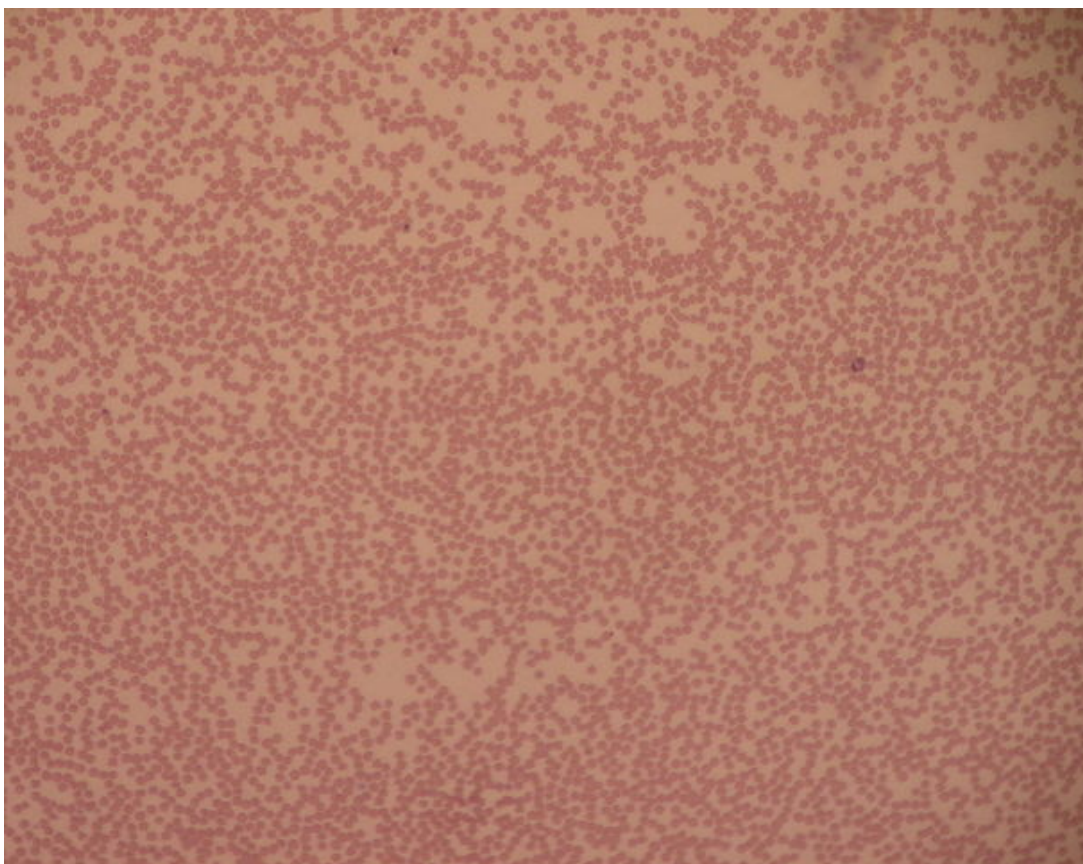


Megaloblastic Anemia (Vitamin B12 or Folate Deficiency Anemia, or Macrocytic Anemia)

[See online here](#)

In practice, anemia associated with many acute and chronic diseases is often reflected by blood count. Therefore, a diagnosis of anemia is recommended because a lowered hemoglobin value is the first important sign of an undetected underlying disease.



Definition of Megaloblastic Anemia

Prevention of **DNA** synthesis in new cells due to multiple factors may impact the growth of **erythrocyte** progenitor cells.

The so-called **erythroblasts** show typical morphological changes, which are called megaloblasts.

Every patient with megaloblastic anemia produces macrocytic erythrocytes, but not every case of **macrocytosis** is associated with **megaloblastic anemia**. The most common causes of megaloblastic anemia include:

- Vitamin B12 deficiency (frequent)
- Folate deficiency (frequent)
- Malignant diseases (moderately frequent)

Vitamin B12 Deficiency (Cobalamin Deficiency)

Definition of vitamin B12 Deficiency

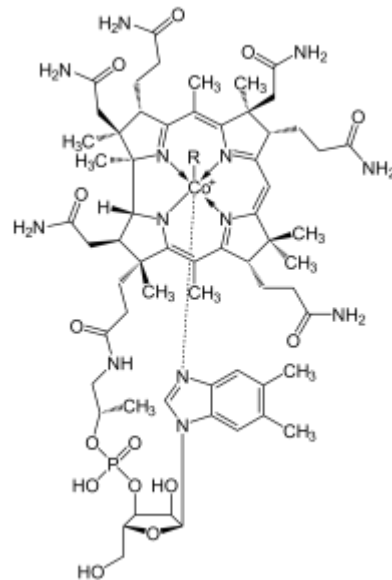


Image: Structural formula of vitamin B12.
By Lecturio

Vitamin B12 deficiency results in **macrocytic-hyperchromic**, and megaloblastic anemia.

The most common etiological factor involves defective absorption of the vitamin. In case the abnormal absorption is caused by **type A gastritis** resulting from **intrinsic factor deficiency**, the disease is known as **pernicious anemia**.

Defective absorption in the area of ileum after **resection**, **Crohn's disease** or **exocrine pancreatic insufficiency** can trigger megaloblastic anemia associated with vitamin B12 deficiency; however, it is not classified as pernicious anemia.

Evidence of autoimmunity alone establishes a diagnosis of pernicious anemia.

Classification	Causes	Discussion
Decreased intake	Pure vegan diet	Breastfed infants of pure vegans
	Malnutrition	Elderly patients
Malabsorption	→ Intrinsic factor	Autoimmune destruction of parietal cells
	→ Gastric acid	Cannot activate pepsinogen
	Intestinal reabsorption	Crohn's disease or celiac disease Bacterial overgrowth Fish tapeworm Chronic pancreatitis
Increased utilization	Pregnancy/ lactation	Deficiency in pure vegan

Vitamin B12 metabolism

Vitamin B12 in meat products
↓
Vitamin B12 binds to R-factor in saliva (protecting from acid destruction)
↓
Gastric acid converts pepsinogen to pepsin, which frees vitamin B12 from ingested protein
↓
Parietal cells (body/fundus) synthesize intrinsic factor (IF)
↓
Pancreatic enzymes cleave off R-factor in the duodenum, and vitamin B12 forms a complex with IF
↓
Vitamin B12: IF complex reabsorbed in the terminal
↓
Vitamin B12-bound transcobalamin II is delivered to liver, marrow, and actively dividing cells

Etiology of vitamin B12 deficiency

The daily intake of vitamin B12, which is also known as **cobalamin**, is only around 2–3 µg. However, defective incorporation, absorption, synthesis or storage of the vitamin can lead to serious symptoms. This defect mainly occurs in areas of the body where the vitamin is essential, especially in the bone marrow.

Insufficient levels of vitamin can have negative effects on **erythropoiesis**. As a **coenzyme** mediating the metabolism of nucleic acids and lipids, vitamin B12 plays an important role in the synthesis of active folic acid. If production is disrupted due to cobalamin deficiency, it leads to defective DNA synthesis, resulting in anemia.

Causes of vitamin B12 deficiency

Vegetarian diets

Vitamin B12 is mainly found in animal products such as meat, fish, milk, and eggs. Therefore, a vegetarian lifestyle that excludes intake of animal products, leads to vitamin B12 deficiency-anemia. However, not every vegetarian necessarily develops anemia.

No other vitamin is stored longer in the liver than vitamin B12, and the B12 supply can last for months, or even years. Therefore, nutritional deficiency of vitamin 12 is rarely the cause of anemia.

Anacidity caused by atrophic gastritis

Gastric anacidity is one of the more common causes of vitamin B12 deficiency, when the release and binding of the vitamin with the transportation proteins is disrupted, leading to defective absorption, and anemia in chronic cases.

Intrinsic factor (type A gastritis)

The transport mechanism can also be disrupted in other places. **T cells** can destroy **parietal cells** in the stomach triggered by autoimmune reactions.

The parietal cells secrete the intrinsic factor, which is necessary for the transportation of vitamin B12. Destruction of the intrinsic factor along with the parietal cells, and synthesis of antibodies inhibit the binding of vitamin B12 to **glycoprotein**. The transportation and resorption of the vitamin are severely disrupted.

Additional factors inhibiting vitamin B12 absorption

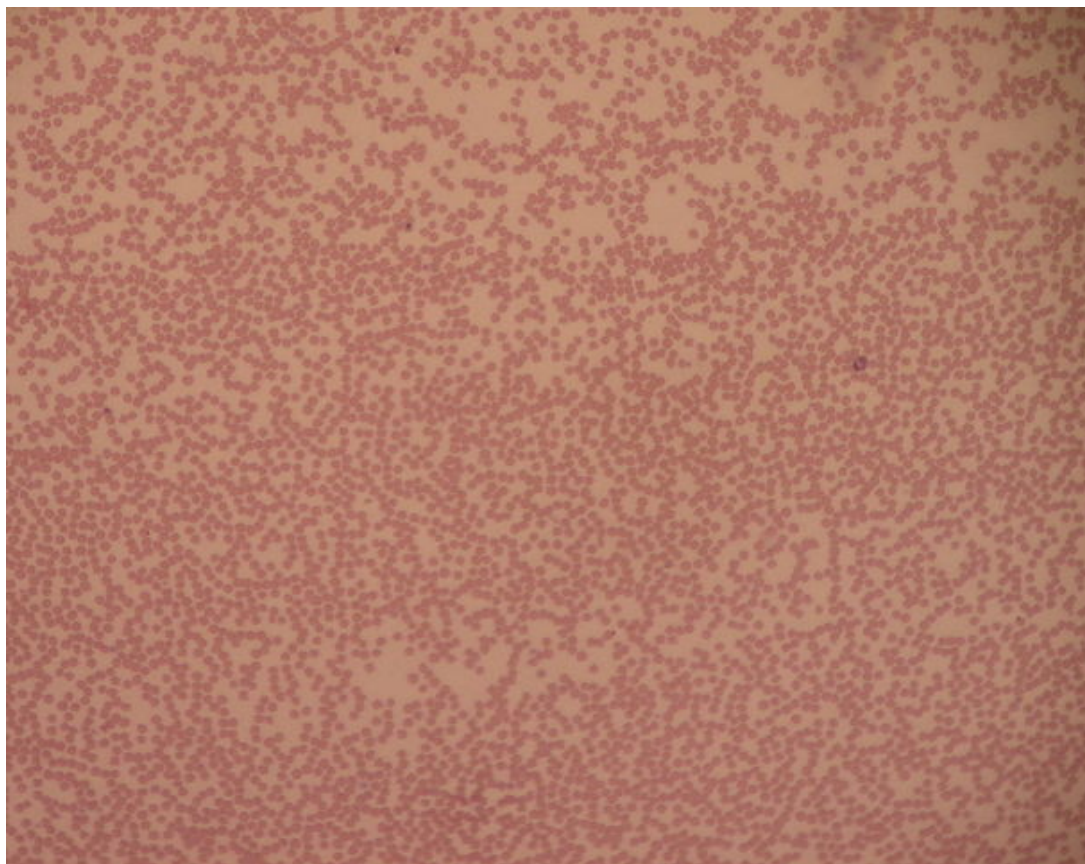
Defective absorption may also occur directly in the **terminal ileum**, where the vitamin is reabsorbed from the intestine. Impaired intestinal absorption is primarily induced by:

- [Crohn's disease](#)
- Resection
- Harmful intestinal bacteria
- Diphyllbothrium

Clinical vitamin B12 deficiency

Subclinical jaundice

In addition to the typical symptoms of anemia such as lethargy, pale skin and pale mucosa, a patient with vitamin B12 deficiency may also manifest symptoms of subclinical jaundice characterized by higher **levels of serum bilirubin**, following defective **erythrocyte turnover** in the bone marrow.



[Image](#): Photo of a 10x field of a blood rub showing significant neutropenia, by Roberto J. Galindo. [License](#): CC BY-SA 3.0

Neutropenia and thrombocytopenia

Since all cells are affected by the disruption, **neutropenia** and **thrombocytopenia** can occur at an advanced stage, resulting in **thrombocytopenic purpura** (hemorrhagic

diathesis) and overall weakening of the immune system.

Subacute combined degeneration of the spinal cord

Compared with other forms of anemia, vitamin B12 deficiency can also trigger neurological disorders ranging from **isolated peripheral neuropathy** to **subacute combined degeneration of the spinal cord**.

Clinical symptoms include memory disruption, loss of concentration and sensitivity, paresthesia and reduced reflexes, and even muscular paralysis. These diseases are induced by prolonged vitamin B12 deficiency, which leads to **demyelination**, especially in the dorsal and lateral columns of the spinal cord.

Further clinical signs, which do not exclude other types of anemia, are:

- Loss of appetite
- Abdominal discomfort
- [Diarrhea](#)
- Obstipation
- Glossodynia and atrophic tongue (Hunter-glossitis)

Diagnosis and differential diagnostics of vitamin B12 deficiency

Measurement of serum levels of vitamin B12

In most cases (90%), a lower level of vitamin B12 in the serum is not reliable in establishing clinical deficiency because it can be skewed by **proliferative diseases of the bone marrow**, or by liver diseases. In addition, patients already manifest symptoms of anemia in the lower normal range of vitamin B12.

In these cases, the serum concentrations of methylmalonic **acid** and **homocysteine**, which are increased in vitamin B12-deficiency-anemia, should be measured.

Blood count

As in most cases, a blood count can reveal the first signs of possible anemia, which normally precede the vitamin B12 levels. A lower value of hemoglobin alone, and in combination with **macrocytosis** and **hyperchromasia**, should indicate a diagnosis of vitamin B 12-deficiency anemia.

Compared with iron-deficiency anemia, all the cells are affected by vitamin B12 deficiency, characterized by lower levels of leukocytes and thrombocytes (**pancytopenia**).

Schilling test

The **Schilling test** uses radioactively-labeled vitamin B12 to distinguish between defective absorption and intrinsic factor deficiency.

Evidence of antibodies

In the case of suspected **pernicious anemia**, antibodies targeting the intrinsic factor as well as the gastric parietal cells should be analyzed.

Gastroscopy

The most common causes of vitamin B12 deficiency can be found in the stomach. Therefore, gastroscopy is indicated for every patient with vitamin B12 deficiency, to establish or rule out gastric carcinoma and **atrophic gastritis**.

Treatment of vitamin B12 deficiency



[Image](#): Hydroxocobalamin injection is a clear red liquid solution of hydroxocobalamin. By Sbharris. License: [CC BY-SA 3.0](#)

The treatment depends on the underlying disease. Additionally, vitamin B12 supplementation using a high dose of **hydroxocobalamin** (1,000 µg) is administered parenterally once a week. After the values reach the normal level, patients are recommended lifelong therapy with 1,000 µg every six months.

Course and prognosis of vitamin B12 deficiency

Diagnosis of the underlying disease followed by treatment via appropriate supplementation of **vitamin B12** can lead to amelioration of anemia within a couple of days.

Untreated neurological symptoms induced by vitamin B12 deficiency can lead to lasting neurological damage. Because of the **atrophic and aplastic changes of the mucosa**, the risk of [stomach carcinoma](#), or other [carcinoid diseases](#) is higher in patients with pernicious anemia.

Note: Type A gastritis is the most common **cause** of vitamin B12 deficiency. In addition to the typical **symptoms of anemia**, the patients also show signs of neurological disruption. Measurement of serum levels of vitamin B12 and antibodies provides path-breaking diagnosis. In addition to treatment of the underlying disease, supplementation with vitamin B12 is necessary.

Folate Deficiency

Definition of folate deficiency

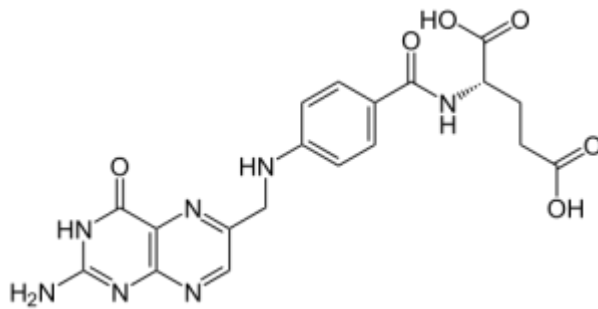


Image: Structural formula of folic acid. By Lecturio

Similar to vitamin B12-deficiency anemia, **folate deficiency** leads to megaloblastic anemia. The most common cause is insufficient nutritional intake of folic acid. The causes include:

- Dietary deficiencies (most common) associated with alcoholism, pregnancy (fetal consumption of folate), and poor dietary practices in the elderly
- Treatment with drugs, especially dihydrofolate (DHFR) inhibitors (methotrexate, trimethoprim)
- Jejunal malabsorption ([celiac disease](#))

Folic acid present in green vegetables and meat products
↓
Polyglutamate converted to monoglutamate by intestinal conjugase in the jejunum
↓
Monoglutamate reabsorbed in jejunum
↓
Only 3-4 month supply of folate in the liver

Etiology of Folate Deficiency

Biochemically, folate represents a whole group of so-called **derivatives of pteridine**, which are produced by plants and microorganisms. Vegetables, salads, fruits, milk, whole-grain products, and offal are good sources of folate acid. Therefore, before pharmacological intervention, substitution with cattle liver was the first choice.

As the recommended daily intake is approx. 400 µg, in patients with poor dietary folate levels, the symptoms of folate deficiency occur within a couple of weeks as the body reserves of 5 mg folate are exhausted rapidly.

In addition to nutritional deficiency of folate, other possible causes are:

- [Liver disease](#)
- [Alcohol abuse](#)
- A large resection of the [small intestine](#)
- Pregnancy
- [Anticonvulsive drug](#)
- Chronic hemolysis
- [Gluten-sensitive enteropathy](#)
- Tropical sprue

- Overcooked food

Clinical manifestations of folate deficiency

Folate deficiency leads to typical symptoms of [anemia](#). Mucosal atrophy in the larynx (**dysphagia**) or the gastrointestinal tract (**meteorism, diarrhea**) are pathognomonic for vitamin B12 deficiency anemia, as well as folate deficiency. However, the folic acid does not play a role in lipid metabolism and, therefore, does not trigger neuropathy.

Diagnosis of folate deficiency

Because blood parameters and findings of bone marrow also reflect vitamin B12 deficiency (**macrocytosis, hyperchromasia**), further testing and analysis of other factors are important to distinguish between the two types of megaloblastic anemia. Therefore, it is important to measure the levels of vitamin B12 to exclude vitamin B12 deficiency anemia. Furthermore, the folate level can be determined, which is not clinically meaningful, because it can be influenced very easily. A single meal enriched with folate can restore the levels to normal. A more reliable parameter is the concentration of folate in the erythrocytes.

Treatment of folate deficiency

Normally, the treatment of disease based on the etiological factors such as [alcohol abuse](#) and **anorexia nervosa**, is enough. However, depending on the severity of the disease, it is not always easy and, therefore, difficult to implement. In such cases, it is important to increase the dose of supplementation. A daily oral intake of 5 mg of folic acid is recommended for prophylaxis.

Complications of folate deficiency

Prolonged and untreated folate deficiency can exacerbate the development of arteriosclerosis, which can increase the risk of myocardial or brain infarction.

Folate insufficiency during pregnancy can lead to **neural tube defects** in the child during embryonic phase. Further, **osteoporosis** may be worsened by folate deficiency.

Note: In the absence of neurological testing via anamnesis and clinical examination, folate deficiency can be confused with vitamin B12 deficiency anemia due to similar hematological and clinical manifestations. Therefore, it is important to understand that folate deficiency alone does not trigger neurological symptoms.

Other Megaloblastic Disorders

Orotic aciduria is an **autosomal recessive disorder** characterized by the inability to convert orotic acid to uridine monophosphate (UMP) via de novo pyrimidine synthesis because of defective UMP synthase.

Clinical manifestations include failure to thrive in children, developmental delay and resistance to treatment with B12 plus folate. No hyperammonemia is observed compared with ornithine transcarbamylase deficiency in which orotic acid is elevated with hyperammonemia.

Treatment involves bypass in uridine monophosphate.

Diamond-Blackfan anemia is characterized by rapid anemia within the first year due to intrinsic erythroid progenitor cells, increased HbF (and decreased total Hb), short stature, craniofacial anomalies, and upper extremity malformations (triphangeal).

References

Davis, L. J., & Brown, A. (1953). *The megaloblastic anaemias*. Springfield, IL: C. Thomas.

Hoffbrand, A. V. (1976). *Megaloblastic anaemia*. London: W.B. Saunders.

Magnus, E. M. (1975). *Folate studies: Folate and vitamin B12 values in relation to bone marrow pattern*.

Rutter, A. (2012). *Anemia (decrease in number of red blood cells)*. New Delhi: World Technologies.

Sippe, G. R. (1947). *Nutritional macrocytic anaemia*. London: Crown Agents for the Colonies.

Legal Note: Unless otherwise stated, all rights reserved by Lecturio GmbH. For further legal regulations see our [legal information page](#).

Notes