

## CASE STUDY

# 90

## VITAMIN B12 DEFICIENCY ANEMIA



For the Patient Case for this case study, see the printed book.

## DISEASE SUMMARY

### Definitions

*Anemia* is defined as an abnormally low number of circulating red blood cells (RBCs) or low concentration of total hemoglobin, or both, resulting in diminished oxygen-carrying capacity of the blood. Anemia is not a disease per se but rather a complication of a disease process or abnormality in body function. Anemia has multiple causes, but one cause is a deficiency of vitamin B12 (also known as cobalamin).

*Vitamin B12* is one of a number of B complex vitamins that is necessary for normal RBC production, nervous system conduction, and DNA (i.e., deoxyribonucleic acid) synthesis. All vitamin B12 comes from dietary sources and the vitamin is present in all foods of animal origin (especially red meat, poultry, fish, eggs, and dairy products). *Vitamin B12* is essential for the synthesis of DNA. When this vitamin is deficient, nuclear maturation and cell division, especially of rapidly proliferating RBCs, fail to occur in the bone marrow. The RBCs that are produced are abnormally large, have flimsy cell membranes, are oval in shape rather than biconcave, and are highly susceptible to *intramedullary hemolysis* (i.e., destruction of RBCs within the bone marrow). In the bone marrow, these large, immature RBCs are known as *megaloblasts*. Following their release into the circulation, they are referred to as *macrocytes*. These RBCs have a short lifespan that can be measured in weeks instead of months.

As a result, *vitamin B12 deficiency anemia* is one type of anemia that results from a reduced rate of RBC production (i.e., *erythropoiesis*) in the bone marrow when a critical nutritional component is deficient.

### Prevalence

The true prevalence of vitamin B12 deficiency in the general population is unknown. The incidence, however, appears to increase with age. In one study, 15% of adults older than age 65 years had laboratory evidence of B12 deficiency. The widespread use of gastric acid-blocking agents, which can lead to decreased B12 levels, may have an underappreciated role in the development of B12 deficiency. Taking the extensive use of these drugs and the aging of the U.S. population into consideration, the actual prevalence of B12 deficiency may be even higher than statistics indicate.

Since the human body stores 3–5 years worth of vitamin B12, a deficiency state typically takes more than 3 years to manifest in adults. Infants and children show signs of deficiency more rapidly, as they have not yet established an extensive reserve.

Deficiency resulting from insufficient dietary intake of B12 is uncommon in the United States but **may be seen in vegetarians who do not consume any animal products.** Older adults who do not eat a variety of foods and people who abuse alcohol are also prone to a B12 deficiency state.

**By far the most common cause of vitamin B12 deficiency anemia in the United States is a condition known as pernicious anemia (PA).** Nearly 2% of all persons over the age of 60 years have PA. The disease occurs in all racial and ethnic groups but develops most often in people of Scandinavian or Celtic (i.e., **English, Irish, or Scottish**) descent. Among these groups, 10–20 cases per 100,000 people occur every year. Although females carry a 50% higher risk in other parts of the world for developing PA, males and females in the United States are equally susceptible to developing this disorder.

## Significance

The significance of vitamin B12 deficiency lies primarily in the troublesome symptoms and complications of the disorder. Anemia often is well tolerated. **Fatigue, weakness, and light-headedness are common symptoms.** **Severe anemia may cause heart failure and retinal hemorrhages.**

Complications of B12 deficiency *exclusive of anemia* are more numerous and serious and include:

- anorexia with weight loss
- burning or soreness of the tongue and mouth with changes in taste
- nausea and vomiting
- neurologic symptoms, such as *paresthesias* (i.e., **numbness or tingling sensations**) in the **fingers and toes, an inability to sense vibrations in the extremities, an unsteady gait, and a poor sense of balance**
- **symptoms that mimic Alzheimer disease in older people (e.g., confusion, memory loss, irritability, difficulty concentrating, and impaired judgment)**
- **psychotic manifestations (e.g., delusions, hallucinations, and paranoia)**
- **spinal cord damage that can result in abdominal rigidity and severe pain, urinary retention that predisposes to urinary tract infections, and an inability to coordinate movements (i.e., ataxia)**

Complications related to the central nervous system may become permanent if treatment is delayed for more than 6 months. Because of the subtle nature of the clinical manifestations, B12 deficiency often goes undiagnosed in the elderly until neurologic changes are irreversible.

**Disease Summary Question 1.** Match each of the symptoms of psychosis listed in the left-hand column directly below with its appropriate definition in the right-hand column.

\_\_\_ paranoia

\_\_\_ hallucinations

\_\_\_ delusions

A. persistent aberrant beliefs or perceptions held inviolable by a person despite evidence that refutes them

B. abnormal condition characterized by an elaborate, suspicious system of thinking that is usually centered on one major theme, such as an unfaithful spouse, being poisoned, or being watched by outer space aliens

C. abnormal sensory perceptions that can occur in any of the senses, do not result from an external stimulus, and occur in the waking state

## Causes and Risk Factors

Vitamin **B12 deficiency is caused by five basic abnormalities: inadequate intake, impaired absorption, impaired plasma transport, and poor utilization or poor separation of the vitamin from ingested animal proteins (i.e., proteolysis).** Specific examples of each of these abnormal

**Disease Summary Table 90.1 Causes and Abnormal Processes in Vitamin B12 Deficiency**

Abnormal Process Causing Vitamin B12 Deficiency	Specific Causes of Vitamin B12 Deficiency
Dietary insufficiency of vitamin B12	<ol style="list-style-type: none"> <li>1. Strict vegetarian diet (usually &gt;5 years)</li> <li>2. Chronic alcoholism</li> </ol>
Insufficient stomach acid or pancreatic enzymes to separate B12 from ingested animal proteins or B12 binding proteins	<ol style="list-style-type: none"> <li>1. Surgical removal of stomach (i.e., <i>gastrectomy</i>)</li> <li>2. Chronic gastritis <ul style="list-style-type: none"> <li>• <i>Helicobacter pylori</i> infection</li> <li>• Chronic alcoholism</li> </ul> </li> <li>3. Use of histamine-2 blocking drugs or proton pump inhibitors to treat gastroesophageal reflux disorder or peptic ulcer disease</li> <li>4. Chronic pancreatic disease (e.g., <i>pancreatitis</i>)</li> </ol>
Impaired absorption of vitamin B12	<ol style="list-style-type: none"> <li>1. IF deficiency <ul style="list-style-type: none"> <li>• Pernicious anemia</li> <li>• Surgical removal of stomach</li> </ul> </li> <li>2. Surgical removal of terminal ileum</li> <li>3. Intrinsic disease of terminal ileum <ul style="list-style-type: none"> <li>• Crohn disease</li> <li>• Celiac disease/sprue (intolerance to wheat products)</li> <li>• Lakefish tapeworms (compete with host for B12)</li> <li>• Bacterial overgrowth (e.g., within intestinal diverticula)</li> </ul> </li> <li>4. Certain medications <ul style="list-style-type: none"> <li>• Cholestyramine</li> <li>• Neomycin</li> <li>• Metformin</li> <li>• Phenformin</li> <li>• Colchicine</li> </ul> </li> </ol>
Abnormality in plasma transport of vitamin B12	Congenital deficiency of plasma protein carrier transcobalamin II
Abnormalities in utilization of vitamin B12	Congenital enzyme deficiencies that result in impaired deoxyadenosylcobalamin or methylcobalamin synthesis

IF, intrinsic factor

processes are shown in Disease Summary Table 90.1. **Absence of intrinsic factor (IF), a protein that is critical in the absorption of vitamin B12, is the most common cause of B12 deficiency in the United States today.**

Major risk factors for vitamin B12 deficiency and anemia include:

- positive family history of PA
- Scandinavian or Celtic descent
- medical history of an autoimmune neuroendocrine disease that includes type 1 diabetes mellitus, Addison disease, Graves disease, or Hashimoto thyroiditis—all of which carry a significant predisposition for PA

**Disease Summary Question 2.** Match each of the autoimmune neuroendocrine diseases listed in the left-hand column directly below with its corresponding abnormal hormone change.

- |                              |                          |
|------------------------------|--------------------------|
| ___ type 1 diabetes mellitus | A. ↑ serum thyroxine     |
| ___ Addison disease          | B. lack of serum insulin |
| ___ Graves disease           | C. ↓ serum thyroxine     |
| ___ Hashimoto thyroiditis    | D. ↓ serum cortisol      |

**Disease Summary Question 3.** Briefly describe the pathophysiology that underlies autoimmune disease.

## Pathophysiology

Vitamin B12 belongs to the family of cobalamins (i.e., organometallic substances with a centrally located cobalt atom) and serves as a cofactor for several important intra-cellular biochemical reactions in humans. As methylcobalamin, the vitamin serves as a cofactor for methionine synthetase in the conversion of homocysteine to methionine. As adenosylcobalamin, vitamin B12 facilitates conversion of methylmalonic acid to succinyl-coenzyme A. Vitamin B12 also promotes thymidine synthase function, DNA synthesis, and normal development of the nucleus in a variety of cell types, including developing RBCs.

After being ingested and separated from animal proteins by the actions of gastric acid and pancreatic enzymes, vitamin B12 is bound to IF, a protein that is produced by gastric parietal cells. Other cobalamin-binding proteins (known as *R factors*) compete with IF for B12. Vitamin B12 that is bound with R factors cannot be absorbed. **The B12-IF complex travels through the small intestine and is absorbed in the terminal ileum by cells with specific receptors for the complex.** The vitamin is then transported through the blood and stored in the liver. The liver may store as many as 5000 µg vitamin B12. Since daily losses of the vitamin are typically only 3–5 µg, a B12 deficiency state may not develop until more than 3 years after vitamin B12 absorption is impaired.

Three plasma transport proteins for B12 have been identified. Transcobalamins I and III are secreted by white blood cells (WBCs). Although approximately 90% of plasma B12 is bound to these two proteins, only transcobalamin II is capable of transporting vitamin B12 into cells for use. **Any process that impairs the ingestion, separation, absorption, plasma transport, or transfer into cells of B12 may result in the clinical manifestations of a vitamin B12 deficiency state.**

Despite defective DNA synthesis in developing RBCs of people who are B12-deficient, ribonucleic acid (RNA)-regulated processes (e.g., hemoglobin synthesis) occur at a normal rate, resulting in a disparity between the development of the nucleus and cytoplasm. Asynchronous nuclear and cytoplasmic maturation results in megaloblastic cells in the bone marrow that contain a nucleus that is immature and much smaller than that of normoblasts. Furthermore, every cell division causes the disparity between nucleus and cytoplasm to become more obvious. **Abnormal development of RBCs results in premature cell death and phagocytosis within the bone marrow. The result is a condition known as megaloblastic anemia.**

Identical processes of defective DNA synthesis and asynchrony in nuclear-cytoplasmic development occur in developing WBCs and megakaryoblasts (i.e., **cells that produce platelets**). Blast cells of the WBC series also tend to be larger than normal. Both developing WBCs and megakaryoblasts also undergo premature cell death in the bone marrow. Thrombocytopenia (i.e., low platelet count) and leukopenia (i.e., low WBC count) are observed in varying degrees. **Other cells throughout the body, especially those with high turnover rates, may also show a significant increase in size and nuclear-cytoplasmic abnormalities. This may explain abnormal changes in the papillae of the tongue (leading to pain and redness) and in the intestinal tract (resulting in diarrhea).**

As a result of the significant degree of cell death that occurs from a B12 deficiency, serum lactic dehydrogenase levels are high and support a diagnosis of B12 deficiency. Furthermore, an elevated serum indirect bilirubin concentration reflects the increased breakdown of hemoglobin. **The skin of Caucasian patients with B12 deficiency anemia becomes sallow (i.e., lemon-yellow) in color. This is the result of both pallor (i.e., pale appearance) of the skin from anemia and the deposition of excess amounts of circulating unprocessed bilirubin in elastic tissues of the skin.**

Myelin is a substance rich in lipid that wraps around neuronal axons and facilitates rapid nerve impulse conduction. There is also evidence that myelin is essential for survival of both axons and neurons. A deficiency of B12 causes abnormal methylation of the protein component of myelin and, consequently, synthesis of abnormal myelin. This phenomenon results in myelin degeneration and produces many of the neurologic complications of B12 deficiency. For example, **demyelination of the peripheral nerves causes paresthesias of the hands and feet. Demyelination of the spinal cord results in loss of vibratory sensations in the arms and legs and, eventually, ataxia.**

The principal abnormality in PA is an absence of IF. The disease is believed to be caused by autoimmune mechanisms because antibodies to gastric parietal cells are present in both the serum and gastric juice of patients with PA. The foreign antigen targeted by these antibodies has been identified as H<sup>+</sup>/K<sup>+</sup>-ATPase, an enzyme that is responsible for the secretion of hydrogen ions by parietal cells in exchange for potassium ions. Pernicious anemia is also

characterized by an infiltration of lymphocytes within the walls of the stomach that is associated with both degeneration of parietal cells and their replacement with mucus-secreting goblet cells—a phenomenon known as *intestinal metaplasia*. The precise mechanism of parietal cell death is unknown, but it is believed to involve signaling through death-inducing pathways and tumor necrosis factor. Contributing further to poor absorption of B12, there are also antibodies present in the gastric juice of individuals with PA that bind with B12 at its IF binding site and, thus, prevent the formation of B12-IF complexes.

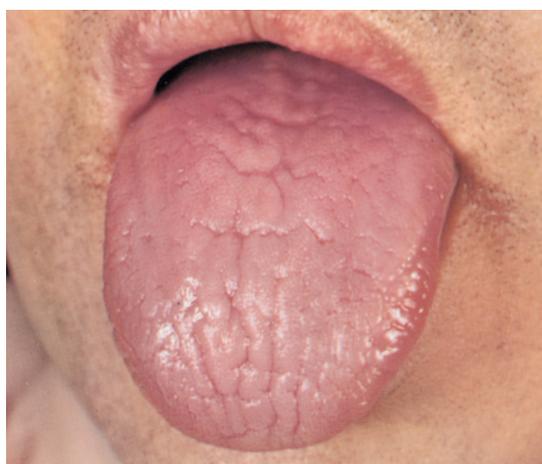
## Diagnosis: Clinical Manifestations and Laboratory Tests

The primary goals of the clinical evaluation are to establish that the patient has a B12 deficiency and, subsequently, determine the specific cause of the B12 deficiency state. The diagnosis is based primarily on the patient's medical and family histories, symptoms, a physical examination with emphasis on neurologic aspects, and a series of blood tests.

A careful dietary history is essential. Both the type and quantity of foods consumed are documented. In the case of an infant with suspected B12 deficiency, a thorough maternal dietary history is obtained. Obtaining an extended family history is also necessary because genetically transmitted deficiencies in transcobalamin II occur in families, usually as an autosomal recessive condition. A medical history of autoimmune disease is important because a positive history is consistent with PA.

In addition to the typical patient symptoms associated with anemia (i.e., fatigue, weakness, and light-headedness), patients with a B12 deficiency often complain of a *sore tongue, poor appetite, and diarrhea*. *Although there are multiple causes of megaloblastic anemia, only B12 deficiency causes associated neurologic abnormalities*. Furthermore, in some cases, abnormal neurologic function may occur in the absence of anemia. Peripheral nerves are usually first affected and patients complain initially of *paresthesias of the hands and feet*. The posterior columns of the spinal cord degenerate with more advanced disease and balance becomes problematic. In the most serious cases, cerebral function is altered, causing dementia, depression, and other neuropsychiatric abnormalities.

The physical examination generally reveals a number of clinical signs that are consistent with a B12 deficiency state. *Caucasian patients have a lemon-yellow, waxy pallor of the skin. Yellowing of the eyes, premature graying of the hair, low-grade fever, and a red, smooth, and shiny tongue (i.e., atrophic glossitis)* may also be observed. Atrophic glossitis is shown in Disease Summary Figure 90.1. *Dyspnea, tachypnea, retinal hemorrhages, hepatomegaly, splenomegaly, and swelling of the ankles and feet (i.e., pedal edema)* are signs that anemia is severe or that heart failure has developed. The neurologic examination may reveal a poor



### DISEASE SUMMARY FIGURE 90.1

Photograph showing a *smooth, red, shiny tongue without papillae* (atrophic glossitis) in a patient with vitamin B12 deficiency. (Reprinted with permission from Weber J, Kelley J. Health Assessment in Nursing, 2<sup>nd</sup> Ed. Philadelphia: Lippincott Williams & Wilkins, 2003.)

**Disease Summary Table 90.2 Laboratory Test Findings Consistent with Vitamin B12 Deficiency**

Laboratory Test	Expected Result in B12 Deficiency
Red blood cell count	Low (anemia)
White blood cell count	Low (leukopenia)
Platelet count	Low (thrombocytopenia)
Reticulocyte count	Low
Hematocrit	Low (anemia)
Mean corpuscular volume	High (macrocytic anemia)
Total hemoglobin concentration	Low (anemia)
Mean corpuscular hemoglobin	High
Mean corpuscular hemoglobin concentration	Normal
Serum lactate dehydrogenase concentration	High
Serum indirect bilirubin concentration	High
Serum folic acid concentration	Normal
Peripheral blood smear (see Disease Summary Figure 87.1)	<ul style="list-style-type: none"> <li>• Macrocytosis</li> <li>• Anisocytosis</li> <li>• Poikilocytosis</li> <li>• Hypersegmented neutrophils and eosinophils</li> <li>• Giant platelets</li> <li>• Normal lymphocytes and plasma cells</li> </ul>
Bone marrow biopsy	<ul style="list-style-type: none"> <li>• Marked red blood cell hypercellularity</li> <li>• Megaloblasts in both red and white blood cell lines</li> </ul>
Serum antibodies to parietal cells	Positive in 90% of patients with pernicious anemia
Serum antibodies to intrinsic factor	Positive in >50% patients with pernicious anemia
Gastric evaluation	<ul style="list-style-type: none"> <li>• Absence of hydrochloric acid (i.e., achlorhydria) in pernicious anemia</li> <li>• Lymphocytes in walls of stomach in pernicious anemia</li> </ul>

sense of vibration or position (early signs of spinal cord demyelination), a positive Babinski reflex, impaired senses, or subnormal deep tendon reflexes. The cardiac examination often identifies a rapid heart rate and heart murmur when the hematocrit is <20%.

**A definitive diagnosis of vitamin B12 deficiency is made when the serum level of vitamin B12 is <100 pg/mL. When the serum B12 level is borderline, diagnosis is best confirmed by either an elevated serum concentration of methylmalonic acid or homocysteine.** In a large study of 406 patients with confirmed B12 deficiency, 98.4% showed elevated serum methylmalonic acid levels and 95.9% demonstrated elevated homocysteine concentrations, resulting in a sensitivity of 99.8% when both metabolites were tested.

Other laboratory findings that are consistent with a diagnosis of B12 deficiency are shown in Disease Summary Table 90.2.

**Disease Summary Question 4.** What are reticulocytes?

**Disease Summary Question 5.** Briefly distinguish between anisocytosis and poikilocytosis.

**Disease Summary Question 6.** Why is it reasonable to test the serum folic acid concentration in a patient who is suspected of having a vitamin B12 deficiency?

**Disease Summary Question 7.** Why is it reasonable to find lymphocytes in the walls of the stomach in patients with pernicious anemia?

**Disease Summary Question 8.** Why is it reasonable to find achlorhydria in patients with pernicious anemia?

**Disease Summary Question 9.** If the father of an unborn child has a single defective gene/mutation for transcobalamin II deficiency and the mother has two normal genes, what is the probability that their unborn child will be transcobalamin II deficient?

**Disease Summary Question 10.** If both the father and mother of an unborn child each have a single defective gene/mutation for transcobalamin II deficiency, what is the probability that their unborn child will be transcobalamin II deficient?

## ■ Appropriate Therapy

Treatment varies with the underlying cause and severity of the vitamin deficiency but always includes vitamin B12 replacement. Hospitalization is only required for patients with life-threatening anemia. On rare occasions, patients with heart failure or coronary insufficiency from anemia may initially require a blood transfusion. **If megaloblastic anemia results from a lack of dietary B12, the condition may be treated initially (when severe) with intramuscular (IM) B12 injections and then maintained with oral B12.** Treatment with vitamin B12 is combined with a more balanced diet that includes good sources of the vitamin. **An oral dose of 100–200 µg B12 weekly often provides adequate maintenance therapy for strict vegetarians. Anemia caused by malabsorption is best treated with B12 injections until the condition improves.** If another medical disorder is interfering with the patient's ability to absorb B12, the condition is usually treated concurrently. For example, **a bacterial infection in the intestinal tract is treated with antibiotics.**

Historically, patients with PA have been treated with IM injections of B12. Depending on severity, an adult dose of 100–1000 µg is given daily or every other day for the first 1–2 weeks, followed by 100–1000 µg given once every 1–3 months for life. Since PA is a lifelong disorder with no cure, **B12 deficiency will recur if patients discontinue long-term therapy.** Limited studies have shown that adequate therapy can also be maintained after initial injected doses (or, in some cases, a single daily oral dose of 1000–2000 µg for 1–2 weeks) by taking 250–1000 µg oral B12 daily for life. Even with total absence of IF, approximately 1% of an oral dose is absorbed by alternate transport mechanisms independent of IF. The minimum daily requirement of B12 is only 1–2 µg. Oral maintenance may be especially necessary for patients who have allergic reactions to B12 injections or who do not wish to tolerate painful injections or bear the higher cost of injection therapy.

**Vitamin B12 is available for use in an injectable form as either cyanocobalamin or hydroxocobalamin.** Both are equally beneficial for prompt treatment of vitamin B12 deficiency anemia and, except for a rare allergic reaction, are generally safe. Theoretical advantages exist for using hydroxocobalamin, because it not only is retained better in the body but also is more available to cells.

Patients respond to therapy with an immediate improvement in their sense of well-being. Hypokalemia (i.e., low serum potassium levels) may complicate the first several days of therapy and even cause sudden death, particularly if anemia is severe. Hypokalemia should be managed with potassium supplementation. **The effectiveness of B12 replacement therapy is measured by an increasing reticulocyte count in the peripheral blood.** A brisk reticulocytosis that represents an increase in normal bone marrow activity occurs within 7 days and blood counts typically normalize within 5–8 weeks. Nervous system manifestations are reversible with B12 replacement only if treatment occurs within 6 months of onset.

Since alcohol interferes with vitamin B12 absorption, patients are strongly encouraged to avoid alcohol during oral B12 therapy. Furthermore, strenuous physical activity is best curtailed in patients with severe anemia until they develop an adequate response to therapy.

## ■ Serious Complications and Prognosis

Prognosis depends primarily on the underlying cause of the deficiency state and the degree of patient compliance with therapy. Some patients who use B12 injections may not readily comply with treatment. With prompt treatment and good patient compliance, outcome is usually excellent.

The majority of patients respond well to replacement therapy. However, continued assessment and monitoring of these patients are essential to prevent relapse due to inadequate therapy. In patients with neurologic signs and symptoms, the reversibility of neurologic damage is slow, with a maximal response that may require up to 6 months. Further substantial increases in recovery are unlikely after 12 months. In 90% of patients with significant neurologic abnormalities, major improvement is seen. The degree of functional recovery is inversely related to the extent of the disease and duration of the clinical manifestations. Patients with signs and symptoms of less than 3 months duration may show complete recovery.

Furthermore, early recognition and treatment of PA provides a normal, and usually uncomplicated, life expectancy. Delayed treatment permits progression of anemia and serious neurologic complications. Untreated PA is fatal and death is often the result of heart failure. Death occurs after a clinical course of remissions and relapses that lasts 1–3 years. Since 1926, when replacement therapy was initiated, mortality has been reduced significantly. Today, death from PA is rare and relapses are usually due to non-compliance with therapy. The incidence of stomach cancer is two- to three-fold greater in patients with PA than in the general population of the same age.

## Suggested Readings

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