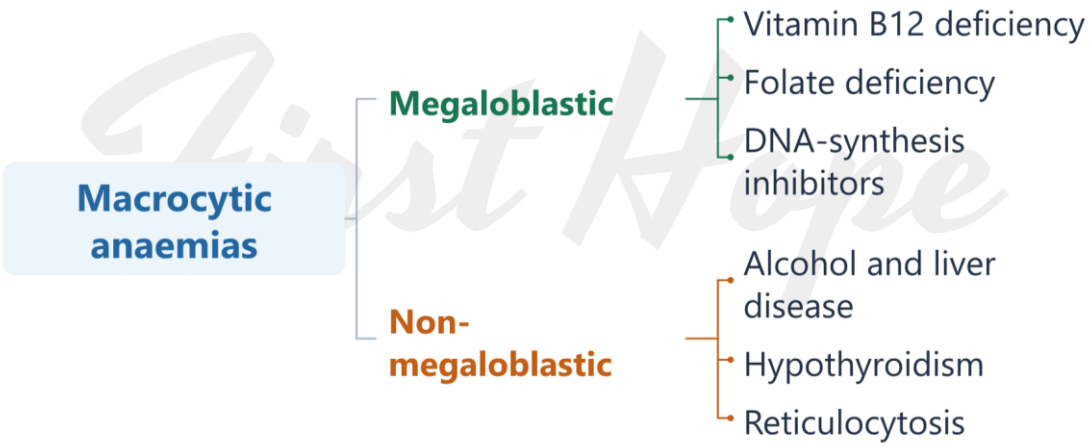
# Pathology - Topic 15 - Macrocytic anemia

## Macrocytosis and Megaloblastic Change

- Macrocytosis describes enlarged red cells, while megaloblastic change describes abnormal maturation caused by impaired DNA synthesis.

### Meaning and Main Categories

- **Macrocytosis** means increased average red-cell volume, usually an MCV above about 100 fL in an adult.
    - Macrocytosis may occur before anaemia and can also occur without anaemia.
- A **megaloblastic anaemia** results from impaired DNA synthesis that delays nuclear maturation in developing blood cells.
    - Cytoplasmic growth continues, creating a mismatch between nuclear and cytoplasmic maturity.
- Not every macrocytic anaemia is megaloblastic, and an apparently normal MCV does not exclude megaloblastic disease when iron deficiency coexists.




### 1. Megaloblastic Causes

- Vitamin B12 deficiency and folate deficiency are the major nutritional causes.
- Drugs that impair folate metabolism or DNA synthesis can produce similar marrow and blood-film changes.
    - Some myeloid neoplasms cause abnormal maturation that can resemble megaloblastic change and require further investigation.

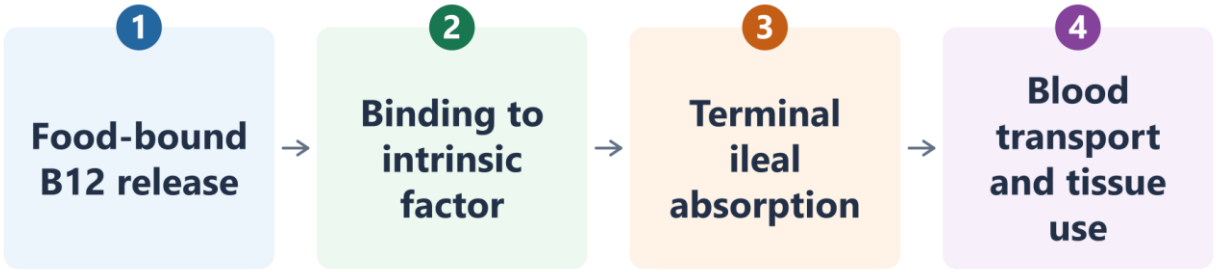
### 2. Non-megaloblastic Causes

- Alcohol exposure, liver disease, hypothyroidism and an increased reticulocyte count can cause macrocytosis without the classic DNA-synthesis defect.
    - Reticulocytes are larger than mature red cells, so a strong marrow response after bleeding or haemolysis can raise the MCV.
- Certain drugs and marrow disorders are additional causes, and the clinical context determines which tests are needed.

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# Vitamin B12 Metabolism and Deficiency

- Vitamin B12 is obtained mainly from animal-derived foods or fortified foods and supplements.




## Gastric and Intestinal Steps

### 1. Release from Food and Intrinsic-Factor Binding

- Gastric acid and pepsin help release food-bound B12, which initially binds to haptocorrin.
- Pancreatic enzymes later digest haptocorrin in the small intestine.
- Freed B12 binds to **intrinsic factor**, a protein secreted by gastric parietal cells.

### 2. Ileal Absorption, Transport and Storage

- The B12–intrinsic-factor complex is absorbed through receptors in the terminal ileum.
- After absorption, B12 binds to transport proteins, including transcobalamin, for delivery to tissues.
- The liver holds substantial stores, so dietary deficiency commonly develops over a long period rather than within a few days.

## Biochemical Roles

- B12 supports the conversion of homocysteine to methionine and helps regenerate usable folate for DNA synthesis.
  - B12 deficiency traps folate in a form that cannot adequately support thymidine production.
- B12 is also required for conversion of methylmalonyl-CoA to succinyl-CoA.
  - Methylmalonic acid therefore rises in B12 deficiency, although renal impairment can also increase its concentration.

## Causes of Vitamin B12 Deficiency

### 1. Reduced Intake

- A prolonged diet with little or no B12-containing food can cause deficiency if suitable supplementation is absent.
  - Infants of severely deficient mothers can become affected more quickly because their stores are limited.

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### 2. Loss of Intrinsic Factor

- Autoimmune destruction of gastric parietal cells and antibodies affecting intrinsic factor can impair B12 absorption.
    - **Pernicious anaemia** is the B12-deficiency anaemia associated with this autoimmune gastric process.
- Gastrectomy and other major gastric operations can also reduce intrinsic-factor availability.

#### Autoimmune Gastric Pathology

- Autoimmune gastritis preferentially damages the body and fundus, causing loss of parietal cells, mucosal atrophy and reduced acid and intrinsic-factor production.
- Reduced acid secretion increases gastrin and may produce enterochromaffin-like-cell hyperplasia.
- Intestinal metaplasia may accompany the atrophic mucosa, and the condition is associated with increased risk of selected gastric neoplasms.
- Iron deficiency may occur before overt B12-deficiency anaemia because reduced acidity impairs food-iron availability.

### 3. Intestinal and Other Causes

- Terminal ileal disease or resection can prevent absorption of the B12–intrinsic-factor complex.
- Bacterial overgrowth, pancreatic insufficiency and selected parasitic infections can interfere with normal absorption.
- Metformin and prolonged acid suppression may contribute in susceptible people, while nitrous oxide can inactivate B12.
    - A medication history is therefore part of the investigation rather than an optional extra.
- Competition for B12 can occur with heavy infestation by a fish tapeworm, while inherited defects of transport or receptor pathways cause rare early presentations.
- Nitrous oxide oxidises active cobalamin and can cause functional deficiency even when a routine serum concentration is not markedly reduced.

## Folate Metabolism and Deficiency

- Folate comes from vegetables, legumes and other foods and is absorbed mainly in the proximal small intestine.

### Dietary Supply and Metabolic Roles

- Body folate stores are smaller than B12 stores, so deficiency can appear within months of inadequate supply.
- Folate is required for reactions that produce purines and thymidylate for DNA synthesis.

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- Poor nutrition, alcohol-related disease, malabsorption and increased demand can cause folate deficiency.
    - Pregnancy and chronic haemolysis increase demand because more cells are being produced.

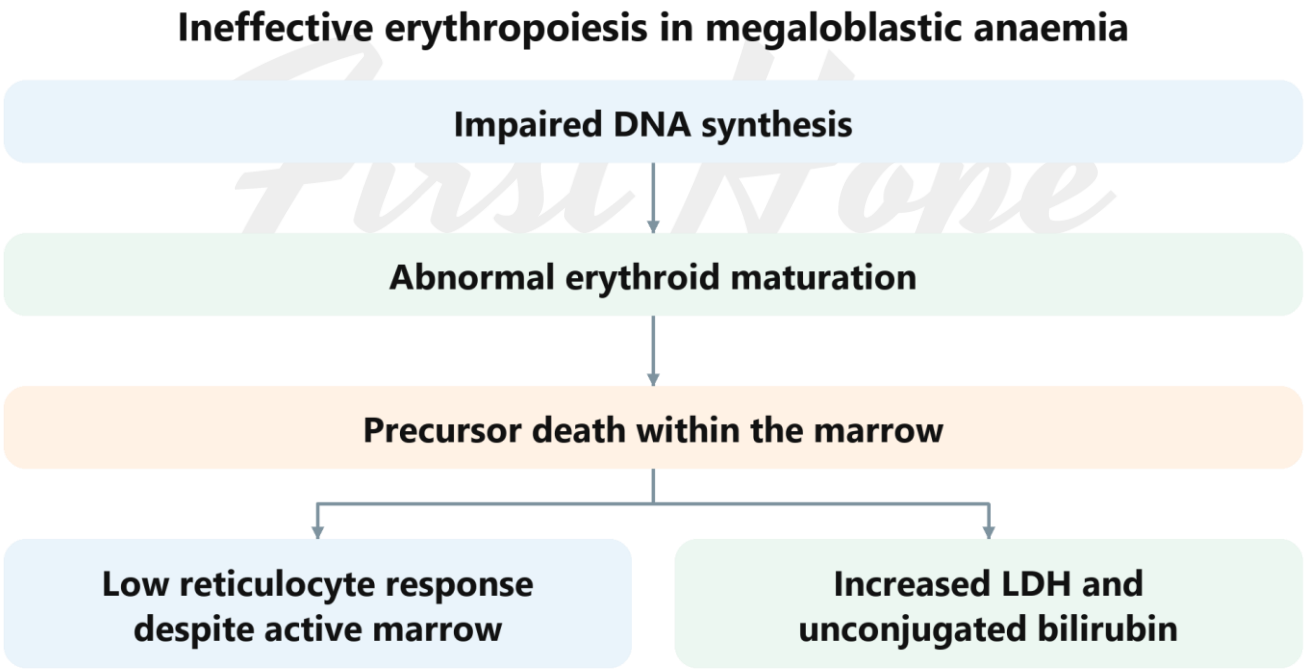
## Factors Reducing Folate Availability

- Methotrexate inhibits dihydrofolate reductase and reduces regeneration of folate cofactors needed for DNA synthesis.
- Heating and food processing can reduce dietary folate availability, contributing to deficiency when the diet is already limited.

# Megaloblastic Anaemia: Pathogenesis and Morphology

- Megaloblastic anaemia results from impaired DNA synthesis, producing abnormal maturation of blood-forming cells.

## Ineffective Blood-Cell Production




- Impaired DNA synthesis affects rapidly dividing cells, especially blood-forming cells and gastrointestinal epithelium.
- Many abnormal precursors die inside the marrow before becoming circulating blood cells.
    - This is **ineffective erythropoiesis**, which explains a low reticulocyte response despite a very active-looking marrow.
- Breakdown of precursors raises LDH and unconjugated bilirubin and can produce mild jaundice.
    - The combination resembles haemolysis, but the low reticulocyte response helps show that much destruction occurs before release into blood.

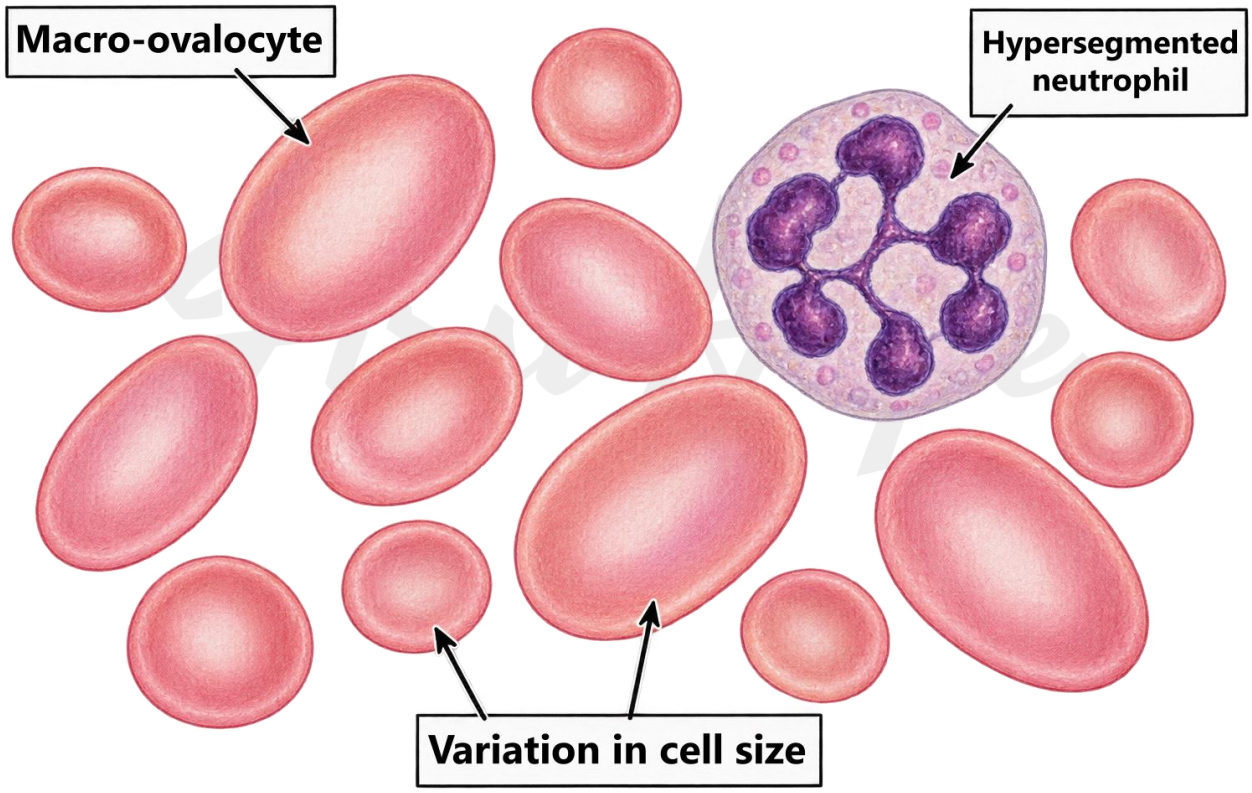
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- Severe disease can reduce white cells and platelets as well as red cells, causing pancytopenia.

### Linking the Biochemical Defect to Megaloblastosis

- Reduced thymidylate availability limits DNA replication and delays progression through the cell cycle.
- RNA and protein synthesis are relatively less impaired, so the cytoplasm continues to mature while the nucleus retains open immature chromatin.
- Ineffective granulopoiesis and megakaryopoiesis explain why severe disease can involve all three blood-cell lineages.
- The erythroid expansion lowers the myeloid-to-erythroid ratio despite failure to produce an adequate circulating reticulocyte response.

## Peripheral Blood Film




*Macro-ovalocytes and a hypersegmented neutrophil in megaloblastic anaemia*

- The typical film shows large oval red cells called **macro-ovalocytes**, with variation in size and shape.
- Neutrophils may have excessive nuclear segmentation, including cells with six or more lobes.
    - Hypersegmentation is a useful clue but must be interpreted with the rest of the smear and clinical information.
- The MCV and RDW are often increased, while the reticulocyte response is low for the degree of anaemia.
    - Coexisting iron deficiency or a recent transfusion may produce a dimorphic population and mask the average increase in size.

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