precursor deoxyuridine monophosphate.

2- 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 by the small intestine

Causes of Vit-B12 and folate deficiency

Vitamin-B_{12} deficiency	Folic acid deficiency
Nutritional deficits, e. g. – Goat milk – Vegetarian diet – Alcoholism	**Nutritional deficits** – Chronic abuse of alcohol
Impaired absorption – Genuine pernicious anemia – Status after gastrectomy – Ileum resection – Crohn disease – Celiac disease, sprue (psilosis) – Intestinal diverticulosis – Insufficiency of the exocrine pancreas – Fish tapeworm	**Impaired absorption** – E. g., sprue (psilosis) **Increased requirement** – Pregnancy – Hemolytic anemia **Interference/antagonism** – Phenylhydantoin – Cytostatic antimetabolic drugs – Trimethoprim (antibacterial combination drug) – Oral contrazeptives – Antidepressants – Alcohol

Table 4.5 Causes of folate deficiency.

Nutritional

Especially old age, institutions, poverty, famine, special diets, goat's milk anaemia, etc.

Malabsorption

Tropical sprue, gluten-induced enteropathy (adult or child). Possible contributory factor to folate deficiency in some patients with partial gastrectomy, extensive jejunal resection or Crohn's disease

Excess utilization

Physiological

Pregnancy and lactation, prematurity

Pathological

Haematological diseases: haemolytic anaemias, myelofibrosis

Malignant disease: carcinoma, lymphoma, myeloma

Inflammatory diseases: Crohn's disease, tuberculosis, rheumatoid arthritis, psoriasis, exfoliative dermatitis, malaria

Excess urinary folate loss

Active liver disease, congestive heart failure

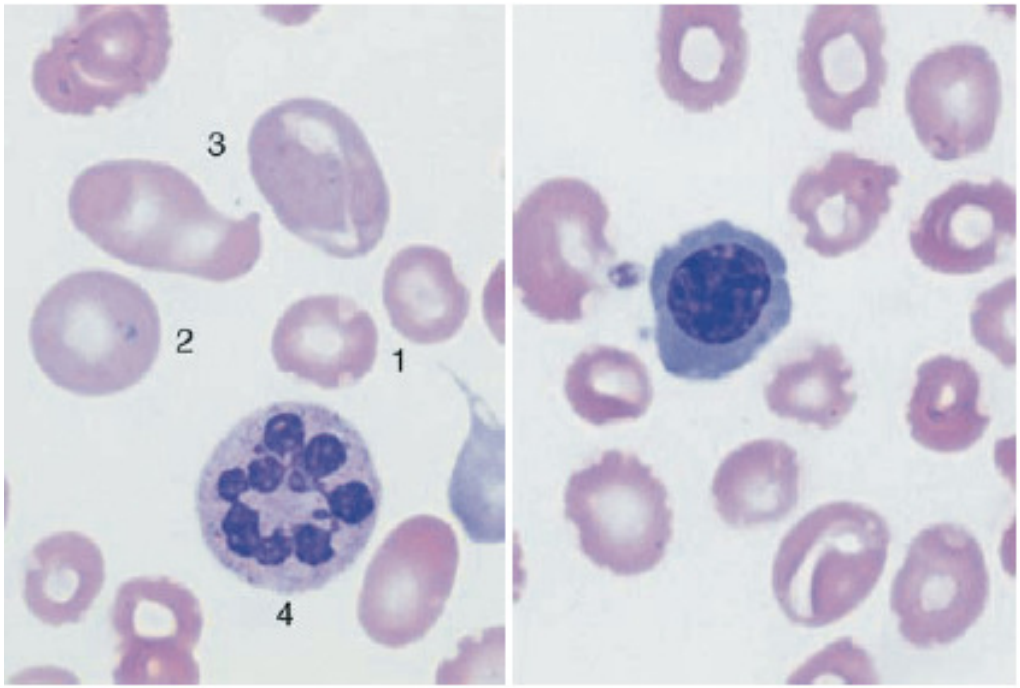
Drugs

Anticonvulsants, sulfasalazine

Mixed

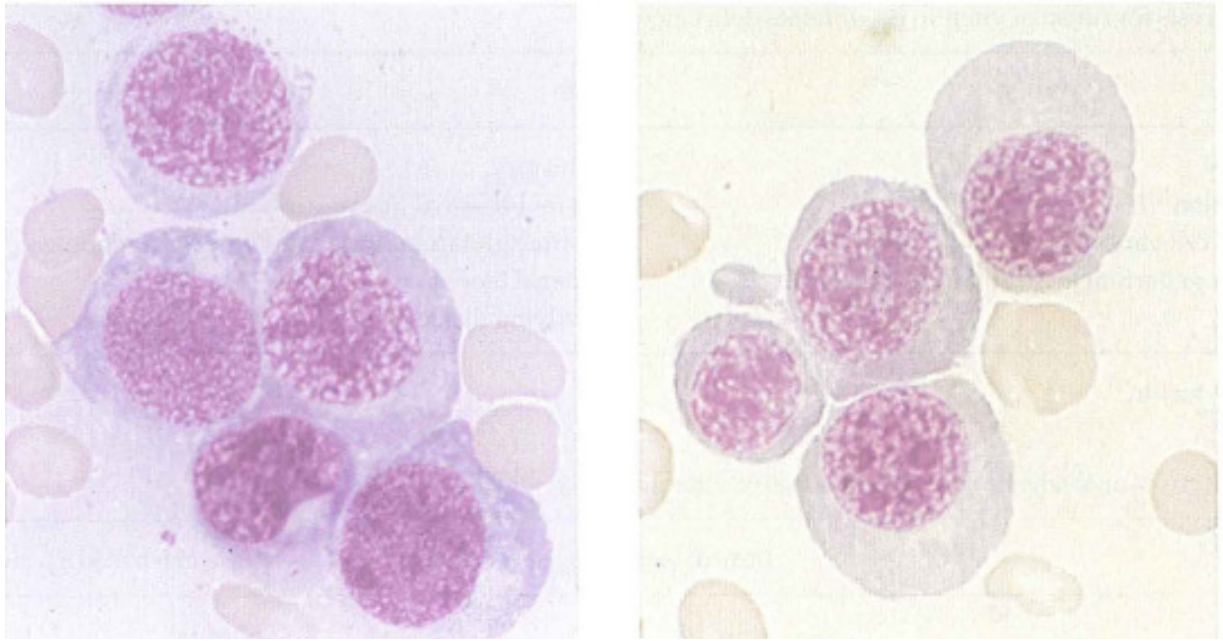
Liver disease, alcoholism, intensive care

Morphology



-In macrocytic anaemia the red cells are abnormally large (mean corpuscular volume, MeV >95 fL).

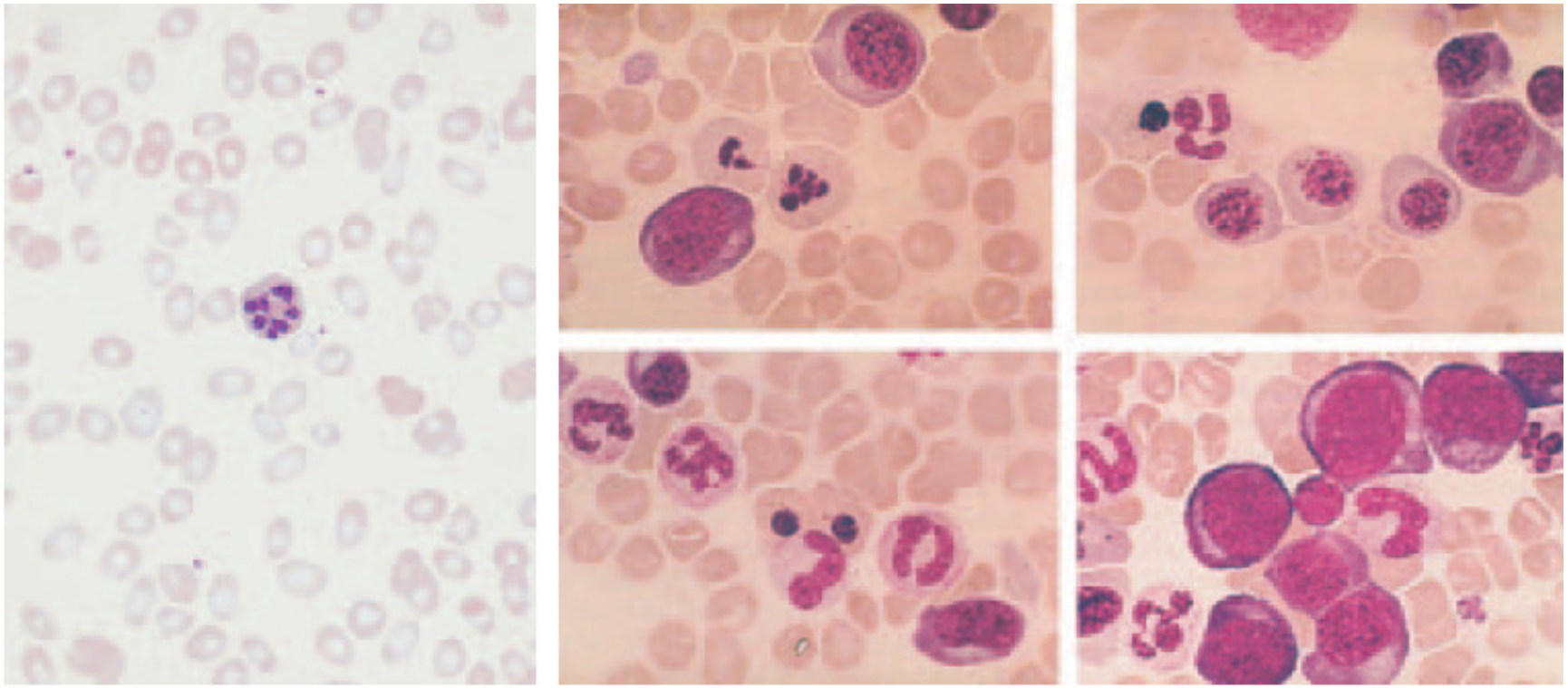
BM showing erythroblasts



-Macrocytic RBC due to megaloblastic anaemia is characterised by the appearance of developing erythroblasts in the bone marrow.
- The cause of the abnormal maturation of the erythroblast nucleus is defective DNA synthesis

A

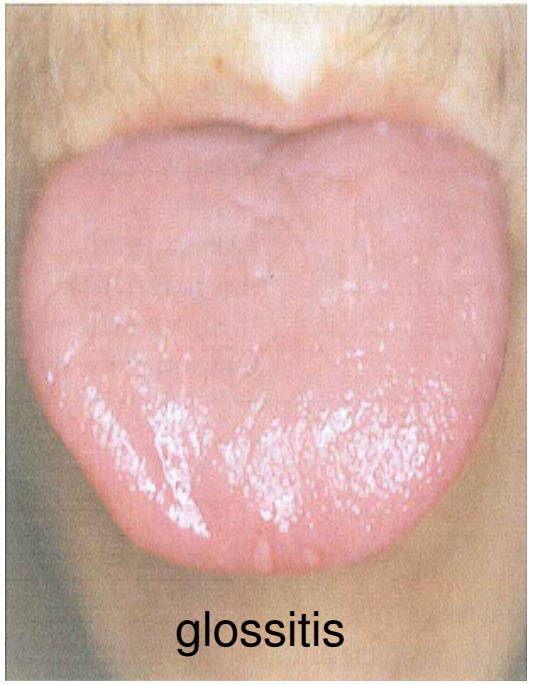
B



(a) The peripheral blood in severe megaloblastic anaemia.

(b) (b) The bone marrow in severe megaloblastic anaemia.

Clinical features of megaloblastic anaemia



glossitis

angular cheilosis

Clinical effects of Vit B12 or folate deficiency

Table 4.6 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 (see text and Chapter 25)

pernicious anaemia

- This is caused by autoimmune attack on the gastric mucosa leading to atrophy of the stomach.
- Secretion of IF is absent or almost absent

Some associations of pernicious anaemia

Table 4.4 Pernicious anaemia: associations.

Female	Vitiligo
Blue eyes	Myxoedema
Early greying	Hashimoto's disease
Northern European	Thyrotoxicosis
Familial	Addison's disease
Blood group A	Hypoparathyroidism
	Hypogammaglobulinaemia
	Carcinoma of the stomach

Laboratory findings

Table 4.7 Laboratory tests for vitamin B_{12} and folate deficiency.

			Result in	
Test	Normal values*		Vitamin B_{12} deficiency	Folate deficiency
Serum vitamin B_{12}	160–925 ng/L	120–680 pmol/L	Low	Normal or borderline
Serum folate	3.0–15.0 µg/L	4–30 nmol/L	Normal or raised	Low
Red cell folate	160–640 µg/L	360–1460 nmol/L	Normal or low	Low