Vitamin B12

Advances and Insights

Rima Obeid (Editor)

CRC Press
Taylor & Francis Group

A SCIENCE PUBLISHERS BOOK

Vitamin B12

Advances and Insights

Vitamin B12

Advances and Insights

Edited by

Rima Obeid

Aarhus Institute of Advanced Studies
University of Aarhus
Høegh-Guldbergs Gade 6B
Aarhus C, Denmark

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

A SCIENCE PUBLISHERS BOOK

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper
Version Date: 20160829

International Standard Book Number-13: 978-1-4987-0699-5 (Hardback)

Library of Congress Cataloging-in-Publication Data

Names: Obeid, Rima, editor.
Title: Vitamin B12 : advances and insights / edited by Rima Obeid.
Other titles: Vitamin B12 (Obeid)
Description: Boca Raton, FL : Taylor & Francis Group, [2016] | Includes bibliographical references and index.
Identifiers: LCCN 2016039101| ISBN 9781498706995 (hardback : alk. paper) | ISBN 9781498707008 (e-book : alk. paper)
Subjects: | MESH: Vitamin B 12 Deficiency | Vitamin B 12--metabolism
Classification: LCC QP772.V52 | NLM WD 120 | DDC 612.3/99--dc23
LC record available at https://lccn.loc.gov/2016039101

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Dedication

To my son, Jean-Paul

Preface

Cobalamin(s) (vitamin B12) have been known for 100 years. Key milestones in the study of cobalamin have been through over 10 decades of trial and error, research and discoveries. Remarkable discoveries in the field have saved many lives and were awarded 2 Nobel Prizes; Minot and Murphy (Nobel Prize in Physiology or Medicine 1934) and Dorothy Hodgkin (Nobel Prize in Chemistry 1964). Still, cobalamin constitutes an amazing area of research with many undiscovered facets.

The health relevance of cobalamin became evident long before discovering its chemical entity. Liver extracts containing few micrograms of the healing factor, cobalamin, were used in the 1920s up to the early 1930s as a life-saving medication against fatal pernicious anemia. The purification and production of large quantities of the 'liver factor' were real challenges, but the biggest challenge was for patients to eat these extracts as an alternative to death. Now that cobalamin has become available as over-the-counter supplements, or as injections containing a few micrograms to milligrams, its relevance to health and disease has gained more importance over the time. Cobalamin's 'lifting effect' has been experienced by millions of patients and doctors. Today, the impact of cobalamin on human health has changed from 'treating a severe disease' to 'prevention of a yet not-manifested condition'. The meaning of cobalamin has now taken new dimensions on a population level after implementing modern laboratory diagnosis tests. Using modern biomarkers has shown that subclinical cobalamin deficiency affects many individuals in critical life phases.

'Vitamin B12: advances and insights' is an extract of knowledge of experienced scientists who have been working on nutritional, structural, chemical, and clinical aspects of the vitamin. This book has introduced an innovative and unclassical approach by addressing 'gaps in knowledge' that surround the topic. These gaps are identified by scientists who are very close to the cobalamin epi-center and intended to provide a direction for future research.

The book is an in-depth study on the vitamin from basic science to modern health challenges. Early knowledge on cobalamin in the light of recent scientific discoveries (Chapter 1); Dietary requirements and nutritional supply (Chapter 2); Cobalamin uptake and intracellular processing (Chapter 3);

Congenital cobalamin disorders (Chapter 4); Acquired causes of cobalamin deficiency and clinical consequences (Chapter 5); Cobalamin deficiency: a public health problem in developing countries (Chapter 6); The role of cobalamin in the nervous system, its relevance to brain aging, and potential mechanisms surrounding this area (Chapters 7 and 8); Cobalamin deficiency biomarkers and diagnosis (Chapter 9); Cobalamin deficiency in critical age phases such as pregnancy, lactation and early life (Chapters 10 and 11); Cobalamin deficiency in the era of folic acid fortification (Chapter 12); Cobalamin unexplained extreme values in clinical practice (Chapter 13); the role of Cobalamin in drug transport and development (Chapter 14).

The target audience for this book are experts and researchers looking for in-depth knowledge in the above mentioned areas of cobalamin science; health care providers who take part in diagnosis, treatment, and prevention of deficiency conditions; policy makers who can influence implementation of diagnosis tools or nutritional policies on a country and population levels; and stakeholders and pharmaceutical companies who are interested in producing diagnosis tools, supplements, fortified foods or other pharmaceutical products that use cobalamin as a drug carrier.

This book is by no mean a complete documentation of what is going on around the topic. However, it constitutes an attempt to grasp the current knowledge on a few areas related to cobalamin and to provide insights into unexplored questions and issues.

Contents

1

Milestones in the Discovery of Pernicious Anemia and its Treatment

Jörn Schneede

OVERVIEW

Pernicious anemia (PA) is a serious form of vitamin B12-deficiency. Vitamin B12 belongs together with heme and chlorophyll to the tetrapyrrole family (Figure 1) (Yin and Bauer 2013). Vitamin B12 is an evolutionarily ancient (≈ 3.8 x 10^9 years old) cofactor that was responsible for energy production through fermentation of small organic molecules in the absence of exogenous electron acceptors in the prokaryotic anaerobic world (Figure 2) (Santander et al. 1997). In the course of evolution siroheme later allowed making use of inorganic electron acceptors, before oxygen production by chlorophyll made aerobic respiration through heme possible. Almost 1% of the genome of S. typhymurium is dedicated to vitamin B12 synthesis and transport (Roth et al. 1996). Though being one of the structurally most complex, non-polymeric biomolecules synthesized by nature, eukaryotic organisms do not produce B12 (Figure 2). As a consequence, this vitamin is essential for human metabolism, albeit only required in trace amounts (possibly as low as 1 µg/d, while the recommended daily allowances in adults are 2.4 µg/d) and functions as cofactor in only two enzymes, methionine synthase and (R)-methylmalonyl-CoA mutase (Helliwell et al. 2011). The remarkable discovery of vitamin B12 was only possible and proceeded by the endeavor to find effective

Department of Clinical Pharmacology. University of Umeå 901 85 Umeå, Sweden.
Email: jorn.schneede@medbio.umu.se

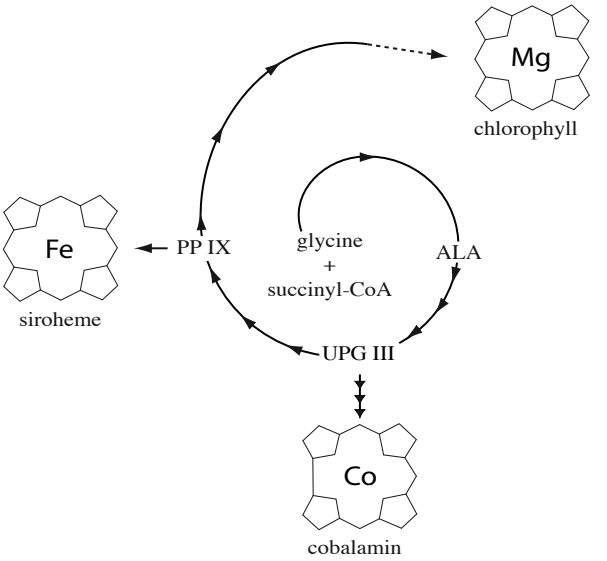

Figure 1. Schematic depiction of the evolutionary development of the tetrapyrrole biosynthetic pathways. Synthesis of tetrapyrrols starts with succinyl-CoA and glycine to form 5-aminolevulinic acid (ALA). Uroporphyrinogen III (UPG III) is used for synthesis of cobalamin (vitamin B12), while protoporphyrin IX (PP IX) is the starting point for siroheme and chlorophyll synthesis. Note the different metal ions bound to the corrin rings: Co, Fe and Mg. Compared to (siro-)heme- and chlorophyll, synthesis of cobalamin is far more complicated and complex, involving considerably more enzymatic steps (at least 25 enzymes uniquely involved), ring contraction, insertion of cobalt, modification of the tetrapyrrole ring and insertion of a nucleotide tail. Adapted and modified from (Yin and Bauer 2013).

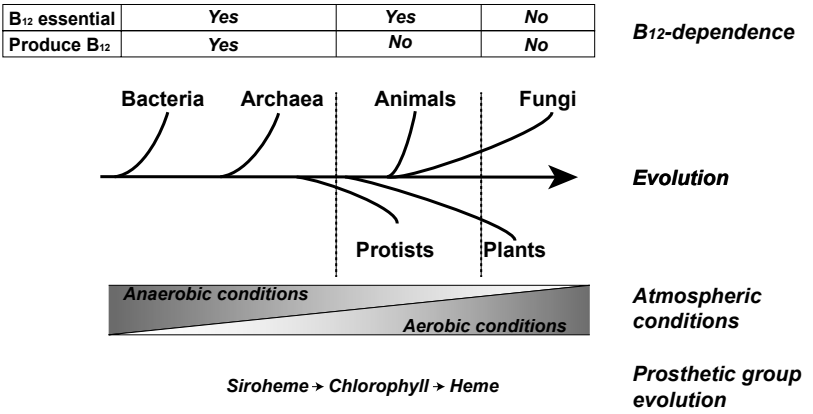

Figure 2. Distribution and dependency on vitamin B12 among different living forms during the evolutionary process and under different atmospheric conditions. Adapted and modified from (Roth et al. 1996).

treatment options for PA, one of the conditions causing severe vitamin B12-deficiency. The scientific progress was, however, slow and stretched over a period of almost 200 years from the first description of PA, to the evolution of theories about possible causes and ultimately the invention of effective treatments. The search for effective treatment options also resulted in the resolution of the pathogenesis of pernicious anemia and ultimately the discovery of B12. Through isolation of an unknown *extrinsic factor* from liver extracts that was accountable for clinical response in pernicious anemia patients it was eventually possibly to elucidate the chemical structure of vitamin B12. In parallel, efforts were started to map the production of vitamin B12 in certain bacteria. The elucidation of the chemical pathways of bacterial production of the vitamin finally made the complete synthesis of the vitamin in the laboratory possible. This enterprise has sometimes been called "Mount Everest of biosynthesis" and it was not before in 2013 that the complete anaerobic pathway of B12-synthesis had been charted (Moore et al. 2013). All in all, vitamin B12 research has resulted in two Nobel prizes-so far. Notwithstanding these achievements, synthesis of the vitamin in the laboratory is far too complicated and resource-demanding for commercial purposes and large-scale industrial production of vitamin B12 is still carried out by aerobic fermentation using *Pseudomonas denitrificans* (Xia et al. 2015) (Figure 3).

The course of history of vitamin B12 can arbitrarily be divided into different eras and stages (Figure 4). During this journey different therapeutic approaches for the treatment of vitamin B12-deficiency were developed, first oral therapy with raw liver, then oral or parenteral administration of liver extracts, followed by more refined liver concentrates that could be injected or taken by mouth with and without addition of intrinsic factor isolated from gastric juice. Later, crystalline B12 (cyanocobalamin) was isolated from the liver or produced by bacterial fermentation. With this advance, parenteral therapy with highly concentrated cobalamin preparations became feasible and affordable. In parallel, there was a continuous development of diagnostic tests for detection of vitamin B12-deficiency (Moridani and Ben-Poorat 2006). Parenteral therapy with intramuscular injections was soon considered the most reliable method of treating pernicious anemia (Bethell et al. 1959). However, recent clinical experience and health technology assessments from Sweden and other countries indicate that oral therapy with vitamin B12 tablets is both clinically feasible and more cost-effective than injections (Berlin et al. 1968b; Kolber and Houle 2014).

The following historical review will present a survey over the history of vitamin B12 and changing concepts for the treatment of vitamin B12-deficiency over the last two centuries.

Figure 3. Fermenter for pharmaceutical production of vitamin B12. Microbial fermentation still is the most commonly used method for industrial scale production of many vitamins, including vitamin B12 (Xia et al. 2015). The picture shows a fermenter for industrial scale production of vitamin B12 under both aerobic and anaerobic conditions. The tank volume of the depicted fermenter can be up to 6.000 liters. In large scale industrial production fermenters of 120.000 liters can be used yielding up to 198 mg/l of B12 (Xia et al. 2015). Reproduced with permission (INOXPA 2015).

1. History of Vitamin B12

1.1 The era before treatment of pernicious anemia was possible

1.1.1 Discovery of pernicious anemia as a first step in identification of vitamin B12

Pernicious anemia, an extreme form of vitamin B12-deficiency, was most likely first portrayed in 1822 by James Combe (1793–1860), a Scottish physician from Edinburgh (Combe 1824). He described the disease history of a 47-year-old man, Alexander Haynes, who suffered from a peculiar, rather

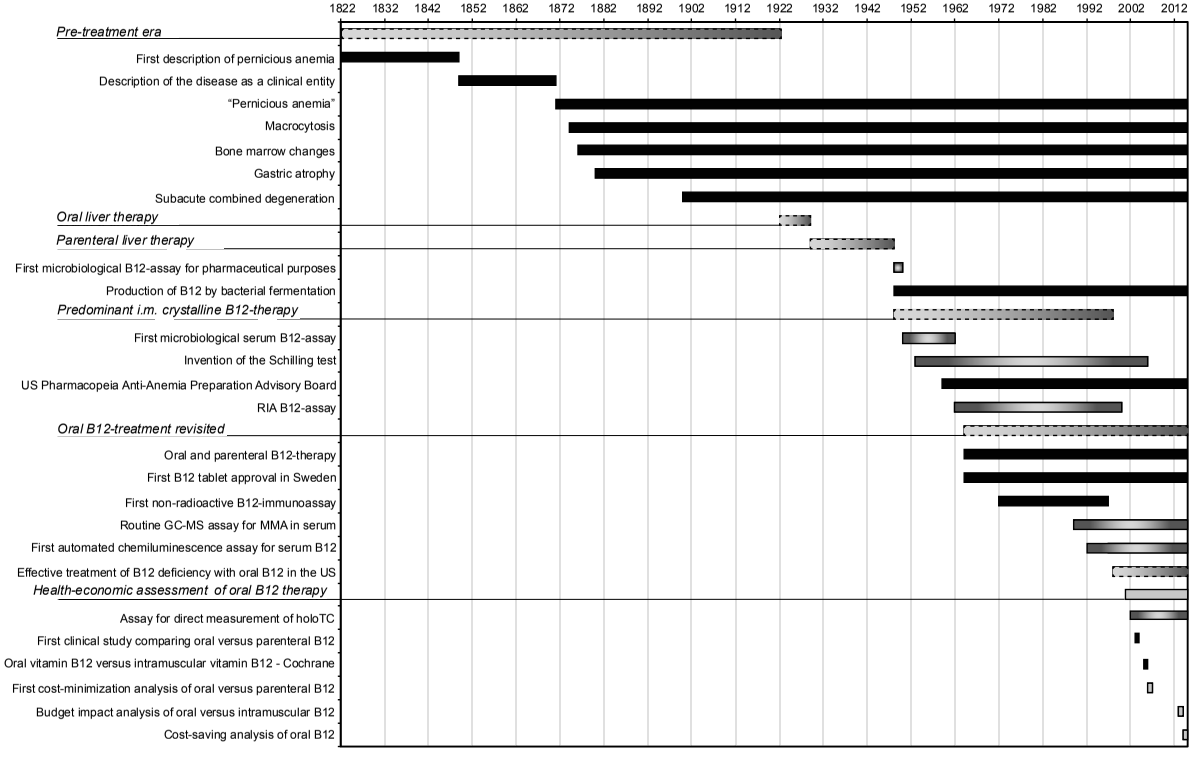

Figure 4. Time lines of different eras in the history of vitamin B12-deficiency and its treatment. The graph portrays an arbitrary division of the history of vitamin B12-deficiency into different eras and milestones of discoveries. Treatment-related accomplishments are depicted by grey gradient bars with dashed-lined borders, major diagnostic achievements by central gradient bars with solid-lined borders and health-economic evaluations of oral vitamin B12 treatment are illustrated by grey bars with solid-lined borders. For about 100 years after the first description of pernicious anemia it was a virtually untreatable, fatal disease. For detailed references see Table 1.

rapidly progressing condition of severe anemia combined with gastrointestinal symptoms. Haynes finally deceased in a state of pulmonary edema within a period of less than seven months after the first contact with Combe. Combe recommended "*chalybeates*,[1] *tonics and a nourishing diet*" to treat the condition, with no success.

After the first description of PA as a clinical entity it would take over 100 years before an effective treatment strategies became available. During this period, PA was considered an untreatable and inevitably lethal ("pernicious") disease. The exact cause of the disease remained obscure for even many more years to come. This disease harvested many casualties. Before effective treatment became available, PA accounted for the death of more than 50,000 people per year in the US alone (Ahrens 1993; Jarcho and Brown 1977).

The constantly fatal outcome of this disease accompanied by lack of conclusive autopsy findings must indeed have been an agonizing experience for doctors at that time, but also spurred scientific efforts to find the cause and potential therapies of this disease. In 1855, Thomas Addison (1793–1860), a London physician, described more details about the disease from observations in 11 patients who were admitted to Guy's Hospital in London (Pearce 2004). Addison reported:

> *"a very remarkable form of general anaemia occurring without any discernable cause whatever."* The patients had *"no previous loss of blood, no exhausting diarrhoea, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous or malignant disease."*

Addison's observations of this "idiopathic anemia" initially received little attention in the scientific community. In 1872, however, Anton Biermer, a German internist working at that time in Zürich, gave a comprehensive description of this disorder during a meeting and used for the first time the expression "progressive pernicious anemia". He chose the phrase "pernicious anemia" (PA) as the disease had an insidious onset with slow progress and because it was deemed to be untreatable and lethal at that time. This time, the disorder received more interest worldwide, which resulted in a large number of publications during the years to follow (Cohnheim 1876; Ehrlich 1880; Eichhorst 1878; Fenwick 1880; Lichtheim 1887). As an acknowledgment of the contribution of both Addison and Biermer, PA is also called "Addison-Biermer disease" (Ewing 1901).

During the years to come the morphological characteristics of PA were identified and described in more detail. Cohnheim (1839–1884) observed increased cellularity in the bone marrow (Cohnheim 1876) and Paul Ehrlich (1854–1915) discovered the occurrence of megaloblasts in the peripheral blood of PA patients in 1880 (Ehrlich 1880). In 1900, Russell described spinal cord

[1] Water from a mineral spring with a high content of iron.

involvement in PA and coined the term "subacute combined degeneration of the spinal cord" (Russell et al. 1900). Moreover, gastric atrophy was detected in PA patients (Fenwick 1880). It was noted that hematologic abnormalities in PA patients resembled tropical sprue, which normally responded to a diet containing milk, meat, cod-liver oil and oranges. This may be the reason why similar treatments were used for patients with PA in the early days (Wills 1948).

Thus, in the period from 1876 to 1900, it became clear that PA was not solely a hematological disease, but also had gastrointestinal and nervous system components (Table 1).

Because of the treacherous start and slow progression of PA, this disease was often misinterpreted, and initial symptoms were often attributed to normal or premature ageing processes (Tobin and Cargnello 1993). Consequently, the disease was often identified at a late stage and many patients only had a short time to live after diagnosis (Combe 1824).

Nowadays it is difficult to imagine the seriousness of untreated pernicious anemia. However, thanks to William P Murphy, one of three laureates sharing the Nobel Prize in Physiology or Medicine in 1934, we are still able to watch a motion picture giving a vivid picture of the graveness of the disease in historic PA patients before and under treatment with liver extracts. The motion picture was presented during Murphy's Nobel Lecture, December 12, 1934 (Murphy 1934). This motion picture has been recently made available to the general public through the Blood journal's website (Kumar et al. 2006).

An overview over the milestones in the discovery of pernicious anemia and vitamin B12 is given in Table 1.

2. Early Treatment Approaches of PA

The first therapeutic approaches to a disease of an unknown cause and pathogenesis were highly experimental and arbitrary, and quite often obscure. Until the discovery that liver contains important nutrients and factors for hematopoiesis, the methods intended to treat pernicious anemia only had temporary effects and were on the whole unsuccessful (Combe 1824; Sinclair 2008). Around 1900 a renowned textbook of hematology considered iron being contraindicated for the treatment of certain forms of anemia where megalocytes with increased hemoglobin content appeared in the peripheral blood. Instead arsenic was supposed to exert almost specific effects and would result in increasing numbers of red cells and in stimulating the production of more uniformly distributed Hb (Ewing 1901). In the eighth edition of Sir William Osler's "*THE PRINCIPLES AND PRACTICE OF MEDICINE—DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE"* from 1915, one of the most authoritative text books at that time, it was suggested—among other remedies—to try Fowler's Solution, sodium cacodylate or *Atoxyl*. Fowler's Solution was an arsenical preparation, which may well have accelerated the death of many PA patients. Also *Atoxyl*, a

Table 1. Historical track record of discovery and treatment of pernicious anemia that later lead to the discovery of vitamin B12.

Era/Discovery	Year	Discovery/Event	Ref.
Pre-treatment, disease finding era. Characterization of the pernicious anemia and early therapeutic approaches	1822	Unexplained cases of anemia, first description of PA	(Combe 1824)
	1849	PA identified as a clinical entity	(Addison 1849)
	1871	15 cases of PA described—PA gained general interest in the medical community for the first time	(Biermer 1872)
	1874	First blood count in PA—observed large size of cells	(Sørensen 1874)
	1876	Bone marrow examination—increased cellularity	(Cohnheim 1876)
	1878	Comprehensive monograph on progressive PA	(Eichhorst 1878)
	1880	Monograph on atrophy of the stomach	(Fenwick 1880)
	1880	Recognition of megaloblasts in the blood of PA patients	(Ehrlich 1880)
	1887	Neurological components of PA	(Lichtheim 1887)
	1900	Subacute combined degeneration of the spinal cord (SCDC)	(Russell et al. 1900)
Oral and parenteral liver treatment and discovery of the pathogenesis of pernicious anemia	1926	Liver therapy of pernicious anemia	(Minot and Murphy 1926)
	1929	Achylia gastrica (atrophic gastritis) associated with PA—intrinsic factor contained in gastric juice	(Castle 1929)
	1947	First (microbiological) assay for quantification of B12	(Shorb 1947b)
Isolation and characterization of B12; predominantly parenteral treatment with crystalline B12	1948	Isolation and crystallization of B12 from liver	(Fantes et al. 1950; Rickes et al. 1948)
	1949	Production of B12 by bacterial fermentation	(Stokstad et al. 1949)
	1952	Assay of cobalamin in human serum	(Ross 1952)
	1953	Schilling test for evaluation of intestinal absorption of B12	(Schilling 1953)
	1954	Complete structure of B12 resolved	(Brink et al. 1954)
Oral treatment revisited. First B12-tablet approved in Sweden and final elucidation of synthesis pathways of B12	1964	First B12 tablet approved by Swedish Medical Products Agency	(Ågren 1964)
	1965	B12-binding proteins described	(Hall and Finkler 1965)
	1973	Total synthesis of vitamin B12 achieved	(Woodward 1973)
	1994	Entire aerobic pathway of B12 synthesis resolved	(Battersby 1994)
	2013	Elucidation of the entire anaerobic pathway of B12 synthesis	(Moore et al. 2013)

precursor of sulfonamide antibiotics, contained arsenic (Riethmiller 2005), which—together with sodium cacodylate—was used for the treatment of syphilis (Nichols 1911). The following quote from Osler's textbook illustrates the prevailing ignorance of the medical community about the proper treatment of PA at that time (Osler 1915):

> *"There are five essentials: first, a diagnosis; secondly, rest in bed for weeks or even months, if possible (thirdly) in the open air; fourthly, all the good food the patient can take; the outlook depends largely on the stomach; fifthly, arsenic; Fowler's solution in increasing dosis beginning with m iii or v (0.2 to 0.3 c.c.) three times a day, and increasing to m i each week until the patient takes m xv (1 c.c.) three times a day. Other forms of arsenic may be tried, as the sodium cacodylate*[2] *or the atoxyl hypodermically. Atoxyl can be given in doses of gr. ss (0.032 gm.) every five days, and the amount is gradually increased. Accessories are oil inunctions; bone-marrow, which has the merit of a recommendation by Galen; in some cases iron seems to do good. Care should be taken of the mouth and teeth. Gastric lavage and irrigations of the colon are useful in some cases.*
>
> *Injections of blood serum and defibrinated blood have been given. The serum is given in small amounts, 10 to 20 c.c., usually into a vein; rabbit serum is perhaps the best. Defibrinated human blood should be given intravenously in large amounts, up to 500 c.c." (Osler 1915).*

Part of the short-lived effectiveness of arsenic for treatment of PA may be explained by liberation of B12 from the body's own cells through arsenic-induced cell-lysis (Dunlop 1973; Riedmann et al. 2015; Weber 1932).

3. Recovery from PA by Liver Treatment

3.1 The discovery and development of oral liver therapy

The First World War triggered research into blood substitutes and ways of improving recovery and hematopoiesis after massive blood loss (Sinclair 2008). This may also have stimulated George Whipple, who was an expert in liver diseases working at the University of California, to examine the liver's role in hematopoiesis. In 1920 he conducted a series of experiments in dogs that had been made anemic through venesectio and investigated the effects of various dietary treatments (Whipple et al. 1920). Interestingly, similar experiments carried out in pancreoectomized dogs resulted in the discovery of insulin by Fredrick Banting and Charles Best at the University of Toronto, Canada, during 1920–1924 (Banting et al. 1991). Whipple later moved to the University of Rochester, School of Medicine and Dentistry in New York State

[2] Chemical compound with the formula $(CH_3)_2AsO_2Na$ at that time used—together with Salvarsan and Atoxyl—for the treatment of syphilis

and continued his research on the effects of dietary regimes including liver, iron pills, arsenic and germanium dioxide for treatment of chronic anemia. Only liver, and especially raw, uncooked liver turned out to be effective in treatment of anemia (Robscheit-Robbins and Whipple 1925). The finding that raw liver was more effective than cooked liver was pure serendipity. Disobeying the instructions of Whipple, a laboratory technicians responsible for the dogs, fed the anemic animals raw liver instead of cooked and a more pronounce hematological effect was observed (Sinclair 2008). We now know that liver is rich in vitamin B12, folate, and other nutrients. Further, vitamin B12 is heat-stable while folate is not. Therefore, the chance finding that raw liver was more effective than cooked liver in restoring hemoglobin levels could indicate that apart from heat-stable vitamin B12 other, heat-labile hematopoietic factors such as folate contained in raw liver might have been responsible for the superior hematological effects in anemic dogs. Still, in 1923 George Minot and William Murphy, two physicians from Bostom, took notice of Whipple's discovery in dogs and decided to try raw liver for the treatment of patients with PA (Sinclair 2008). In 1926, Minot and Murphy presented their results of the first 45 patients who had been given a high protein diet that included 100–240 g of liver and 120 g of meat for between six weeks and two years at a meeting of the Association of American Physicians in Boston (Minot and Murphy 1926).

Interestingly, Minot had learnt a method of counting reticulocytes in the meanwhile that allowed him to study early hematological responses to liver treatment (Sinclair 2008). Minot and Murphy observed raised reticulocyte counts within four to ten days after starting the diet (Kumar et al. 2006). Other signs of hematological response such as increased hemoglobin levels and red cell counts and improvement of jaundice in addition to neurological recovery followed later during therapy.

3.2 Rather die than being treated with raw liver that tasted dreadful

Raw liver was assumed to contain a yet unidentified *extrinsic factor* responsible for the clinical effects. However, this diet tasted dreadful. David Hilbert (1862–1943), one of the greatest mathematicians of the first half of the twentieth century and director of the Mathematical Institute of Göttingen (Reid 1996) was diagnosed with pernicious anemia during autumn 1925. The disease had gone undetected for a long time because the first symptoms—taking into account his age of 65 y—had been interpreted as a merely age-related phenomenon. At the time of diagnosis, however, Hilbert was no longer able to leave his house because he was too weak to walk and he taught his students at home. The doctors gave him at best a few months or even weeks to live. A pharmacologist friend in Göttingen by chance read the paper of Minot and Murphy in JAMA from 1926 (Minot and Murphy 1926). By the intervention of Marianne Landau, daughter of the Nobel laureate Paul Ehrlich, contact was established with several Harvard professors in mathematics who finally could convince Minot

to send experimental liver extracts from the United States despite the scarcity of the preparations. Until the arrival of the liver extracts, Hilbert had, however, to follow the original raw liver diet. A colleague of Hilbert, EU Condon, visiting Göttingen in the summer of 1926, heard Hilbert complain that he would rather die than eat that much raw liver. Yet, his condition improved almost immediately upon the liver therapy (Reid 1986).

3.3 Nobel Prize in Medicine in 1934 and development of oral and parenteral liver treatment

Vitamin B12 research resulted in two Nobel prizes. On December 10, 1934, the Caroline Institute awarded the Nobel Prize in Physiology or Medicine to three American investigators: George R. Minot and William P Murphy of the Harvard Medical School (Boston, MA) and George H Whipple of the University of Rochester School of Medicine and Dentistry (Rochester, NY), "in recognition of their discoveries respecting liver therapy in anaemias." On December 12, 1934, Murphy presented this motion picture (Murphy 2006) as part of his Nobel lecture (Murphy 1934). He introduced the movie with the following words:

> *"Rather than enlarge further upon the details and results of the treatment of pernicious anemia, I shall now present, with your permission, a motion picture which will illustrate many points more clearly than I could discuss them here."*

The motion picture, made at the Peter Bent Brigham Hospital in Boston emphasizes the superiority of parenteral to oral therapy with liver extract in the treatment of PA. The movie consists of two parts. In the first part hematologic and neurologic signs and symptoms in PA are illustrated and a synopsis of normal hematopoiesis as well as pathology seen in PA is given. Further, different treatment schemes with whole liver, oral liver extracts, and concentrated extracts for intramuscular injections are compared. The second part depicts the improvement in the peripheral smear with liver therapy, and the greater clinical effectiveness of parenteral therapy compared with oral treatment with liver or liver extracts. Even a cost-effectiveness analysis of the parenteral treatment is presented and the importance of maintenance therapy is highlighted. Oral liver therapy was used in clinical practice for a relatively short period of about seven years before it was substituted by parenteral therapy and at the time of the Nobel lecture oral liver therapy had been more or less replaced by intramuscular injections of liver extracts (Figure 4). Liver extraction methods were rather crude at that time (Gänsslen 1930) and preparations certainly contained other hematopoietic factors in addition to vitamin B12 (Okuda 1999). Ironically, improved purification of liver extracts may have removed these additional hematopoietic factors and contributed to the lower potency and greater batch variability of the

preparations during the course of the years between 1940 and 1948 (Mollin 1950). Until that time, the "extrinsic factor" contained in liver and curing PA still remained undiscovered.

4. Isolation and Crystallization of Vitamin B12

The discovery of the unknown liver factor, i.e., vitamin B12, was delayed because no quantitative *in vitro* tests were available at that time to measure the potency of the different liver extracts. Thus, the only way to evaluate the effectiveness of the extracts was to test them on patients with PA, which was time-consuming (Rickes et al. 1948; Shive 2002; Vora 1956). The discovery of a microbiological assay for the measurement of vitamin B12 activity in 1947 (Shorb 1947a; Shorb 1947b) accelerated the isolation of the *extrinsic factor* contained in liver that was responsible for the alleviating the clinical symptoms. Vitamin B12 in the liver extract was able to enhance the growth of the bacteria, and the growth rate could be used as a measure of the amount of the unknown factor in the extract. Unfortunately, extraction and isolation of crystalline vitamin B12 from liver was highly inefficacious. One and a half tons of beef liver was needed to produce 1 gram of vitamin B12. Finally, in 1948 two independent groups, Folkers and co-workers at Merck, United States, and Lester-Smith and co-workers at Glaxo, England, succeeded in isolating the *extrinsic factor* in 2 different crystalline forms (hydroxyl and cyano-cobalamin) and they named it vitamin B12 (Wagner and Folkers 1963). Vitamin B12 received its name (B12) just after folate (vitamin B9) had been discovered and thus it was given the number 12 in the B-group. The gaps in the numbering of the B-vitamin complex are due to the fact that a number of substances initially mistaken for vitamins were gradually removed from the group of B-vitamins (Elliot 2008).

4.1 Second Nobel Prize in Chemistry in 1955 and the discovery of the chemical structure of vitamin B12

The final product of the extraction, vitamin B12, turned out to be odor- and tasteless, bright red needle-shaped crystals (Howard 2003). However, it took seven more years before the exact chemical structure was finally resolved through X-ray crystallography by Dorothy Hodgkin in 1955 (Brink et al. 1954; Hodgkin et al. 1955). About ten million calculations had been necessary to clarify the structure of this factor. For this achievement Dorothy Crowfoot Hodgkin received the Nobel Prize in 1964. During the 1950's studies on isolates of various bacteria and molds primarily used for antibiotic production, and rumen microorganisms revealed that many of these microbes were also able to synthesize vitamin B12 (Halbrook et al. 1950; Johnson et al. 1956).

Still, the complete laboratory chemical synthesis of vitamin B12 was not accomplished before 1972 (Woodward 1973). Total chemical synthesis requires

more than 70 steps and is extremely resource demanding. Microorganisms are far more efficient at synthesis of this vitamin and bacterial fermentation remains the main source of production of vitamin B12 at industrial scale even today (Xia et al. 2015) (Figure 3).

5. Oral Treatment Revisited

5.1 Oral or parenteral treatment with liver extracts

Even though the exact cause of PA remained unknown for many years to come, involvement of the gastric ventricle in the pathogenesis of this disease was anticipated as early as in 1880 (Fenwick 1880). Gastric atrophy and achlorhydria were common findings in pernicious anemia patients. In 1926, it was clear that liver obviously contained an, at that time, unidentified *extrinsic* (food/liver) *factor* accountable for the clinical response, but for more effective oral treatment in addition an *intrinsic* (gastric) *factor* was needed and this factor was most likely contained in the gastric juice of healthy humans or animals (Castle 1929).

In 1927, Castle performed the first experiments that demonstrated the existence of an additional endogenous gastric substance involved in the pathogenesis of PA, which he called the *intrinsic factor* (Castle 1929).

Castle found that neither normal human gastric juice nor nearly raw hamburger meat alone could induce a reticulocyte response in PA patients. However, hamburger meat that had stayed in Castle's own stomach for 1 h before it was regurgitated and then fed to PA patients via a nasogastric tube triggered a reticulocyte response. Castle stated:

> *'that in contrast to the conditions within the stomach of the pernicious anaemia patient, there is found within the normal stomach during digestion of beef muscle some substance capable of promptly and markedly relieving the anaemia of these patients'* (Castle 1929).

Development of processed liver concentrates for oral administration followed. However, oral treatment demanded relatively high doses and was thus very expensive (Ungley 1955). It turned out that the potency of the liver extracts could be improved by adding the yet unidentified *intrinsic factor* (Castle 1953), which was supplied as liquefied stomach contents of a healthy normal person or desiccated hog's stomach (Glass and Boyd 1953). However, all of these preparations tasted dreadful and the period of exclusively oral treatment of PA with liver or liver extracts was soon replaced by more "palatable" parenteral regimes with injectable liver extracts (Schultzer 1934). Parenteral treatment had additional advantages as it was—at that time—considerably cheaper compared to oral therapy due to lower dose-demands and no *intrinsic factor* was needed (Ungley 1950a; Ungley 1950b). However, injectable liver extracts also had serious side effects, sometimes even fatal, and

the potency unfortunately showed considerable variability between vendors as well as over time resulting in many relapses during maintenance therapy (Anonymous 1965; Mollin 1950). Moreover, the cleaner the liver extracts became the poorer was their potency as other potentially active factors such as folate and iron from crude liver extracts gradually disappeared (Conley and Krevans 1955). By the end of the 1940s pure crystalline cyanocobalamin (vitamin B12) was preferred over liver extracts for treatment of PA (Blackburn et al. 1952; Blackburn et al. 1955; Wagner and Folkers 1963).

Since then, parenteral supplementation with crystalline cyanocobalalmin has been the mainstay of treatment of most forms of vitamin B12 deficiency in the majority of countries world-wide (Stabler 2013). Adherence to this therapeutic tradition is most likely also a result of the 1959 US Pharmacopeia Anti-Anemia Preparations Advisory Board recommendation, which advised against the use of oral therapy for pernicious anemia, mostly because of its unpredictable efficacy (Bethell et al. 1959). Typically, arguments against oral cyanocobalamin therapy were based on findings of inadequately low serum cobalamin concentrations achieved in patients taking oral vitamin B12 doses of 100–250 µg/d without *intrinsic factor* (Glass and Boyd 1953). According to our current knowledge, when oral doses > 10 µg/d are used, only approximately 1.5% of the dose is expected to be absorbed through passive diffusion, thus explaining the relatively low efficacy of doses < 500 µg/d in treatment of PA.

5.2 Oral treatment with crystalline vitamin B12 with and without intrinsic factor

Parallel with the parenteral use of crystalline vitamin B12, investigators searched for oral alternatives to liver extracts and experimented with oral use of small amounts of crystalline vitamin B12 in combination with *intrinsic factor* from various sources to improve bioavailability (Blackburn et al. 1955). By the end of the 1950s more efficient, large-scale industrial production of vitamin B12 by microbial fermentation was accomplished, securing the supply of inexpensive cyanocobalamin (Mervyn and Smith 1964). This opened up for the use of higher oral doses of cyanocobalamin without *intrinsic factor* despite poor bioavailability (Waife et al. 1963). During the 1950's a large number of dose-finding studies of oral therapy with crystalline B12 were performed with and without addition of intrinsic factor and clinical responses were monitored thoroughly (Brody et al. 1959; Chalmers and Hall 1954; Chalmers and Shinton 1958; Conley and Krevans 1955; Doscherholmen and Hagen 1957; Gaffney et al. 1959; McIntyre et al. 1960; Reisner et al. 1955; Ross et al. 1954; Schwartz et al. 1959; Shinton 1961; Spies et al. 1949; Ungley 1950a; Ungley 1950b; Ungley 1950c; Ungley and Childs 1950; Waife et al. 1963). The required oral doses varied considerably between the studies and ranged from repeated daily doses of 50–100 µg (Brody et al. 1959) to 1000 µg per week (Reisner et al. 1955)

to at highest 3000 µg/d (Ungley 1950a). Consistently, it was found that oral doses needed to be 30–60 times higher than parenteral doses in patients with pernicious anemia (Chalmers and Hall 1954; Spies et al. 1949). In Sweden, during the late 1950's and early 1960's basic research was carried out studying the feasibility of oral treatment of pernicious anemia with tablets containing very high doses of cyanocobalamin without an intrinsic factor (Berlin et al. 1965; Berlin et al. 1966; Berlin et al. 1968b; Berlin et al. 1958; Berlin et al. 1961). Little by little, this research provided convincing evidence from long-term follow-up of pernicious anemia patients, showing that oral treatment with vitamin B12-tablets was indeed possible and reliable (Berlin et al. 1965; Berlin et al. 1968b). Vitamin B12 tablets were approved by the Swedish Medical Products Agency in 1964 (Ågren 1964). Since then, vitamin B12-substitution with tablets has gradually replaced parenteral therapy in Sweden, where vitamin B12 tablets constitute more than 80% of vitamin B12-prescription drugs (Nilsson et al. 2005).

6. The Pharmacology of Oral Vitamin B12

To understand the feasibility of oral vitamin B12-treatment it is necessary to recognize the clinical pharmacology of vitamin B12, which is quite complex. Most of the work on vitamin B12 pharmacokinetics was carried out during the 1960s (Adams et al. 1971; Ardeman et al. 1964; Boddy et al. 1968; Gottlieb et al. 1965; Herbert 1968; Hertz et al. 1964; Heyssel et al. 1966; Skouby 1966). Physiological losses of vitamin B12 through renal and biliary elimination routes are minimal and daily losses in healthy subjects account for only 0.1–0.2% of the total body reserves of 3–5 mg, and merely this portions needs to be replenished (Table 3) (Combs 2008). Therefore, the daily cobalamin requirements in order to maintain normal vitamin status in healthy subjects are extremely low. The recommended daily allowance (RDA) for adults is 2.4 µg/d as set by the US Institute of Medicine in 1998.

6.1 Pharmacokinetics

Absorption, transport and cellular uptake as well as retention in the body depend on a number of transporters, binding proteins and receptors that all have a high specificity for vitamin B12 (Table 2).

The free binding capacity of most of the binding proteins is adapted to the physiologically low vitamin B12-supply and demands. Therefore, the free binding capacity of B12 binders is generally low as regards to both active intestinal absorption and transport in the blood. In line with this, the maximum capacity of active intrinsic factor-mediated absorption of vitamin B12 is only 2.5 to 3.0 µg per serving (Heyssel et al. 1966). It takes about 4–6 hours before maximum active absorption capacity is completely restored (Heyssel et al. 1966). Further, the unsaturated vitamin B12 binding capacity in human plasma

Table 2. Main proteins involved in vitamin B12 homeostasis and transport.*

	Binding proteins or transporters			Receptor proteins		
	IF	HC	TCII	Cubilin/ amnion-less	Megalin	TC-receptor CD320
Main function:						
Intestinal absorption	x			x		
Blood transport		x	x			
Cellular uptake			x		x	x
Entero-hepatic circulation	x		x	x		
Renal tubular re-absorption			x		x	x
Biliary elimination		x				

* The table is based on data from the following references (Banerjee et al. 2009; Birn 2006; Fyfe et al. 2004; Grasbeck 2006; Herbert 1994; Kanazawa et al. 1983; Quadros and Sequeira 2013; Schjonsby 1989). IF = intrinsic factor; HC = haptocorrin; TCII = transcobalamin II; TC-receptor = transcobalamin receptor

ranges from 230 to 1380 pmol/l (Herbert 1968), mostly constituted of apo-transcobalamin II (apo TC-II) (Markle 1996; Obeid et al. 2006; Teplitsky et al. 2003). This corresponds to a total binding capacity of only 3 to 5 µg of newly absorbed cobalamin (Gottlieb et al. 1965). Vitamin B12 unbound to transporters or plasma proteins is subject to glomerular filtration and rapid renal excretion (Herbert 1968). This limits maximum (active) absorption and body retention when vitamin B12 is supplemented in pharmacological doses (Table 3). Further, the bioavailability and total body retention of vitamin B12 not only depends on the route of administration, oral or parenteral, the capacity of vitamin B12 binding proteins, but also on the formulation of vitamin B12 preparations (i.e., cyano- and hydroxocobalamin) (Adams et al. 1971; Boddy et al. 1968; Hertz et al. 1964; Skouby 1966) (Table 3). At high doses oral bioavailability or retention of *i.m.* vitamin B12 is very similar in healthy subjects and patients suffering from PA (Table 3, Figure 4).

6.1.1 Oral absorption

Gastric dysfunction such as chronic atrophic gastritis is a major cause of reduced oral up-take of cobalamin from food sources (food cobalamin malabsorption) (Nielsen et al. 2012). Interestingly, reduced availability of the intrinsic factor due to gastric atrophy is not a rate-limiting factor in this process. The stomach appears to have a large reserve capacity for *intrinsic factor* secretion and daily production of *intrinsic factor* suffices for uptake of 100–150 µg/d (Ardeman et al. 1964). Only extreme forms of atrophic gastritis and selective destruction of

Table 3. Bioavailability and retention of cobalamin.

	Healthy subject		**Pernicious anemia patient**	
Daily loss*	≈ 1µg/d		≈ 2 µg/d	
RDA	2.4 µg/d		1000 µg/d p.o. 1000 µg/90 days i.m.	
Bioavailability of a single oral dose µg (% of the dose)				
0.5 µg	0.38 µg (75%)		0.006 µg (1.2%)	
1–2 µg	0.5–1 µg (50%)		0.012–0.024 µg (1.2%)	
10 µg	1.6 µg (16%)		0.12 µg (1.2%)	
50 µg	2.0 µg (4%)		0.6 µg (1.2%)	
500 µg	10 µg (2%)		6 µg (1.2%)	
1000 µg	≈ 14 µg (1.4%)		≈ 12 (1.2%)	
Retention of a single i.m. dose (% of the dose)	CN-Cbl	OH-Cbl	CN-Cbl	OH-Cbl
3 µg	100%	100%	100%	100%
10 µg	97%	98%	98%	98%
25 µg	95%	96%	96%	98%
40 µg	93%	94%	94%	96%
100 µg	55%	90%	60%	94%
500 µg	20%	50%	30%	55%
1000 µg	15%	30%	20%	35%

* Mainly represented by vitamin excreted in urine and bile. RDA, Recommended Dietary Allowance. This table is a compilation of data from the following studies (Ardeman et al. 1964; Berlin et al. 1968a; Heyssel et al. 1966; Scott 1997).

gastric parietal cells by autoantibodies in pernicious anemia can reduce *intrinsic factor* production to a significant level. Nevertheless, atrophic gastritis per se may limit the bioavailability of oral vitamin B-12 through other mechanisms, such as impaired release of the vitamin from food proteins due to impaired acid secretion and reduced digestion by pepsin (Selhub et al. 2000). These restraints do of course not apply for crystalline vitamin B12 tablets. The rate-limiting factor of oral bioavailability of low doses of food vitamin B12 is primarily saturation of ileal receptors, which recognize the cobalamin-*intrinsic factor* complex (Heyssel et al. 1966). The active transport of the cobalamin-*intrinsic factor*-complex is easily saturable. The maximum amount of vitamin B12 that can be absorbed from a single meal is about 2 µg (Scott 1997; Watanabe 2007) and the fractional absorption decreases as oral doses are increased. About 50% of a single oral dose of 1 µg is retained, 20% of a 5 µg dose, and only 5% of a 25 mg dose (Table 3). To improve oral bioavailability of vitamin B12 repeated daily dosing at least 4–6 hours apart without concomitant food intake would appear advantageous (Berlin et al. 1968a; Brody et al. 1959; Heyssel et al. 1966). At oral doses of 500–1000 µg and above a constant fraction of

cobalamin, approximately 1.5 of the dose, is absorbed by simple diffusion from the lumen to the intestinal epithelium independent of *intrinsic factor* (Berlin et al. 1968a). In pernicious anemia active uptake of vitamin B12 through ileal receptors does not occur due to lack of *intrinsic factor*, but passive absorption by simple diffusion is more than adequate to meet the daily requirements for patients without *intrinsic factor* when daily oral dosages of 1000 µg are ingested (Berlin et al. 1968a). When using low oral doses of vitamin B12 a saturation of the plasma total vitamin B12 binding capacity is normally not achieved. However, at oral doses exceeding 1–10 mg significant urinary excretion of newly absorbed vitamin B12 is observed (Berlin et al. 1968a).

At increasing oral doses the absolute and relative difference in vitamin B12 uptake between healthy subjects and patients with pernicious anemia becomes narrower (Berlin et al. 1968a) (Figure 5).

6.2 Pharmacodynamics

Vitamin B12 is essential for cell growth and replication and participates in transmethylation reactions during the synthesis of methionine, choline, creatinine and nucleic acids. Vitamin B12 supplements reverse the hematopoietic and, if started timely, neurological symptoms of vitamin B12

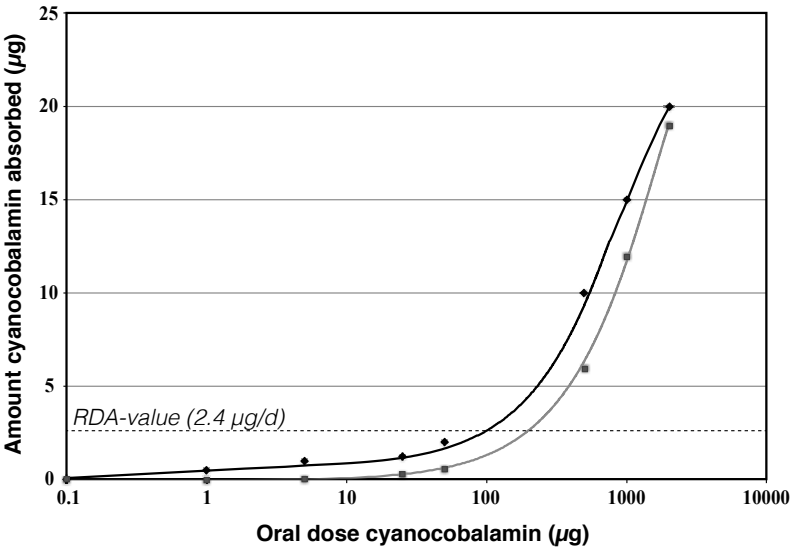

Figure 5. Schematic representation of estimated vitamin B12-uptake at different oral doses (per serving) in healthy subjects (black color, black diamond symbols) and cyanocobalamin tablets patients with pernicious anemia (grey color, solid grey square symbols) based on data from literature (Doscherholmen and Hagen 1957; Gaffney et al. 1959). The figure illustrates the dual mechanism of active (saturable) and passive absorption of oral cyanocobalamin (Doscherholmen and Hagen 1957) and that similar absolute amounts of cyanocobalamin are absorbed in healthy subjects and patients suffering from PA when very high oral doses are used.

deficiency (Stabler 2013). Vitamin B12 does not exert direct pharmacodynamic activity, but acts as a co-factor in two different forms, methylcobalamin and 5-deoxyadenosincobalamin, for the enzymes methionine synthase and methylmalonyl-CoA mutase, respectively (Banerjee 2006). In addition, vitamin B12 has repeatedly been proposed as a carrier molecule for up-take and targeting of drugs to certain tissues (Clardy-James et al. 2013).

6.3 Side effects

Generally, both oral vitamin B12 and vitamin B12-injections are well tolerated. However, injection site reactions including pain, erythema, pruritus, induration, swelling, and necrosis can occur (2013) causing patient discomfort and inconvenience (van Walraven et al. 2001a; van Walraven et al. 2001b). Oral supplementation reduces the risk of injection complications such as infections or cyst formations and nerve injuries are avoided. In addition, the risk of allergic reactions is lower with oral administration (Bilwani et al. 2005). Finally, oral treatment is preferred to intramuscular injections in patients on anticoagulation therapy as there is increased risk of hematoma formation when i.m. injections have to be performed regularly (Kim and Hyung 2011).

7. Diagnostic Achievements in the Course of Discovery of PA

Milestones in the development of diagnostic procedures for vitamin B12-deficiency are depicted by central gradient bars with solid-lined borders in Figure 4. Development of assays for identification and quantification of the putative *extrinsic factor* were crucial for final isolation of vitamin B12 from liver extracts, and measuring its concentration in these extracts (Vora 1956) and later diagnostically in blood samples. Before that, the potency of liver extracts assumed to contain the vital *extrinsic factor* that cured anemia had to be tested on the basis of the hematological response in affected patients, which was very time-consuming and not without risks (Shive 2002; Vora 1956). However, in 1947/48 important observations of Shorb of a linear relationship between the amount of a presumed growth factor for *Lactobacillus lactis* Dorner in liver extracts and the potency of the same factor for the treatment of patients suffering from pernicious anemia resulted in the first microbial vitamin B12-assay (Shorb 1947a; Shorb 1947b; Shorb 1948). Having a quantitative *in vitro* assay that allowed testing the biological activity of the extracts greatly accelerated the successful isolation of vitamin B12 (Ahrens 1993).

Soon, the same principle of microbial assays was found to be useful for measuring of vitamin B12 concentrations in serum and other body fluids. Measuring blood concentrations of vitamin B12 soon became the first step in diagnosing PA (Ross 1952).

However, even microbial assays were laborious had many limitations such as multiple steps and long incubation times, difficulties to automate the assay,

risk of microbial contamination, and suppression of growth by antibiotics and cytotoxic drugs and were relatively soon abandoned from the clinical routine laboratory (O'Sullivan et al. 1992). Today, microbiological assays for vitamin B12 are adapted to microtiter plate format and carried out by robotic workstations and are mainly used for scientific purposes (Molloy and Scott 1997; O'Broin and Kelleher 1992; Taneja et al. 2007).

In the 1960s, radioimmunoassays, RIAs, were introduced using ^{57}Co-cyanocobalamin and *intrinsic factor* and R-binder as binders (Moridani and Ben-Poorat 2006; O'Sullivan et al. 1992). RIA tests had the drawback of demanding manual sample pretreatment, radiation exposure risk and costs associated with disposal of the radioimmunoassay components (Kuemmerle et al. 1992; Moridani and Ben-Poorat 2006). By 2007, the manufacturer of the most commonly used RIA-assay, the Bio-Rad RIA, discontinued the production (Yetley et al. 2011). The first automated, non-isotopic chemiluminescence assays for measuring vitamin B12 in serum were developed in the early 1990s (Kuemmerle et al. 1992). Current automated routine assays are mostly based on these non-isotopic procedures using chemiluminescence or more recently electroluminescence detection and exhibit relatively good measuring agreement between the methods (Karmi et al. 2011; Vogeser and Lorenzl 2007).

In parallel, alternative or complementary tests to serum vitamin B12 assays were developed, including more sensitive and specific functional markers of vitamin B12 status such as methylmalonic acid and homocysteine that increase in blood and urine of people with deficiency. By the end of the 1980s and through the 1990s different methods for determination of the functional vitamin B12-marker methylmalonic acid (MMA) became available, including GC-MS, HPLC, capillary electrophoresis, LC-MS and LC-MS-MS techniques (Stabler et al. 1986; Schneede and Ueland 1993; Schneede and Ueland 1995; Windelberg et al. 2005; Lakso et al. 2008). Together with total homocysteine, MMA nowadays represents one of the cornerstones of vitamin B12 deficiency diagnostic tests (Langan and Zawistoski 2011; Remacha et al. 2014; Risch et al. 2015).

During the same period, the concept of holotranscobalamin (holoTC) as a measure of biologically active cobalamin was developed (Carmel 1985; Herbert et al. 1990; Herzlich and Herbert 1988; Lindemans et al. 1983; Remacha et al. 2014). Vitamin B12 in serum is carried by two binding proteins, transcobalamin and haptocorrin. Although the fraction of transcobalamin-bound vitamin B12 (holoTC) in relation to total vitamin B12 is small (≈ 20–30 %), holoTC is considered representing newly absorbed vitamin B12 and being responsible for delivering cobalamin to cells through a receptor mediated up-take. HoloTC is considered being the functionally active fraction of the vitamin (Carmel 2011; Nexö and Hoffmann-Lucke 2011). The first commercial RIA-assay for determination of holoTC became available in 2002 (Ulleland et al. 2002) and has now been replaced by an automated sandwich microparticle enzyme immunoassay that can be run on standard analytical platforms (Brady et al. 2008). The clinical utility of the holo-TC test has been evaluated during the

recent years and its place in vitamin B12-diagnostics is still under debate (Herrmann and Obeid 2013; Remacha et al. 2014; Risch et al. 2015).

Another landmark in revealing the cause of vitamin B12-deficiency through diagnostic test was the Schilling test. The Schilling test was introduced by Schilling in 1953 and was designed to assess the ability of the patient to absorb small oral doses of radioactively labeled vitamin B12 (Schilling 1953). This test remained the mainstay of diagnostic tests for detection and differentiation of potential causes of vitamin B12 deficiency for more than five decades until it was abandoned due to high costs, lack of sensitivity under certain conditions and terminated production of cobalt radioisotopes and labeled cobalamin forms (Moridani and Ben-Poorat 2006; Palmer et al. 2012; Yetley et al. 2011). More recently, a non-radioactive vitamin B12 absorption test (CobaSorb) has been developed, but also this test has several limitations and has not achieved widespread adoption so far (Hardlei et al. 2010; Hvas et al. 2011; Hvas et al. 2007).

8. Health-economic Assessments of Oral B12 Treatment

Vitamin B12-treatment was from the very beginning not just a matter of clinical effectiveness, but also cost-effectiveness (Kumar et al. 2006). Already in 1934 Murphy addressed in his Nobel lecture cost-aspects of liver-treatment and potential savings with liver extracts for intramuscular use compared to peroral treatment (Murphy 1934). The first modern health-economic assessment of oral versus parenteral B12 supplementation that also included a sensitivity analysis was performed in 2001 (Figure 4) (van Walraven et al. 2001a), grey bars with solid-lined borders in Figure 4. Sensitivity analysis indicated that the number of injection-associated physician visits that could be avoided by switching patients to oral therapy had major impact on the cost-effectiveness. Later, publications on cost minimization analyses (Vidal-Alaball et al. 2006) and cost-saving analyses (Houle et al. 2014) as well as budget impact analyses (Masucci and Goeree 2013) performed in the UK, Canada and Spain followed.

Nowadays, the switch to oral vitamin B12 supplementation with tablets is generally considered feasible and a cost-effective alternative to parenteral treatment (Kolber and Houle 2014; Kwong et al. 2005).

9. Summary

Vitamin B12 is an archaic vitamin in many aspects. As other vitamins, vitamin B12 is vital for all higher organisms and functions as cofactor. Humans require dietary supply of these organic micronutrients, but microorganisms and many plants synthesize de novo the cofactors they need. Vitamin B12 is also an ancient molecule, as it was first synthesized by prokaryotic cells. Conceivably, the history of vitamin B12 deficiency and PA in humans has to be considerably shorter than the history of the vitamin itself, and can arbitrarily be divided

into different epochs. It is almost 200 years since the first description of PA and the pre-treatment era stretches over 100 years before effective treatment options were developed (Figure 4). Oral treatment with raw or slightly cooked liver or liver extracts followed, but was soon abandoned due to high costs and unacceptable taste. The epoch of oral liver therapy was succeeded by a period of intramuscular administration of liver extracts, which lasted for about 20 years. With the isolation and characterization of the *extrinsic factor* (B12) from liver and the advent of large-scale, cost-effective production of vitamin B12 by bacterial fermentation (Xia et al. 2015) it was possible to use pure crystalline vitamin B12 for intramuscular administration, which still is the predominant treatment option of vitamin B12 deficiency world-wide today. The introduction and approval of high-dose vitamin B12 tablets in Sweden in the early 1960's ushered in the renaissance of oral treatment of vitamin B12-deficiency. The need to diagnose PA and other causes of vitamin B12 deficiency triggered the development of a range of diagnostic tests, some of them now constitute the basis of diagnostic strategies in clinical routine. During the last decade several health-economic assessments have confirmed the cost-effectiveness of oral vitamin B12 treatment over parenteral therapy. Industrial production by bacterial fermentation and the return of oral treatment vitamin B12 deficiency underscore the archaic nature of this precious co-factor. Almost 200 years after discovering PA and after approximately 70 years of efforts to find the cause of PA and to understand the synthesis of vitamin B12, large parts of the puzzle now seem to have been solved, but in fact many questions on vitamin B12 deficiency are still unanswered and warrant further investigations (Gräsbeck 2013).

Keywords: Vitamin B12 deficiency, cobalamin, history, management, diagnostics, supplementation, homocysteine, methylmalonic acid, holo-transcobalamin, health economics.

Abbreviations

PA	:	Pernicious anaemia
HC	:	Haptocorrin
TCII	:	Transcobalamin II
HoloTC	:	holotranscobalamin
RDA	:	Recommended Daily Allowance

References

Adams JF, Ross SK, Mervyn L, Boddy K and King P. 1971. Absorption of cyanocobalamin, coenzyme B 12, methylcobalamin, and hydroxocobalamin at different dose levels. Scandinavian journal of Gastroenterology. 6(3): 249–252.

Addison T. 1849. Chronic suprarenal insufficiency, usually due to tuberculosis of suprarenal Capsule. London Medical Gazette. 43: 517–518.

Ågren A. 1964. Farmacevtiska specialiteten Behepan tabletter 1 mg, file number 7399. Stockholm: Kungliga Medicinalstyrelsen (Swedish Medical Products Agency). p 1–20.
Ahrens RA. 1993. Mary Shaw Shorb (1907–1990). J Nutr. 123(5): 791–796.
Anonymous. 1965. Research News. Section II Development of the institute's research activities. The institute and research on pernicious anemia. Research News Ann Arbor: Office of Research Administration, the University of Michigan. Ann Arbor. pp. 15–19.
Ardeman S, Chanarin I and Doyle JC. 1964. Studies on secretion of gastric intrinsic factor in man. British Medical Journal. 2(5409): 600–603.
Banerjee R. 2006. B12 Trafficking in Mammals: A Case for Coenzyme Escort Service. ACS Chemical Biology. 1(3): 149–159.
Banerjee R, Gherasim C and Padovani D. 2009. The tinker, tailor, soldier in intracellular B12 trafficking. Current Opinion in Chemical Biology. 13(4): 484–491.
Banting FG, Best CH, Collip JB, Campbell WR and Fletcher AA. 1991. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. 1922. CMAJ: Canadian Medical Association Journal. 145(10): 1281–1286.
Battersby AR. 1994. How nature builds the pigments of life: the conquest of vitamin B12. Science (New York, NY). 264(5165): 1551–1557.
Berlin H, Berlin R and Brante G. 1965. [Peroral Treatment of Pernicious Anemia with High Doses of Vitamin B12 without Intrinsic Factor]. Lakartidningen. 62: 773–781.
Berlin H, Berlin R and Brante G. 1966. Crude or refined intrinsic factor in preparations for the oral treatment of pernicious anaemia. Scandinavian Journal of Haematology. 3(3): 236–244.
Berlin H, Berlin R and Brante G. 1968a. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Medica Scandinavica. 184(4): 247–258.
Berlin H, Berlin R and Brante G. 1968b. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Medica Scandinavica. 184: 247–258.
Berlin H, Berlin R, Brante G and Sjoberg SG. 1958. Studies on intrinsic factor and pernicious anemia. I. Oral uptake of vitamin B12 in pernicious anemia with increasing doses of an intrinsic factor concentrate. Scand J Clin Lab Invest. 10(3): 278–282.
Berlin R, Berlin H and Brante G. 1961. The absorption of IF-bound and free B12 in various clinical conditions. Second European Symposium on Vitamin B12 and Intrinsic Factor. Hamburg: Enke Verlag Stuttgart.
Bethell FH, Castle WB, Conley CL and London IM. 1959. Present status of treatment of pernicious anemia. J Am Med Assoc. 171: 2092–2094.
Biermer AM. 1872. Über eine eigenthümliche Form von progressiver, perniciöser Anaemie. Correspondenz-Blatt für Schweizer Aerzte. 2(1): 15–17.
Bilwani F, Adil SN, Sheikh U, Humera A and Khurshid M. 2005. Anaphylactic reaction after intramuscular injection of cyanocobalamin (vitamin B12): a case report. JPMA The Journal of the Pakistan Medical Association. 55(5): 217–219.
Birn H. 2006. The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins. American Journal of Physiology Renal Physiology. 291(1): F22-36-F22-36.
Blackburn EK, Burke J, Roseman C and Wayne EJ. 1952. Comparison of liver extract and vitamin B12 (cyanocobalamin) in maintenance treatment of pernicious anaemia. British Medical Journal. 2(4778): 245–248.
Blackburn EK, Cohen H and Wilson GM. 1955. Oral treatment of pernicious anaemia with a combined vitamin B12 and intrinsic factor preparation. British Medical Journal. 2(4937): 461–463.
Boddy K, King P, Mervyn L, Macleod A and Adams JF. 1968. Retention of cyanocobalamin, hydroxocobalamin, and coenzyme B12 after parenteral administration. Lancet 2(7570): 710–712.
Brady J, Wilson L, McGregor L, Valente E and Orning L. 2008. Active B12: a rapid, automated assay for holotranscobalamin on the Abbott AxSYM analyzer. Clinical Chemistry. 54(3): 567–573.
Brink C, Hodgkin DC, Lindsey J, Pickworth J, Robertson JR and White JG. 1954. X-ray crystallographic evidence on the structure of vitamin B12. Nature. 174(4443): 1169–1171.

Brody EA, Estren S and Wasserman LR. 1959. Treatment of pernicious anemia by oral administration of vitamin B12 without added intrinsic factor. The New England Journal of Medicine. 260(8): 361–367.
Carmel R. 1985. The distribution of endogenous cobalamin among cobalamin-binding proteins in the blood in normal and abnormal states. Am J Clin Nutr. 41(4): 713–719.
Carmel R. 2011. Biomarkers of cobalamin (vitamin B-12) status in the epidemiologic setting: a critical overview of context, applications, and performance characteristics of cobalamin, methylmalonic acid, and holotranscobalamin II. Am J Clin Nutr. 94(1): 348s–358s.
Castle WB. 1929. The Aetiological Relationship of Achylia Gastrica to Pernicious Anaemia. Proc R Soc Med. 22(9): 1214–1216.
Castle WB. 1953. Development of knowledge concerning the gastric intrinsic factor and its relation to pernicious anemia. The New England Journal of Medicine. 249(15): 603–614.
Chalmers JN and Hall ZM. 1954. Treatment of pernicious anaemia with oral vitamin B12 without known source of intrinsic factor. British Medical Journal. 1(4872): 1179–1181.
Chalmers JN and Shinton NK. 1958. Absorption of orally administered vitamin B12 in pernicious anaemia. Lancet. 2(7060): 1298–1302.
Clardy-James S, Chepurny OG, Leech CA, Holz GG and Doyle RP. 2013. Synthesis, characterization and pharmacodynamics of vitamin-B12 -conjugated glucagon-like Peptide-1. Chem Med Chem. 8(4): 582–586.
Cohnheim JF. 1876. Erkrankungen des Knochenmarkes bei perniziöser Anämie. Virchows Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin. 68: 291–293.
Combe JS. 1824. History of a case of anaemia. Transactions of the Medico-Chirurgical Society of Edinburgh. 1(August 2.): 194–204.
Combs GF. 2008. Chapter 17: Vitamin B12. The vitamins: fundamental aspects in nutrition and health. 3rd ed. ed. Oxford: Academic. pp. 384–385.
Conley CL and Krevans JR. 1955. New developments in the diagnosis and treatment of pernicious anemia. Annals of Internal Medicine. 43(4): 758–766.
Doscherholmen A and Hagen PS. 1957. A dual mechanism of vitamin B12 plasma absorption. The Journal of clinical investigation 36(11): 1551–1557.
Dunlop DM. 1973. Medicines in our time. The Rock Carling Fellowship. London: Nuffield Provincial Hospitals Trust. pp. 1–12.
Ehrlich P. 1880. Über Regeneration und Degeneration der rothen Blutscheiben bei Anämien. Berliner Klinische Wochenschrift. 117: 405.
Eichhorst H. 1878. Die progressive perniziöse Anämie: eine klinische und kritische Untersuchung. Leipzig: Veit & Comp. xi, 375 p., 373 leaves of plates.
Elliot CM. 2008. Vitamin B : new research. New York: Nova Biomedical Books. xiv, 234 p.
Ewing J. 1901. Clinical pathology of the blood; a treatise on the general principles and special applications of hematology: Philadelphia, Lea Brothers & Co. 489 p.
Fantes KH, Page JE, Parker LFJ and Smith EL. 1950. Crystalline Anti-Pernicious Anaemia Factor from Liver. Proceedings of the Royal Society of London B: Biological Sciences. 136(885): 592–609.
Fenwick S. 1880. On Atrophy of the Stomach and on the nervous affections of the digestive organs. J. & A. Churchill: London. 242 p.
Fyfe JC, Madsen M, Hojrup P, Christensen EI, Tanner SM, de la Chapelle A, He Q and Moestrup SK. 2004. The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless. Blood. 103(5): 1573–1579.
Gaffney GW, Watkin DM and Chow BF. 1959. Vitamin B12 absorption: relationship between oral administration and urinary excretion of cobalt 60-labeled cyanocobalamin following a parenteral dose; study of doses of 2 to 250 mu g in 148 apparently health men 20 to 92 years old. J Lab Clin Med. 53(4): 525–534.
Gänsslen M. 1930. Ein Hochwirksamer, Injizierbarer Leberextrakt. Klin Wochenschr. 9(45): 2099–2102.
Glass GBJ and Boyd LJ. 1953. Oral Treatment of Pernicious Anemia with Small Doses of Vitamin B12 Combined with Mucinous Materials Derived from the Hog Stomach. Blood. 8(10): 867–892.

Gottlieb C, Lau K-S, Wasserman LR and Herbert V. 1965. Rapid Charcoal Assay for Intrinsic Factor (IF), Gastric Juice Unsaturated B12 Binding Capacity, Antibody to IF, and Serum Unsaturated B12 Binding Capacity. Blood. 25(6): 875–884.

Grasbeck R. 2006. Imerslund-Grasbeck syndrome (selective vitamin B(12) malabsorption with proteinuria). Orphanet Journal of Rare Diseases. 1: 17.

Gräsbeck R. 2013. Hooked to vitamin B12 since 1955: a historical perspective. Biochimie. 95(5): 970–975.

Halbrook ER, Cords F, Winter AR and Sutton TS. 1950. Vitamin B12 production by microorganisms isolated from poultry house litter and droppings. J Nutr. 41(4): 555–563.

Hall CA and Finkler AE. 1965. The Dynamics of Transcobalamin Ii. A Vitamin B12 Binding Substance in Plasma. J Lab Clin Med. 65: 459–468.

Hardlei TF, Mørkbak AL, Bor MV, Bailey LB, Hvas A-M and Nexo E. 2010. Assessment of vitamin B(12) absorption based on the accumulation of orally administered cyanocobalamin on transcobalamin. Clinical Chemistry. 56(3): 432–436.

Helliwell KE, Wheeler GL, Leptos KC, Goldstein RE and Smith AG. 2011. Insights into the evolution of vitamin B12 auxotrophy from sequenced algal genomes. Mol Biol Evol. 28(10): 2921–2933.

Herbert V. 1968. Diagnostic and Prognostic Values of Measurement of Serum Vitamin B12-Binding Proteins. Blood. 32(2): 305–312.

Herbert V. 1994. Staging vitamin B-12 (cobalamin) status in vegetarians. Am J Clin Nutr. 59(5 Suppl): 1213s–1222s.

Herbert V, Fong W, Gulle V and Stopler T. 1990. Low holotranscobalamin II is the earliest serum marker for subnormal vitamin B12 (cobalamin) absorption in patients with AIDS. American Journal of Hematology. 34(2): 132–139.

Herrmann W and Obeid R. 2013. Utility and limitations of biochemical markers of vitamin B12 deficiency. European Journal of Clinical Investigation. 43(3): 231–237.

Hertz H, Kristensen HP and Hoff-Jorgensen E. 1964. Studies on vitamin B12 retention. Comparison of retention following intramuscular injection of cyanocobalamin and hydroxocobalamin. Scand J Haematol. 1: 5–15.

Herzlich B and Herbert V. 1988. Depletion of serum holotranscobalamin II. An early sign of negative vitamin B12 balance. Laboratory investigation; A Journal of Technical Methods and Pathology. 58(3): 332–337.

Heyssel RM, Bozian RC, Darby WJ and Bell MC. 1966. Vitamin B12 turnover in man. The assimilation of vitamin B12 from natural foodstuff by man and estimates of minimal daily dietary requirements. Am J Clin Nutr. 18(3): 176–184.

Hodgkin DG, Pickworth J, Robertson JH, Trueblood KN, Prosen RJ and White JG. 1955. The crystal structure of the hexacarboxylic acid derived from B12 and the molecular structure of the vitamin. Nature. 176(4477): 325–328.

Houle SK, Kolber MR and Chuck AW. 2014. Should vitamin B12 tablets be included in more Canadian drug formularies? An economic model of the cost-saving potential from increased utilisation of oral versus intramuscular vitamin B12 maintenance therapy for Alberta seniors. BMJ open. 4(5): e004501.

Howard JAK. 2003. Dorothy Hodgkin and her contributions to biochemistry. Nature Reviews Molecular Cell Biology. 4: 891–896.

Hvas A-M, Morkbak AL, Hardlei TF and Nexo E. 2011. The vitamin B12 absorption test, CobaSorb, identifies patients not requiring vitamin B12 injection therapy. Scandinavian Journal of Clinical and Laboratory Investigation. 71(5): 432–438.

Hvas A-M, Morkbak AL and Nexo E. 2007. Plasma holotranscobalamin compared with plasma cobalamins for assessment of vitamin B12 absorption; optimisation of a non-radioactive vitamin B12 absorption test (CobaSorb). Clinica Chimica Acta; International Journal of Clinical Chemistry. 376(1-2): 150–154.

INOXPA. 2015. INOXPA—Fermenter. In: http: //www.inoxpa.com/uploads/producte/Fermentador/Fermenter-INOXPA.jpg, editor. http: //wwwinoxpacom/uploads/producte/Fermentador/Fermenter-INOXPAjpg. http: //www.inoxpa.com/uploads/producte/Fermentador/Fermenter-INOXPA.jpg.

Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. 1998. Dietary Reference

Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline: The National Academies Press.
Jarcho S and Brown G. 1977. Medicine and Health Care. New York: Ayer Co Pub. 398 p.
Johnson RR, Bentley OG and Moxon AL. 1956. Synthesis *in vitro* and *in vivo* of Co60 containing vitamin B12-active substances by rumen microorganisms. J Biol Chem. 218(1): 379–390.
Kanazawa S, Herbert V, Herzlich B, Drivas G and Manusselis C. 1983. Removal of cobalamin analogue in bile by enterohepatic circulation of vitamin B12. Lancet. 1(8326 Pt 1): 707–708.
Karmi O, Zayed A, Baraghethi S, Qadi M and Ghanem R. 2011. Measurement of vitamin B12 concentration: A review on the available methods. The IIOAB Journal. 2(2): 23–32.
Kim HI and Hyung WJ. 2011. Oral vitamin B12 therapy after total gastrectomy. Annals of surgical oncology 18 Suppl 3: 199.
Kolber MR and Houle SK. 2014. Oral vitamin B12: a cost-effective alternative. Canadian family physician Medecin de famille canadien. 60(2): 111–112.
Kuemmerle SC, Boltinghouse GL, Delby SM, Lane TL and Simondsen RP. 1992. Automated assay of vitamin B-12 by the Abbott IMx analyzer. Clinical Chemistry. 38(10): 2073–2077.
Kumar N, Boes CJ and Samuels MA. 2006. Liver therapy in anemia: a motion picture by William P. Murphy. Blood. 107(12): 4970.
Kwong JC, Carr D, Dhalla IA, Tom-Kun D and Upshur RE. 2005. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. BMC family Practice. 6(1): 8.
Lakso HA, Appelblad P and Schneede J. 2008. Quantification of methylmalonic acid in human plasma with hydrophilic interaction liquid chromatography separation and mass spectrometric detection. Clinical Chemistry. 54(12): 2028–2035.
Langan RC and Zawistoski KJ. 2011. Update on vitamin B12 deficiency. American Family Physician. 83(12): 1425–1430.
Lichtheim L. 1887. Zur Kenntnis der perniziösen Anämie. Schweizerische Medizinische Wochenschrift 34.
Lindemans J, Schoester M and van Kapel J. 1983. Application of a simple immunoadsorption assay for the measurement of saturated and unsaturated transcobalamin II and R-binders. Clinica Chimica Acta; International Journal of Clinical Chemistry. 132(1): 53–61.
Markle HV. 1996. Cobalamin. Critical Reviews in Clinical Laboratory Sciences. 33(4): 247–356.
Masucci L and Goeree R. 2013. Vitamin B12 intramuscular injections versus oral supplements: a budget impact analysis. Ontario health technology assessment series. 13(24): 1–24.
McIntyre PA, Hahn R, Masters JM and Krevans JR. 1960. Treatment of pernicious anemia with orally administered cyanocobalamin (vitamin b12). Archives of Internal Medicine. 106(2): 280–292.
Mervyn L and Smith EL. 1964. The biochemistry of vitamin B12 fermentation. Progress in Industrial Microbiology. 5: 151–201.
Minot GR and Murphy WP. 1926. Treatment of pernicious anemia by a special diet. Jama. 87(7): 470–476.
Mollin DL. 1950. Treatment of pernicious anaemia with parenteral liver extract; a review of 51 patients between 1940 and 1948. Lancet 1(6615): 1064–1068.
Molloy AM and Scott JM. 1997. Microbiological assay for serum, plasma, and red cell folate using cryopreserved, microtiter plate method. Methods in Enzymology. 281: 43–53.
Moore SJ, Lawrence AD, Biedendieck R, Deery E, Frank S, Howard MJ, Rigby SEJ and Warren MJ. 2013. Elucidation of the anaerobic pathway for the corrin component of cobalamin (vitamin B12). Proceedings of the National Academy of Sciences. 110(37): 14906–14911.
Moridani M and Ben-Poorat S. 2006. Laboratory Investigation of Vitamin B12 Deficiency. Lab Medicine. 37(3): 166–174.
Murphy WP. 1934. Nobel Lecture: Pernicious Anemia. Stockholm: Nobelprize.org. Nobel Media AB 2014.
Murphy WP. 2006. Liver therapy in anemia: a motion picture by William P. Murphy. Supplemental materials for: Kumar et al, Blood, Volume 107, Issue 12,4970: http: //bloodjournal.hematologylibrary.org/content/107/12/4970.1/suppl/DC1. Washington: Blood. Journal of The American Society of Hematology.
Nexo E and Hoffmann-Lucke E. 2011. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. Am J Clin Nutr. 94(1): 359s–365s.

Nichols HJ. 1911. Salvarsan and sodium cacodylate. Journal of the American Medical Association. LVI(7): 492–495.
Nielsen MJ, Rasmussen MR, Andersen CB, Nexo E and Moestrup SK. 2012. Vitamin B12 transport from food to the body's cells—a sophisticated, multistep pathway. Nat Rev Gastroenterol Hepatol. 9(6): 345–354.
Nilsson M, Norberg B, Hultdin J, Sandstrom H, Westman G and Lokk J. 2005. Medical intelligence in Sweden. Vitamin B12: oral compared with parenteral? Postgraduate Medical Journal. 81(953): 191–193.
O'Broin S and Kelleher B. 1992. Microbiological assay on microtitre plates of folate in serum and red cells. Journal of Clinical Pathology. 45(4): 344–347.
O'Sullivan JJ, Leeming RJ, Lynch SS and Pollock A. 1992. Radioimmunoassay that measures serum vitamin B12. Journal of Clinical Pathology. 45(4): 328–331.
Obeid R, Morkbak AL, Munz W, Nexo E and Herrmann W. 2006. The cobalamin-binding proteins transcobalamin and haptocorrin in maternal and cord blood sera at birth. Clinical Chemistry. 52(2): 263–269.
Okuda K. 1999. Discovery of vitamin B12 in the liver and its absorption factor in the stomach: a historical review. J Gastroenterol Hepatol. 14(4): 301–308.
Osler W. 1915. The principles and practice of medicine. New York: D. Appleton and Company. 1225 p.
Palmer WC, Crozier JA and Petrucelli OM. 2012. 79-year-old woman with forgetfulness. Mayo Clinic Proceedings. 87(4): 408–411.
Pearce JMS. 2004. Thomas Addison (1793–1860). Journal of the Royal Society of Medicine. 97(6): 297–300.
Quadros EV and Sequeira JM. 2013. Cellular Uptake of Cobalamin: Transcobalamin and the TCblR/CD320 Receptor. Biochimie. 95(5): 1008–1018.
Reid C. 1986. Hilbert-Courant. New York: Springer-Verlag. xiv, 547 p., 546 p. of plates p.
Reid C. 1996. Hilbert. New York: Copernicus. ix, 228 p. p.
Reisner EH, Jr., Weiner L, Schittone MT and Henck EA. 1955. Oral treatment of pernicious anemia with vitamin B12 without intrinsic factor. The New England Journal of Medicine. 253(12): 502–506.
Remacha AF, Sarda MP, Canals C, Queralto JM, Zapico E, Remacha J and Carrascosa C. 2014. Role of serum holotranscobalamin (holoTC) in the diagnosis of patients with low serum cobalamin. Comparison with methylmalonic acid and homocysteine. Annals of Hematology. 93(4): 565–569.
Rickes EL, Brink NG, Koniuszy FR, Wood TR and Folkers K. 1948. Crystalline Vitamin B12. Science (New York, NY). 107(2781): 396–397.
Riedmann C, Ma Y, Melikishvili M, Godfrey S, Zhang Z, Chen K, Rouchka E and Fondufe-Mittendorf Y. 2015. Inorganic Arsenic-induced cellular transformation is coupled with genome wide changes in chromatin structure, transcriptome and splicing patterns. BMC Genomics. 16(1): 212.
Riethmiller S. 2005. From Atoxyl to Salvarsan: searching for the magic bullet. Chemotherapy. 51(5): 234–242.
Risch M, Meier DW, Sakem B, Medina Escobar P, Risch C, Nydegger U and Risch L. 2015. Vitamin B12 and folate levels in healthy Swiss senior citizens: a prospective study evaluating reference intervals and decision limits. BMC Geriatrics. 15: 82.
Robscheit-Robbins FS and Whipple GH. 1925. BLOOD REGENERATION IN SEVERE ANEMIA: II. Favorable Influence of Liver, Heart and Skeletal Muscle in Diet. American Journal of Physiology—Legacy Content. 72(3): 408–418.
Ross GI. 1952. Vitamin B12 assay in body fluids using Euglena gracilis. Journal of Clinical Pathology. 5(3): 250–256.
Ross GI, Mollin DL, Cox EV and Ungley CC. 1954. Hematologic responses and concentration of vitamin B12 in serum and urine following oral administration of vitamin B12 without intrinsic factor. Blood. 9(5): 473–488.
Roth JR, Lawrence JG and Bobik TA. 1996. Cobalamin (coenzyme B12): synthesis and biological significance. Annu Rev Microbiol. 50: 137–181.

Russell JSR, Batten FE and Collier J. 1900. Subacute combined degeneration of the spinal cord. Brain. 23(1): 39–110.
Santander PJ, Roessner CA, Stolowich NJ, Holderman MT and Scott AI. 1997. How corrinoids are synthesized without oxygen: nature's first pathway to vitamin B12. Chem Biol. 4(9): 659–666.
Schilling RF. 1953. Intrinsic factor studies II. The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B12. The Journal of Laboratory and Clinical Medicine. 42(6): 860–866.
Schjonsby H. 1989. Vitamin B12 absorption and malabsorption. Gut. 30(12): 1686–1691.
Schneede J and Ueland PM. 1993. Automated assay of methylmalonic acid in serum and urine by derivatization with 1-pyrenyldiazomethane, liquid chromatography, and fluorescence detection. Clinical Chemistry. 39(3): 392–399.
Schneede J and Ueland PM. 1995. Application of capillary electrophoresis with laser-induced fluorescence detection for routine determination of methylmalonic acid in human serum. Analytical Chemistry. 67(5): 812–819.
Schultzer P. 1934. Intramuscular Injections of Liver Extract for Initial and Maintenance Treatment of Pernicious Anemia. Acta medica Scandinavica. 82(5-6): 393–418.
Schwartz M, Lous P and Meulengracht E. 1959. [Vitamin B12 absorption in pernicious anemia; studies on the treatment-induced deficiency of vitamin B12 absorption after protracted therapy with some new combination preparations]. Ugeskr Laeger 121(10): 353–358.
Scott JM. 1997. Bioavailability of vitamin B12. Eur J Clin Nutr. 51 Suppl 1: S49–53.
Selhub J, Bagley LC, Miller J and Rosenberg IH. 2000. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr. 71(2): 614S–620S.
Shinton NK. 1961. Oral Treatment of Pernicious Anaemia with Vitamin-B(12)-Peptide. British Medical Journal. 1(5239): 1579–1582.
Shive W. 2002. Karl August Folkers 1906–1997. Biographical Memoirs. Washington D.C.: National Academies Press. p 101–115.
Shorb MS. 1947a. Unidentified essential growth factors for Lactobacillus lactis found in refined liver extracts and in certain natural materials. J Bacteriol. 53(5): 669.
Shorb MS. 1947b. Unidentified growth factors for Lactobacillus lactis in refined liver extracts. J Biol Chem 169(2): 455.
Shorb MS. 1948. Activity of Vitamin B12 for the Growth of Lactobacillus lactis. Science (New York, NY). 107(2781): 397–398.
Sinclair L. 2008. Recognizing, treating and understanding pernicious anaemia. Journal of the Royal Society of Medicine. 101(5): 262–264.
Skouby AP. 1966. Retention and distribution of B12 activity, and requirement for B12, following parenteral administration of hydroxocobalamin (Vibeden). Acta Medica Scandinavica. 180(1): 95–105.
Sørensen ST. 1874. Tællinger af blodlegemer i 3 tilfælde af excessiv oligocythaemi. Hospitals Tidende. 1: 513–521.
Spies TD, Stone RE, and et al. 1949. Vitamin B12 by mouth in pernicious and nutritional macrocytic anaemia and sprue. Lancet. 2(6576): 454–456.
Stabler SP. 2013. Vitamin B12 Deficiency. New England Journal of Medicine. 368(2): 149–160.
Stabler SP, Marcell PD, Podell ER, Allen RH and Lindenbaum J. 1986. Assay of methylmalonic acid in the serum of patients with cobalamin deficiency using capillary gas chromatography-mass spectrometry. The Journal of Clinical Investigation. 77(5): 1606–1612.
Stokstad ELR, Jukes TH, Pierce J, Page AC and Franklin AL. 1949. THE MULTIPLE NATURE OF THE ANIMAL PROTEIN FACTOR. Journal of Biological Chemistry. 180(2): 647–654.
Taneja S, Bhandari N, Strand TA, Sommerfelt H, Refsum H, Ueland PM, Schneede J, Bahl R and Bhan MK. 2007. Cobalamin and folate status in infants and young children in a low-to-middle income community in India. Am J Clin Nutr. 86(5): 1302–1309.
Teplitsky V, Huminer D, Zoldan J, Pitlik S, Shohat M and Mittelman M. 2003. Hereditary partial transcobalamin II deficiency with neurologic, mental and hematologic abnormalities in children and adults. The Israel Medical Association Journal : IMAJ. 5(12): 868–872.
Tobin DJ and Cargnello JA. 1993. Partial reversal of canities in a 22-year-old normal chinese male. Archives of Dermatology. 129(6): 789–791.

Ulleland M, Eilertsen I, Quadros EV, Rothenberg SP, Fedosov SN, Sundrehagen E and Orning L. 2002. Direct assay for cobalamin bound to transcobalamin (holo-transcobalamin) in serum. Clinical Chemistry. 48(3): 526–532.

Ungley CC. 1950a. Absorption of vitamin B12 in pernicious anaemia. I. Oral administration without a source of intrinsic factor. British Medical Journal. 2(4685): 905–908.

Ungley CC. 1950b. Absorption of vitamin B12 in pernicious anemia. II. Oral administration with normal gastric juice. British Medical Journal. 2(4685): 908–911.

Ungley CC. 1950c. Absorption of vitamin B12 in pernicious anemia. IV. Administration into buccal cavity, into washed segment of intestine, or after partial sterilization of bowel. British Medical Journal. 2(4685): 915–919.

Ungley CC. 1955. The chemotherapeutic action of vitamin B12. In: Harris RS, Marian GF, and Thimann KV, editors. VITAMINS AND HORMONES. New York: Academic Press. pp. 139–213.

Ungley CC and Childs GA. 1950. Absorption of vitamin B12 in pernicious anemia. III. Failure of fresh milk or concentrated whey to function as Castle's intrinsic factor or to potentiate the action of orally administered vitamin B12. British Medical Journal. 2(4685): 911–915.

van Walraven C, Austin P and Naylor CD. 2001a. Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills? Canadian Family Physician Medecin de Famille Canadien. 47: 79–86.

van Walraven CG, Austin P and Naylor CD. 2001b. Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills? Canadian Family Physician. 47: 79–86.

Vidal-Alaball J, Butler CC and Potter CC. 2006. Comparing costs of intramuscular and oral vitamin B12 administration in primary care: a cost-minimization analysis. The European Journal of General Practice. 12(4): 169–173.

Vogeser M and Lorenzl S. 2007. Comparison of automated assays for the determination of vitamin B12 in serum. Clinical Biochemistry. 40(16-17): 1342–1345.

Vora VC. 1956. Vitamin B12—Its chemistry, production & assay. J Sci Industr Res. 15A: 552–561.

Wagner AF and Folkers K. 1963. Vitamin B12. In: Florkin M, and Stotz EH, editors. Comprehensive Biochemistry Water-Soluble Vitamins, Hormones, Antibiotics. 1 ed. New York: Elsevier. pp. 103–115.

Waife SO, Jansen CJ, Jr., Crabtree RE, Grinnan EL and Fouts PJ. 1963. Oral vitamin B12 without intrinsic factor in the treatment of pernicious anemia. Annals of internal medicine 58: 810–817.

Watanabe F. 2007. Vitamin B12 sources and bioavailability. Exp Biol Med (Maywood). 232(10): 1266–1274.

Weber FP. 1932. An old Case of Pernicious Anæmia. Proceedings of the Royal Society of Medicine. 25(6): 800–801.

Whipple GH, Robscheit FS and Hooper CW. 1920. BLOOD REGENERATION FOLLOWING SIMPLE ANEMIA: IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets. American Journal of Physiology—Legacy Content. 53(2): 236–262.

Wills L. 1948. Pernicious anemia, nutritional macrocytic anemia, and tropical sprue. Blood. 3(1): 36–56.

Windelberg A, Arseth O, Kvalheim G and Ueland PM. 2005. Automated assay for the determination of methylmalonic acid, total homocysteine, and related amino acids in human serum or plasma by means of methylchloroformate derivatization and gas chromatography-mass spectrometry. Clinical Chemistry. 51(11): 2103–2109.

Woodward RB. 1973. The total synthesis of vitamin B 12. Pure Appl Chem. 33(1): 145–177.

Xia W, Chen W, Peng W-f and Li K-t. 2015. Industrial vitamin B12 production by Pseudomonas denitrificans using maltose syrup and corn steep liquor as the cost-effective fermentation substrates. Bioprocess Biosyst Eng. 38(6): 1065–1073.

Yetley EA, Pfeiffer CM, Phinney KW, Bailey RL, Blackmore S, Bock JL, Brody LC, Carmel R, Curtin LR, Durazo-Arvizu RA et al. 2011. Biomarkers of vitamin B-12 status in NHANES: a roundtable summary. Am J Clin Nutr. 94(1): 313s–321s.

Yin L and Bauer CE. 2013. Controlling the delicate balance of tetrapyrrole biosynthesis. Philosophical Transactions of the Royal Society of London B: Biological Sciences. 368(1622)

Milestones in the Discovery of Pernicious Anemia and its Treatment

Adams J. F. Ross S.K. , Mervyn L. , Boddy K. and King P. . 1971. Absorption of cyanocobalamin, coenzyme B 12, methylcobalamin, and hydroxocobalamin at different dose levels. Scandinavian journal of Gastroenterology. 6 (3): 249252.

Addison T. 1849. Chronic suprarenal insufficiency, usually due to tuberculosis of suprarenal Capsule. London Medical Gazette. 43: 517518.

23 gren A. 1964. Farmacevtiska specialiteten Behepan tabletter 1 mg, file number 7399. Stockholm: Kungliga Medicinalstyrelsen (Swedish Medical Products Agency) p 120.

Ahrens R. A. 1993. Mary Shaw Shorb (1907-1990). J Nutr. 123 (5): 791796.

Anonymous . 1965. Research News. Section II Development of the institutes research activities. The institute and research on pernicious anemia. Research News Ann Arbor: Office of Research Administration, the University of Michigan. Ann Arbor. pp. 1519.

Ardeman, S. Chanarin I. and Doyle J.C. . 1964. Studies on secretion of gastric intrinsic factor in man. British Medical Journal. 2 (5409): 600603.

Banerjee R. 2006. B12 Trafficking in Mammals: A Case for Coenzyme Escort Service. ACS Chemical Biology. 1 (3): 149159.

Banerjee R. , Gherasim C. and Padovani D. . 2009. The tinker, tailor, soldier in intracellular B12 trafficking. Current Opinion in Chemical Biology. 13 (4): 484491.

Banting F.G. , Best C.H. , Collip J.B. , Campbell W.R. and Fletcher A.A. , . 1991. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. 1922. CMAJ: Canadian Medical Association Journal. 145(10): 12811286.

Battersby A.R. . 1994. How nature builds the pigments of life: the conquest of vitamin B12. Science (New York, NY). 264(5165): 15511557.

Berlin H. , Berlin R. and Brante G. . 1965. Peroral Treatment of Pernicious Anemia with High Doses of Vitamin B12 without Intrinsic Factor. Lakartidningen. 62: 773781.

Berlin H. , Berlin R. and Brante G. . 1966. Crude or refined intrinsic factor in preparations for the oral treatment of pernicious anaemia. Scandinavian Journal of Haematology. 3 (3): 236244.

Berlin, H. , R. Berlin and G. Brante . 1968a. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Medica Scandinavica. 184 (4): 247258.

Berlin H. , Berlin R. and G. Brante . 1968b. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Medica Scandinavica. 184: 247258.

Berlin, H. , Berlin R. , Brante G. and Sjoberg S. G. . 1958. Studies on intrinsic factor and pernicious anemia. I. Oral uptake of vitamin B12 in pernicious anemia with increasing doses of an intrinsic factor concentrate. Scand J Clin Lab Invest. 10 (3): 278282.

Berlin R. , Berlin H. and Brante G. . 1961. The absorption of IF-bound and free B12 in various clinical conditions. Second European Symposium on Vitamin B12 and Intrinsic Factor. Hamburg: Enke Verlag Stuttgart.

Bethell F. H. , Castle W.B. , Conley C.L. and London I.M. . 1959. Present status of treatment of pernicious anemia. J Am Med Assoc. 171: 20922094.

Biermer A.M. 1872. ber eine eigenthmliche Form von progressiver, pernicioser Anaemie. Correspondenz-Blatt fr Schweizer Aerzte. 2 (1): 1517.

Bilwani F. , Adil S.N. , Sheikh U. , Humera A. and Khurshid M. . 2005. Anaphylactic reaction after intramuscular injection of cyanocobalamin (vitamin B12): a case report. JPMA The Journal of the Pakistan Medical Association. 55 (5): 217219.

Birn H. . 2006. The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins. American Journal of Physiology Renal Physiology. 291(1): F2236-F22-36.

Blackburn E.K. , Burke J. , Roseman C. and Wayne E.J. . 1952. Comparison of liver extract and vitamin B12 (cyanocobalamin) in maintenance treatment of pernicious anaemia. British Medical Journal. 2 (4778): 245248.

Blackburn E.K. , Cohen H. and Wilson G.M. . 1955. Oral treatment of pernicious anaemia with a combined vitamin B12 and intrinsic factor preparation. British Medical Journal. 2 (4937): 461463.

Boddy K. , King P. , Mervyn L. , Macleod A. and Adams J.F. . 1968. Retention of cyanocobalamin, hydroxocobalamin, and coenzyme B12 after parenteral administration. Lancet 2 (7570): 710712.

Brady J. , Wilson L. , McGregor L. , Valente E. and Orning L. . 2008. Active B12: a rapid, automated assay for holotranscobalamin on the Abbott AxSYM analyzer. Clinical Chemistry. 54 (3): 567573.

Brink C. , Hodgkin D.C. , Lindsey J. , Pickworth J. , Robertson J.R. and White J.G. . 1954. X-ray crystallographic evidence on the structure of vitamin B12. Nature. 174 (4443): 11691171.

24 Brody E.A. , Estren S. and Wasserman L.R. . 1959. Treatment of pernicious anemia by oral administration of vitamin B12 without added intrinsic factor. The New England Journal of Medicine. 260 (8): 361367.

Carmel R. 1985. The distribution of endogenous cobalamin among cobalamin-binding proteins in the blood in normal and abnormal states. Am J Clin Nutr. 41 (4): 713719.

Carmel R. 2011. Biomarkers of cobalamin (vitamin B-12) status in the epidemiologic setting: a critical overview of context, applications, and performance characteristics of cobalamin, methylmalonic acid, and holotranscobalamin II. Am J Clin Nutr. 94 (1): 348s358s.

Castle W. B. 1929. The Aetiological Relationship of Achylia Gastrica to Pernicious Anaemia. Proc R Soc Med. 22 (9): 12141216.

Castle W. B. 1953. Development of knowledge concerning the gastric intrinsic factor and its relation to pernicious anemia. The New England Journal of Medicine. 249 (15): 603614.

Chalmers J. N. and Hall Z.M. . 1954. Treatment of pernicious anaemia with oral vitamin B12 without known source of intrinsic factor. British Medical Journal. 1 (4872): 11791181.

Chalmers J. N. and Shinton N.K. . 1958. Absorption of orally administered vitamin B12 in pernicious anaemia. Lancet. 2 (7060): 12981302.

Clardy-James S. , Chepurny O.G. , Leech C.A. , Holz G.G. and Doyle R.P. . 2013. Synthesis, characterization and pharmacodynamics of vitamin-B12 -conjugated glucagon-like Peptide-1. Chem Med Chem. 8 (4): 582586.

Cohnheim, J.F. 1876. Erkrankungen des Knochenmarkes bei perniziser Anmie. Virchows Archiv fr Pathologische Anatomie und Physiologie und fr Klinische Medizin. 68: 291293.

Combe J.S. . 1824. History of a case of anaemia, Transactions of the Medico-Chirurgical Society of Edinburgh. 1(August 2.): 194204.

Combs G.F. . 2008. Chapter 17: Vitamin B12. The vitamins: fundamental aspects in nutrition and health. 3rd ed. ed. Oxford: Academic. pp. 384385.

Conley C.L. and Krevans J.R. . 1955. New developments in the diagnosis and treatment of pernicious anemia. Annals of Internal Medicine. 43 (4): 758766.

Doscherholmen A. and Hagen P.S. . 1957. A dual mechanism of vitamin B12 plasma absorption. The Journal of clinical investigation 36 (11): 15511557.

Dunlop D.M. 1973. Medicines in our time. The Rock Carling Fellowship. London: Nuffield Provincial Hospitals Trust, pp. 112.

Ehrlich, P. 1880. ber Regeneration und Degeneration der rothen Blutscheiben bei Anmien. Berliner Klinische Wochenschrift. 117: 405.

Eichhorst H. . 1878. Die progressive pernizise Anmie: eine klinische und kritische Untersuchung. Leipzig: Veit & Comp. xi, 375 p., 373 leaves of plates.

Elliot C.M. 2008. Vitamin B : new research. New York, NY: Nova Biomedical Books. xiv, 234 p.-.
Ewing J. . 1901. Clinical pathology of the blood; a treatise on the general principles and special applications of hematology: Philadelphia, PA, Lea Brothers & Co. 489 p.
Fantes K.H. , Page J.E. , Parker L.F.J. and Smith E.L. . 1950. Crystalline Anti-Pernicious Anaemia Factor from Liver. Proceedings of the Royal Society of London B: Biological Sciences. 136 (885): 592609.
Fenwick S. 1880. On Atrophy of the Stomach and on the nervous affections of the digestive organs. J. & A. Churchill: London. 242 p.
Fyfe J.C. , Madsen M. , Hojrup P. , Christensen E.I. , Tanner S.M. , de la Chapelle A. , He Q. and Moestrup S.K. . 2004. The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless. Blood. 103 (5): 15731579.
Gaffney G.W. , Watkin D.M. and Chow B.F. . 1959. Vitamin B12 absorption: relationship between oral administration and urinary excretion of cobalt 60-labeled cyanocobalamin following a parenteral dose; study of doses of 2 to 250 mu g in 148 apparently health men 20 to 92 years old. J Lab Clin Med. 53 (4): 525534.
Gnsslen M. 1930. Ein Hochwirksamer. Injizierbarer Leberextrakt. Klin Wochenschr. 9 (45): 20992102.
Glass G.B.J. and Boyd L.J. . 1953. Oral Treatment of Pernicious Anemia with Small Doses of Vitamin B12 Combined with Mucinous Materials Derived from the Hog Stomach. Blood. 8 (10): 867892.
25 Gottlieb C. , Lau K.-S. , Wasserman L.R. and Herbert V. . 1965. Rapid Charcoal Assay for Intrinsic Factor (IF), Gastric Juice Unsaturated B12 Binding Capacity, Antibody to IF, and Serum Unsaturated B12 Binding Capacity. Blood. 25 (6): 875884.
Grasbeck R. 2006. Imerslund-Grasbeck syndrome (selective vitamin B(12) malabsorption with proteinuria). Orphanet Journal of Rare Diseases. 1: 17.
Grsbeck R. 2013. Hooked to vitamin B12 since 1955: a historical perspective. Biochimie. 95 (5): 970975.
Halbrook, E.R. , Cords F. , Winter A.R. and Sutton T.S. . 1950. Vitamin B12 production by microorganisms isolated from poultry house litter and droppings. J Nutr. 41 (4): 555563.
Hall, C.A. , and Finkler A.E. . 1965. The Dynamics of Transcobalamin Ii. A Vitamin B12 Binding Substance in Plasma. J Lab Clin Med. 65: 459468.
Hardlei T.F. , Morkbak A.L. , Bor M.V. , Bailey L.B. , Hvas A.-M. and Nexo E. . 2010. Assessment of vitamin B(12) absorption based on the accumulation of orally administered cyanocobalamin on transcobalamin. Clinical Chemistry. 56 (3): 432436.
Helliwell K.E. , Wheeler G.L. , Leptos K.C. , Goldstein R.E. and Smith A.G. . 2011. Insights into the evolution of vitamin B12 auxotrophy from sequenced algal genomes. Mol Biol Evol. 28 (10): 29212933.
Herbert V. 1968. Diagnostic and Prognostic Values of Measurement of Serum Vitamin B12-Binding Proteins. Blood. 32 (2): 305312.
Herbert V. 1994. Staging vitamin B-12 (cobalamin) status in vegetarians. Am J Clin Nutr. 59 (5 Suppl): 1213s1222s.
Herbert V. , Fong W. Gulle V. and Stopler T. . 1990. Low holotranscobalamin II is the earliest serum marker for subnormal vitamin B12 (cobalamin) absorption in patients with AIDS. American Journal of Hematology. 34 (2): 132139.
Herrmann W. and Obeid R. . 2013. Utility and limitations of biochemical markers of vitamin B12 deficiency. European Journal of Clinical Investigation. 43 (3): 231237.
Hertz H. , Kristensen H.P. and Hoff-Jorgensen E. . 1964. Studies on vitamin B12 retention. Comparison of retention following intramuscular injection of cyanocobalamin and hydroxocobalamin. Scand J Haematol. 1: 515.
Herzlich B. and Herbert V. . 1988. Depletion of serum holotranscobalamin II. An early sign of negative vitamin B12 balance. Laboratory investigation; A Journal of Technical Methods and Pathology 58 (3): 332337.
Heyssel R. M. , Bozian R.C. , Darby W.J. and Bell M.C. . 1966. Vitamin B12 turnover in man. The assimilation of vitamin B12 from natural foodstuff by man and estimates of minimal daily dietary requirements. Am J Clin Nutr. 18 (3): 176184.
Hodgkin D.G. , Pickworth J. , Robertson J.H. , Trueblood K.N. , Prosen R.J. , and White J.G. . 1955. The crystal structure of the hexacarboxylic acid derived from B12 and the molecular structure of the vitamin. Nature. 176 (4477): 325328.
Houle S.K. , Kolber M.R. and Chuck A.W. . 2014. Should vitamin B12 tablets be included in more Canadian drug formularies? An economic model of the cost-saving potential from increased utilisation of oral versus intramuscular vitamin B12 maintenance therapy for Alberta seniors. BMJ open. 4 (5): e004501.
Howard J.A.K. 2003. Dorothy Hodgkin and her contributions to biochemistry. Nature Reviews Molecular Cell Biology. 4: 891896.
Hvas A.-M. , Morkbak A.L. , Hardlei T.F. and Nexo E. . 2011. The vitamin B12 absorption test, CobaSorb, identifies patients not requiring vitamin B12 injection therapy. Scandinavian Journal of Clinical and Laboratory Investigation. 71 (5): 432438.
Hvas A.-M. , Morkbak A.L. and Nexo E. . 2007. Plasma holotranscobalamin compared with plasma cobalamins for assessment of vitamin B12 absorption; optimisation of a non-radioactive vitamin B12 absorption test (CobaSorb). Clinica Chimica Acta; International Journal of Clinical Chemistry. 376 (12): 150154.
INOXPA. 2015. INOXPAFermenter. In: http://www.inoxpa.com/uploads/producte/Fermentador/Fermenter-INOXPA.jpg, editor. http://wwwinoxpacom/uploads/producte/Fermentador/Fermenter-INOXPAjpg. http://www.inoxpa.com/uploads/producte/Fermentador/Fermenter-INOXPA.jpg.
Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. 1998. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline: The National Academies Press.
26 Jarcho S. and Brown G. . 1977. Medicine and Health Care. New York, NY: Ayer Co Pub. 398p.
Johnson R.R. , Bentley O.G. and Moxon A.L. . 1956. Synthesis in vitro and in vivo of Co60 containing vitamin B12-active substances by rumen microorganisms. J Biol Chem. 218(1): 379390.
Kanazawa S. , Herbert V. , Herzlich B. , Drivas G. and Manusselis C. . 1983. Removal of cobalamin analogue in bile by enterohepatic circulation of vitamin B12. Lancet. 1 (8326 Pt 1): 707708.
Karmi O. , Zayed A. , Baraghethi S. , Qadi M. and Ghanem R. . 2011. Measurement of vitamin B12 concentration: A review on the available methods. The IIOAB Journal. 2 (2): 2332.
Kim H.I. and Hyung W.J. . 2011. Oral vitamin B12 therapy after total gastrectomy. Annals of surgical oncology 18 (Suppl 3): 199.
Kolber M.R. and Houle S.K. . 2014. Oral vitamin B12: a cost-effective alternative. Canadian family physician Medecin de famille canadien. 60 (2): 111112.
Kuemmerle S.C. , Boltinghouse G.L. , Delby S.M. , Lane T.L. and Simondsen R.P. . 1992. Automated assay of vitamin B-12 by the Abbott IMx analyzer. Clinical Chemistry. 38 (10): 20732077.
Kumar N. , Boes C.J. and Samuels M.A. . 2006. Liver therapy in anemia: a motion picture by William P. Murphy. Blood. 107 (12): 4970.
Kwong J.C. , Carr D. , Dhalla I.A. , Tom-Kun D. and Upshur R.E. . 2005. Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. BMC family Practice. 6 (1): 8.
Lakso H. A. , Appelblad P. and Schneede J. . 2008. Quantification of methylmalonic acid in human plasma with hydrophilic interaction liquid chromatography separation and mass spectrometric detection. Clinical Chemistry. 54 (12): 20282035.
Langan R. C. , and Zawistoski K.J. . 2011. Update on vitamin B12 deficiency. American Family Physician. 83 (12): 14251430.
Lichtheim L. . 1887. Zur Kenntnis der pernizisen Anmie. Schweizerische Medizinische Wochenschrift 34.

Lindemans J. , Schoester M. and van Kapel J. . 1983. Application of a simple immunoadsorption assay for the measurement of saturated and unsaturated transcobalamin II and R-binders. Clinica Chimica Acta; International Journal of Clinical Chemistry. 132 (1): 5361.
Masucci L. and Goeree R. . 2013. Vitamin B12 intramuscular injections versus oral supplements: a budget impact analysis. Ontario health technology assessment series. 13(24): 124.
McIntyre P.A. , Hahn R. , Masters J.M. and Krevans J.R. . 1960. Treatment of pernicious anemia with orally administered cyanocobalamin (vitamin b12). Archives of Internal Medicine. 106 (2): 280292.
Mervyn L. and Smith E.L. . 1964. The biochemistry of vitamin B12 fermentation. Progress in Industrial Microbiology. 5: 151201.
Minot G.R. and Murphy W.P. . 1926. Treatment of pernicious anemia by a special diet. Jama. 87 (7): 470476.
Mollin D.L. 1950. Treatment of pernicious anaemia with parenteral liver extract; a review of 51 patients between 1940 and 1948. Lancet 1 (6615): 10641068.
Molloy A.M. and Scott J.M. . 1997. Microbiological assay for serum, plasma, and red cell folate using cryopreserved, microtiter plate method. Methods in Enzymology. 281: 4353.
Moore S.J. , Lawrence A.D. , Biedendieck R. , Deery E. , Frank S. , Howard M.J. , Rigby S.E.J. and Warren M.J. . 2013. Elucidation of the anaerobic pathway for the corrin component of cobalamin (vitamin B12). Proceedings of the National Academy of Sciences. 110 (37): 1490614911.
Moridani M. and Ben-Poorat S. . 2006. Laboratory Investigation of Vitamin B12 Deficiency. Lab Medicine. 37 (3): 166174.
Murphy W.P. . 1934. Nobel Lecture: Pernicious Anemia. Stockholm: Nobelprize.org. Nobel Media AB 2014.
Murphy W.P. . 2006. Liver therapy in anemia: a motion picture by P. William Murphy . Supplemental materials for: Kumar et al, Blood, Volume 107, Issue 12,4970: http: http:////bloodjournal. hematologylibrary.org/content/107/12/4970.1/suppl/DC1. Washington: Blood. Journal of The American Society of Hematology.
Nexo E. and Hoffmann-Lucke E. . 2011. Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility. Am J Clin Nutr. 94 (1): 359s365s.
27 Nichols H.J. . 1911. Salvarsan and sodium cacodylate. Journal of the American Medical Association. LVI(7): 492495.
Nielsen M.J. , Rasmussen M.R. , Andersen C.B. , Nexo E. and Moestrup S.K. . 2012. Vitamin B12 transport from food to the bodys cellsa sophisticated, multistep pathway. Nat Rev Gastroenterol Hepatol. 9 (6): 345354.
Nilsson M. , Norberg B. , Hultdin J. , Sandstrom H. , Westman G. and Lokk J. . 2005. Medical intelligence in Sweden. Vitamin B12: oral compared with parenteral? Postgraduate Medical Journal. 81 (953): 191193.
OBroin S. and Kelleher B. . 1992. Microbiological assay on microtitre plates of folate in serum and red cells. Journal of Clinical Pathology. 45 (4): 344347.
OSullivan J.J. , Leeming R.J. , Lynch S.S. and Pollock A. . 1992. Radioimmunoassay that measures serum vitamin B12. Journal of Clinical Pathology. 45 (4): 328331.
Obeid R. , Morkbak A. L. , Munz W. , Nexo E. and Herrmann W. . 2006. The cobalamin-binding proteins transcobalamin and haptocorrin in maternal and cord blood sera at birth. Clinical Chemistry. 52 (2): 263269.
Okuda K. 1999. Discovery of vitamin B12 in the liver and its absorption factor in the stomach: a historical review. J Gastroenterol Hepatol. 14 (4): 301308.
Osler W. 1915. The principles and practice of medicine. New York, NY: D. Appleton and Company. 1225 p.
Palmer W.C. , Crozier J.A. and Petrucelli O.M. . 2012. 79-year-old woman with forgetfulness. Mayo Clinic Proceedings. 87 (4): 408411.
Pearce, J.M.S. 2004. Thomas Addison (1793-1860). Journal of the Royal Society of Medicine. 97 (6): 297300.
Quadros E.V. , and Sequeira J.M. . 2013. Cellular Uptake of Cobalamin: Transcobalamin and the TCblR/CD320 Receptor. Biochimie. 95 (5): 10081018.
Reid C. 1986. Hilbert-Courant. New York: Springer-Verlag. xiv, 547 p., 546 p. of plates p.
Reid C. . 1986. Hilbert-Courant. New York, NY: Springer-Verlag. xiv, 547 p., 546 p. of plates p.
Reid, C. 1996. Hilbert, 228. New York, NY: Copernicus. ix.
Reisner E. H., Jr. , Weiner L. , Schittone M.T. and Henck E.A. . 1955. Oral treatment of pernicious anemia with vitamin B12 without intrinsic factor. The New England Journal of Medicine. 253 (12): 502506.
Remacha A.F. , Sarda M.P. , Canals C. , Queralto J.M. , Zapico E. , Remacha J. and Carrascosa C. . 2014. Role of serum holotranscobalamin (holoTC) in the diagnosis of patients with low serum cobalamin. Comparison with methylmalonic acid and homocysteine. Annals of Hematology. 93 (4): 565569.
Rickes E.L. , Brink N.G. , Koniuszy F.R. , Wood T.R. and Folkers K. . 1948. Crystalline Vitamin B12. Science (New York, NY). 107(2781): 396397.
Riedmann C. , Ma Y. , Melikishvili M. , Godfrey S. , Zhang Z. , Chen K. , Rouchka E. and Fondufe- Mittendorf Y. . 2015. Inorganic Arsenic-induced cellular transformation is coupled with genome wide changes in chromatin structure, transcriptome and splicing patterns. BMC Genomics. 16 (1): 212.
Riethmiller S. 2005. From Atoxyl to Salvarsan: searching for the magic bullet. Chemotherapy. 51 (5): 234242.
Risch M. , Meier D.W. , Sakem B. , Medina Escobar P. , Risch C. , Nydegger U. and Risch L. . 2015. Vitamin B12 and folate levels in healthy Swiss senior citizens: a prospective study evaluating reference intervals and decision limits. BMC Geriatrics. 15: 82.
Robscheit-Robbins F.S. and Whipple G.H. . 1925. BLOOD REGENERATION IN SEVERE ANEMIA: II. Favorable Influence of Liver, Heart and Skeletal Muscle in Diet. American Journal of PhysiologyLegacy Content. 72(3): 408418.
Ross G.I. 1952. Vitamin B12 assay in body fluids using Euglena gracilis. Journal of Clinical Pathology. 5 (3): 250256.
Ross G.I. , Mollin D.L. , Cox E.V. and Ungley C.C. . 1954. Hematologic responses and concentration of vitamin B12 in serum and urine following oral administration of vitamin B12 without intrinsic factor. Blood. 9 (5): 473488.
Roth J.R. , Lawrence J.G. and Bobik T.A. . 1996. Cobalamin (coenzyme B12): synthesis and biological significance. Annu Rev Microbiol. 50: 137181.
28 Russell J.S.R. , Batten F.E. and Collier J. . 1900. Subacute combined degeneration of the spinal cord. Brain. 23 (1): 39110.
Santander P.J. , Roessner C.A. , Stolowich N.J. , Holderman M.T. and Scott A.I. . 1997. How corrinoids are synthesized without oxygen: natures first pathway to vitamin B12. Chem Biol. 4 (9): 659666.
Schilling R.F. 1953. Intrinsic factor studies II. The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B12. The Journal of Laboratory and Clinical Medicine. 42 (6): 860866.
Schjonsby H. 1989. Vitamin B12 absorption and malabsorption. Gut. 30 (12): 16861691.
Schneede J. and Ueland P.M. . 1993. Automated assay of methylmalonic acid in serum and urine by derivatization with 1-pyrenyldiazomethane, liquid chromatography, and fluorescence detection. Clinical Chemistry. 39(3): 392399.
Schneede J. and Ueland P.M. . 1995. Application of capillary electrophoresis with laser-induced fluorescence detection for routine determination of methylmalonic acid in human serum. Analytical Chemistry. 67 (5): 812819.
Schultzer P. 1934. Intramuscular Injections of Liver Extract for Initial and Maintenance Treatment of Pernicious Anemia. Acta medica Scandinavica. 82 (56): 393418.

Schwartz M. , Lous P. and Meulengracht E. . 1959. Vitamin B12 absorption in pernicious anemia; studies on the treatment-induced deficiency of vitamin B12 absorption after protracted therapy with some new combination preparations. Ugeskr Laeger 121 (10): 353358.
Scott J.M. 1997. Bioavailability of vitamin B12. Eur J Clin Nutr. 51 (Suppl 1): S4953.
Selhub J. , Bagley L.C. , Miller J. and Rosenberg I.H. . 2000. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr. 71 (2): 614S620S.
Shinton N.K. 1961. Oral Treatment of Pernicious Anaemia with Vitamin-B(12)-Peptide. British Medical Journal. 1 (5239): 15791582.
Shive W. 2002. Karl August Folkers 19061997, 101115. Biographical Memoirs. Washington D.C.: National Academies Press.
Shorb M.S. 1947a. Unidentified essential growth factors for Lactobacillus lactis found in refined liver extracts and in certain natural materials. J Bacteriol. 53 (5): 669.
Shorb M.S. 1947b. Unidentified growth factors for Lactobacillus lactis in refined liver extracts. J Biol Chem 169 (2): 455.
Shorb M.S. . 1948. Activity of Vitamin B12 for the Growth of Lactobacillus lactis. Science (New York, NY). 107(2781): 397398.
Sinclair L. 2008. Recognizing, treating and understanding pernicious anaemia. Journal of the Royal Society of Medicine. 101 (5): 262264.
Skouby A.P. 1966. Retention and distribution of B12 activity, and requirement for B12, following parenteral administration of hydroxocobalamin (Vibeden). Acta Medica Scandinavica. 180 (1): 95105.
Sorensen, S.T. 1874. Tcllinger af blodlegemer i 3 tilfclde af excessiv oligocythaemi. Hospitals Tidende. 1: 513521.
Spies, T.D. , Stone R.E. , et al. 1949. Vitamin B12 by mouth in pernicious and nutritional macrocytic anaemia and sprue. Lancet. 2 (6576): 454456.
Stabler S.P. 2013. Vitamin B12 Deficiency. New England Journal of Medicine. 368 (2): 149160.
Stabler S.P. , Marcell P.D. , Podell E.R. , Allen R.H. and Lindenbaum J. . 1986. Assay of methylmalonic acid in the serum of patients with cobalamin deficiency using capillary gas chromatography-mass spectrometry. The Journal of Clinical Investigation. 77(5): 16061612.
Stokstad E.L.R. , Jukes T.H. , Pierce J. , Page A.C. and Franklin A.L. . 1949. THE MULTIPLE NATURE OF THE ANIMAL PROTEIN FACTOR. Journal of Biological Chemistry. 180 (2): 647654.
Taneja S. , Bhandari N. , Strand T.A. , Sommerfelt H. , Refsum H. , Ueland P.M. , Schneede J. , Bahl R. and Bhan M.K. . 2007. Cobalamin and folate status in infants and young children in a low-to-middle income community in India. Am J Clin Nutr. 86 (5): 13021309.
Teplitsky V. , Huminer D. , Zoldan J. , Pitlik S. , Shohat M. and Mittelman M. . 2003. Hereditary partial transcobalamin II deficiency with neurologic, mental and hematologic abnormalities in children and adults. The Israel Medical Association Journal : IMAJ. 5 (12): 868872.
Tobin, D.J. and Cargnello J.A. . 1993. Partial reversal of canities in a 22-year-old normal chinese male. Archives of Dermatology. 129 (6): 789791.
29 Ulleland M. , Eilertsen I. , Quadros E.V. , Rothenberg S.P. , Fedosov S.N. , Sundrehagen E. , and Orning L. . 2002. Direct assay for cobalamin bound to transcobalamin (holo-transcobalamin) in serum. Clinical Chemistry. 48 (3): 526532.
Ungley C.C. 1950a. Absorption of vitamin B12 in pernicious anaemia. I. Oral administration without a source of intrinsic factor. British Medical Journal. 2 (4685): 905908.
Ungley C.C. 1950b. Absorption of vitamin B12 in pernicious anemia. II. Oral administration with normal gastric juice. British Medical Journal. 2 (4685): 908911.
Ungley, C.C. 1950c. Absorption of vitamin B12 in pernicious anemia. IV. Administration into buccal cavity, into washed segment of intestine, or after partial sterilization of bowel. British Medical Journal. 2 (4685): 915919.
Ungley, C.C. 1955. The chemotherapeutic action of vitamin B12. In: R.S. Harris , G.F. Marian and K.V. Thimann , editors. Vitamins And Hormones. New York, NY: Academic Press. pp. 139213.
Ungley, C.C. and Childs G.A. . 1950. Absorption of vitamin B12 in pernicious anemia. III. Failure of fresh milk or concentrated whey to function as Castles intrinsic factor or to potentiate the action of orally administered vitamin B12. British Medical Journal. 2 (4685): 911915.
van Walraven C. , Austin P. and Naylor C. D. . 2001a. Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills? Canadian Family Physician Medecin de Famille Canadien. 47: 7986.
van Walraven C.G. , Austin P. and Naylor C.D. . 2001b. Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills? Canadian Family Physician. 47: 7986.
Vidal-Alaball J. , Butler C.C. , and Potter C. C. . 2006. Comparing costs of intramuscular and oral vitamin B12 administration in primary care: a cost-minimization analysis. The European Journal of General Practice. 12 (4): 169173.
Vogeser M. and Lorenzl S. . 2007. Comparison of automated assays for the determination of vitamin B12 in serum. Clinical Biochemistry. 40 (1617): 13421345.
Vora V.C. . 1956. Vitamin B12Its chemistry, production & assay. J Sci Industr Res. 15A: 552561.
Wagner A.F. and Folkers K. . 1963. Vitamin B12. In: Florkin M. , and Stotz E.H. , editors. Comprehensive Biochemistry Water-Soluble Vitamins, Hormones, Antibiotics. 1 ed. New York, NY: Elsevier. pp. 103115.
Waife S.O. , Jansen C.J., Jr. , Crabtree R.E. , Grinnan E. L. and Fouts P.J. . 1963. Oral vitamin B12 without intrinsic factor in the treatment of pernicious anemia. Annals of internal medicine 58: 810817.
Watanabe F. 2007. Vitamin B12 sources and bioavailability. Exp Biol Med (Maywood). 232 (10): 12661274.
Weber F. P. 1932. An old Case of Pernicious Anemia. Proceedings of the Royal Society of Medicine. 25 (6): 800801.
Whipple G.H. , Robscheit F.S. and Hooper C.W. . 1920. BLOOD REGENERATION FOLLOWING SIMPLE ANEMIA: IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets. American Journal of PhysiologyLegacy Content. 53(2): 236262.
Wills L. 1948. Pernicious anemia, nutritional macrocytic anemia, and tropical sprue. Blood. 3 (1): 3656.
Windelberg A. , Arseth O. , Kvalheim G. and Ueland P.M. . 2005. Automated assay for the determination of methylmalonic acid, total homocysteine, and related amino acids in human serum or plasma by means of methylchloroformate derivatization and gas chromatography-mass spectrometry. Clinical Chemistry. 51 (11): 21032109.
Woodward R.B. 1973. The total synthesis of vitamin B 12. Pure Appl Chem. 33 (1): 145177.
Xia W. , Chen W. , W-f Peng and K-t. L.i. . 2015. Industrial vitamin B12 production by Pseudomonas denitrificans using maltose syrup and corn steep liquor as the cost-effective fermentation substrates. Bioprocess Biosyst Eng. 38 (6): 10651073.
Yetley E.A. , Pfeiffer C.M. , Phinney K.W. , Bailey R.L. , Blackmore S. , Bock J.L. , Brody L.C. , Carmel R. , Curtin L.R. , Durazo-Arvizu R.A. , et al. 2011. Biomarkers of vitamin B-12 status in NHANES: a roundtable summary. Am J Clin Nutr. 94 (1): 313s321s.
Yin L. and Bauer C. E. . 2013. Controlling the delicate balance of tetrapyrrole biosynthesis. Philosophical Transactions of the Royal Society of London B: Biological Sciences. 368 (1622).

Nutritional and Biochemical Aspects of Cobalamin Throughout Life

Aimone-Gastin, I. , Pierson H. , Jeandel C. , J. P. Bronowicki , Plenat F. , Lambert D. , Nabet-Belleville F. , and Gueant J.L. . 1997. Prospective evaluation of protein bound vitamin B12 (cobalamin) malabsorption in the elderly using trout flesh labelled in vivo with 57Co-cobalamin. Gut. 41: 475479.

Allen, L. H. 2010. Bioavailability of vitamin B12. Int J Vitam Nutr Res. 80: 330335.

Bae, S. , West A.A. , Yan J. , Jiang X. , Perry C.A. , Malysheva O. , Stabler S.P. , Allen R.H. , and Caudill M.A. . 2015. Vitamin B12 status differs among pregnant, lactating, and control women with equivalent nutrient intakes. J Nutr. 145: 15071514.

Bjorkenheim, B. 1966. Optic neuropathy caused by vitamin-B12 deficiency in carriers of the fish tapeworm, Diphyllobothrium latum. Lancet. 1: 688690.

Bor, M. V. , Lydeking-Olsen E. , Moller J. , and Nexo E. . 2006. A daily intake of approximately 6 microg vitamin B12 appears to saturate all the vitamin B12-related variables in Danish postmenopausal women. Am J Clin Nutr. 83: 5258.

Brenner, M. , Kim J.G. , Mahon S.B. , Lee J. , Kreuter K.A. , Blackledge W. , Mukai D. , Patterson S. , Mohammad O. , Sharma V.S. , and Boss G.R. . 2010. Intramuscular cobinamide sulfite in a rabbit model of sublethal cyanide toxicity. Ann Emerg Med. 55: 352363.

Brouwer-Brolsma, E. M. , Dhonukshe-Rutten R.A. , van Wijngaarden J.P. , Zwaluw N.L. , Velde N. , and de Groot L.C. . 2015. Dietary sources of vitamin B12 and their association with vitamin B12 status markers in healthy older adults in the B-PROOF study. Nutrients. 7: 77817797.

Carmel, R. 1995. Malabsorption of food cobalamin. Baillieres Clin Haematol. 8: 639655.

Casterline, J. E. , Allen L.H. , and Ruel M.T. . 1997. Vitamin B12 deficiency is very prevalent in lactating Guatemalan women and their infants at three months postpartum. J Nutr. 127: 19661972.

Czerwonga, M. , Szterk A. , and Waszkiewicz-Robak B. . 2014. Vitamin B12 content in raw and cooked beef. Meat Sci. 96: 13711375.

Dagnelie, P. C. , van Staveren W.A. , and van den Berg H. . 1991. Vitamin B12 from algae appears not to be bioavailable. Am J Clin Nutr. 53: 695697.

de Jager, C. A. , Oulhaj A. , Jacoby R. , Refsum H. , and Smith A.D. . 2012. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 27: 592600.

Doscherholmen, A. , McMahon J. , and Economon P. . 1981. Vitamin B12 absorption from fish. Proc Soc Exp Biol Med. 167: 480484.

Doscherholmen, A. , McMahon J. , and Ripley D. . 1975. Vitamin B12 absorption from eggs. Proc Soc Exp Biol Med. 149: 987990.

43 Doscherholmen, A. , McMahon J. , and Ripley D. . 1978. Vitamin B12 assimilation from chicken meat. Am J Clin Nutr. 31: 825830.

Dror, D. K. , and Allen L.H. . 2008. Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms. Nutr Rev. 66: 250255.

Duggan, C. , Srinivasan K. , Thomas T. , Samuel T. , Rajendran R. , Muthayya S. , Finkelstein J.L. , Lukose A. , Fawzi W. , Allen L.H. , Bosch R.J. , and Kurpad A.V. . 2014. Vitamin B12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B12 status. J Nutr. 144: 758764.

Farquharson, J. , and Adams J.F. . 1976. The forms of vitamin B12 in foods. Br J Nutr. 36: 127136.

Fedosov, S. N. 2012. Physiological and molecular aspects of cobalamin transport. Subcell Biochem. 56: 347367.

Fedosov, S. N. , Petersen T.E. , and Nexo E. . 1996. Transcobalamin from cow milk: isolation and physicochemical properties. Biochim Biophys Acta. 1292: 113119.

Gille, D. , and Schmid A. . 2015. Vitamin B12 in meat and dairy products. Nutr Rev. 73: 106115.

Gimsing P. and Nexo E. . 1983. The forms of cobalamin in biological materials. pp. 7-30. In: The Cobalamins by Hall CA, Churchill Livingstone, Edinburgh London Melbourne and New York. Chapter 1 ed.

Greibe, E. , Andreasen B.H. , Lildballe D.L. , Morkbak A.L. , Hvas A.M. , and Nexo E. . 2011. Uptake of cobalamin and markers of cobalamin status: a longitudinal study of healthy pregnant women. Clin Chem Lab Med. 49: 18771882.

Greibe, E. , Lildballe D.L. , Streym S. , Vestergaard P. , Rejnmark L. , Mosekilde L. , and Nexo E. . 2013a. Cobalamin and haptocorrin in human milk and cobalamin-related variables in mother and child: a 9-mo longitudinal study. Am J Clin Nutr. 98: 389395.

Greibe, E. , Trolle B. , Bor M.V. , Lauszus F.F. , and Nexo E. . 2013b. Metformin lowers serum cobalamin without changing other markers of cobalamin status: a study on women with polycystic ovary syndrome. Nutrients. 5: 24752482.

Gu, Q. , Zhang C. , Song D. , Li P. , and Zhu X. . 2015. Enhancing vitamin B12 content in soy-yogurt by Lactobacillus reuteri. Int J Food Microbiol. 206: 5659.

Hardlei, T. F. , Obeid R. , Herrmann W. , and Nexo E. . 2013. Cobalamin analogues in humans: a study on maternal and cord blood. PLoS One. 8: e61194.

Herbert V. 1996. Vitamin B12. In: Present Knowledge in Nutrition (7th edition) by Ziegler E.E. , Filer L.J. , International Life Science Institute (ILSI), Washington DC, Chapter 20.

Herrmann, W. , Schorr H. , Obeid R. , and Geisel J. . 2003. Vitamin B12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr. 78: 131136.

Heyssel, R. M. , Bozian R.C. , Darby W.J. , and Bell M.C. . 1966. Vitamin B12 turnover in man. The assimilation of vitamin B12 from natural foodstuff by man and estimates of minimal daily dietary requirements. Am J Clin Nutr. 18: 176184.

Jerneren, F. , Elshorbagy A.K. , Oulhaj A. , Smith S.M. , Refsum H. , and Smith A.D. . 2015. Brain atrophy in cognitively impaired elderly: the importance of long-chain omega-3 fatty acids and B vitamin status in a randomized controlled trial. Am J Clin Nutr. 102: 215221.

Khodabandehloo, N. , Vakili M. , Hashemian Z. , and Zare Z.H. . 2015. Determining functional vitamin B12 deficiency in the elderly. Iran Red Crescent Med J. 17: e13138.

Koehler, K. M. , Romero L.J. , Stauber P.M. , Pareo-Tubbeh S.L. , Liang H.C. , Baumgartner R.N. , Garry P.J. , Allen R.H. , and Stabler S.P. . 1996. Vitamin supplementation and other variables affecting serum homocysteine and methylmalonic acid concentrations in elderly men and women. J Am Coll Nutr. 15: 364376.

Kornerup L.S. , Juul C.B. , Fedosov S.N. , Heegaard C.W. , Greibe E. and Nexo E. . 2015. Absorption and retention of free and milk protein-bound cyano- and hydroxocobalamins. An experimental study in rats. Biochimie.

Kountouras, J. , Gavalas E. , Boziki M. , and Zavos C. . 2007. Helicobacter pylori may be involved in cognitive impairment and dementia development through induction of atrophic gastritis, vitamin B12 folate deficiency, and hyperhomocysteinemia sequence. Am J Clin Nutr. 86: 805806.

44 Kwok, T. , Chook P. , Qiao M. , Tam L. , Poon Y.K. , Ahuja A.T. , Woo J. , Celermajer D.S. , and Woo K.S. . 2012. Vitamin B12 supplementation improves arterial function in vegetarians with subnormal vitamin B12 status. J Nutr Health Aging. 16: 569573.

Lildballe, D. L. , Hardlei T.F. , Allen L.H. , and Nexo E. . 2009. High concentrations of haptocorrin interfere with routine measurement of cobalamins in human serum and milk. A problem and its solution. Clin Chem Lab Med. 47: 182187.

Lildballe D.L. and Nexo E. . 2013. Analysis of cobalamins (vitamin B12) in human samples: An overview of methodology. In: B Vitamins and Folate: Chemistry, Analysis, Function and Effects, Chapter 26.

Lindenbaum, J. , Rosenberg I.H. , Wilson P.W. , Stabler S.P. , and Allen R.H. . 1994. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr. 60: 211.

Majchrzak, D. , Singer I. , Manner M. , Rust P. , Genser D. , Wagner K.H. , and Elmadfa I. . 2006. B-vitamin status and concentrations of homocysteine in Austrian omnivores, vegetarians and vegans. Ann Nutr Metab. 50: 485491.
Matte, J. J. , Guay F. , and Girard C.L. . 2012. Bioavailability of vitamin B12 in cows milk. Br J Nutr. 107: 6166.
McLean, E. D. , Allen L.H. , Neumann C.G. , Peerson J.M. , Siekmann J.H. , Murphy S.P. , Bwibo N.O. , and Demment M.W. . 2007. Low plasma vitamin B12 in Kenyan school children is highly prevalent and improved by supplemental animal source foods. J Nutr. 137: 676682.
Miceli, E. , Lenti M.V. , Padula D. , Luinetti O. , Vattiato C. , Monti C.M. , Di S.M. , and Corazza G.R. . 2012. Common features of patients with autoimmune atrophic gastritis. Clin Gastroenterol Hepatol. 10: 812814.
Naik, S. , Bhide V. , Babhulkar A. , Mahalle N. , Parab S. , Thakre R. , and Kulkarni M. . 2013. Daily milk intake improves vitamin B12 status in young vegetarian Indians: an intervention trial. Nutr J. 12: 136.
Nishioka, M. , Kanosue F. , Yabuta Y. , and Watanabe F. . 2011. Loss of vitamin B(12) in fish (round herring) meats during various cooking treatments. J Nutr Sci Vitaminol (Tokyo). 57: 432436.
Obeid, R. , Jung J. , Falk J. , Herrmann W. , Geisel J. , Friesenhahn-Ochs B. , Lammert F. , Fassbender K. , and Kostopoulos P. . 2012. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. Biochimie.
Pennypacker, L. C. , Allen R.H. , Kelly J.P. , Matthews L.M. , Grigsby J. , Kaye K. , Lindenbaum J. , and Stabler S.P. . 1992. High prevalence of cobalamin deficiency in elderly outpatients. J Am Geriatr Soc. 40: 11971204.
Refsum, H. , Yajnik C.S. , Gadkari M. , Schneede J. , Vollset S.E. , Orning L. , Guttormsen A.B. , Joglekar A. , Sayyad M.G. , Ulvik A. , and Ueland P.M. . 2001. Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of cobalamin deficiency in Asian Indians. Am J Clin Nutr. 74: 233241.
Rojas Hernandez, C. M. , and Oo T.H. . 2015. Advances in mechanisms, diagnosis, and treatment of pernicious anemia. Discov Med. 19: 159168.
Rozgony, N. R. , Fang C. , Kuczmarski M.F. , and Bob H. . 2010. Vitamin B(12) deficiency is linked with long-term use of proton pump inhibitors in institutionalized older adults: could a cyanocobalamin nasal spray be beneficial? J Nutr Elder. 29: 8799.
Russell, R. M. , Baik H. , and Kehayias J.J. . 2001. Older men and women efficiently absorb vitamin B12 from milk and fortified bread. J Nutr. 131: 291293.
Schjonsby, H. 1989. Vitamin B12 absorption and malabsorption. Gut. 30: 16861691.
Siddiqua, T. J. , Ahmad S.M. , Ahsan K.B. , Rashid M. , Roy A. , Rahman S.M. , Shahab-Ferdows S. , Hampel D. , Ahmed T. , Allen L.H. , and Raqib R. . 2015. Vitamin B12 supplementation during pregnancy and postpartum improves B12 status of both mothers and infants but vaccine response in mothers only: a randomized clinical trial in Bangladesh. Eur J Nutr.
Stabler, S. P. 2013. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 368: 149160.
Stabler, S.P. , and Allen R.H. . 2004. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr 24: 299326.
Strand, T.A. , Taneja S. , Kumar T. , Manger M.S. , Refsum H. , Yajnik C.S. , and Bhandari N. . 2015. Vitamin B12, folic acid, and growth in 6- to 30-month-old children: a randomized controlled trial. Pediatrics. 135: e918e926.
45 The Danish National Food Institute, DF. 2015. The Danish National Food Institute, DTU Food, Food Composition Databank - Version 7.01.
Tomkin, G. H. , Hadden D.R. , Weaver J.A. , and Montgomery D.A. . 1971. Vitamin-B12 status of patients on long-term metformin therapy. Br Med J. 2: 685687.
Tucker, K. L. , Rich S. , Rosenberg I. , Jacques P. , Dallai G. , Wilson P.W. , and Selhub J. . 2000. Plasma vitamin B12 concentrations relate to intake source in the Framingham offspring study. Am J Clin Nutr. 71: 514522.
van den Berg, H. , Daqnelie P.C. , and van Staveren W.A. . 1988. Vitamin B12 and seaweed. Lancet. 1: 242243.
Vogiatzoglou, A. , Smith A.D. , Nurk E. , Berstad P. , Drevon C.A. , Ueland P.M. , Vollset S.E. , Tell G.S. , and Refsum H. . 2009. Dietary sources of vitamin B12 and their association with plasma vitamin B12 concentrations in the general population: the Hordaland Homocysteine Study. Am J Clin Nutr. 89: 10781087.
Watanabe, F. 2007. Vitamin B12 sources and bioavailability. Exp Biol Med (Maywood). 232: 12661274.
Wong, C. W. 2015. Vitamin B12 deficiency in the elderly: is it worth screening? Hong Kong Med J. 21: 155164.
Xia, L. , Cregan A.G. , Berben L.A. , and Brasch N.E. . 2004. Studies on the formation of glutathionylcobalamin: any free intracellular aquacobalamin is likely to be rapidly and irreversibly converted to glutathionylcobalamin. Inorg Chem. 43: 68486857.

Intracellular Processing and Utilization of Cobalamins

Acquaviva, C. , Benoist J.F. , Pereira S. , Callebaut I. , Koskas T. , Porquet D. , and Elion J. . 2005. Molecular basis of methylmalonyl-CoA mutase apoenzyme defect in 40 European patients affected by mut(o) and mut-forms of methylmalonic acidemia: identification of 29 novel mutations in the MUT gene. Hum Mutat. 25 (2): 167176.
Allen, R. H. , and Stabler S.P. . 2008. Identification and quantitation of cobalamin and cobalamin analogues in human feces. Am J Clin Nutr. 87 (5): 13241335.
Amagasaki, T. , Green R. , and Jacobsen D.W. . 1990. Expression of transcobalamin II receptors by human leukemia K562 and HL-60 cells. Blood. 76 (7): 13801386.
Andrews, E. , Jansen R. , Crane A.M. , Cholin S. , McDonnell D. , and Ledley F.D. . 1993. Expression of recombinant human methylmalonyl-CoA mutase: in primary mut fibroblasts and Saccharomyces cerevisiae . Biochem Med Metab Biol. 50 (2): 135144.
Ast, T. , Nicolaou A. , Anderson M.M. , James C. , and Gibbons W.A. . 1994. Purification, properties and inhibition of rat liver cytosolic vitamin B12-dependent methionine synthase. Biochem Soc Trans. 22 (2): 217S.
Atkinson, C. , Miousse I.R. , Watkins D. , Rosenblatt D.S. , and Raiman J.A. . 2014. Clinical, biochemical, and molecular presentation in a patient with the cblD-homocystinuria inborn error of cobalamin metabolism. JIMD Rep. 17: 7781.
Backe, P. H. , Ytre-Arne M. , Rohr A.K. , Brodtkorb E. , Fowler B. , Rootwelt H. , Bjoras M. , and Morkrid L. . 2013. Novel deletion mutation identified in a patient with late-onset combined methylmalonic acidemia and homocystinuria, cblC type. JIMD Rep. 11: 7985.
Bandarian, V. , Pattridge K.A. , Lennon B.W. , Huddler D.P. , Matthews R.G. , and Ludwig M.L. . 2002. Domain alternation switches B(12)-dependent methionine synthase to the activation conformation. Nat Struct Biol. 9 (1): 5356.
Banerjee R. 1999. Chemistry and Biochemistry of B12. In: R. Banerjee (ed.). John Wiley and Sons, New York, NY, 921 pp.
Banerjee, R. 2003. Radical carbon skeleton rearrangements: catalysis by coenzyme B12-dependent mutases. Chem Rev. 103 (6): 20832094.
Banerjee, R. 2006. B12 trafficking in mammals: A for coenzyme escort service. ACS Chem Biol. 1 (3): 149159.
83 Banerjee, R. , Chen Z. , and Gulati S. . 1997. Methionine synthase from pig liver. Methods Enzymol. 281: 189196.

Banerjee, R. V. , and Matthews R.G. . 1990. Cobalamin-dependent methionine synthase. FASEB J. 4 (5): 14501459.
Bommer, M. , Kunze C. , Fesseler J. , Schubert T. , Diekert G. , and Dobbek H. . 2014. Structural basis for organohalide respiration. Science. 346 (6208): 455458.
Bose, S. , Kalra S. , Yammani R.R. , Ahuja R. , and Seetharam B. . 2007. Plasma membrane delivery, endocytosis and turnover of transcobalamin receptor in polarized human intestinal epithelial cells. J Physiol. 581 (Pt 2): 457466.
Bose, S. , Seetharam S. , Dahms N.M. , and Seetharam B. . 1997. Bipolar functional expression of transcobalamin II receptor in human intestinal epithelial Caco-2 cells. J Biol Chem. 272 (6): 35383543.
Brouwer, M. , Chamulitrat W. , Ferruzzi G. , Sauls D.L. , and Weinberg J.B. . 1996. Nitric oxide interactions with cobalamins: biochemical and functional consequences. Blood. 88 (5): 18571864.
Brown, K. L. , and Brooks H.B. . 1991. Effects of axial ligation on the thermolysis of benzyl- and neopentylcobamides: analysis of the base-on effect. Inorg Chem. 30 (18): 34203430.
Carmel, R. , Karnaze D.S. , and Weiner J.M. . 1988. Neurologic abnormalities in cobalamin deficiency are associated with higher cobalamin analogue values than are hematologic abnormalities. J Lab Clin Med. 111 (1): 5762.
Carrillo-Carrasco, N. , Chandler R.J. , and Venditti C.P. . 2012. Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management. J Inherit Metab Dis. 35 (1): 91102.
Caterino, M. , Pastore A. , Strozziero M.G. , Di Giovamberardino G. , Imperlini E. , Scolamiero E. , Ingenito L. , Boenzi S. , Ceravolo F. , Martinelli D. , et al. 2015. The proteome of cblC defect: in vivo elucidation of altered cellular pathways in humans. J Inherit Metab Dis. 38 (5): 969979.
Chang, H. 2005. Gene symbol: MUT. Disease: Methylmalonic aciduria. Hum Genet. 117 (23): 299.
Chen, L. H. , Liu M.L. , Hwang H.Y. , Chen L.S. , Korenberg J. , and Shane B. . 1997. Human methionine synthase. cDNA cloning, gene localization, and expression. J Biol Chem. 272 (6): 36283634.
Chen, Z. , Crippen K. , Gulati S. , and Banerjee R. . 1994. Purification and kinetic mechanism of a mammalian methionine synthase from pig liver. J Biol Chem. 269 (44): 2719327197.
Chowdhury, S. , and Banerjee R. . 2000. Thermodynamic and kinetic characterization of Co-C bond homolysis catalyzed by coenzyme B12-dependent methylmalonyl-CoA mutase. Biochemistry. 39 (27): 79988006.
Christensen, B. , and Ueland P.M. . 1993. Methionine synthase inactivation by nitrous oxide during methionine loading of normal human fibroblasts. Homocysteine remethylation as determinant of enzyme inactivation and homocysteine export. J Pharmacol Exp Ther. 267 (3): 12981303.
Chu, R. C. , Begley J.A. , Colligan P.D. , and Hall C.A. . 1993. The methylcobalamin metabolism of cultured human fibroblasts. Metabolism. 42 (3): 315319.
Coelho, D. , Kim J.C. , Miousse I.R. , Fung S. , du Moulin M. , Buers I. , Suormala T. , Burda P. , Frapolli M. , Stucki M. , et al. 2012. Mutations in ABCD4 cause a new inborn error of vitamin B12 metabolism. Nat Genet. 44 (10): 11521155.
Coelho, D. , Suormala T. , Stucki M. , Lerner-Ellis J.P. , Rosenblatt D.S. , Newbold R.F. , Baumgartner M.R. , and Fowler B. . 2008. Gene identification for the cblD defect of vitamin B12 metabolism. N Engl J Med. 358 (14): 14541464.
Croft, M. T. , Lawrence A.D. , Raux-Deery E. , Warren M.J. , and Smith A.G. . 2005. Algae acquire vitamin B12 through a symbiotic relationship with bacteria. Nature. 438 (7064): 9093.
Dan, N. , and Cutler D.F. . 1994. Transcytosis and processing of intrinsic factor-cobalamin in Caco-2 cells. J Biol Chem. 269 (29): 1884918855.
Danishpajooh, I. O. , Gudi T. , Chen Y. , Kharitonov V.G. , Sharma V.S. , and Boss G.R. . 2001. Nitric oxide inhibits methionine synthase activity in vivo and disrupts carbon flow through the folate pathway. J Biol Chem. 276 (29): 2729627303.
Deme, J. C. , Miousse I.R. , Plesa M. , Kim J.C. , Hancock M.A. , Mah W. , Rosenblatt D.S. , and Coulton J.W. . 2012. Structural features of recombinant MMADHC isoforms and their interactions with MMACHC, proteins of mammalian vitamin B12 metabolism. Mol Genet Metab. 107 (3): 352362.
84 Dillon, M. J. , England J.M. , Gompertz D. , Goodey P.A. , Grant D.B. , Hussein H.A. , Linnell J.C. , Matthews D.M. , Mudd S.H. , Newns G.H. , et al. 1974. Mental retardation, megaloblastic anaemia, methylmalonic aciduria and abnormal homocysteine metabolism due to an error in vitamin B12 metabolism. Clin Sci Mol Med. 47 (1): 4361.
Dobson, C. M. , Wai T. , Leclerc D. , Kadir H. , Narang M. , Lerner-Ellis J.P. , Hudson T.J. , Rosenblatt D.S. , and Gravel R.A. . 2002a. Identification of the gene responsible for the cblB complementation group of vitamin B12-dependent methylmalonic aciduria. Hum Mol Genet. 11 (26): 33613369.
Dobson, C. M. , Wai T. , Leclerc D. , Wilson A. , Wu X. , Dore C. , Hudson T. , Rosenblatt D.S. , and Gravel R.A. . 2002b. Identification of the gene responsible for the cblA complementation group of vitamin B12-responsive methylmalonic acidemia based on analysis of prokaryotic gene arrangements. Proc Natl Acad Sci U S A. 99 (24): 1555415559.
Drennan, C. L. , Huang S. , Drummond J.T. , Matthews R.G. , and Lidwig M.L. . 1994. How a protein binds B12: A 3.0 A X-ray structure of B12-binding domains of methionine synthase. Science. 266 (5191): 16691674.
Drummond, J. T. , Huang S. , Blumenthal R.M. , and Matthews R.G. . 1993. Assignment of enzymatic function to specific protein regions of cobalamin-dependent methionine synthase from Escherichia coli . Biochemistry. 32 (36): 92909295.
Eschenmoser, A. 2011. Etiology of potentially primordial biomolecular structures: from vitamin B12 to the nucleic acids and an inquiry into the chemistry of lifes origin: a retrospective. Angew Chem Int Ed Engl. 50 (52): 1241212472.
Fenton, W. A. , Ambani L.M. , and Rosenberg L.E. . 1976. Uptake of hydroxocobalamin by rat liver mitochondria. Binding to a mitochondrial protein. J Biol Chem. 251 (21): 66166623.
Fenton, W. A. , Hack A.M. , Willard H.F. , Gertler A. , and Rosenberg L.E. . 1982. Purification and properties of methylmalonyl coenzyme A mutase from human liver. Arch Biochem Biophys. 214 (2): 815823.
Fenton, W. A. , and Rosenberg L.E. . 1978. Mitochondrial metabolism of hydroxocobalamin: synthesis of adenosylcobalamin by intact rat liver mitochondria. Arch Biochem Biophys. 189 (2): 441447.
Fenton, W. A. , and Rosenberg L.E. . 1981. The defect in the cbl B class of human methylmalonic acidemia: deficiency of cob(I)alamin adenosyltransferase activity in extracts of cultured fibroblasts. Biochem Biophys Res Commun. 98 (1): 283289.
Fofou-Caillierez, M. B. , Mrabet N.T. , Chery C. , Dreumont N. , Flayac J. , Pupavac M. , Paoli J. , Alberto J.M. , Coelho D. , Camadro J.M. , et al. 2013. Interaction between methionine synthase isoforms and MMACHC: characterization in cblG-variant, cblG and cblC inherited causes of megaloblastic anaemia. Hum Mol Genet. 22 (22): 45914601.
Fong, J. H. , Shoemaker B.A. , Garbuzynskiy S.O. , Lobanov M.Y. , Galzitskaya O.V. , and Panchenko A.R. . 2009. Intrinsic disorder in protein interactions: insights from a comprehensive structural analysis. PLoS Comput Biol. 5 (3): e1000316.
Froese, D. S. , and Gravel R.A. . 2010. Genetic disorders of vitamin B12 metabolism: eight complementation groupseight genes. Expert Rev Mol Med. 12: e37.
Froese, D. S. , Healy S. , McDonald M. , Kochan G. , Oppermann U. , Niesen F.H. , and Gravel R.A. . 2010a. Thermolability of mutant MMACHC protein in the vitamin B12-responsive cblC disorder. Mol Genet Metab. 100 (1): 2936.
Froese, D. S. , Kochan G. , Muniz J.R. , Wu X. , Gileadi C. , Ugochukwu E. , Krysztofinska E. , Gravel R.A. , Oppermann U. , and Yue W.W. . 2010b. Structures of the human GTPase MMAA and vitamin B12-dependent methylmalonyl-CoA mutase and insight into their

complex formation. J Biol Chem. 285 (49): 3820438213.
Froese, D. S. , Krojer T. , Wu X. , Shrestha R. , Kiyani W. , von Delft F. , Gravel R.A. , Oppermann U. , and Yue W.W. . 2012. Structure of MMACHC reveals an arginine-rich pocket and a domain-swapped dimer for its B12 processing function. Biochemistry. 51 (25): 50835090.
Froese, D. S. , Wu X. , Zhang J. , Dumas R. , Schoel W.M. , Amrein M. , and Gravel R.A. . 2008. Restricted role for methionine synthase reductase defined by subcellular localization. Mol Genet Metab. 94 (1): 6877.
Froese, D. S. , Zhang J. , Healy S. , and Gravel R.A. . 2009. Mechanism of vitamin B12-responsiveness in cblC methylmalonic aciduria with homocystinuria. Mol Genet Metab. 98 (4): 338343.
85 Gailus, S. , Hohne W. , Gasnier B. , Nurnberg P. , Fowler B. , and Rutsch F. . 2010a. Insights into lysosomal cobalamin trafficking: lessons learned from cblF disease. J Mol Med (Berl). 88 (5): 459466.
Gailus, S. , Suormala T. , Malerczyk-Aktas A.G. , Toliat M.R. , Wittkampf T. , Stucki M. , Nurnberg P. , Fowler B. , Hennermann J.B. , and Rutsch F. . 2010b. A novel mutation in LMBRD1 causes the cblF defect of vitamin B(12) metabolism in a Turkish patient. J Inherit Metab Dis. 33 (1): 1724.
Geno, M. K. , and Halpern J. . 1987. Why does nature not use the porphyrin ligand in vitamin B12? J Am Chem Soc. 109 (4): 12381240.
Gherasim, C. , Hannibal L. , Rajagopalan D. , Jacobsen D.W. , and Banerjee R. . 2013a. The C-terminal domain of CblD interacts with CblC and influences intracellular cobalamin partitioning. Biochimie. 95 (5): 10231032.
Gherasim, C. , Lofgren M. , and Banerjee R. . 2013b. Navigating the B12 road: assimilation, delivery, and disorders of cobalamin. J Biol Chem. 288 (19): 1318613193.
Gherasim, C. , Ruetz M. , Li Z. , Hudolin S. , and Banerjee R. . 2015. Pathogenic mutations differentially affect the catalytic activities of the human B12-processing chaperone CblC and increase futile redox cycling. J Biol Chem. 290 (18): 1139311402.
Gimsing, P. 1995. Cobalamin forms and analogues in plasma and myeloid cells during chronic myelogenous leukaemia related to clinical condition. Br J Haematol. 89 (4): 812819.
Gimsing, P. , and Beck W.S. . 1989. Cobalamin analogues in plasma. An in vitro phenomenon? Scand J Clin Lab Invest Suppl. 194: 3740.
Gravel, R. A. , Mahoney M.J. , Ruddle F.H. , and Rosenberg L.E. . 1975. Genetic complementation in heterokaryons of human fibroblasts defective in cobalamin metabolism. Proc Natl Acad Sci U S A. 72 (8): 31813185.
Gueant, J. L. , Gerard A. , Monin B. , Champigneulle B. , Gerard H. , and Nicolas J.P. . 1988. Radioautographic localisation of iodinated human intrinsic factor in the guinea pig ileum using electron microscopy. Gut. 29 (10): 13701378.
Gulati, S. , Baker P. , Li Y.N. , Fowler B. , Kruger W. , Brody L.C. , and Banerjee R. . 1996. Defects in human methionine synthase in cblG patients. Hum Mol Genet. 5 (12): 18591865.
Gulati, S. , Chen Z. , Brody L.C. , Rosenblatt D.S. , and Banerjee R. . 1997. Defects in auxiliary redox proteins lead to functional methionine synthase deficiency. J Biol Chem. 272 (31): 1917119175.
Gunasekaran, K. , Tsai C.J. , Kumar S. , Zanuy D. , and Nussinov R. . 2003. Extended disordered proteins: targeting function with less scaffold. Trends Biochem Sci. 28 (2): 8185.
Hakami, N. , Neiman P.E. , Canellos G.P. , and Lazerson J. . 1971. Neonatal megaloblastic anemia due to inherited transcobalamin II deficiency in two siblings. N Engl J Med. 285 (21): 11631170.
Hannibal, L. , DiBello P.M. , and Jacobsen D.W. . 2013. Proteomics of vitamin B12 processing. Clin Chem Lab Med. 51 (3): 477488.
Hannibal, L. , DiBello P.M. , Yu M. , Miller A. , Wang S. , Willard B. , Rosenblatt D.S. , and Jacobsen D.W. . 2011. The MMACHC proteome: hallmarks of functional cobalamin deficiency in humans. Mol Genet Metab. 103 (3): 226239.
Hannibal, L. , Kim J. , Brasch N.E. , Wang S. , Rosenblatt D.S. , Banerjee R. , and Jacobsen D.W. . 2009. Processing of alkylcobalamins in mammalian cells: A role for the MMACHC (cblC) gene product. Mol Genet Metab. 97 (4): 260266.
Haque, M. M. , Bayachou M. , Tejero J. , Kenney C.T. , Pearl N.M. , Im S.C. , Waskell L. , and Stuehr D.J. . 2014. Distinct conformational behaviors of four mammalian dual-flavin reductases (cytochrome P450 reductase, methionine synthase reductase, neuronal nitric oxide synthase, endothelial nitric oxide synthase) determine their unique catalytic profiles. FEBS J. 281 (23): 53255340.
Harding, C. O. , Arnold G. , Barness L.A. , Wolff J.A. , and Rosenblatt D.S. . 1997. Functional methionine synthase deficiency due to cblG disorder: a report of two patients and a review. Am J Med Genet. 71 (4): 384390.
Hardlei, T. F. , Obeid R. , Herrmann W. , and Nexo E. . 2013. Cobalamin analogues in humans: a study on maternal and cord blood. PLoS One. 8 (4): e61194.
Hodgkin, D. C. , Pickworth J. , Robertson J.H. , Trueblood K.N. , Prosen R.J. , and White J.G. . 1955. Structure of vitamin B12. The crystal structure of the hexacarboxylic acid derived from B12 and the molecular structure of the vitamin. Nature. 176 (4477): 325328.
Hubbard, P. A. , Padovani D. , Labunska T. , Mahlstedt S.A. , Banerjee R. , and Drennan C.L. . 2007. Crystal structure and mutagenesis of the metallochaperone MeaB: insight into the causes of methylmalonic aciduria. J Biol Chem. 282 (43): 3130831316.
86 Hunter G. A. and Ferreira G. C. . 2009. 5-aminolevulinate synthase: catalysis of the first step of heme biosynthesis. Cell Mol Biol (Noisy-le-grand). 55(1): 102110.
Idriss, J. M. , and Jonas A.J. . 1991. Vitamin B12 transport by rat liver lysosomal membrane vesicles. J Biol Chem. 266 (15): 94389441.
Jacobsen, D. W. , Montejano Y.D. , Vitols K.S. , and Huennekens F.M. . 1980. Adherence of L1210 murine leukemia cells to sephacryl-aminopropylcobalamin beads treated with transcobalamin-II. Blood. 55 (1): 160163.
James, K. J. , Hancock M.A. , Gagnon J.N. , and Coulton J.W. . 2009. TonB interacts with BtuF, the Escherichia coli periplasmic binding protein for cyanocobalamin. Biochemistry. 48 (39): 92129220.
Jarrett, J. T. , Amaratunga M. , Drennan C.L. , Scholten J.D. , Sands R.H. , Ludwig M.L. , and Matthews R.G. . 1996. Mutations in the B12-binding region of methionine synthase: how the protein controls methylcobalamin reactivity. Biochemistry. 35 (7): 24642475.
Jencks, W. P. 1975. Binding energy, specificity, and enzymic catalysis: the circe effect. Adv Enzymol Relat Areas Mol Biol. 43: 219410.
Jeong, J. , Ha T.S. , and Kim J. . 2011. Protection of aquo/hydroxocobalamin from reduced glutathione by a B12 trafficking chaperone. BMB Rep. 44 (3): 170175.
Jeong, J. , and Kim J. . 2011. Glutathione increases the binding affinity of a bovine B12 trafficking chaperone bCblC for vitamin B12. Biochem Biophys Res Commun. 412 (2): 360365.
Jiang, W. , Nakayama Y. , Sequeira J.M. , and Quadros E.V. . 2013. Mapping the functional domains of TCblR/CD320, the receptor for cellular uptake of transcobalamin-bound cobalamin. FASEB J. 27 (8): 29882994.
Jorge-Finnigan, A. , Gamez A. , Perez B. , Ugarte M. , and Richard E. . 2010. Different altered pattern expression of genes related to apoptosis in isolated methylmalonic aciduria cblB type and combined with homocystinuria cblC type. Biochim Biophys Acta. 1802 (11): 959967.
Jusufi, J. , Suormala T. , Burda P. , Fowler B. , Froese D.S. , and Baumgartner M.R. . 2014. Characterization of functional domains of the cblD (MMADHC) gene product. J Inherit Metab Dis. 37 (5): 841849.
Kajiura, H. , Mori K. , Tobimatsu T. , and Toraya T. . 2001. Characterization and mechanism of action of a reactivating factor for adenosylcobalamin-dependent glycerol dehydratase. J Biol Chem. 276 (39): 3651436519.
Kambo, A. , Sharma V.S. , Casteel D.E. , Woods V.L. Jr , Pilz R.B. , and Boss G.R. . 2005. Nitric oxide inhibits mammalian methylmalonyl-CoA mutase. J Biol Chem. 280 (11): 1007310082.

Kierstein, S. , Peters U. , Habermann F.A. , Fries R. , and Brenig B. . 2003. Assignment of the methylmalonyl- CoA mutase gene (MUT) to porcine chromosome 7q13>q14 by in situ hybridization and analysis of radiation hybrid panels. Cytogenet Genome Res. 101 (1): 92F.
Kim, J. , Gherasim C. , and Banerjee R. . 2008. Decyanation of vitamin B12 by a trafficking chaperone. Proc Natl Acad Sci U S A. 105 (38): 1455114554.
Kim, J. , Hannibal L. , Gherasim C. , Jacobsen D.W. , and Banerjee R. . 2009. A human vitamin B12 trafficking protein uses glutathione transferase activity for processing alkylcobalamins. J Biol Chem. 284 (48): 3341833424.
Kishimoto, T. , Tavassoli M. , Green R. , and Jacobsen D.W. . 1987. Receptors for transferrin and transcobalamin II display segregated distribution on microvilli of leukemia L1210 cells. Biochem Biophys Res Commun. 146 (3): 11021108.
Kolhouse, J. F. , Utley C. , and Allen R.H. . 1980. Isolation and characterization of methylmalonyl-CoA mutase from human placenta. J Biol Chem. 255 (7): 27082712.
Kolhouse, J. F. , Utley C. , Stabler S.P. , and Allen R.H. . 1991. Mechanism of conversion of human apo- to holomethionine synthase by various forms of cobalamin. J Biol Chem. 266 (34): 2301023015.
Kondo, H. , Osborne M.L. , Kolhouse J.F. , Binder M.J. , Podell E.R. , Utley C.S. , Abrams R.S. , and Allen R.H. . 1981. Nitrous oxide has multiple deleterious effects on cobalamin metabolism and causes decreases in activities of both mammalian cobalamin-dependent enzymes in rats. J Clin Invest. 67 (5): 12701283.
Korotkova, N. , and Lidstrom M.E. . 2004. MeaB is a component of the methylmalonyl-CoA mutase complex required for protection of the enzyme from inactivation. J Biol Chem. 279 (14): 1365213658.
Koutmos, M. , Gherasim C. , Smith J.L. , and Banerjee R. . 2011. Structural basis of multifunctionality in a vitamin B12-processing enzyme. J Biol Chem. 286 (34): 2978029787.
87 Kraeutler, B. , Konrat R. , Stupperich E. , Faerber G. , Gruber K. , and Kratky C. . 1994. Direct evidence for the conformational deformation of the corrin ring by the nucleotide base in vitamin B12: Synthesis and solution spectroscopic and crystal structure analysis of Co.beta.- cyanoimidazolylcobamide. Inorg Chem. 33 (18): 41284139.
Laframboise, R. , Cooper B.A. , and Rosenblatt D.S. . 1992. Malabsorption of vitamin B12 from the intestine in a child with cblF disease: evidence for lysosomal-mediated absorption. Blood. 80 (1): 291292.
Leal, N. A. , Park S.D. , Kima P.E. , and Bobik T.A. . 2003. Identification of the human and bovine ATP:Cob(I) alamin adenosyltransferase cDNAs based on complementation of a bacterial mutant. J Biol Chem. 278 (11): 92279234.
Leclerc, D. , Campeau E. , Goyette P. , Adjalla C.E. , Christensen B. , Ross M. , Eydoux P. , Rosenblatt D.S. , Rozen R. , and Gravel R.A. . 1996. Human methionine synthase: cDNA cloning and identification of mutations in patients of the cblG complementation group of folate/cobalamin disorders. Hum Mol Genet. 5 (12): 18671874.
Leclerc, D. , Odievre M. , Wu Q. , Wilson A. , Huizenga J.J. , Rozen R. , Scherer S.W. , and Gravel R.A. . 1999. Molecular cloning, expression and physical mapping of the human methionine synthase reductase gene. Gene. 240 (1): 7588.
Leclerc, D. , Wilson A. , Dumas R. , Gafuik C. , Song D. , Watkins D. , Heng H.H. , Rommens J.M. , Scherer S.W. , Rosenblatt D.S. , et al. 1998. Cloning and mapping of a cDNA for methionine synthase reductase, a flavoprotein defective in patients with homocystinuria. Proc Natl Acad Sci U S A. 95 (6): 30593064.
Ledley, F. D. , Lumetta M. , Nguyen P.N. , Kolhouse J.F. , and Allen R.H. . 1988a. Molecular cloning of L-methylmalonyl-CoA mutase: gene transfer and analysis of mut cell lines. Proc Natl Acad Sci U S A. 85 (10): 35183521.
Ledley, F. D. , Lumetta M.R. , Zoghbi H.Y. , VanTuinen P. , Ledbetter S.A. , and Ledbetter D.H. . 1988b. Mapping of human methylmalonyl CoA mutase (MUT) locus on chromosome 6. Am J Hum Genet. 42 (6): 839846.
Lenhert, P. G. , and Hodgkin D.C. . 1961. Structure of the 5,6-dimethylbenzimidazolylcobamide coenzyme. Nature. 192: 937938.
Lerner-Ellis, J. P. , Anastasio N. , Liu J. , Coelho D. , Suormala T. , Stucki M. , Loewy A.D. , Gurd S. , Grundberg E. , Morel C.F. , et al. 2009. Spectrum of mutations in MMACHC, allelic expression, and evidence for genotype-phenotype correlations. Hum Mutat. 30 (7): 10721081.
Lerner-Ellis, J. P. , Dobson C.M. , Wai T. , Watkins D. , Tirone J.C. , Leclerc D. , Dore C. , Lepage P. , Gravel R.A. , and Rosenblatt D.S. . 2004. Mutations in the MMAA gene in patients with the cblA disorder of vitamin B12 metabolism. Hum Mutat. 24 (6): 509516.
Lerner-Ellis, J. P. , Tirone J.C. , Pawelek P.D. , Dore C. , Atkinson J.L. , Watkins D. , Morel C.F. , Fujiwara T.M. , Moras E. , Hosack A.R. , et al. 2006. Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. Nat Genet. 38 (1): 93100.
Li, Y. N. , Gulati S. , Baker P.J. , Brody L.C. , Banerjee R. , and Kruger W.D. . 1996. Cloning, mapping and RNA analysis of the human methionine synthase gene. Hum Mol Genet. 5 (12): 18511858.
Li, Z. , Gherasim C. , Lesniak N.A. , and Banerjee R. . 2014a. Glutathione-dependent one-electron transfer reactions catalyzed by a B12 trafficking protein. J Biol Chem. 289 (23): 1648716497.
Li, Z. , Lesniak N.A. , and Banerjee R. . 2014b. Unusual aerobic stabilization of cob(I)alamin by a B12- trafficking protein allows chemoenzymatic synthesis of organocobalamins. J Am Chem Soc. 136 (46): 1610816111.
Lienhart, W.-D. , Gudipati V. , and Macheroux P. . 2013. The human flavoproteome. Arch Biochem Biophys. 535 (2): 150162.
Linnell, J. C. , Matthews D.M. , Mudd S.H. , Uhlendorf B.W. , and Wise I.J. . 1976. Cobalamins in fibroblasts cultured from normal control subjects and patients with methylmalonic aciduria. Pediatr Res. 10 (3): 179183.
Loewy, A. D. , Niles K.M. , Anastasio N. , Watkins D. , Lavoie J. , Lerner-Ellis J.P. , Pastinen T. , Trasler J.M. , and Rosenblatt D.S. . 2009. Epigenetic modification of the gene for the vitamin B12 chaperone MMACHC can result in increased tumorigenicity and methionine dependence. Mol Genet Metab. 96 (4): 261267.
Lofgren, M. , Koutmos M. , and Banerjee R. . 2013a. Autoinhibition and signaling by the switch II motif in the G-protein chaperone of a radical B12 enzyme. J Biol Chem. 288 (43): 3098030989.
88 Lofgren, M. , Padovani D. , Koutmos M. , and Banerjee R. . 2013b. A switch III motif relays signaling between a B12 enzyme and its G-protein chaperone. Nat Chem Biol. 9 (9): 535539.
Loughlin, R. E. , Elford H.L. , and Buchanan J.M. . 1964. Enzymatic synthesis of the methyl group of methionine. Vii. isolation of a cobalamin-containing transmethylase (5-Methyltetrahydro- Folate-Homocysteine) from mammalian liver. J Biol Chem. 239: 28882895.
MacDonald, M. , Wiltse H. , Bever J. , and Rosenblatt D.S. . 1992. Clinical heterogeneity in two patients with cblF disease [Abstract]. Am J Hum Genet. 51: A353.
Mah, W. , Deme J.C. , Watkins D. , Fung S. , Janer A. , Shoubridge E.A. , Rosenblatt D.S. , and Coulton J.W. . 2013. Subcellular location of MMACHC and MMADHC, two human proteins central to intracellular vitamin B12 metabolism. Mol Genet Metab. 108 (2): 112118.
Mahoney, M. J. , Hart A.C. , Steen V.D. , and Rosenberg L.E. . 1975. Methylmalonicacidemia: biochemical heterogeneity in defects of 5-deoxyadenosylcobalamin synthesis. Proc Natl Acad Sci U S A. 72 (7): 27992803.
Mahoney, M. J. , and Rosenberg L.E. . 1971. Synthesis of cobalamin coenzymes by human cells in tissue culture. J Lab Clin Med. 78 (2): 302308.
Mahoney, M. J. , Rosenberg L.E. , Mudd S.H. , and Uhlendorf B.W. . 1971. Defective metabolism of vitamin B12 in fibroblasts from children with methylmalonic aciduria. Biochem Biophys Res Commun. 44 (2): 375381.
Martens, J. H. , Barg H. , Warren M.J. , and Jahn D. . 2002. Microbial production of vitamin B12. Appl Microbiol Biotechnol. 58 (3): 275285.
Marzilli, L. G. , Toscano P.J. , Randaccio L. , Bresciani-Pahor N. , and Calligaris M. . 1979. An unusually long cobalt-carbon bond. Molecular structure of trans-bis(dimethylglyoximato)(isopropyl) (pyridine)cobalt(III). Implications with regard to the conformational trigger

mechanism of cobalt-carbon bond cleavage in coenzyme B12. J Am Chem Soc. 101 (22): 67546756.
Matthews, R. G. , and 2001. Cobalamin-dependent methyltransferases. Acc Chem Res. 34(8): 681689. Matthews RG, Koutmos M and Datta S. . 2008. Cobalamin-dependent and cobamide-dependent methyltransferases. Curr Opin Struct Biol. 18 (6): 658666.
Mc Guire, P. J. , Parikh A. , and Diaz G.A. . 2009. Profiling of oxidative stress in patients with inborn errors of metabolism. Mol Genet Metab. 98 (12): 173180.
McLean, G. R. , Pathare P.M. , Wilbur D.S. , Morgan A.C. , Woodhouse C.S. , Schrader J.W. , and Ziltener H.J. . 1997. Cobalamin analogues modulate the growth of leukemia cells in vitro . Cancer Res. 57 (18): 40154022.
Mellman, I. , Willard H.F. , Youngdahl-Turner P. , and Rosenberg L.E. . 1979a. Cobalamin coenzyme synthesis in normal and mutant human fibroblasts. Evidence for a processing enzyme activity deficient in cblC cells. J Biol Chem. 254 (23): 1184711853.
Mellman, I. S. , Lin P.F. , Ruddle F.H. , and Rosenberg L.E. . 1979b. Genetic control of cobalamin binding in normal and mutant cells: assignment of the gene for 5-methyltetrahydrofolate:L- homocysteine S-methyltransferase to human chromosome 1. Proc Natl Acad Sci U S A. 76 (1): 405409.
Miousse, I. R. , Watkins D. , Coelho D. , Rupar T. , Crombez E.A. , Vilain E. , Bernstein J.A. , Cowan T. , Lee- Messer C. , Enns G.M. , et al. 2009. Clinical and molecular heterogeneity in patients with the cblD inborn error of cobalamin metabolism. J Pediatr. 154 (4): 551556.
Moore, S. J. , Lawrence A.D. , Biedendieck R. , Deery E. , Frank S. , Howard M.J. , Rigby S.E. , and Warren M.J. . 2013. Elucidation of the anaerobic pathway for the corrin component of cobalamin (vitamin B12). Proc Natl Acad Sci U S A. 110 (37): 1490614911.
Moreira, E. S. , Brasch N.E. , and Yun J. . 2011. Vitamin B12 protects against superoxide-induced cell injury in human aortic endothelial cells. Free Radic Biol Med. 51 (4): 876883.
Morita, H. , Kurihara H. , Sugiyama T. , Hamada C. , Kurihara Y. , Shindo T. , Oh-hashi Y. , and Yazaki Y. . 1999. Polymorphism of the methionine synthase gene : association with homocysteine metabolism and late-onset vascular diseases in the Japanese population. Arterioscler Thromb Vasc Biol. 19 (2): 298302.
Morrow 3rd, G. , Mahoney M.J. , Mathews C. , and Lebowitz J. . 1975. Studies of methylmalonyl coenzyme A carbonylmutase activity in methylmalonic acidemia. I. Correlation of clinical, hepatic, and fibroblast data. Pediatr Res. 9 (8): 641644.
89 Mudd, S. H. , Levy H.L. , Abeles R.H. , and Jennedy J.P. Jr . 1969. A derangement in B12 metabolism leading to homocystinemia, cystathioninemia and methylmalonic aciduria. Biochem Biophys Res Commun. 35 (1): 121126.
Mudd, S. H. , Uhlendorf B.W. , and Hinds K.R. . 1970. Deranged B12 metabolism: studies of fibroblasts grown in tissue culture. Biochem Med. 4 (3): 215239.
Muir, M. , and Landon M. . 1985. Endogenous origin of microbiologically-inactive cobalamins (cobalamin analogues) in the human fetus. Br J Haematol. 61 (2): 303306.
Ng, F. T. T. , and Rempel G.L. . 1982. Ligand effects on transition metal-alkyl bond dissociation energies. J Am Chem Soc. 104 (2): 621623.
Nicolaou, A. , Ast T. , Garcia C.V. , Anderson M.M. , Gibbons J.M. , and Gibbons W.A. . 1994. In vitro NO and N2O inhibition of the branch point enzyme vitamin B12 dependent methionine synthase from rat brain synaptosomes. Biochem Soc Trans. 22 (3): 296S.
Nicolaou, A. , Kenyon S.H. , Gibbons J.M. , Ast T. , and Gibbons W.A. . 1996. In vitro inactivation of mammalian methionine synthase by nitric oxide. Eur J Clin Invest. 26 (2): 167170.
Nicolaou, A. , Waterfield C.J. , Kenyon S.H. , and Gibbons W.A. . 1997. The inactivation of methionine synthase in isolated rat hepatocytes by sodium nitroprusside. Eur J Biochem. 244 (3): 876882.
Okada, K. , Tanaka H. , Temporin K. , Okamoto M. , Kuroda Y. , Moritomo H. , Murase T. , and Yoshikawa H. . 2011. Akt/ mammalian target of rapamycin signaling pathway regulates neurite outgrowth in cerebellar granule neurons stimulated by methylcobalamin. Neurosci Lett. 495 (3): 201204.
Olteanu, H. , and Banerjee R. . 2001. Human methionine synthase reductase, a soluble P-450 reductaselike dual flavoprotein, is sufficient for NADPH-dependent methionine synthase activation. J Biol Chem. 276 (38): 3555835563.
Olteanu, H. , Munson T. , and Banerjee R. . 2002. Differences in the efficiency of reductive activation of methionine synthase and exogenous electron acceptors between the common polymorphic variants of human methionine synthase reductase. Biochemistry. 41 (45): 1337813385.
Orozco-Barrios, C. E. , Battaglia-Hsu S.F. , Arango-Rodriguez M.L. , Ayala-Davila J. , Chery C. , Alberto J.M. , Schroeder H. , Daval J.L. , Martinez-Fong D. , and Gueant J.L. . 2009. Vitamin B12- impaired metabolism produces apoptosis and Parkinson phenotype in rats expressing the transcobalamin-oleosin chimera in substantia nigra. PLoS One. 4 (12): e8268.
Padmakumar, R. , Padmakumar R. , and Banerjee R. . 1997. Evidence that cobalt-carbon bond homolysis is coupled to hydrogen atom abstraction from substrate in methylmalonyl-CoA mutase. Biochemistry. 36 (12): 37133718.
Padovani, D. , and Banerjee R. . 2006. Assembly and protection of the radical enzyme, methylmalonyl- CoA mutase, by its chaperone. Biochemistry. 45 (30): 93009306.
Padovani, D. , and Banerjee R. . 2009a. A G-protein editor gates coenzyme B12 loading and is corrupted in methylmalonic aciduria. Proc Natl Acad Sci U S A. 106 (51): 2156721572.
Padovani, D. , and Banerjee R. . 2009b. A rotary mechanism for coenzyme B12 synthesis by adenosyltransferase. Biochemistry. 48 (23): 53505357.
Padovani, D. , Labunska T. , and Banerjee R. . 2006. Energetics of interaction between the G-protein chaperone, MeaB, and B12-dependent methylmalonyl-CoA mutase. J Biol Chem. 281 (26): 1783817844.
Park, J. , Jeong J. , and Kim J. . 2012. Destabilization of a bovine B12 trafficking chaperone protein by oxidized form of glutathione. Biochem Biophys Res Commun. 420 (3): 547551.
Park, J. , and Kim J. . 2015. Characterization of a B12 trafficking chaperone protein from caenorhabditis elegans . Protein Pept Lett. 22 (1): 3138.
Pastore, A. , Martinelli D. , Piemonte F. , Tozzi G. , Boenzi S. , Di Giovamberardino G. , Petrillo S. , Bertini E. , and Dionisi-Vici C. . 2014. Glutathione metabolism in cobalamin deficiency type C (cblC). J Inherit Metab Dis. 37 (1): 125129.
Payne, K. A. , Quezada C.P. , Fisher K. , Dunstan M.S. , Collins F.A. , Sjuts H. , Levy C. , Hay S. , Rigby S.E. , and Leys D. . 2015. Reductive dehalogenase structure suggests a mechanism for B12-dependent dehalogenation. Nature. 517 (7535): 513516.
Pezacka, E. , Denison C. , Green R. , and Jacobsen D. . 1988. Biosynthesis of methylcobalamin: chemical model studies with thiol-cobalamin adducts and S-adenosylmethionine. J Cell Physiol. 107: 860a.
Pezacka, E. , Green R. , and Jacobsen D.W. . 1990. Glutathionylcobalamin as an intermediate in the formation of cobalamin coenzymes. Biochem Biophys Res Commun. 169 (2): 443450.
90 Pezacka, E. H. 1993. Identification and characterization of two enzymes involved in the intracellular metabolism of cobalamin. Cyanocobalamin beta-ligand transferase and microsomal cob(III) alamin reductase. Biochim Biophys Acta. 1157 (2): 167177.
Pezacka, E. H. , Jacobsen D.W. , Luce K. , and Green R. . 1992. Glial cells as a model for the role of cobalamin in the nervous system: impaired synthesis of cobalamin coenzymes in cultured human astrocytes following short-term cobalamin-deprivation. Biochem Biophys Res Commun. 184 (2): 832839.
Pezacka E.H. and Rosenblatt D.S. . 1994. Intracellular metabolism of cobalamin. Altered activities of p-axial-ligand transferase and microsomal cob(III)alamin reductase in cblC and cblD fibroblasts. Advances in Thomas Addisons Diseases. H.R. Bhatt , V.H.T. James ,

G.M. Besser , G.F. Bottazzo and H. Keen (eds.). Bristol. J. Endocrinol. pp. 315323.
Plesa, M. , Kim J. , Paquette S.G. , Gagnon H. , Ng-Thow-Hing C. , Gibbs B.F. , Hancock M.A. , Rosenblatt D.S. , and Coulton J.W. . 2011. Interaction between MMACHC and MMADHC, two human proteins participating in intracellular vitamin B12 metabolism. Mol Genet Metab. 102 (2): 139148.
Pons, L. , Guy M. , Lambert D. , Hatier R. , and Gueant J. . 2000. Transcytosis and coenzymatic conversion of [(57)Co]cobalamin bound to either endogenous transcobalamin II or exogenous intrinsic factor in caco-2 cells. Cell Physiol Biochem. 10 (3): 135148.
Quadros, E. V. , Lai S.C. , Nakayama Y. , Sequeira J.M. , Hannibal L. , Wang S. , Jacobsen D.W. , Fedosov S. , Wright E. , Gallagher R.C. , et al. 2010. Positive newborn screen for methylmalonic aciduria identifies the first mutation in TCblR/CD320, the gene for cellular uptake of transcobalamin- bound vitamin B(12). Hum Mutat. 31 (8): 924929.
Quadros, E. V. , Nakayama Y. , and Sequeira J.M. . 2009. The protein and the gene encoding the receptor for the cellular uptake of transcobalamin-bound cobalamin. Blood. 113 (1): 186192.
Quadros, E. V. , and Sequeira J.M. . 2013. Cellular uptake of cobalamin: transcobalamin and the TCblR/ CD320 receptor. Biochimie. 95 (5): 10081018.
Quintana, A. M. , Geiger E.A. , Achilly N. , Rosenblatt D.S. , Maclean K.N. , Stabler S.P. , Artinger K.B. , Appel B. , and Shaikh T.H. . 2014. Hcfc1b, a zebrafish ortholog of HCFC1, regulates craniofacial development by modulating mmachc expression. Dev Biol. 396 (1): 94106.
Ramanujam, K. S. , Seetharam S. , Dahms N.M. , and Seetharam B. . 1991a. Functional expression of intrinsic factor-cobalamin receptor by renal proximal tubular epithelial cells. J Biol Chem. 266 (20): 1313513140.
Ramanujam, K. S. , Seetharam S. , Dahms N.M. , and Seetharam B. . 1994. Effect of processing inhibitors on cobalamin (vitamin B12) transcytosis in polarized opossum kidney cells. Arch Biochem Biophys. 315 (1): 815.
Ramanujam, K. S. , Seetharam S. , Ramasamy M. , and Seetharam B. . 1991b. Expression of cobalamin transport proteins and cobalamin transcytosis by colon adenocarcinoma cells. Am J Physiol. 260 (3 Pt 1): G416422.
Ramanujam, K. S. , Seetharam S. , and Seetharam B. . 1992. Leupeptin and ammonium chloride inhibit intrinsic factor mediated transcytosis of [57Co]cobalamin across polarized renal epithelial cells. Biochem Biophys Res Commun. 182 (2): 439446.
Raux, E. , Lanois A. , Rambach A. , Warren M.J. , and Thermes C. . 1998. Cobalamin (vitamin B12) biosynthesis: functional characterization of the Bacillus megaterium cbi genes required to convert uroporphyrinogen III into cobyrinic acid a, c-diamide. Biochem J. 335 (Pt 1): 167173.
Richard, E. , Alvarez-Barrientos A. , Perez B. , Desviat L.R. , and Ugarte M. . 2007. Methylmalonic acidaemia leads to increased production of reactive oxygen species and induction of apoptosis through the mitochondrial/caspase pathway. J Pathol. 213 (4): 453461.
Richard, E. , Jorge-Finnigan A. , Garcia-Villoria J. , Merinero B. , Desviat L.R. , Gort L. , Briones P. , Leal F. , Perez-Cerda C. , Ribes A. , et al. 2009. Genetic and cellular studies of oxidative stress in methylmalonic aciduria (MMA) cobalamin deficiency type C (cblC) with homocystinuria (MMACHC). Hum Mutat. 30 (11): 15581566.
Rosenberg, L. E. , Patel L. , and Lilljeqvist A.C. . 1975. Absence of an intracellular cobalamin-binding protein in cultured fibroblasts from patients with defective synthesis of 5-deoxyadenosylcobalamin and methylcobalamin. Proc Natl Acad Sci U S A. 72 (11): 46174621.
Rosenblatt, D. S. , Hosack A. , Matiaszuk N.V. , Cooper B.A. , and Laframboise R. . 1985. Defect in vitamin B12 release from lysosomes: newly described inborn error of vitamin B12 metabolism. Science. 228 (4705): 13191321.
91 Rosenblatt, D. S. , Laframboise R. , Pichette J. , Langevin P. , Cooper B.A. , and Costa T. . 1986. New disorder of vitamin B12 metabolism (cobalamin F) presenting as methylmalonic aciduria. Pediatrics. 78 (1): 5154.
Rosenblatt, D. S. , and Whitehead V.M. . 1999. Cobalamin and folate deficiency: acquired and hereditary disorders in children. Semin Hematol. 36 (1): 1934.
Roth, J. R. , Lawrence J.G. , and Bobik T.A. . 1996. Cobalamin (coenzyme B12): synthesis and biological significance. Annu Rev Microbiol. 50: 137181.
Rutsch, F. , Gailus S. , Miousse I.R. , Suormala T. , Sagne C. , Toliat M.R. , Nurnberg G. , Wittkampf T. , Buers I. , Sharifi A. , et al. 2009. Identification of a putative lysosomal cobalamin exporter altered in the cblF defect of vitamin B12 metabolism. Nat Genet. 41 (2): 234239.
Rutsch, F. , Gailus S. , Suormala T. , and Fowler B. . 2011. LMBRD1: the gene for the cblF defect of vitamin B12 metabolism. J Inherit Metab Dis. 34 (1): 121126.
Sakamoto, O. , Ohura T. , Matsubara Y. , Takayanagi M. , and Tsuchiya S. . 2007. Mutation and haplotype analyses of the MUT gene in Japanese patients with methylmalonic acidemia. J Hum Genet. 52 (1): 4855.
Saridakis, V. , Yakunin A. , Xu X. , Anandakumar P. , Pennycooke M. , Gu J. , Cheung F. , Lew J.M. , Sanishvili R. , Joachimiak A. , et al. 2004. The structural basis for methylmalonic aciduria. The crystal structure of archaeal ATP:cobalamin adenosyltransferase. J Biol Chem. 279 (22): 2364623653.
Scalabrino, G. 2009. The multi-faceted basis of vitamin B12 (cobalamin) neurotrophism in adult central nervous system: Lessons learned from its deficiency. Prog Neurobiol. 88 (3): 203220.
Schubert, H. L. , and Hill C.P. . 2006. Structure of ATP-bound human ATP:cobalamin adenosyltransferase. Biochemistry. 45 (51): 1518815196.
Seifert, C. , Bowien S. , Gottschalk G. , and Daniel R. . 2001. Identification and expression of the genes and purification and characterization of the gene products involved in reactivation of coenzyme B12-dependent glycerol dehydratase of Citrobacter freundii . Eur J Biochem. 268 (8): 23692378.
Shih, V. E. , Axel S.M. , Tewksbury J.C. , Watkins D. , Cooper B.A. , and Rosenblatt D.S. . 1989. Defective lysosomal release of vitamin B12 (cb1F): a hereditary cobalamin metabolic disorder associated with sudden death. Am J Med Genet. 33 (4): 555563.
Sillaots, S. L. , Hall C.A. , Hurteloup V. , and Rosenblatt D.S. . 1992. Heterogeneity in cblG: differential retention of cobalamin on methionine synthase. Biochem Med Metab Biol. 47 (3): 242249.
Soda, R. , Tavassoli M. , and Jacobsen D.W. . 1985. Receptor distribution and the endothelial uptake of transcobalamin II in liver cell suspensions. Blood. 65 (4): 795802.
Sponne, I. E. , Gaire D. , Stabler S.P. , Droesch S. , Barbe F.M. , Allen R.H. , Lambert D.A. , and Nicolas J.P. . 2000. Inhibition of vitamin B12 metabolism by OH-cobalamin c-lactam in rat oligodendrocytes in culture: a model for studying neuropathy due to vitamin B12 deficiency. Neurosci Lett. 288 (3): 191194.
St Maurice, M. , Mera P. , Park K. , Brunold T.C. , Escalante-Semerena J.C. , and Rayment I. . 2008. Structural characterization of a human-type corrinoid adenosyltransferase confirms that coenzyme B12 is synthesized through a four-coordinate intermediate. Biochemistry. 47 (21): 57555766.
Stabler, S. P. , Brass E.P. , Marcell P.D. , and Allen R.H. . 1991. Inhibition of cobalamin-dependent enzymes by cobalamin analogues in rats. J Clin Invest. 87 (4): 14221430.
Stich, T. A. , Buan N.R. , and Brunold T.C. . 2004. Spectroscopic and computational studies of Co2+corrinoids: spectral and electronic properties of the biologically relevant base-on and base-off forms of Co2+cobalamin. J Am Chem Soc. 126 (31): 97359749.
Stich, T. A. , Yamanishi M. , Banerjee R. , and Brunold T.C. . 2005. Spectroscopic evidence for the formation of a four-coordinate Co2+ cobalamin species upon binding to the human ATP:cobalamin adenosyltransferase. J Am Chem Soc. 127 (21): 76607661.
Stockler, S. , Corvera S. , Lambright D. , Fogarty K. , Nosova E. , Leonard D. , Steinfeld R. , Ackerley C. , Shyr C. , Au N. , et al. 2014. Single point mutation in Rabenosyn-5 in a female with intractable seizures and evidence of defective endocytotic trafficking. Orphanet J

Rare Dis. 9: 141.
Strope, S. , Rivi R. , Metzger T. , Manova K. , and Lacy E. . 2004. Mouse amnionless, which is required for primitive streak assembly, mediates cell-surface localization and endocytic function of cubilin on visceral endoderm and kidney proximal tubules. Development. 131 (19): 47874795.
Stucki, M. , Coelho D. , Suormala T. , Burda P. , Fowler B. , and Baumgartner M.R. . 2012. Molecular mechanisms leading to three different phenotypes in the cblD defect of intracellular cobalamin metabolism. Hum Mol Genet. 21 (6): 14101418.
92 Suarez-Moreira, E. , Yun J. , Birch C.S. , Williams J.H. , McCaddon A. , and Brasch N.E. . 2009. Vitamin B12 and redox homeostasis: cob(II)alamin reacts with superoxide at rates approaching superoxide dismutase (SOD). J Am Chem Soc. 131 (42): 1507815079.
Sugase, K. , Dyson H.J. , and Wright P.E. . 2007. Mechanism of coupled folding and binding of an intrinsically disordered protein. Nature. 447 (7147): 10211025.
Suormala, T. , Baumgartner M.R. , Coelho D. , Zavadakova P. , Kozich V. , Koch H.G. , Berghauser M. , Wraith J.E. , Burlina A. , Sewell A. , et al. 2004. The cblD defect causes either isolated or combined deficiency of methylcobalamin and adenosylcobalamin synthesis. J Biol Chem. 279 (41): 4274242749.
Takahashi, K. , Tavassoli M. , and Jacobsen D.W. . 1980. Receptor binding and internalization of immobilized transcobalamin II by mouse leukaemia cells. Nature. 288 (5792): 713715.
Toraya, T. 2000. Radical catalysis of B12 enzymes: structure, mechanism, inactivation, and reactivation of diol and glycerol dehydratases. Cell Mol Life Sci. 57 (1): 106127.
Trakadis, Y. J. , Alfares A. , Bodamer O.A. , Buyukavci M. , Christodoulou J. , Connor P. , Glamuzina E. , Gonzalez-Fernandez F. , Bibi H. , Echenne B. , et al. 2014. Update on transcobalamin deficiency: clinical presentation, treatment and outcome. J Inherit Metab Dis. 37 (3): 461473.
Utley, C. S. , Marcell P.D. , Allen R.H. , Antony A.C. , and Kolhouse J.F. . 1985. Isolation and characterization of methionine synthetase from human placenta. J Biol Chem. 260 (25): 1365613665.
Vassiliadis, A. , Rosenblatt D.S. , Cooper B.A. , and Bergeron J.J. . 1991. Lysosomal cobalamin accumulation in fibroblasts from a patient with an inborn error of cobalamin metabolism (cblF complementation group): visualization by electron microscope radioautography. Exp Cell Res. 195 (2): 295302.
Warren, M. J. 2006. Finding the final pieces of the vitamin B12 biosynthetic jigsaw. Proc Natl Acad Sci U S A. 103 (13): 47994800.
Warren, M. J. , Raux E. , Schubert H.L. , and Escalante-Semerena J.C. . 2002. The biosynthesis of adenosylcobalamin (vitamin B12). Nat Prod Rep. 19 (4): 390412.
Watanabe, F. , Nakano Y. , Maruno S. , Tachikake N. , Tamura Y. , and Kitaoka S. . 1989. NADH- and NADPH-linked aquacobalamin reductases occur in both mitochondrial and microsomal membranes of rat liver. Biochem Biophys Res Commun. 165 (2): 675679.
Watanabe, F. , Saido H. , Yamaji R. , Miyatake K. , Isegawa Y. , Ito A. , Yubisui T. , Rosenblatt D.S. , and Nakano Y. . 1996. Mitochondrial NADH- or NADPH-linked aquacobalamin reductase activity is low in human skin fibroblasts with defects in synthesis of cobalamin coenzymes. J Nutr. 126 (12): 29472951.
Watkins, D. , and Rosenblatt D.S. . 1986. Failure of lysosomal release of vitamin B12: a new complementation group causing methylmalonic aciduria (cblF). Am J Hum Genet. 39 (3): 404408.
Watkins, D. , and Rosenblatt D.S. . 1989. Functional methionine synthase deficiency (cblE and cblG): clinical and biochemical heterogeneity. Am J Med Genet. 34 (3): 427434.
Watkins, D. , and Rosenblatt D.S. . 2011. Inborn errors of cobalamin absorption and metabolism. Am J Med Genet C Semin Med Genet. 157C (1): 3344.
Watkins, D. , Ru M. , Hwang H.Y. , Kim C.D. , Murray A. , Philip N.S. , Kim W. , Legakis H. , Wai T. , Hilton J.F. , et al. 2002. Hyperhomocysteinemia due to methionine synthase deficiency, cblG: structure of the MTR gene, genotype diversity, and recognition of a common mutation, P1173L. Am J Hum Genet. 71 (1): 143153.
Wilkemeyer, M. F. , Crane A.M. , and Ledley F.D. . 1991. Differential diagnosis of mut and cbl methylmalonic aciduria by DNA-mediated gene transfer in primary fibroblasts. J Clin Invest. 87 (3): 915918.
Willard, H. F. , Mellman I.S. , and Rosenberg L.E. . 1978. Genetic complementation among inherited deficiencies of methylmalonyl-CoA mutase activity: evidence for a new class of human cobalamin mutant. Am J Hum Genet. 30 (1): 113.
Willard, H. F. , and Rosenberg L.E. . 1979. Inborn errors of cobalamin metabolism: effect of cobalamin supplementation in culture on methylmalonyl CoA mutase activity in normal and mutant human fibroblasts. Biochem Genet. 17 (12): 5775.
Wilson, A. , Leclerc D. , Saberi F. , Campeau E. , Hwang H.Y. , Shane B. , Phillips J.A. 3rd , Rosenblatt D.S. , and Gravel R.A. . 1998. Functionally null mutations in patients with the cblG-variant form of methionine synthase deficiency. Am J Hum Genet. 63 (2): 409414.
93 Wolthers, K. R. , Basran J. , Munro A.W. , and Scrutton N.S. . 2003. Molecular dissection of human methionine synthase reductase: determination of the flavin redox potentials in full-length enzyme and isolated flavin-binding domains. Biochemistry. 42 (13): 39113920.
Wolthers, K. R. , Lou X. , Toogood H.S. , Leys D. , and Scrutton N.S. . 2007a. Mechanism of coenzyme binding to human methionine synthase reductase revealed through the crystal structure of the FNR-like module and isothermal titration calorimetry. Biochemistry. 46 (42): 1183311844.
Wolthers, K. R. , Toogood H.S. , Jowitt T.A. , Marshall K.R. , Leys D. , and Scrutton N.S. . 2007b. Crystal structure and solution characterization of the activation domain of human methionine synthase. FEBS J. 274 (3): 738750.
Wolthers, K. R. , and Scrutton N.S. . 2004. Electron transfer in human methionine synthase reductase studied by stopped-flow spectrophotometry. Biochemistry. 43 (2): 490500.
Wolthers, K. R. , and Scrutton N.S. . 2007. Protein interactions in the human methionine synthase- methionine synthase reductase complex and implications for the mechanism of enzyme reactivation. Biochemistry. 46 (23): 66966709.
Wolthers, K. R. , and Scrutton N.S. . 2009. Cobalamin uptake and reactivation occurs through specific protein interactions in the methionine synthase-methionine synthase reductase complex. FEBS J. 276 (7): 19421951.
Yamada, K. , Gherasim C. , Banerjee R. , and Koutmos M. . 2015. Structure of Human B12 trafficking protein CblD reveals molecular mimicry and identifies a new subfamily of Nitro-FMN reductases. J Biol Chem. 290 (49): 291552916.
Yamada, K. , Gravel R.A. , Toraya T. , and Matthews R.G. . 2006. Human methionine synthase reductase is a molecular chaperone for human methionine synthase. Proc Natl Acad Sci U S A. 103 (25): 94769481.
Yamada, R. , Shimizu S. , and Fukui S. . 1968. Disproportionation of vitamin B12r under various mild conditions. Biochemistry. 7 (5): 17131719.
Yamanishi, M. , Labunska T. , and Banerjee R. . 2005. Mirror base-off conformation of coenzyme B12 in human adenosyltransferase and its downstream target, methylmalonyl-CoA mutase. J Am Chem Soc. 127 (2): 526527.
Yu, H.C. , Sloan J.L. , Scharer G. , Brebner A. , Quintana A.M. , Achilly N.P. , Manoli I. , Coughlin C.R. 2nd , Geiger E.A. , Schneck U. , et al. 2013. An X-linked cobalamin disorder caused by mutations in transcriptional coregulator HCFC1. Am J Hum Genet. 93 (3): 506514.
Zhang, J. , Wu X. , Padovani D. , Schubert H.L. , and Gravel R.A. . 2009. Ligand-binding by catalytically inactive mutants of the cblB complementation group defective in human ATP:cob(I)alamin adenosyltransferase. Mol Genet Metab. 98 (3): 278284.
Zheng, D. , Yan L. , and Birke R.L. . 2002. Electrochemical and spectral studies of the reactions of aquocobalamin with nitric oxide and nitrite ion. Inorg Chem. 41 (9): 25482555.

Inherited Defects of Cobalamin Metabolism

Alfares, A. , Dempsey Nunez L. , Al-Thihli K. , Mitchell J. , Melanon S. , Anastasio N. , Ha K.C.H. , Majewski J. , Rosenblatt D.S. , and Braverman N. 2011. Combined malonic and methylmalonic aciduria: exome sequencing reveals mutations in the ACSF3 gene in patients with a non-classic phenotype. J Med Genet. 48: 602605.

Andersson, H. C. , and Shapira E. 1998. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). J Pediatr. 132: 121124.

Atkinson, C. , Miousse I.R. , Watkins D. , Rosenblatt D.S. , and Raiman J.A.J. 2014. Clinical, biochemical, and molecular presentation in a patient with the cblD-homocystinuria inborn error of cobalamin metabolism. JIMD Rep. 17: 7781.

Baker, E. H. , Sloan J.L. , Hauser N.S. , Gropman A.L. , Adams D.R. , Toro C. , Manoli I. , and Venditti C.P. 2015. MRI characteristics of globus pallidus infarcts in isolated methylmalonic acidemia. Am J Neuroradiol. 36: 194201.

Batshaw, M. L. , Thomas G.H. , Cohen S.R. , Matalon R. , and Mahoney M.J. 1984. Treatment of the cbl B form of methylmalonic acidaemia with adenosylcobalamin. J Inher Metab Dis. 7: 6568.

Carrillo-Carrasco, N. , Chandler R.J. , and Venditti C.P. 2012. Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentation, diagnosis and management. J Inher Metab Dis. 35: 91102.

Carrillo-Carrasco, N. , Sloan J. , Valle D. , Hamosh A. , and Venditti C.P. 2009. Hydroxocobalamin dose escalation improves metabolic control in cblC. J Inher Metab Dis. 32: 728731.

Carrillo-Carrasco, N. , and Venditti C.P. 2012. Combined methylmalonic acidemia and homocystinuria, cblC type. II. Complications, pathophysiology, and outcomes. J Inher Metab Dis. 35: 103114.

Cerone, R. , Schiaffino M.C. , Caruso U. , Lupino S. , and Gatti R. 1999. Minor facial anomalies in combined methylmalonic aciduria and homocystinuria due to a defect in cobalamin metabolism. J Inher Metab Dis. 22: 247250.

Cheng, K. H. , Liu M.Y. , Kao C.H. , Chen Y.J. , Hsiao K.J. , Liu T.T. , Lin H.Y. , Huang C.H. , Chiang C.C. , Ho H.J. , Lin S.P. , Lee N.C. , Hwu W.L. , Lin J.L. , Hung P.Y. , and Niu D.M. 2010. Newborn screening for methylmalonic acid by tandem mass spectroscopy: 7 years experience from two centers in Taiwan. J Chin Med Assoc. 73: 314318.

Coelho, D. , Kim J.C. , Miousse I.R. , Fung S. , Du Moulin M. , Buers I. , Suormala T. , Burda P. , Frapolli M. , Stucki M. , Nrnberg P. , Thiele H. , Robenek H. , Hhne W. , Longo N. , Pasquali M. , Mengel E. , Watkins D. , Shoubridge E.A. , Majewski J. , Rosenblatt D.S. , Fowler B. , Rutsch F. , and Baumgartner M.R. 2012. Mutations in ABCD4 cause a new inborn error of vitamin B12 metabolism. Nature Genet. 44: 11521155.

Coelho, D. , Suormala T. , Stucki M. , Lerner-Ellis J.P. , Rosenblatt D.S. , Newbold R.F. , Baumgartner M.R. , and Fowler B. 2008. Gene identification for the cblD defect of vitamin B12 metabolism. N Engl J Med. 358: 14541464.

110 Cosson, M. A. , Benoist J.F. , Touati G. , Dchaux M. , Royer N. , Grandin L. , Jais J.P. , Boddaert N. , Barbier V. , Desguerre I. , Campeau P.M. , Rabier D. , Valayannopoulos V. , Niaudet P. , and de Lonlay P. 2009. Long-term outcome in methylmalonic aciduria: a series of 30 French patients. Mol Genet Metab. 97: 172178.

Coulombe, J. T. , Shih V.E. , and Levy H.L. 1981. Massachusetts metabolic disorders screening program. II. Methylmalonic aciduria. Pediatrics. 67: 2631.

Cusmano-Ozog, K. , Lorey F. , Levine S. , Martin M. , Nicholas E. , Packman S. , Rosenblatt D.S. , Cederbaum S. , Cowan T.M. , and Enns G.M. 2007. Cobalamin C disease identified by expanded newborn screening: the California experience. Mol Genet Metab. 90: 240.

Dobson, C. M. , Gradinger A. , Longo N. , Wu X. , Leclerc D. , Lerner-Ellis J. , Lemieux M. , Belair C. , Watkins D. , Rosenblatt D.S. , and Gravel R.A. 2006. Homozygous nonsense mutation in the MCEE gene and siRNA suppression of methylmalonyl-CoA epimerase expression: a novel cause of mild methylmalonic aciduria. Mol Genet Metab. 88: 327333.

Fischer, S. , Huemer M. , Baumgartner M. , Deodato F. , Ballhausen D. , Boneh A. , Burlina A.B. , Cerone R. , Garcia P. , Gkcay G. , Grnewald S. , Hberle J. , Jaeken J. , Ketteridge D. , Lindner M. , Mandel H. , Martinelli D. , Martins E.G. , Schwab K.O. , Gruenert S.C. , Schwahn B. , Sztriha L. , Tomaske M. , Trefz F. , Vilarinho L. , Rosenblatt D.S. , Fowler B. , and Dionisi-Vici C. 2014. Clinical presentation and outcome in a series of 88 patients with the cblC defect. J Inher Metab Dis. 37: 831840.

Fowler, B. , Leonard J.V. , and Baumgartner M.R. 2008. Causes and diagnostic approaches to methylmalonic acidurias. J Inher Metab Dis. 31: 350360.

Grard, M. , Morin G. , Bourillon A. , Colson C. , Mathieu S. , Rabier D. , Billette de Villemeur T. , Ogier de Baulny H. , and Benoist J.F. 2015. Multiple congenital anomalies in two boys with mutations in HCFC1 and cobalamin disorder. Eur J Med Genet. 58: 148153.

Gold, R. , Bogdahn U. , Kappos L. , Toyka K.V. , Baumgartner E.R. , Fowler B. , and Wendel U. 1996. Hereditary defect of cobalamin metabolism (homocystinuria and methylmalonic aciduria) of juvenile onset. J Neurol Neurosurg Psych. 60: 107108.

Gravel, R. A. , Mahoney M.J. , Ruddle F.H. , and Rosenberg L.E. 1975. Genetic complementation in heterokaryons of human fibroblasts defective in cobalamin metabolism. Proc Natl Acad Sci USA 72: 31813185.

Gu, W. , Koh W. , Blumenfeld Y.J. , El-Sayed Y.Y. , Hudgens L. , Hintz S.R. , and Quake S.R. 2014. Noninvasive prenatal diagnosis in a fetus at risk for methylmalonic acidemia. Genet Med. 16: 564567.

Gulati, S. , Baker P. , Li Y.N. , Fowler B. , Kruger W. , Brody L.C. , and Banerjee R. 1996. Defects in human methionine synthase in cblG patients. Hum Molec Genet. 5: 18591865.

Homolova, K. , Zavadakova P. , Doktor T.K. , Schroeder L.D. , Kozich V. , and Andresen B.S. 2010. The deep intronic c.903+469T>C mutation in the MTRR gene creates an SF2/ASF binding exonic splicing enhancer, which leads to pseudoexon activation and causes the cblE type of homocystinuria. Hum Mut. 31: 437444.

Hrster, F. , Baumgartner M.R. , Viardot C. , Suormala T. , Burgard P. , Fowler B. , Hoffmann G.F. , Garbade S.F. , Klker S. , and Baumgartner E.R. 2007. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut0, mut-, cblA, cblB). Pediatr Res. 62: 225230.

Huemer, M. , Brer C. , Jesina P. , Kozich V. , Landolt M.A. , Suormala T. , Fowler B. , Augoustides- Savopoulou P. , Blair E. , Brennerova K. , Broomfield A. , De Meirleir L. , Gkcay G. , Hennermann J. , Jardine P. , Koch J. , Lorenzl S. , Lotz-Havla A.S. , Noss J. , Parini R. , Peters H. , Plecko B. , Ramos F.J. , Schlune A. , Tsiakas K. , Zerjav Tansek M. , and Baumgartner M.R. 2014a. Clinical onset and course, response to treatment and outcome in 24 patients with the cblE or cblG remethylation defect complemented by genetic and in vitro enzyme study data. J Inher Metab Dis. doi:10.1007/s10545-014-9803-7.

Huemer, M. , Scholl-Brgi S. , Hadaya K. , Kern I. , Beer R. , Sepp K. , Fowler B. , Baumgartner M.R. , and Karali D. 2014b. Three new cases of late-onset cblC defect and review of the literature illustrating when to consider inborn errors of metabolism beyond infancy. Orphanet J Rare Dis. 9: 161.

Huemer, M. , Simma B. , Fowler B. , Suormala T. , Bodamer O.A. , and Sass J.O. 2005. Prenatal and postnatal treatment in cobalamin C defect. J Pediatr. 147: 469472.

Karth, P. , Singh R. , Kim J. , and Costakos D. 2012. Bilateral central retinal artery occlusions in an infant with hyperhomocysteinemia. J AAPOS. 16: 398400.

111 Kim, J. C. , Lee N.C. , Hwu P.W. , Chien Y.H. , Fahiminiya S. , Majewski J. , Watkins D. , and Rosenblatt D.S. 2012. Late onset of symptoms in an atypical patient with the cblJ inborn error of vitamin B12 metabolism: diagnosis and novel mutation revealed by exome sequencing. Mol Genet Metab. 107: 664668.

Kmhoff, M. , Roofthooft M.T. , Westra D. , Teertstra T.K. , Losito A. , N. C. A. J. van de Car , and Berger R.M.F. 2013. Combined pulmonary arterial hypertension and renal thrombotic microangiopathy in cobalamin C deficiency. Pediatrics. 132: e540e544.
Ktena Y.P. , Paul S.M. , Hauser N.S. , Sloan J.L. , Gropman A. , Manoli I. and Venditti C.P. 2015. Delineating the spectrum of impairments, disabilities, and rehabilitation needs in methylmalonic acidemia (MMA). Am J Med Genet. A doi: http://10.1002/ajmg.a.37127.
Leclerc, D. , Campeau E. , Goyette P. , Adjalla C.E. , Christensen B. , Ross M. , Eydoux P. , Rosenblatt D.S. , Rozen R. , and Gravel R.A. 1996. Human methionine synthase: cDNA cloning and identification of mutations in patients of the cblG complementation group of folate/cobalamin disorders. Hum Molec Genet. 5: 18671874.
Leclerc, D. , Wilson A. , Dumas R. , Gafuik C. , Song D. , Watkins D. , Heng H.H.Q. , Rommens J.M. , Scherer S.W. , Rosenblatt D.S. , and Gravel R.A. 1998. Cloning and mapping of a cDNA for methionine synthase reductase, a flavoprotein defective in patients with homocystinuria. Proc Natl Acad Sci USA 95: 30593064.
Lemieux, B. , Auray-Blais C. , Gigure R. , Shapcott D. , and Scriver C.R. 1988. Newborn urine screening experience with over one million infants in the Quebec Network of Genetic Medicine. J Inher Metab Dis. 11: 4555.
Lerner-Ellis, J. P. , Tirone J.C. , Pawelek P.D. , Dor C. , Atkinson J.L. , Watkins D. , Morel C.F. , Fujiwara T.M. , Moras E. , Hosack A.R. , Dunbar G.V. , Antonicka H. , Forgetta V. , Dobson C.M. , Leclerc D. , Gravel R.A. , Shoubridge E.A. , Coulton J.W. , Lepage P. , Rommens J.M. , Morgan K. , and Rosenblatt D.S. 2006. Identification of the gene responsible for methylmalonic aciduria and homocystinuria, cblC type. Nature Genet. 38: 93100.
Lin, H. J. , Neidich J.A. , Salazar D. , Thomas-Johnson E. , Ferreira B.F. , Kwong A.M. , Lin A.M. , Jonas A.J. , Levine S. , Lorey F. , and Rosenblatt D.S. 2009. Asymptomatic maternal combined homocystinuria and methylmalonic aciduria (cblC) detected through low carnitine levels on newborn screening. J Pediatr. 155: 924927.
Liu, M. Y. , Yang Y.L. , Chang Y.C. , Chiang S.H. , Lin S.P. , Han L.S. , Qi Y. , Hsiao K.J. , and Liu T.T. 2010. Mutation spectrum of MMACHC in Chinese patients with combined methylmalonic aciduria and homocystinuria. J Hum Genet. 55: 621626.
Matsui, S. M. , Mahoney M.J. , and Rosenberg L.E. 1983. The natural history of the inherited methylmalonic acidemias. N Engl J Med. 308: 857861.
Mitchell, G. A. , Watkins D. , Melanon S.B. , Rosenblatt D.S. , Geoffroy G. , Orquin J. , Homsy M.B. , and Dallaire L. 1986. Clinical heterogeneity in cobalamin C variant of combined homocystinuria and methylmalonic aciduria. J Pediatr. 108: 410415.
Montgomery, J. A. , Mamer O.A. , and Scriver C.R. 1983. Metabolism of methylmalonic acid in rats. Is methylmalonyl-coenzyme a racemase deficiency symptomatic in man? J Clin Invest. 72: 19371947.
Morath, M. A. , Hrster F. , and Sauer S.W. 2013. Renal dysfunction in methylmalonic aciduias: review for the pediatric nephrologist. Pediatr Nephrol. 28: 227235.
Morel, C. F. , Lerner-Ellis J.P. , and Rosenblatt D.S. 2006. Combined methylmalonic aciduria and homocystinuria (cblC): phenotype-genotype correlations and ethnic-specific observations. Mol Genet Metab. 88: 315321.
Morel, C. F. , Watkins D. , Scott P. , Rinaldo P. , and Rosenblatt D.S. 2005. Prenatal diagnosis for methylmalonic acidemia and inborn errors of vitamin B12 metabolism and transport. Mol Genet Metab. 86: 160171.
Niemi, A. K. , Kim I.K. , Krueger C.E. , Cowan T.M. , Baugh N. , Farrell R. , Bonham C.A. , Concepcian W. , Esquivel C.O. , and Enns G.M. 2015. Treatment of methylmalonic acidemia by liver or combined liver-kidney transplantation. J Pediatr. doi:10.1016/j.peds.2015.01.051.
Nizon, M. , Ottolenghi C. , Valayannopoulos V. , Arnoux J.B. , Barbier V. , Habarou F. , Desguerre I. , Boddaert N. , Bonnefont J.P. , Acqaviva C. , Benoist J.F. , Rabier D. , Touati G. , and de Lonlay P. 2013. Long-term neurological outcome of a cohort of 80 patients with classical organic acidurias. Orphanet J Rare Dis. 8: 148.
112 Oladipo, O. , Rosenblatt D.S. , Watkins D. , Miousse I.R. , Sprietsma L. , Dietzen D.J. , and Shinawi M. 2011. Cobalamin F disease detected by newborn screening and follow-up on a 14-year-old patient. Pediatrics. 128: e1636e1640.
OShea, C. J. , Sloan J.L. , Wiggs E.A. , Pao M. , Gropman A. , Baker E.H. , Manoli I. , Venditti C.P. , and Snow J. 2012. Neurocognitive phenotype of isolated methylmalonic acidemia. Pediatrics. 129: e1541e1551.
Ostergaard, E. 2008. Disorders caused by deficiency of succinate-CoA ligase. J Inher Metab Dis. 31: 226229.
Pangilinan, F. , Mitchell A. , VanderMeer J. , Molloy A.M. , Troendle J. , Conley M. , Kirke P.N. , Sutton M. , Seqeira J.M. , Quadros E.V. , Mills J.M. , and Brody L.C. 2010. Transcobalamin II receptor polymorphisms are associated with increased risk for neural tube defects. J Med Genet. 47: 677685.
Powers, J. M. , Rosenblatt D.S. , Schmidt R.E. , Cross A.H. , Black J.T. , Moser A.B. , Moser H.W. , and Morgan D.J. 2001. Neurological and neuropathologic heterogeneity in two brothers with cobalamin C deficiency. Ann Neurol. 49: 396400.
Profitlich, L. E. , Kirmse B. , Wasserstein M.P. , Diaz G.A. , and Srivastava S. 2009. High prevalence of structural heart disease in children with cblC-type methylmalonic aciduria and homocystinuria. Mol Genet Metab. 98: 344348.
Quadros, E. V. , Lai S.C. , Nakayama Y. , Sequeira J.M. , Hannibal L. , Wang S. , Jacobsen D.W. , Fedosov S.N. , Wright E. , Gallagher R.C. , Anastasio N. , Watkins D. , and Rosenblatt D.S. 2010. Positive newborn screen for methylmalonic aciduria identifies the first mutation in TCblR/CD320, the gene for cellular uptake of transcobalamin-bound vitamin B12. Hum Mut. 31: 924929.
Robb, R. M. , Dowton S.B. , Fulton A.B. , and Levy H.L. 1984. Retinal degeneration in vitamin B12 disorder associated with methylmalonic aciduria and sulfur amino acid abnormalities. Am J Ophthalmol. 97: 691696.
Rosenblatt, D. S. , Aspler A.L. , Shevell M.I. , Pletcher B.A. , Fenton W.A. , and Seashore M.R. 1997. Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC) . J Inher Metab Dis. 20: 528538.
Rosenblatt, D. S. , Cooper B.A. , Pottier A. , Lue-Shing H. , Matiaszuk N. , and Grauer K. 1984. Altered vitamin B12 metabolism in fibroblasts from a patient with megaloblastic anemia and homocystinuria due to a new defect in methionine biosynthesis. J Clin Invest. 74: 21492156.
Rosenblatt, D. S. , Cooper B.A. , Schmutz S.M. , Zaleski W.A. , and Casey R.E. 1985. Prenatal vitamin B12 therapy of a fetus with methylcobalamin deficiency (cobalamin E disease). Lancet. 325: 11271129.
Rosenblatt, D. S. , Hosack A. , Matiaszuk N.V. , Cooper B.A. , and Laframboise R. 1985. Defect in vitamin B12 release from lysosomes: newly described inborn error of vitamin B12 metabolism. Science. 228: 13191321.
Rosenblatt D.S. and Watkins D. 2010. Prenatal diagnosis of miscellaneous biochemical disorders. pp. 614-627. In: A. Milunsky and J.M. Milunsky (eds.). Genetic Disorders and the Fetus. Diagnosis, Prevention and Treatment. Wiley-Blackwell, London.
Rutsch, F. , Gailus S. , Miousse I.R. , Suormala T. , Sagn C. , Reza Toliat M. , Nrnber G. , Wittkampf T. , Buers I. , Sharifi A. , Stucki M. , Becker C. , Baumgartner M. , Robenek H. , Marquardt T. , Hhne W. , Gasnier B. , Rosenblatt D.S. , Fowler B. , and Nrnberg P. 2009. Identification of a putative lysosomal cobalamin exporter mutated in the cblF inborn error of vitamin B12 metabolism. Nature Genet. 41: 234239.
Schimel, A. M. , and Mets M.B. 2006. The natural history of retinal degeneration in association with cobalamin C (cblC) disease. Ophthalmic Genet. 27: 914.
Shinnar, S. , and Singer H.S. 1984. Cobalamin C mutation (methylmalonic aciduria and homocystinuria) in adolescence. A treatable cause of dementia and myelopathy. N Engl J Med. 311: 451454.
Sloan, J. L. , Johnston J.J. , Manoli I. , Chandler R.J. , Krause C. , Carrillo-Carrasco N. , Chandrasekaran S.D. , Sysol J.R. , OBrien K. , Hauser N.S. , Sapp J.C. , Dorward H.M. , Huizing M. , NIH Intramural Sequencing Center Group, Barshop B.A. , Berry S.A. , James P.M. , Champaigne N.L. , de Lonlay P. , Valayannopoulos V. , Geschwind M.D. , Gavrilov D.K. , Nyhan W.L. , Biesecker L.G. , and Venditti C.P.

2011. Exome sequencing identifies ACSF3 as a cause of combined malonic and methylmalonic aciduria. Nature Genet. 43: 883886.
113 Sloan, J. L. , Manoli I. , and Venditti C.P. 2015. Liver or combined liver-kidney transplantation for patients with isolated methylmalonic acidemia: who and when? J Pediatr. 166: 14551461.
Suormala, T. , Baumgartner M.R. , Coelho D. , Zavadakova P. , Kozich V. , Koch H.G. , Berghauser M. , Wraith J.E. , Burlina A. , Sewell A. , Herwig J. , and Fowler B. 2004. The cblD defect causes either isolated or combined deficiency of methylcobalamin and adenosylcobalamin synthesis. J Biol Chem. 279: 4274242749.
Takeichi, T. , Hsu C.K. , Yang H.S. , Chen H.Y. , Wong T.W. , Tsai W.L. , Chao S.C. , Lee J.Y. , Akiyama M. , Simpson M.A. , and McGrath J.A. 2015. Progressive hyperpigmentation in a Taiwanese child due to an inborn error of vitamin B12 metabolism (cblJ). Br J Dermatol. 172: 11111115.
Thauvin-Robinet, C. , Roze E. , Couvreur G. , Horellou M.H. , Sedel F. , Grabli D. , Bruneteau G. , Toneti C. , Masurel-Paulet A. , Perennou D. , Moreau T. , Giroud M. , Ogier de Baulny H. , Giraudier S. , and Faivre L. 2008. The adolescent and adult form of cobalamin C disease: clinical and molecular spectrum. J Neurol Neurosurg Psych. 79: 725728.
Tortorelli, S. , Turgeon C.T. , Lim J.S. , Baumgart S. , Day-Salvatore D.L. , Abdenur J. , Bernstein J.A. , Lorey F. , Lichter-Konecki U. , Oglesbee D. , Raymond K. , Matern D. , Schimmenti L. , Rinaldo P. , and Gavrilov D.K. 2010. Two-tier approach to the newborn screening of methylenetetrahydrofolate reductase deficiency and other remethylation disorders with tandem mass spectrometry. J Pediatr. 157: 271275.
Turgeon, C. T. , Magera M.J. , Cuthbert C.D. , Loken P.R. , Gavrilov D.K. , Tortorelli S. , Raymond K.M. , Oglesbee D. , Rinaldo P. , and Matern D. 2010. Determination of total homocysteine, methylmalonic acid, and 2-methylcitric acid in dried blood spots by tandem mass spectroscopy. Clin Chem. 56: 16861695.
Vilaseca, M. A. , Vilarinho L. , Zavadakova P. , Vela E. , Cleto E. , Pineda M. , Coimbra E. , Suormala T. , Fowler B. , and Kozich V. 2003. CblE type of homocystinuria: mild clinical phenotype in two patients homozygous for a novel mutation in the MTRR gene. J Inher Metab Dis. 26: 361369.
Watkins, D. , Matiaszuk N. , and Rosenblatt D.S. 2000. Complementation studies in the cblA class of inborn error of cobalamin metabolism: evidence for interallelic complementation and for a new complementation class (cblH) . J Med Genet. 37: 510513.
Watkins, D. , and Rosenblatt D.S. 1986. Failure of lysosomal release of vitamin B12: a new complementation group causing methylmalonic aciduria. Am J Hum Genet. 39: 404408.
Watkins, D. , and Rosenblatt D.S. 1988. Genetic heterogeneity among patients with methylcobalamin deficiency. Definition of two complementation groups, cblE and cblG. J Clin Invest. 81: 16901694.
Watkins, D. , and Rosenblatt D.S. 1989. Functional methionine synthase deficiency (cblE and cblG): clinical and biochemical heterogeneity. Am J Med Genet. 34: 427434.
Watkins, D. , Ru M. , Hwang H.Y. , Kim C.D. , Murray A. , Philip N.S. , Kim W. , Legakis H. , Wai T. , Hilton J.F. , Ge B. , Dor C. , Hosack A. , Wilson A. , Gravel R.A. , Shane B. , Hudson T.J. , and Rosenblatt D.S. 2002. Hyperhomocysteinemia due to methionine synthase deficiency, cblG: structure of the MTR gene, genotype diversity, and recognition of a common mutation, P1173L. Am J Hum Genet. 71: 143153.
Weisfeld-Adams, J. D. , McCourt E.A. , Diaz G.A. , and Oliver S.C. 2015. Ocular disease in the cobalamin C defect: a review of the literature and a suggested framework for clinical surveillance. Mol Genet Metab. doi:10.1016/j.ymgme.2015.01.012.
Wilcken, B. , Wiley V. , Hammond J. , and Carpenter K. 2003. Screening of newborns for inborn errors of metabolism by tandem mass spectrometry. N Engl J Med. 348: 23042312.
Willard, H. F. , Mellman I.S. , and Rosenberg L.E. 1978. Genetic complementation among inherited deficiencies of methylmalonyl-CoA mutase activity: evidence for a new class of human cobalamin mutant. Am J Hum Genet. 30: 113.
Wong, D. , Tortorelli S. , Bishop L. , Sellars E.A. , Schimmenti L.A. , Gallant N. , Prada C.E. , Hopkins R.J. , Leslie N.D. , Berry S.A. , Rosenblatt D.S. , Fair A.L. , Matern D. , Raymond K. , Oglesbee D. , Rinaldo P. , and Gavrilov D. 2015. Outcomes of four patients with homocyateine remethuylation disorders detected by newborn screening. Genet Med. doi:10.1038/gim.2015.45.
114 Gavrilov, D. 2015. Outcomes of four patients with homocyateine remethuylation disorders detected by newborn screening. Genet Med. doi:10.1038/gim.2015.45.
Worgan, L. C. , Niles K. , Tirone J.C. , Hofmann A. , Verner A. , Sammak A. , Kucic T. , Lepage P. , and Rosenblatt D.S. 2006. Spectrum of mutations in mut methylmalonic acidemia and identification of a common Hispanic mutation and haplotype. Hum Mutat. 27: 3143.
Yu, H. C. , Sloan J.L. , Scharer G. , Brebner A. , Quintana A. , Achilly N.P. , Manoli I. , Coughlin C.R. , Geiger E.A. , Schneck U. , Watkins D. , Suormala T. , Van Hove J.L.K. , Fowler B. , Baumgartner M.R. , Rosenblatt D.S. , Venditti C.P. , and Shaikh T.M. 2013. An X-linked cobalamin disorder caused by mutations in transcriptional coregulator HCFC1 . Am J Hum Genet. 93: 506514.
Zhang, Y. , Yang Y. , Hasegawa Y. , Yamaguchi S. , Shi C. , Song J. , Sayami S. , Liu P. , Yan R. , Dong J. , and Qin J. 2008. Prenatal diagnosis of methylmalonic aciduria by analysis of organic acids and total homocysteine in amniotic fluid. Chin Med J. 121: 216219.

Conditions and Diseases that Cause Vitamin B12 Deficiency: Form Metabolism to Diseases

Ahuja, R. , Yammani R. , Bauer J.A. , Kalra S. , Seetharam S. , and Seetharam B. 2008. Interactions of cubilin with megalin and the product of the amnionless gene (AMN): effect on its stability. Biochem J. 410 (2): 3018.
Aminoff, M. , Carter J.E. , Chadwick R.B. , Johnson C. , Grasbeck R. , Abdelaal M.A. , et al 1999. Mutations in CUBN, encoding the intrinsic factor-vitamin B12 receptor, cubilin, cause hereditary megaloblastic anaemia 1. Nat Genet. 21 (3): 30913.
Andrs, E. , Affenberger S. , Vinzio S. , Kurtz J.E. , Noel E. , Kaltenbach G. , et al 2005. Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. Am J Med. 118 (10): 11549.
Andrs, E. , Affenberger S. , Zimmer J. , Vinzio S. , Grosu D. , Pistol G. , et al 2006. Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency. Clin Lab Haematol. 28 (1): 506.
Andrs, E. , Fothergill H. , and Mecili M. 2010. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opinion Pharmacotherapy. 11 (3): 24956.
Andrs, E. , Goichot B. , and Schlienger J.L. 2000. Food-cobalamin malabsorption: a usual cause of vitamin B12 deficiency. Arch Intern Med. 160 (11): 20612.
Andrs, E. , Henoun Loukili N. , Noel E. , Maloisel F. , Vinzio S. , Kaltenbach G. , et al 2005. Oral cobalamin (daily dose of 1000 pg) therapy for the treatment of patients with pernicious anemia. An open label study of 10 patients. Curr Ther. Research. 66 (10): 1322.
Andrs, E. , Kurtz J.E. , Perrin A.E. , Maloisel F. , Demangeat C. , Goichot B. , et al 2001. Oral cobalamin therapy for the treatment of patients with food-cobalamin malabsorption. Am J Med. 111 (9): 1269.
Andrs, E. , Loukili N.H. , Noel E. , Kaltenbach G. , Abdelgheni M.B. , Perrin A.E. , et al 2004. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ. 171 (3): 2514.

Andrs, E. , Noel E. , and Goichot B. 2002. Metformin-associated vitamin B12 deficiency. Arch Intern Med. 162 (19): 22512.
Andrs E. , Vogel T. , Federici L. , Zimmer J. and Kaltenbach G. 2008. Update on oral cyanocobalamin (vitamin B12) treatment in elderly patients. Drugs Aging. (1); 25: 927-32.
Bauman, W. A. , Shaw S. , Jayatilleke E. , Spungen A.M. , and Herbert V. 2000. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 23 (9): 122731.
Birn, H. , Verroust P.J. , Nexo E. , Hager H. , Jacobsen C. , Christensen E.I. , et al 1997. Characterization of an epithelial approximately 460-kDa protein that facilitates endocytosis of intrinsic factorvitamin B12 and binds receptor-associated protein. J Biol Chem. 272 (42): 26497504.
129 Birn, H. 2006. The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins. Am J Physiol Renal Physiol. 291 (1): F2236.
Bolaman, Z. , Kadikoylu G. , Yukselen V. , Yavasoglu I. , Barutca S. , and Senturk T. 2003. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study. Clin Ther. 25: 312434.
Carmel, R. 1983. R-binder deficiency. A clinically benign cause of cobalamin pseudodeficiency. JAMA. 250 (14): 188690.
Carmel, R. 1995. Malabsorption of food cobalamin. Baillieres Clin Haematol. 8 (3): 63955.
Carmel, R. 2003. Mild transcobalamin I (haptocorrin) deficiency and low serum cobalamin concentrations. Clin Chem. 49 (8): 136774.
Christensen, E. I. , and Birn H. 2002. Megalin and cubilin: multifunctional endocytic receptors. Nat Rev Mol Cell Biol. 3 (4): 25666.
Dali-Youcef N. and Andrs E. 2009. An update on cobalamin deficiency in adults. QJM. (7); 102: 17-28.
Fowler, B. 1998. Genetic defects of folate and cobalamin metabolism. Eur J Pediatr. 157 (Suppl 2): S606.
Fyfe, J. C. , Madsen M. , Hojrup P. , Christensen E.I. , Tanner S.M. , de la Chapelle A. , et al 2004. The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless. Blood. 103 (5): 15739.
Grasbeck, R. 1960. Familiar selective vitamin B12 malabsorption with proteinuria. A pernicious anemia-like syndrome. Nord Med. 63 (2): 3223.
He, Q. , Madsen M. , Kilkenney A. , Gregory B. , Christensen E.I. , Vorum H. , et al 2005. Amnionless function is required for cubilin brush-border expression and intrinsic factor-cobalamin (vitamin B12) absorption in vivo . Blood. 106 (4): 144753.
Imerslund, O. 1960. Idiopathic chronic megaloblastic anemia in children. Acta Paediatr. 49 (Suppl 119): 1115.
Jung, S. B. , Nagaraja V. , Kapur A. , and Eslick G.D. 2015. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Intern Med J. 45 (4): 40916.
Kantarci, S. , Al-Gazali L. , Hill R.S. , Donnai D. , Black G.C. , Bieth E. , et al 2007. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico- renal syndromes. Nat Genet. 39 (8): 9579.
Kaptan, K. , Beyan C. , Ural A.U. , Cetin T. , Avcu F. , Gulsen M. , et al 2000. Helicobacter pyloriis it a novel causative agent in Vitamin B12 deficiency? Arch Intern Med. 160 (9): 134953.
Kozyraki, R. , Kristiansen M. , Silahtaroglu A. , Hansen C. , Jacobsen C. , Tommerup N. , et al 1998. The human intrinsic factor-vitamin B12 receptor, cubilin: molecular characterization and chromosomal mapping of the gene to 10p within the autosomal recessive megaloblastic anemia (MGA1) region. Blood. 91 (10): 3593600.
Kristiansen, M. , Aminoff M. , Jacobsen C. , de La Chapelle A. , Krahe R. , Verroust P.J. , et al 2000. Cubilin P1297L mutation associated with hereditary megaloblastic anemia 1 causes impaired recognition of intrinsic factor-vitamin B(12) by cubilin. Blood. 96 (2): 4059.
Kristiansen, M. , Kozyraki R. , Jacobsen C. , Nexo E. , Verroust P.J. , and Moestrup S.K. 1999. Molecular dissection of the intrinsic factor-vitamin B12 receptor, cubilin, discloses regions important for membrane association and ligand binding. J Biol Chem. 274 (29): 205404.
Kuzminski, A. M. , Del Giacco E.I. , Allen R.H. , Stabler S.P. , and Lindenbaum J. 1998. Effective treatment of cobalamin deficiency with oral cobalamin. Blood. 92: 11918.
Lane, L. A. , and Rojas-Fernandez C. 2002. Treatment of vitamin B12 deficiency anemia: oral versus parenteral therapy. Ann Pharmacother. 36: 126872.
Li, N. , Rosenblatt D.S. , Kamen B.A. , Seetharam S. , and Seetharam B. 1994. Identification of two mutant alleles of transcobalamin II in an affected family. Hum Mol Genet. 3 (10): 183540.
Lindenbaum, J. , Rosenberg I.H. , Wilson P.W. , Stabler S.P. , and Allen R.H. 1994. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr. 60 (1): 211.
Markle, H. V. 1996. Cobalamin. Crit Rev Clin Lab Sci. 33 (4): 247356.
Matthews, J. H. 1995. Cobalamin and folate deficiency in the elderly. Baillieres Clin Haematol. 8 (3): 67997.
130 Medicine I. 1998. Dietary reference intake of thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, panthotenic acid, biotin and choline Food and Nutrition Board, Washington DC National Academies Press.
Moestrup, S. K. , Birn H. , Fischer P.B. , Petersen C.M. , Verroust P.J. , Sim R.B. , et al 1996. Megalin-mediated endocytosis of transcobalamin-vitamin-B12 complexes suggests a role of the receptor in vitamin-B12 homeostasis. Proc Natl Acad Sci USA 93 (16): 86127.
Nicolas J.P. and Gueant J.L. 1994. Absorption, distribution and excretion of vitamin B12. Ann Gastroenterol Hepatol (Paris). 30(6): 270-6, 81; discussion 81-2.
Pawlak, R. , Lester S.E. , and Babatunde T. 2014. The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. Eur J Clin Nutr. 68 (5): 5418.
Quadros, E. V. 2010. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol. 148 (2): 195204.
Rojas Hernandez, C. M. , and Oo T.H. 2015. Advances in mechanisms, diagnosis, and treatment of pernicious anemia. Discov Med. 19 (104): 15968.
Saito, A. , Pietromonaco S. , Loo A.K. , and Farquhar M.G. 1994. Complete cloning and sequencing of rat gp330/megalin, a distinctive member of the low density lipoprotein receptor gene family. Proc Natl Acad Sci USA 91 (21): 97259.
Slot, W. B. , Merkus F.W. , Van Deventer S.J. , and Tytgat G.N. 1997. Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. Gastroenterology. 113: 4303.
Stabler, S. P. 2013. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 368 (2): 14960.
Tanner, S. M. , Li Z. , Perko J.D. , Oner C. , Cetin M. , Altay C. , et al 2005. Hereditary juvenile cobalamin deficiency caused by mutations in the intrinsic factor gene. Proc Natl Acad Sci USA 102 (11): 41303.
Teplitsky, V. , Huminer D. , Zoldan J. , Pitlik S. , Shohat M. , and Mittelman M. 2003. Hereditary partial transcobalamin II deficiency with neurologic, mental and hematologic abnormalities in children and adults. Isr Med Assoc J. 5 (12): 86872.
Toh, B. H. , van Driel I.R. , and Gleeson P.A. 1997. Pernicious anemia. N Engl J Med. 337 (20): 14418.
van Asselt, D. Z. , Blom H.J. , Zuiderent R. , Wevers R.A. , Jakobs C. , van den Broek W.J. , et al 2000. Clinical significance of low cobalamin levels in older hospital patients. Neth J Med. 57 (2): 419.
Vidal-Alaball J. , Butler C.C. , Cannings-John R. , Goringe A. , Hood K. , McCaddon A. et al 2005. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 20: CD004655.
Yammani, R. R. , Seetharam S. , Dahms N.M. , and Seetharam B. 2003. Transcobalamin II receptor interacts with megalin in the renal apical brush border membrane. J Membr Biol. 193 (1): 5766.

Vitamin B12 Deficiency in Developing and Newly Industrialising Countries

Abdollahi, Z. , Elmadfa I. , Djazayeri A. , Sadeghian S. , Freisling H. , Mazandarani, F.S. , and Mohamed K. 2008. Folate, vitamin B12 and homocysteine status in women of childbearing age: baseline data of folic acid wheat flour fortification in Iran. Ann Nutr Metab. 53: 143150.

Adaikalakoteswari, A. , Jayashri R. , Sukumar N. , Venkataraman H. , Pradeepa R. , Gokulakrishnan K. , Anjana, R.M. , McTernan, P.G. , Tripathi G. , Patel V. , Kumar S. , Mohan V. , and Saravanan P. 2014. Vitamin B12 deficiency is associated with adverse lipid profile in Europeans and Indians with type 2 diabetes. Cardiovasc Diabetol. 13: 129.

Allen, L.H. 2004. Folate and vitamin B12 status in the Americas. Nutr Rev. 62: S29S33.

Allen L.H. 2008. Causes of vitamin B12 and folate deficiency. Food Nutr Bull. 29: S2034; discussion S35-7.

Antony, A.C. 2003. Vegetarianism and vitamin B12 (cobalamin) deficiency. Am J Clin Nutr. 78: 36.

Ayesh, M.H. , Jadalah K. , Awadi E. , Alawneh K. , and Khassawneh B. 2013. Association between vitamin B12 level and anti-parietal cells and anti-intrinsic factor antibodies among adult Jordanian patients with Helicobacter pylori infection. Braz J Infect Dis. 17: 629632.

Balci, Y.I. , Ergin A. , Karabulut A. , Polat A. , Dogan M. , and Kktac K. 2014. Serum vitamin B12 and folate concentrations and the effect of the Mediterranean diet on vulnerable populations. Pediatr Hematol Oncol. 31: 6267.

Barnab, A. , Alssio, A.C. , Bittar, L.F. , de MoraesMazetto B. , Bicudo, A.M. , de Paula, E.V. , Hoehr, N.F. , and Annichino-Bizzacchi, J.M. 2015. Folate, vitamin B12 and Homocysteine status in the postfolic acid fortification era in different subgroups of the Brazilian population attended to at a public health care center. Nutr J. 14: 19.

Bhate, V. , Deshpande S. , Bhat D. , Joshi N. , Ladkat R. , Watve S. , Fall C. , de Jager, C.A. , Refsum H. , and Yajnik C. 2008. Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children. Food Nutr Bull. 29: 249254.

Bhate, V.K. , Joshi, S.M. , Ladkat, R.S. , Deshmukh, U.S. , Lubree, H.G. , Katre, P.A. , Bhat, D.S. , Rush, E.C. , and Yajnik, C.S. 2012. Vitamin B12 and folate during pregnancy and offspring motor, mental and social development at 2 years of age. J Dev Orig Health Dis. 3: 123130.

Bondevik, G.T. , Schneede J. , Refsum H. , Lie, R.T. , Ulstein M. , and Kvale G. 2001. Homocysteine and methylmalonic acid levels in pregnant Nepali women. Should cobalamin supplementation be considered? Eur J Clin Nutr. 55: 85664.

Boushey, C.J. , Beresford, S.A. , Omenn, G.S. , and Motulsky, A.G. 1995. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 274: 10491057.

Brito, A. , Mujica-Coopman, M.F. , Lopez de Romana D. , Cori H. , and Allen, L.H. 2015. Folate and vitamin B12 status in Latin America and the caribbean: An Update. Food Nutr Bull. 36: S109118.

Brouwer-Brolsma, E.M. , Dhonukshe-Rutten, R.A. , van Wijngaarden, J.P. , Zwaluw, N.L. , Velde Nv , and de Groot, L.C. 2015. Dietary sources of vitamin B12 and their association with vitamin B12 status markers in healthy older adults in the B-PROOF study. Nutrients. 7: 77817797.

Cobayashi, F. , Tomita, L.Y. , Augusto, R.A. , DAlmeida V. , and Cardoso, M.A. 2015. ACTION Study Team. Genetic and environmental factors associated with vitamin B12 status in Amazonian children. Public Health Nutr. 18: 220210.

Christian, A.M. , Krishnaveni, G.V. , Kehoe, S.H. , Veena, S.R. , Khanum R. , Marley-Zagar E. , Edwards P. , Margetts, B.M. , and Fall, C.H. 2015. Contribution of food sources to the vitamin B12 status of South Indian children from a birth cohort recruited in the city of Mysore. Public Health Nutr. 18: 596609.

Dali-Youcef, N. , and Andres E. 2009. An update on cobalamin deficiency in adults. QJM. 102: 1728.

Dang, S. , Yan H. , Zeng L. , Wang Q. , Li Q. , Xiao S. , and Fan X. 2014. The status of vitamin B12 and folate among Chinese women: a population-based cross-sectional study in northwest China. PLoS One. 9: e112586.

Deegan, K.L. , Jones, K.M. , Zuleta C. , Ramirez-Zea M. , Lildballe, D.L. , Nexo E. , and Allen, L.H. 2012. Breast milk vitamin B12 concentrations in Guatemalan women are correlated with maternal but not infant vitamin B12 status at 12 months postpartum. J Nutr. 142: 112116.

Deodhar, A.D. , and Ramakrishnan, C.V. 1959. Studies on human lactation. II. Effect of socio-economic status on the vitamin content of human milk. Indian J Med Res. 47: 352355.

146 Deshmukh, U.S. , Joglekar, C.V. , Lubree, H.G. , Ramdas, L.V. , Bhat, D.S. , Naik, S.S. , Hardikar, P.S. , Raut, D.A. , Konde, T.B. , Wills, A.K. , Jackson, A.A. , Refsum H. , Nanivadekar, A.S. , Fall, C.H. , and Yajnik, C.S. 2010. Effect of physiological doses of oral vitamin B12 on plasma homocysteineA randomized, placebo-controlled, double-blind trial in India. Eur J Clin Nutr. 64: 495502.

Dhonukshe-Rutten, R.A. , van Zutphen M. , de Groot, L.C. , Eussen, S.J. , Blom, H.J. , and van Staveren, W.A. 2005. Effect of supplementation with cobalamin carried either by a milk product or a capsule in mildly cobalamin-deficient elderly Dutch persons. Am J Clin Nutr. 82: 568574.

Dror, D.K. , and Allen, L.H. 2011. The importance of milk and other animal-source foods for children in low-income countries. Food Nutr Bull. 32: 227243.

Duggan, C. , Srinivasan K. , Thomas T. , Samuel T. , Rajendran R. , Muthayya S. , Finkelstein, J.L. , Lukose A. , Fawzi W. , Allen, L.H. , Bosch, R.J. , and Kurpad, A.V. 2014. Vitamin B12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B12 status. J Nutr. 144: 75864.

Dwarkanath, P. , Barzilay, J.R. , Thomas T. , Thomas A. , Bhat S. , and Kurpad, A.V. 2013. High folate and low vitamin B12 intakes during pregnancy are associated with small-for-gestational age infants in South Indian women: a prospective observational cohort study. Am J Clin Nutr. 98: 14508.

Fakhrzadeh, H. , Ghotbi S. , Pourebrahim R. , Nouri M. , Heshmat R. , Bandarian F. , Shafaee A. , and Larijani B. 2006. Total plasma homocysteine, folate, and vitamin B12 status in healthy Iranian adults: the Tehranhomocysteine survey (2003-2004)/a crosssectional population based study. BMC Public Health. 6: 29.

Fernndez-Baares F1, Monzn H and Forn M., 2009. A short review of malabsorption and anemia. World J Gastroenterol. 15: 46444652.

Finkelstein, J.L. , Layden, A.J. , and Stover, P.J. 2015. Vitamin B12 and perinatal health. Adv Nutr. 6: 552563.

Galukande, M. , Jombwe J. , Fualal J. , Baingana R. , and Gakwaya A. 2011. Reference values for serum levels of folic acid and vitamin B12 in a young adult Ugandan population. Afr Health Sci. 11: 240243.

Godbole, K. , Gayathri P. , Ghule S. , Sasirekha, B.V. , Kanitkar-Damle A. , Memane N. , Suresh S. , Sheth J. , Chandak, G.R. , and Yajnik, C.S. 2011. Maternal one-carbon metabolism, MTHFR and TCN2 genotypes and neural tube defects in India. Birth Defects Res A Clin Mol Teratol. 91: 848856.

Goraya, J.S. , Kaur S. , and Mehra B. 2015. Neurology of nutritional vitamin B12 deficiency in infants: Case series from India and literature review. J Child Neurol. 30: 18311837.

Greibe, E. , Lildballe, D.L. , Streym S. , Vestergaard P. , Rejnmark L. , Mosekilde L. , and Nexo E. 2013. Cobalamin and haptocorrin in human milk and cobalamin-related variables in mother and child: a 9-mo longitudinal study. Am J Clin Nutr. 98: 389395.

Gupta Bansal, P. , Singh Toteja G. , Bhatia N. , Kishore Vikram N. , Siddhu A. , Kumar Garg A. , and Roy A. Kumar 2015. Deficiencies of serum ferritin and vitamin B12, but not folate, are common in adolescent girls residing in a slum in Delhi. Int J Vitam Nutr Res. 85: 1422.

Haan, M.N. , Miller, J.W. , Aiello, A.E. , Whitmer, R.A. , Jagust, W.J. , Mungas, D.M. , Allen, L.H. , and Green R. 2007. Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. Am J Clin Nutr. 85: 5117.

Halicioglu, O. , Sutcuoglu S. , Koc F. , Ozturk C. , Albudak E. , Colak A. , Sahin E. , and AsikAkman S. 2012. Vitamin B12 and folate statuses are associated with diet in pregnant women, but not with anthropometric measurements in term newborns. J Matern Fetal Neonatal Med. 25: 16181621.
Hazra, A. , Kraft P. , Lazarus R. , Chen C. , Chanock, S.J. , Jacques P. , Selhub J. , and Hunter, D.J. 2009. Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. Hum Mol Genet. 18: 467787.
Hazra A. , Kraft P. , Selhub J. , Giovannucci E.L. , Thomas G. , Hoover R.N. , Chanock S.J. and Hunter D.J. . Common variants of FUT2 are associated with plasma vitamin B12 levels. Nat Genet. 40: 11602.
Herrmann, W. , Obeid R. , and Jouma M. 2003. Hyperhomocysteinemia and vitamin B12 deficiency are more striking in Syrians than in Germans-causes and implications. Atherosclerosis. 166: 143150.
Huo, Y. , Li J. , Qin X. , Huang Y. , Wang X. , Gottesman, R.F. , Tang G. , Wang B. , Chen D. , He M. , Fu J. , Cai Y. , Shi X. , Zhang Y. , Cui Y. , Sun N. , Li X. , Cheng X. , Wang J. , Yang X. , Yang T. , Xiao C. , Zhao G. , Dong Q. , Zhu D. , Wang X. , Ge J. , Zhao L. , Hu D. , Liu L. , and Hou, F.F. 2015. CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA. 313: 132535.
147 Torsvik, Ingrid Kristin , Per Magne Ueland , Trond Markestad , and ivind Midttun and Anne-Lise Bjorke Monsen 2015. Motor development related to duration of exclusive breastfeeding, B vitamin status and B12 supplementation in infants with a birth weight between 2000-3000 g, results from a randomized intervention trial. BMC Pediatr. 15: 218.
Jathar, V.S. , Kamath, S.A. , Parikh, M.N. , Rege, D.V. , and Satoskar, R.S. 1970. Maternal milk and serum vitamin B12, folic acid, and protein levels in Indian subjects. Arch Dis Child. 45: 236241.
Kapil, U. , and Sareen N. 2014. Prevalence of ferritin, folate and vitamin B12 deficiencies amongst children in 5-18 years of age in Delhi. Indian J Pediatr. 81: 312.
Kehoe, S.H. , Chopra H. , Sahariah, S.A. , Bhat D. , Munshi, R.P. , Panchal F. , Young S. , Brown N. , Tarwande D. , Gandhi M. , Margetts, B.M. , Potdar, R.D. , and Fall, C.H. 2015. Effects of a food-based intervention on markers of micronutrient status among Indian women of low socio-economic status. Br J Nutr. 113: 81321.
Khodabandehloo, N. , Vakili M. , Hashemian Z. , and Zardini H. Zare 2015. Determining functional vitamin B12 deficiency in the elderly. Iran Red Crescent Med J. 17: e13138.
Koc, A. , Kocyigit A. , Soran M. , Demir N. , Sevinc E. , Erel O. , and Mil Z. 2006. High frequency of maternal vitamin B12 deficiency as an important cause of infantile vitamin B12 deficiency in Sanliurfa province of Turkey. Eur J Nutr. 45: 2917.
Krishnaveni, G.V. , Hill, J.C. , Veena, S.R. , Bhat, D.S. , Wills, A.K. , Karat, C.L. , Yajnik, C.S. , and Fall, C.H. 2009. Low plasma vitamin B12 in pregnancy is associated with gestational diabesity and later diabetes. Diabetologia. 52: 23502358.
Kumar, J. , Garg G. , Sundaramoorthy E. , Prasad, P.V. , Karthikeyan G. , Ramakrishnan L. , Ghosh S. , and Sengupta S. 2009. Vitamin B12 deficiency is associated with coronary artery disease in an Indian population. Clin Chem Lab Med. 47: 334338.
Kuriyan, R. , Thankachan P. , Selvam S. , Pauline M. , Srinivasan K. , Kamath-Jha S. , Vinoy S. , Misra S. , Finnegan Y. , and Kurpad, A.V. 2016. The effects of regular consumption of a multiple micronutrient fortified milk beverage on the micronutrient status of school children and on their mental and physical performance. Clin Nutr. 35: 1908.
Kvestad, I. , Taneja S. , Kumar T. , Hysing M. , Refsum H. , Yajnik, C.S. , Bhandari N. , and Strand, T.A. 2015. Folate and Vitamin B12 Study Group. Vitamin B12 and Folic Acid Improve Gross Motor and Problem-Solving Skills in Young North Indian Children: A Randomized Placebo-Controlled Trial. PLoS One. 10: e0129915.
Kwak, C.S. , Lee, M.S. , Oh Se In , and Park, S.C. 2010. Discovery of novel sources of vitamin B12 in traditional Korean foods from nutritional surveys of centenarians. Curr Gerontol Geriatr Res. 2010: 374897.
LeBlanc, J.G. , Laino, J.E. , del Valle, M.J. , Vannini V. , van Sinderen D. , Taranto, M.P. , de Valdez, G.F. , de Giori, G.S. , and Sesma F. 2011. B-group vitamin production by lactic acid bacteriacurrent knowledge and potential applications. J Appl Microbiol. 111: 12971309.
Lildballe, D.L. , Hardlei, T.F. , Allen, L.H. , and Nexo E. 2009. High concentrations of haptocorrin interfere with routine measurement of cobalamins in human serum and milk. A problem and its solution. Clin Chem Lab Med. 47: 182187.
Lubree, H.G. , Katre, P.A. , Joshi, S.M. , Bhat, D.S. , Deshmukh, U.S. , Memane, N.S. , Otiv, S.R. , Rush, E.C. , and Yajnik, C.S. 2012. Childs homocysteine concentration at 2 years is influenced by pregnancy vitamin B12 and folate status. J Dev Orig Health Dis. 3: 3238.
McLaren, D.S. 1981. The luxus vitaminsA and B12. Am J Clin Nutr. 34: 16116.
McLean, E. , de Benoist B. , and Allen, L.H. 2008. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. Food Nutr Bull. (2 Suppl): S3851.
McLean, E.D. , Allen, L.H. , Neumann, C.G. , Peerson, J.M. , Siekmann, J.H. , Murphy, S.P. , Bwibo, N.O. , and Demment, M.W. 2007. Low plasma vitamin B12 in Kenyan school children is highly prevalent and improved by supplemental animal source foods. J Nutr. 137: 67682.
Mohammad, M.A. , Molloy A. , Scott J. , and Hussein L. 2006. Plasma cobalamin and folate and their metabolic markers methylmalonic acid and total homocysteine among Egyptian children before and after nutritional supplementation with the probiotic bacteria Lactobacillus acidophilus in yoghurt matrix. Int J Food Sci Nutr. 57: 470480.
148 Monsen, A.L. , Refsum H. , Markestad T. , and Ueland, P.M. 2003. Cobalamin status and its biochemical markers methylmalonic acid and homocysteine in different age groups from 4 days to 19 years. Clin Chem. 49: 206775.
Murphy, M.M. , Molloy, A.M. , Ueland, P.M. , Fernandez-Ballart, J.D. , Schneede J. , Arija V. , and Scott, J.M. 2007. Longitudinal study of the effect of pregnancy on maternal and fetal cobalamin status in healthy women and their offspring. J Nutr. 137: 18637.
Muthayya, S. , Kurpad, A.V. , Duggan, C.P. , Bosch, R.J. , Dwarkanath P. , Mhaskar A. , Mhaskar R. , Thomas A. , Vaz M. , Bhat S. , and Fawzi, W.W. 2006. Low maternal vitamin B12 status is associated with intrauterine growth retardation in urban South Indians. Eur J Clin Nutr. 60: 791801.
Naik, S. , Bhide V. , Babhulkar A. , Mahalle N. , Parab S. , Thakre R. , and Kulkarni M. 2013. Daily milk intake improves vitamin B12 status in young vegetarian Indians: an intervention trial. Nutr J. 12: 136.
Ndeezi, G. , Tumwine, J.K. , Ndugwa, C.M. , Bolann, B.J. , and Tylleskar T. 2011. Multiple micronutrient supplementation improves vitamin B12 and folate concentrations of HIV infected children in Uganda: a randomized controlled trial. Nutr J. 10: 56.
Neumann, C.G. , Oace, S.M. , Chaparro, M.P. , Herman D. , Drorbaugh N. , and Bwibo, N.O. 2013. Low vitamin B12 intake during pregnancy and lactation and low breastmilk vitamin 12 content in rural Kenyan women consuming predominantly maize diets. Food Nutr Bull. 34: 151159.
Pasricha, S.R. , Black J. , Muthayya S. , Shet A. , Bhat V. , Nagaraj S. , Prashanth, N.S. , Sudarshan H. , Biggs, B.A. , and Shet, A.S. 2010. Determinants of anemia among young children in rural India. Pediatrics. 126: e1409.
Pasricha, S.R. , Shet, A.S. , Black, J.F. , Sudarshan H. , Prashanth, N.S. , and Biggs, B.A. 2011. Vitamin B12, folate, iron, and vitamin A concentrations in rural Indian children are associated with continued breastfeeding, complementary diet, and maternal nutrition. Am J Clin Nutr. 94: 135870.
Pathak, P. , Kapil U. , Yajnik, C.S. , Kapoor, S.K. , Dwivedi, S.N. , and Singh R. 2007. Iron, folate, and vitamin B12 stores among pregnant women in a rural area of Haryana State. India. Food Nutr Bull. 28: 435438.
Pawlak, R. , Parrott, S.J. , Raj S. , Cullum-Dugan D. , and Lucus D. 2013. How prevalent is vitamin B(12) deficiency among vegetarians? Nutr Rev. 71: 1107.

Potdar, R.D. , Sahariah, S.A. , Gandhi M. , Kehoe, S.H. , Brown N. , Sane H. , Dayama M. , Jha S. , Lawande A. , Coakley, P.J. , Marley-Zagar E. , Chopra H. , Shivshankaran D. , Chheda-Gala P. , Muley-Lotankar P. , Subbulakshmi G. , Wills, A.K. , Cox, V.A. , Taskar V. , Barker, D.J. , Jackson, A.A. , Margetts, B.M. , and Fall, C.H. 2014. Improving womens diet quality preconceptionally and during gestation: effects on birth weight and prevalence of low birth weight-a randomized controlled efficacy trial in India (Mumbai Maternal Nutrition Project). Am J Clin Nutr. 100: 12571268.
Ramrez-Vlez, R. , Correa-Bautista, J.E. , Martnez-Torres J. , Meneses-Echvez, J.F. , and Lobelo F. 2016. Vitamin B12 concentrations in pregnant Colombian women: analysis of nationwide data 2010. BMC Pregnancy Childbirth. 16: 26.
Rao, S. , Yajnik, C.S. , Kanade A. , Fall, C.H. , Margetts, B.M. , Jackson, A.A. , Shier R. , Joshi S. , Rege S. , Lubree H. , and Desai B. 2001. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune Maternal Nutrition Study. J Nutr. 131: 12171224.
Refsum, H. , Yajnik, C.S. , Gadkari M. , Schneede J. , Vollset, S.E. , Orning L. , Guttormsen, A.B. , Joglekar A. , Sayyad, M.G. , Ulvik A. , and Ueland, P.M. 2001. Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of cobalamin deficiency in Asian Indians. Am J Clin Nutr. 74: 233241.
Rosenthal, J. , Lopez-Pazos E. , Dowling, N.F. , Pfeiffer, C.M. , Mulinare J. , Vellozzi C. , Zhang M. , Lavoie, D.J. , Molina R. , Ramirez N. , and Reeve, M.E. 2015. Folate and Vitamin B12 Deficiency Among Non-pregnant Women of Childbearing-Age in Guatemala 2009-2010: Prevalence and Identification of Vulnerable Populations. Matern Child Health J. 19: 227285.
Rush, E.C. , Chhichhia P. , Hinckson E. , and Nabiryo C. 2009. Dietary patterns and vitamin B(12) status of migrant Indian preadolescent girls. Eur J Clin Nutr. 63: 5857.
Samuel, T.M. , Duggan C. , Thomas T. , Bosch R. , Rajendran R. , Virtanen, S.M. , Srinivasan K. , and Kurpad, A.V. 2013. Vitamin B(12) intake and status in early pregnancy among urban South Indian women. Ann Nutr Metab. 62: 11322.
149 Shamah-Levy, T. , Villalpando S. , Mejia-Rodriguez F. , Cuevas-Nasu L. , Gaona-Pineda, E.B. , RangelBaltazar E. , and Zambrano-Mujica N. 2015. Prevalence of iron, folate, and vitamin B12 deficiencies in 20 to 49 years old women: Ensanut 2012. Salud Publica Mex. 57: 38593.
Shobha, V. , Tarey, S.D. , Singh, R.G. , Shetty P. , Unni, U.S. , Srinivasan K. , and Kurpad, A.V. 2011. Vitamin B12 deficiency & levels of metabolites in an apparently normal urban south Indian elderly population. Indian J Med Res. 134: 432439.
Siekmann, J.H. , Allen, L.H. , Bwibo, N.O. , Demment, M.W. , Murphy, S.P. , and Neumann, C.G. 2003. Kenyan school children have multiple micronutrient deficiencies, but increased plasma vitamin B12 is the only detectable micronutrient response to meat or milk supplementation. J Nutr. 133 (11 Suppl 2): 3972S3980S.
Stewart, C.P. , Christian P. , Schulze, K.J. , Arguello M. , LeClerq, S.C. , Khatry, S.K. , and West, K.P. Jr 2011. Low maternal vitamin B12 status is associated with offspring insulin resistance regardless of antenatal micronutrient supplementation in rural Nepal. J Nutr. 141: 19127.
Strand, T.A. , Taneja S. , Ueland, P.M. , Refsum H. , Bahl R. , Schneede J. , Sommerfelt H. , and Bhandari N. 2013. Cobalamin and folate status predicts mental development scores in North Indian children 12-18 mo of age. Am J Clin Nutr. 97: 3107.
Taneja, S. , Bhandari N. , Strand, T.A. , Sommerfelt H. , Refsum H. , Ueland, P.M. , Schneede J. , Bahl R. , and Bhan, M.K. 2007. Cobalamin and folate status in infants and young children in a low-to-middle income community in India. Am J Clin Nutr. 86: 13029.
Taneja, S. , Strand, T.A. , Kumar T. , Mahesh M. , Mohan S. , Manger, M.S. , Refsum H. , Yajnik, C.S. , and Bhandari N. 2013. Folic acid and vitamin B12 supplementation and common infections in 6-30-mo-old children in India: a randomized placebo-controlled trial. Am J Clin Nutr. 98: 7317.
Tang, K.F. , Li, Y.L. , and Wang, H.Y. 2015. Quantitative assessment of maternal biomarkers related to one-carbon metabolism and neural tube defects. Sci Rep. 5: 8510.
Tapola, N.S. , Karvonen, H.M. , Niskanen, L.K. , and Sarkkinen, E.S. 2004. Mineral water fortified with folic acid, vitamins B6, B12, D and calcium improves folate status and decreases plasma homocysteine concentration in men and women. Eur J Clin Nutr. 58: 376385.
Thomas, D. , Chandra J. , Sharma S. , Jain A. , and Pemde, H.K. 2015. Determinants of nutritional Anemia in adolescents. Indian Pediatr. 52: 8679.
Thomas, M.R. , Sneed, S.M. , Wei C. , Nail, P.A. , and Wilson M. 1980. Sprinkle EE 3rd. The effects of vitamin C, vitamin B6, vitamin B12, folic acid, riboflavin, and thiamin on the breast milk and maternal status of well-nourished women at 6 months postpartum. Am J Clin Nutr. 33: 21516.
Torheim, L.E. , Ferguson, E.L. , Penrose K. , and Arimond M. 2010. Women in resource-poor settings are at risk of inadequate intakes of multiple micronutrients. J Nutr. 140: S2051S2058.
Tucker, K.L. , Rich S. , Rosenberg I. , Jacques P. , Dallal G. , Wilson, P.W. , and Selhub J. 2000. Plasma vitamin B12 concentrations relate to intake source in the Framingham Offspring study. Am J Clin Nutr. 71: 514522.
Ulak, M. , Chandyo, R.K. , Adhikari, R.K. , Sharma, P.R. , Sommerfelt H. , Refsum H. , and Strand, T.A. 2014. Cobalamin and folate status in 6 to 35 months old children presenting with acute diarrhea in Bhaktapur. Nepal. PLoS One. 9: e90079.
VanderJagt, D.J. , I. A. O. Ujah , Ikeh, E.I. , Bryant J. , Pam V. , Hilgart A. , Crossey, M.J. , and Glew, R.H. 2011. Assessment of the vitamin B12 status of pregnant women in Nigeria using plasma holotranscobalamin. Obstet Gynecol. 2011: 365894.
Villalpando, S. , Cruz Vde L. , Shamah-Levy T. , Rebollar R. , and Contreras-Manzano A. 2015. Nutritional status of iron, vitamin B12, folate, retinol and anemia in children 1 to 11 years old: Results of the Ensanut 2012. Salud Publica Mex. 57: 37284.
Watanabe, F. 2007. Vitamin B12 sources and bioavailability. Exp Biol Med. 232: 12661274.
Winkels, R.M. , Brouwer, I.A. , Clarke R. , Katan, M.B. , and Verhoef P. 2008. Bread cofortified with folic acid and vitamin B12 improves the folate and vitamin B12 status of healthy older people: a randomized controlled trial. Am J Clin Nutr. 88: 348355.
Yajnik, C.S. , Deshpande, S.S. , Jackson, A.A. , Refsum H. , Rao S. , Fisher, D.J. , Bhat, D.S. , Naik, S.S. , Coyaji, K.J. , Joglekar, C.V. , Joshi N. , Lubree, H.G. , Deshpande, V.U. , Rege, S.S. , and Fall, C.H. 2008. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: The Pune Maternal Nutrition Study. Diabetologia. 51: 2938.
150 Yajnik, C.S. , Deshpande, S.S. , Lubree, H.G. , Naik, S.S. , Bhat, D.S. , Uradey, B.S. , Deshpande, J.A. , Rege, S.S. , Refsum H. , and Yudkin, J.S. 2006. Vitamin B12 Deficiency and Hyperhomocysteinemia in rural and Urban Indians. J Assoc Physicians India. 54: 77582.
Yajnik, C.S. , Chandak, G.R. , Joglekar C. , Katre P. , Bhat, D.S. , Singh, S.N. , Janipalli, C.S. , Refsum H. , Krishnaveni G. , Veena S. , Osmond C. , and Fall, C.H. 2014. Maternal homocysteine in pregnancy and offspring birthweight: epidemiological associations and Mendelian randomization analysis. Int J Epidemiol. 43: 148797.
Yusufji, D. , Mathan, V.I. , and Baker, S.J. 1973. Iron, folate, and vitamin B12 nutrition in pregnancy: a study of 1000 women from southern India. Bull World Health Organ. 48: 1522.
Zhang, W. , Li Y. , Wang, T.D. , Meng, H.X. , Min, G.W. , Fang, Y.L. , Niu, X.Y. , Ma, L.S. , Guo, J.H. , Zhang J. , Sun, M.Z. , and Li, C.X. 2014. Nutritional status of the elderly in rural North China: a cross-sectional study. J Nutr Health Aging. 18: 730736.

Vitamin B12 in Neurology and Aging

Abraham, N.S. 2012. Proton pump inhibitors: potential adverse effects. Curr Opin Gastroenterol. 28 (6): 615620.

Adams, R.D. , and Kubik C.S. 1944. Subacute degeneration of the brain in pernicious anaemia. N Engl J Med. 231: 19.

Addison, T. 1849. Anemia: Disease of the suprarenal capsules. Lond Med Gaz. 43: 517.

Allain, P. , Le Bouil A. , Cordillet E. , Le Quay L. , Bagheri H. , and Montastruc J.L. 1995. Sulfate and cysteine levels in the plasma of patients with Parkinsons disease. Neurotoxicology. 16 (3): 527529.

Allen, R.H. , Lindenbaum J. , and Stabler S.P. 1995. High prevalence of cobalamin deficiency in the elderly. Trans Am Clin Climatol Assoc. 107: 3745.

171 Allen, R.H. , and Stabler S.P. 2008. Identification and quantitation of cobalamin and cobalamin analogues in human feces. Am J Clin Nutr. 87 (5): 13241335.

Baik, H.W. , and Russell R.M. 1999. Vitamin B12 deficiency in the elderly. Annu Rev Nutr. 19: 357377.

Banerjee, R.V. , and Matthews R.G. 1990. Cobalamin-dependent methionine synthase. FASEB J. 4 (5): 14501459.

Bateman, R.J. , Xiong C. , Benzinger T.L. , Fagan A.M. , Goate A. , Fox N.C. , Marcus D.S. , Cairns N.J. , Xie X. , Blazey T.M. , et al 2012. Clinical and biomarker changes in dominantly inherited Alzheimers Disease. N Engl J Med. 367 (9): 795804.

Bates, C.J. , Schneede J. , Mishra G. , Prentice A. , and Mansoor M.A. 2003. Relationship between methylmalonic acid, homocysteine, vitamin B12 intake and status and socio-economic indices, in a subset of participants in the British National Diet and Nutrition Survey of people aged 65 y and over. Eur J Clin Nutr. 57 (2): 349357.

Beck, W.S. 1988. Cobalamin and the nervous system. N Engl J Med. 318 (26): 17521754.

Bell, I.R. , Edman J.S. , Marby D.W. , Satlin A. , Dreier T. , Liptzin B. , and Cole J.O. 1990. Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population. Biol Psychiatry. 27 (2): 125137.

Bjorkegren, K. , and Svardsudd K. 2001. Serum cobalamin, folate, methylmalonic acid and total homocysteine as vitamin B12 and folate tissue deficiency markers amongst elderly Swedesa population-based study. J Intern Med. 249 (5): 423432.

Blandini, F. , Fancellu R. , Martignoni E. , Mangiagalli A. , Pacchetti C. , Samuele A. , and Nappi G. 2001. Plasma homocysteine and l-dopa metabolism in patients with Parkinson disease. Clin Chem. 47 (6): 11021104.

Bottiglieri, T. , Godfrey P. , Flynn T. , Carney M.W. , Toone B.K. , and Reynolds E.H. 1990. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. J Neurol Neurosurg Psychiatry. 53 (12): 10961098.

Budge, M. , Johnston C. , Hogervorst E. , de Jager C. , Milwain E. , Iversen S.D. , Barnetson L. , King E. , and Smith A.D. 2000. Plasma total homocysteine and cognitive performance in a volunteer elderly population. Ann NY Acad Sci. 903: 407410.

Byrne, E.J. 1987. Reversible dementia. Int J Geriatr Psychiatry. 2: 7381.

Carkeet, C. , Dueker S.R. , Lango J. , Buchholz B.A. , Miller J.W. , Green R. , Hammock B.D. , Roth J.R. , and Anderson P.J. 2006. Human vitamin B12 absorption measurement by accelerator mass spectrometry using specifically labeled (14)C-cobalamin. Proc Natl Acad Sci U S A. 103 (15): 56945699.

Carmel, R. 1988. Pernicious anemia. The expected findings of very low serum cobalamin levels, anemia, and macrocytosis are often lacking. Arch Intern Med. 148 (8): 17121714.

Carmel, R. 1990. Subtle and atypical cobalamin deficiency states. Am J Hematol. 34 (2): 108114.

Carmel, R. 2000. Current concepts in cobalamin deficiency. Annu Rev Med. 51: 357375.

Carmel, R. , Gott P.S. , Waters C.H. , Cairo K. , Green R. , Bondareff W. , DeGiorgio C.M. , Cummings J.L. , Jacobsen D.W. , Buckwalter G. , et al 1995. The frequently low cobalamin levels in dementia usually signify treatable metabolic, neurologic and electrophysiologic abnormalities. Eur J Haematol. 54 (4): 245253.

Chiu, H. F. K. 1996. Vitamin B12 deficiency and dementia. Int J Geriatr Psychiatry. 11: 851858.

Clarke, R. , Grimley Evans J. , Schneede J. , Nexo E. , Bates C. , Fletcher A. , Prentice A. , Johnston C. , Ueland P.M. , Refsum H. , et al 2004. Vitamin B12 and folate deficiency in later life. Age Ageing. 33 (1): 3441.

Clarke, R. , Smith A.D. , Jobst K.A. , Refsum H. , Sutton L. , and Ueland P.M. 1998. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol. 55 (11): 14491455.

Cole, M.G. , and Prchal J.F. 1984. Low serum vitamin B12 in Alzheimer-type dementia. Age Ageing. 13 (2): 101105.

de Jager, C. , Oulhaj A. , Jacoby R. , Refsum H. , and Smith A.D. 2012. Cognitive and clinical outcomes of homocysteine lowering B vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 27 (6): 592600.

Den Heijer, T. , Vermeer S.E. , Clarke R. , Oudkerk M. , Koudstaal P.J. , Hofman A. , and Breteler M.M. 2003. Homocysteine and brain atrophy on MRI of non-demented elderly. Brain. 126 (Pt 1): 170175.

172 Douaud, G. , Refsum H. , de Jager C.A. , Jacoby R. , Nichols T.E. , Smith S.M. , and Smith A.D. 2013. Preventing Alzheimers disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci U S A. 110 (23): 95239528.

Droller, H. , and Dossett J. 1959. Vitamin B12 levels in senile dementia and confusional states. Geriatrics. 14 (6): 367373.

Eastley, R. , Wilcock G.K. , and Bucks R.S. 2000. Vitamin B12 deficiency in dementia and cognitive impairment: the effects of treatment on neuropsychological function. Int J Geriatr Psychiatry. 15 (3): 226233.

Elmore, C.L. , and Matthews R.G. 2007. The many flavors of hyperhomocyst(e)inemia: insights from transgenic and inhibitor-based mouse models of disrupted one-carbon metabolism. Antioxid Redox Signal. 9 (11): 19111921.

Elsborg, L. , Lund V. , and Bastrup-Madsen P. 1976. Serum vitamn B12 levels in the aged. Acta Med Scand. 200: 309314.

Evans, D.L. , Edelsohn G.A. , and Golden R.N. 1983. Organic psychosis without anemia or spinal cord symptoms in patients with vitamin B12 deficiency. Am J Psychiatry. 140 (2): 218221.

Fedosov, S.N. 2010. Metabolic signs of vitamin B(12) deficiency in humans: computational model and its implications for diagnostics. Metabolism. 59 (8): 11241138.

Fedosov, S.N. , Brito A. , Miller J.W. , Green R. , and Allen L.H. 2015. Combined indicator of vitamin B12 status: modification for missing biomarkers and folate status and recommendations for revised cut-points. Clinical Chemistry and Laboratory Medicine: CCLM/FESCC 53 (8): 12151225.

Ferraro, A. , Arieti S. , and English W.H. 1945. Cerebral changes in the course of pernicious anaemia and their relationship to psychiatric symptoms. J Neuropathol Exp Neurol. 4 (3): 217239.

Fuchs, D. , Jaeger M. , Widner B. , Wirleitner B. , Artner-Dworzak E. , and Leblhuber F. 2001. Is hyperhomocysteinemia due to the oxidative depletion of folate rather than to insufficient dietary intake? Clin Chem Lab Med. 39 (8): 691694.

Fuso, A. , and Scarpa S. 2011. One-carbon metabolism and Alzheimers disease: is it all a methylation matter? Neurobiol Aging. 32 (7): 11925.

Garrod, M.G. , Green R. , Allen L.H. , Mungas D.M. , Jagust W.J. , Haan M.N. , and Miller J.W. 2008. Fraction of total plasma vitamin B12 bound to transcobalamin correlates with cognitive function in elderly Latinos with depressive symptoms. Clinical Chemistry. 54 (7): 12101217.
Gimsing, P. , Melgaard B. , Andersen K. , Vilstrup H. , and Hippe E. 1989. Vitamin B12 and folate function in chronic alcoholic men with peripheral neuropathy and encephalopathy. J Nutr. 119 (3): 416424.
Goodkin, D.E. , Jacobsen D.W. , Galvez N. , Daughtry M. , Secic M. , and Green R. 1994. Serum cobalamin deficiency is uncommon in multiple sclerosis. Arch Neurol. 51 (11): 11101114.
Green, R. , and Miller J.W. 2014. Vitamin B12. In Handbook of Vitamins. 5th ed, edited by Zempleni J. , Suttie J.W. , Gregory J.F. III and Stover P. , 447489. Boca Raton, FL: CRC Press.
Haan, M.N. , Miller J.W. , Aiello A.E. , Whitmer R.A. , Jagust W.J. , Mungas D.M. , Allen L.H. , and Green R. 2007. Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. Am J Clin Nutr. 85 (2): 511517.
Healton, E.B. , Savage D.G. , Brust J.C. , Garrett T.J. , and Lindenbaum J. 1991. Neurologic aspects of cobalamin deficiency. Medicine (Baltimore). 70 (4): 229245.
Hector, M. , and Burton J.R. 1988. What are the psychiatric manifestations of vitamin B12 deficiency? J Am Geriatr Soc. 36 (12): 11051112.
Herbert, V. 1987. The 1986 Herman award lecture. Nutrition science as a continually unfolding story: the folate and vitamin B12 paradigm. Am J Clin Nutr. 46 (3): 387402.
Hogervorst, E. , Ribeiro H.M. , Molyneux A. , Budge M. , and Smith A.D. 2002. Plasma homocysteine levels, cerebrovascular risk factors, and cerebral white matter changes (leukoaraiosis) in patients with Alzheimer disease. Arch Neurol. 59 (5): 787793.
Holmes, J. 1956. Cerebral manifestations of vitamin B12 deficiency. BMJ. 2: 1394.
Hooper, M. , Hudson P. , Porter F. , and McCaddon A. 2014. Patient journeys: diagnosis and treatment of pernicious anaemia. Br J Nurs. 23 (7): 376381.
Hooshmand, B. , Solomon A. , Kareholt I. , Leiviska J. , Rusanen M. , Ahtiluoto S. , Winblad B. , Laatikainen T. , Soininen H. , and Kivipelto M. 2010. Homocysteine and holotranscobalamin and the risk of Alzheimer disease: a longitudinal study. Neurology. 75 (16): 14081414.
173 Hooshmand, B. , Solomon A. , Kareholt I. , Rusanen M. , Hanninen T. , Leiviska J. , Winblad B. , Laatikainen T. , Soininen H. , and Kivipelto M. 2012. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. J Intern Med. 271 (2): 204212.
Howard, J.M. , Azen C. , Jacobsen D.W. , Green R. , and Carmel R. 1998. Dietary intake of cobalamin in elderly people who have abnormal serum cobalamin, methylmalonic acid and homocysteine levels. Eur J Clin Nutr. 52 (8): 582587.
Hvas, A.M. , and Nexo E. 2005. Holotranscobalamina first choice assay for diagnosing early vitamin B12 deficiency? J Intern Med. 257 (3): 289298.
Ikeda, T. , Furukawa Y. , Mashimoto S. , Takahashi K. , and Yamada M. 1990. Vitamin B12 levels in serum and cerebrospinal fluid of people with Alzheimers disease. Acta Psychiatr Scand. 82 (4): 327329.
Inada, M. , Toyoshima M. , and Kameyama M. 1982. Cobalamin contents of the brains in some clinical and pathologic states. Int J Vitam Nutr Res. 52 (4): 423429.
Johnston, C.S. , and Thomas J.A. 1997. Holotranscobalamin II levels in plasma are related to dementia in older people. J Am Geriatr Soc. 45 (6): 779780.
Joosten, E. , Lesaffre E. , Riezler R. , Ghekiere V. , Dereymaeker L. , Pelemans W. , and Dejaeger E. 1997. Is metabolic evidence for vitamin B12 and folate deficiency more frequent in elderly patients with Alzheimers disease? J Gerontol A Biol Sci Med Sci. 52 (2): M76M79.
Joosten, E. , Pelemans W. , Devos P. , Lesaffre E. , Goossens W. , Criel A. , and Verhaeghe R. 1993. Cobalamin absorption and serum homocysteine and methylmalonic acid in elderly subjects with low serum cobalamin. Eur J Haematol. 51 (1): 2530.
Karnaze, D.S. , and Carmel R. 1987. Low serum cobalamin levels in primary degenerative dementia. Do some patients harbor atypical cobalamin deficiency states? Arch Intern Med. 147 (3): 429431.
Kennedy, A.M. , Newman S. , McCaddon A. , Ball J. , Roques P. , Mullan M. , Hardy J. , Chartier-Harlin M.C. , Frackowiak R.S. , Warrington E.K. , et al 1993. Familial Alzheimers disease. A pedigree with a mis-sense mutation in the amyloid precursor protein gene (amyloid precursor protein 717 valine>glycine). Brain. 116 (Pt 2): 309324.
Krasinski, S.D. , Russell R.M. , Samloff I.M. , Jacob R.A. , Dallal G.E. , McGandy R.B. , and Hartz S.C. 1986. Fundic atrophic gastritis in an elderly population. Effect on hemoglobin and several serum nutritional indicators. J Am Geriatr Soc. 34 (11): 800806.
Kubova, H. , Folbergrova J. , and Mares P. 1995. Seizures induced by homocysteine in rats during ontogenesis. Epilepsia. 36 (8): 750756.
Kuhn, W. , Roebroek R. , Blom H. , van Oppenraaij D. , and Muller T. 1998. Hyperhomocysteinaemia in Parkinsons disease. J Neurol. 245 (12): 811812.
Lamberti, P. , Zoccolella S. , Armenise E. , Lamberti S.V. , Fraddosio A. , de Mari M. , Iliceto G. , and Livrea P. 2005. Hyperhomocysteinemia in L-dopa treated Parkinsons disease patients: effect of cobalamin and folate administration. Eur J Neurol. 12 (5): 365368.
Larner, A.J. , and Rakshi J.S. 2001. Vitamin B12 deficiency and dementia. Eur J Neurol. 8 (6): 730731.
Leblhuber, F. , Walli J. , Artner-Dworzak E. , Vrecko K. , Widner B. , Reibnegger G. , and Fuchs D. 2000. Hyperhomocysteinemia in dementia. J Neural Transm. 107 (12): 14691474.
Lehmann, M. , Gottfries C.G. , and Regland B. 1999. Identification of cognitive impairment in the elderly: homocysteine is an early marker. Dement Geriatr Cogn Disord. 10 (1): 1220.
Levin, J. , Botzel K. , Giese A. , Vogeser M. , and Lorenzl S. 2010. Elevated levels of methylmalonate and homocysteine in Parkinsons disease, progressive supranuclear palsy and amyotrophic lateral sclerosis. Dement Geriatr Cogn Disord. 29 (6): 553559.
Lewis, M.S. , Miller L.S. , Johnson M.A. , Dolce E.B. , Allen R.H. , and Stabler S.P. 2005. Elevated methylmalonic acid is related to cognitive impairment in older adults enrolled in an elderly nutrition program. J Nutr Elder. 24 (3): 4765.
Lildballe, D.L. , Fedosov S. , Sherliker P. , Hin H. , Clarke R. , and Nexo E. 2011. Association of cognitive impairment with combinations of vitamin B12-related parameters. Clin Chem. 57 (10): 14361443.
Lindenbaum, J. , Healton E.B. , Savage D.G. , Brust J.C. , Garrett T.J. , Podell E.R. , Marcell P.D. , Stabler S.P. , and Allen R.H. 1988. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 318 (26): 17201728.
174 Lindenbaum, J. , Rosenberg I.H. , Wilson P.W. , Stabler S.P. , and Allen R.H. 1994. Prevalence of cobalamin deficiency in the Framingham elderly population. Am J Clin Nutr. 60 (1): 211.
Liu, Q. , Li S. , Quan H. , and Li J. 2014. Vitamin B12 status in metformin treated patients: systematic review. PLoS One. 9 (6): e100379.
Lucas, S.M. , Rothwell N.J. , and Gibson R.M. 2006. The role of inflammation in CNS injury and disease. Br J Pharmacol 147 (Suppl. 1): S232S240.
Marcus, D.L. , Shadick N. , Crantz J. , Gray M. , Hernandez F. , and Freedman M.L. 1987. Low serum B12 levels in a hematologically normal elderly subpopulation. J Am Geriatr Soc. 35 (7): 635638.

Martin, D.C. , Francis J. , Protetch J. , and Huff F.J. 1992. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. J Am Geriatr Soc. 40 (2): 168172.
McCaddon, A. 2013. Vitamin B12 in neurology and ageing. Clinical and genetic aspects. Biochimie. 95 (5): 10661076.
McCaddon, A. , Davies G. , Hudson P. , Tandy S. , and Cattell H. 1998. Total serum homocysteine in senile dementia of Alzheimer type. Int J Geriatr Psychiatry. 13 (4): 235239.
McCaddon, A. , and Hudson P. 2007a. Alzheimers disease, oxidative stress and B-vitamin depletion. Future Neurology. 2 (5): 537547.
McCaddon, A. , Hudson P. , Abrahamsson L. , Olofsson H. , and Regland B. 2001. Analogues, ageing and aberrant assimilation of vitamin B12 in Alzheimers disease. Dement Geriatr Cogn Disord. 12 (2): 133137.
McCaddon, A. , and Hudson P.R. 2007b. Methylation and phosphorylation: a tangled relationship? Clin Chem. 53 (6): 9991000.
McCaddon, A. , and Kelly C.L. 1992. Alzheimers disease: a cobalaminergic hypothesis. Med Hypotheses. 37 (3): 161165.
McCaddon, A. , and Kelly C.L. 1994. Familial Alzheimers disease and vitamin B12 deficiency. Age Ageing. 23 (4): 334337.
McCaddon, A. , McCracken C. , Carr D. , Hudson P. , Moat S. , Ellis R. , Sequeira J. , and Quadros E. 2013. Transcobalamin receptor polymorphisms in the medical research council cognitive function and ageing study (MRC CFAS). J Inherit Metab Dis. 36 (Suppl 1): S155.
McCaddon, A. , and Miller J.W. 2015. Assessing the association between homocysteine and cognition: reflections on Bradford Hill, meta-analyses, and causality. Nutr Rev. 73 (10): 723735.
McCaddon, A. , Regland B. , Hudson P. , and Davies G. 2002. Functional vitamin B(12) deficiency and Alzheimer disease. Neurology. 58 (9): 13951399.
McCaddon, A. , Tandy S. , Hudson P. , Gray R. , Davies G. , Hill D. , and Duguid J. 2004. Absence of macrocytic anaemia in Alzheimers Disease. Clin Lab Haematol 26 (4): 25963.
McCracken, C. , Hudson P. , Ellis R. , and McCaddon A. 2006. Methylmalonic acid and cognitive function in the medical research council cognitive function and ageing study. Am J Clin Nutr. 84 (6): 14061411.
McEvoy, A.W. , Fenwick J.D. , Boddy K. , and James O.F. 1982. Vitamin B12 absorption from the gut does not decline with age in normal elderly humans. Age Ageing. 11 (3): 180183.
McGing, P. , Reed B. , Weir D.G. , and Scott J.M. 1978. The effect of vitamin B12 inhibition in vivo: impaired folate polyglutamate biosynthesis indicating that 5-methyltetrahydropteroylglutamate is not its usual substrate. Biochem Biophys Res Commun. 82 (2): 540546.
Metz, J. , Bell A.H. , Flicker L. , Bottiglieri T. , Ibrahim J. , Seal E. , Schultz D. , Savoia H. , and McGrath K.M. 1996. The significance of subnormal serum vitamin B12 concentration in older people: a case control study. J Am Geriatr Soc. 44 (11): 13551361.
Miller, J.W. 2002. Homocysteine, folate deficiency, and Parkinsons disease. Nutr Rev. 60 (12): 410413.
Miller, J.W. , Garrod M.G. , Allen L.H. , Haan M.N. , and Green R. 2009. Metabolic evidence of vitamin B12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate. Am J Clin Nutr. 90 (6): 15861592.
Miller, J.W. , Garrod M.G. , Rockwood A.L. , Kushnir M.M. , Allen L.H. , Haan M.N. , and Green R. 2006. Measurement of total vitamin B12 and holotranscobalamin, singly and in combination, in screening for metabolic vitamin B12 deficiency. Clin Chem. 52 (2): 278285.
175 Miller, J.W. , Green R. , Ramos M.I. , Allen L.H. , Mungas D.M. , Jagust W.J. , and Haan M.N. 2003a. Homocysteine and cognitive function in the Sacramento Area Latino Study on Aging. Am J Clin Nutr. 78 (3): 441447.
Miller, J.W. , Selhub J. , Nadeau M.R. , Thomas C.A. , Feldman R.G. , and Wolf P.A. 2003b. Effect of L-dopa on plasma homocysteine in PD patients: relationship to B-vitamin status. Neurology. 60 (7): 11251129.
Morris, M.S. , Jacques P.F. , Rosenberg I.H. , and Selhub J. 2007. Folate and vitamin B12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 85 (1): 193200.
Morris, M.S. , Selhub J. , and Jacques P.F. 2012. Vitamin B12 and folate status in relation to decline in scores on the mini-mental state examination in the Framingham heart study. Journal of the American Geriatrics Society. 60 (8): 14571464.
Muller, T. , Werne B. , Fowler B. , and Kuhn W. 1999. Nigral endothelial dysfunction, homocysteine, and Parkinsons disease. Lancet. 354 (9173): 126127.
Muller, T. , Woitalla D. , Hauptmann B. , Fowler B. , and Kuhn W. 2001. Decrease of methionine and S-adenosylmethionine and increase of homocysteine in treated patients with Parkinsons disease. Neurosci Lett. 308 (1): 5456.
Nilsson, K. , Gustafson L. , Faldt R. , Anderson A. , Vaara I. , Nilsson R. , Alm B. , and Hultberg B. 1997. Plasma methylmalonic acid in relation to serum cobalamin and plasma homocysteine in a psychogeriatric population and the effect of cobalamin treatment. Int J Geriatr Psychiatry. 12 (1): 6772.
Nilsson-Ehle, H. 1998. Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy. Drugs Aging. 12 (4): 277292.
Nilsson-Ehle, H. , Jagenburg R. , Landahl S. , Lindstedt S. , Svanborg A. , and Westin J. 1991. Serum cobalamins in the elderly: a longitudinal study of a representative population sample from age 70 to 81. Eur J Haematol. 47 (1): 1016.
OSuilleabhain, P.E. , Sung V. , Hernandez C. , Lacritz L. , Dewey R.B. Jr , Bottiglieri T. , and Diaz-Arrastia R. 2004. Elevated plasma homocysteine level in patients with Parkinson disease: motor, affective, and cognitive associations. Arch Neurol. 61 (6): 865868.
Obeid, R. , Kasoha M. , Knapp J.P. , Kostopoulos P. , Becker G. , Fassbender K. , and Herrmann W. 2007. Folate and methylation status in relation to phosphorylated tau protein(181P) and {beta}- amyloid(1-42) in cerebrospinal fluid. Clin Chem. 53 (6): 11291136.
Oulhaj, A. , Refsum H. , Beaumont H. , Williams J. , King E. , Jacoby R. , and Smith A.D. 2010. Homocysteine as a predictor of cognitive decline in Alzheimers disease. Int J Geriatr Psychiatry. 25 (1): 8290.
Pennypacker, L.C. , Allen R.H. , Kelly J.P. , Matthews L.M. , Grigsby J. , Kaye K. , Lindenbaum J. , and Stabler S.P. 1992. High prevalence of cobalamin deficiency in elderly outpatients. J Am Geriatr Soc. 40 (12): 11971204.
Prins, N.D. , Den Heijer T. , Hofman A. , Koudstaal P.J. , Jolles J. , Clarke R. , and Breteler M.M. 2002. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology. 59 (9): 13751380.
Ramsaransing, G.S. , Fokkema M.R. , Teelken A. , Arutjunyan A.V. , Koch M. , and De Keyser J. 2006. Plasma homocysteine levels in multiple sclerosis. J Neurol Neurosurg Psychiatry. 77 (2): 189192.
Ravaglia, G. , Forti P. , Maioli F. , Martelli M. , Servadei L. , Brunetti N. , Porcellini E. , and Licastro F. 2005. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr. 82 (3): 636643.
Refsum, H. , and Smith A.D. 2003. Low vitamin B12 status in confirmed Alzheimers disease as revealed by serum holotranscobalamin. J Neurol Neurosurg Psychiatry. 74 (7): 959961.
Regland, B. , Abrahamsson L. , Blennow K. , Gottfries C.G. , and Wallin A. 1992. Vitamin B12 in CSF: reduced CSF/serum B12 ratio in demented men. Acta Neurol Scand. 85 (4): 276281.
Regland, B. , Abrahamsson L. , Gottfries C.G. , and Magnus E. 1990. Vitamin B12 analogues, homocysteine, methylmalonic acid, and transcobalamins in the study of vitamin B12 deficiency in primary degenerative dementia. Dementia. 1: 272277.
Regland, B. , and Gottfries C.G. 1992. Slowed synthesis of DNA and methionine is a pathogenetic mechanism common to dementia in Downs syndrome, AIDS and Alzheimers disease? Med Hypotheses. 38 (1): 1119.
176 Regland, B. , Gottfries C.G. , Oreland L. , and Svennerholm L. 1988. Low B12 levels related to high activity of platelet MAO in patients with dementia disorders. A retrospective study. Acta Psychiatr Scand. 78 (4): 451457.

Renvall, M.J. , Spindler A.A. , Ramsdell J.W. , and Paskvan M. 1989. Nutritional status of free-living Alzheimers patients. Am J Med Sci. 298 (1): 2027.
Reynolds, E.H. 1992. Multiple sclerosis and vitamin B12 metabolism. J Neuroimmunol. 40 (23): 225230.
Reynolds, E.H. 2002. Benefits and risks of folic acid to the nervous system. J Neurol Neurosurg Psychiatry. 72 (5): 567571.
Reynolds, E.H. , Bottiglieri T. , Laundy M. , Crellin R.F. , and Kirker S.G. 1992. Vitamin B12 metabolism in multiple sclerosis. Arch Neurol. 49 (6): 649652.
Rosenberg, I.H. , and Miller J. 1992. Nutritional factors in physical and cognitive functions of elderly people. Am J Clin Nutr. 55: 1237s1243s.
Russell, J.D. , Batten F.E. , and Collier J. 1900. Subacute combined degeneration of the cord. Brain. 23: 3962.
Russo, C. , Morabito F. , Luise F. , Piromalli A. , Battaglia L. , Vinci A. , Trapani L. , M.V. V de , Morabito P. , Condino F. , et al 2008. Hyperhomocysteinemia is associated with cognitive impairment in multiple sclerosis. J Neurol. 255 (1): 6469.
Sachdev, P.S. 2005. Homocysteine and brain atrophy. Prog Neuropsychopharmacol Biol Psychiatry. 29 (7): 115261.
Savage, D.G. , and Lindenbaum J. 1995. Neurological complications of acquired cobalamin deficiency: clinical aspects. Baillieres Clin Haematol. 8 (3): 657678.
Scalabrino, G. , Veber D. , and Mutti E. 2008. Experimental and clinical evidence of the role of cytokines and growth factors in the pathogenesis of acquired cobalamin-deficient leukoneuropathy. Brain Res Rev. 59 (1): 4254.
Scarlett, J.D. , Read H. , and ODea K. 1992. Protein-bound cobalamin absorption declines in the elderly. Am J Hematol. 39 (2): 7983.
Scherer, K. 2003. Images in clinical medicine. Neurologic manifestations of vitamin B12 deficiency. N Engl J Med. 348 (22): 2208.
Schwaninger, M. , Ringleb P. , Winter R. , Kohl B. , Fiehn W. , Rieser P.A. , and Walter-Sack I. 1999. Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. Epilepsia. 40 (3): 345350.
Selhub, J. , Morris M.S. , and Jacques P.F. 2007. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci USA 104 (50): 1999520000.
Selhub, J. , Troen A. , and Rosenberg I.H. 2010. B vitamins and the aging brain. Nutr Rev 68 (Suppl. 2): S112S118.
Seshadri, S. , Beiser A. , Selhub J. , Jacques P.F. , Rosenberg I.H. , DAgostino R.B. , Wilson P.W. , and Wolf P.A. 2002. Plasma homocysteine as a risk factor for dementia and Alzheimers disease. N Engl J Med. 346 (7): 476483.
Smith, A.D. 2006. Prevention of dementia: a role for B vitamins? Nutr Health. 18 (3): 225226.
Smith, A.D. , and Refsum H. 2012. Do we need to reconsider the desirable blood level of vitamin B12? J Intern Med. 271 (2): 179182.
Smith, A.D. , Smith S.M. , de Jager C. , Whitbread P. , Johnston C. , Agacinski G. , Oulhaj A. , Bradley K.M. , Jacoby R. , and Refsum H. 2010. Homocysteine-lowering by B-vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. 5 (9): e12244.
Sontag, E. , Nunbhakdi-Craig V. , Sontag J.M. , Diaz-Arrastia R. , Ogris E. , Dayal S. , Lentz S.R. , Arning E. , and Bottiglieri T. 2007. Protein phosphatase 2A methyltransferase links homocysteine metabolism with tau and amyloid precursor protein regulation. J Neurosci. 27 (11): 27512759.
Stabler, S.P. , Lindenbaum J. , and Allen R.H. 1997. Vitamin B12 deficiency in the elderly: current dilemmas. Am J Clin Nutr. 66 (4): 741749.
Stanger, O. , Fowler B. , Piertzik K. , Huemer M. , Haschke-Becher E. , Semmler A. , Lorenzl S. , and Linnebank M. 2009. Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. Expert Rev Neurother. 9 (9): 13931412.
177 Tangney, C.C. , Tang Y. , Evans D.A. , and Morris M.C. 2009. Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline. Neurology. 72 (4): 361367.
Teunisse, S. , Bollen A.E. , van Gool W.A. , and Walstra G.J. 1996. Dementia and subnormal levels of vitamin B12: effects of replacement therapy on dementia. J Neurol. 243 (7): 522529.
Teunissen, C.E. , Killestein J. , Kragt J.J. , Polman C.H. , Dijkstra C.D. , and Blom H.J. 2008. Serum homocysteine levels in relation to clinical progression in multiple sclerosis. J Neurol Neurosurg Psychiatry. 79 (12): 13491353.
Teunissen, C.E. , Van Boxtel M.P. , Jolles J. , De Vente J. , Vreeling F. , Verhey F. , Polman C.H. , Dijkstra C.D. , and Blom H.J. 2005. Homocysteine in relation to cognitive performance in pathological and non-pathological conditions. Clin Chem Lab Med. 43 (10): 10891095.
Thompson, W.G. , Cassino C. , Babitz L. , Meola T. , Berman R. , Lipkin M. Jr , and Freedman M. 1989. Hypersegmented neutrophils and vitamin B12 deficiency. Hypersegmentation in B12 deficiency. Acta Haematol. 81 (4): 186191.
Toth, C. , Breithaupt K. , Ge S. , Duan Y. , Terris J.M. , Thiessen A. , Wiebe S. , Zochodne D.W. , and Suchowersky O. 2010. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. Ann Neurol. 68 (1): 2836.
Triantafyllou, N. , Evangelopoulos M.E. , Kimiskidis V.K. , Kararizou E. , Boufidou F. , Fountoulakis K.N. , Siamouli M. , Nikolaou C. , Sfagos C. , Vlaikidis N. , et al 2008. Increased plasma homocysteine levels in patients with multiple sclerosis and depression. Ann Gen Psychiatry. 7: 17.
Tucker, K.L. , Rich S. , Rosenberg I. , Jacques P. , Dallal G. , Wilson P.W. , and Selhub J. 2000. Plasma vitamin B12 concentrations relate to intake source in the Framingham Offspring study. Am J Clin Nutr. 71 (2): 514522.
van Asselt, D.Z. , De Groot L.C. , van Staveren W.A. , Blom H.J. , Wevers R.A. , Biemond I. , and Hoefnagels W.H. 1998. Role of cobalamin intake and atrophic gastritis in mild cobalamin deficiency in older Dutch subjects. Am J Clin Nutr. 68 (2): 328334.
van Asselt, D.Z. , van den Broek W.J. , Lamers C.B. , Corstens F.H. , and Hoefnagels W.H. 1996. Free and protein-bound cobalamin absorption in healthy middle-aged and older subjects. J Am Geriatr Soc. 44 (8): 949953.
Van Tiggelen, C. J. M. 1983. Alzheimers disease/alcohol dementia: association with zinc deficiency and cerebral vitamin B12 deficiency. J Orthomolecular Psychiatry. 13: 97104.
Vogiatzoglou, A. , Oulhaj A. , Smith A.D. , Nurk E. , Drevon C.A. , Ueland P.M. , Vollset S.E. , Tell G.S. , and Refsum H. 2009. Determinants of plasma methylmalonic acid in a large population: implications for assessment of vitamin B12 status. Clin Chem. 55 (12): 21982206.
Weir, D.G. , and Scott J.M. 1999. Brain function in the elderly: role of vitamin B12 and folate. Br Med Bull. 55 (3): 669682.
Yao, Y. , Yao S.L. , Yao S.S. , Yao G. , and Lou W. 1992. Prevalence of vitamin B12 deficiency among geriatric outpatients. J Fam Pract. 35 (5): 524528.
Zoccolella, S. , Lamberti S.V. , Iliceto G. , Santamato A. , Lamberti P. , and Logroscino G. 2010. Hyperhomocysteinemia in L-dopa treated patients with Parkinsons disease: potential implications in cognitive dysfunction and dementia? Curr Med Chem. 17 (28): 32533261.
Zoccolella, S. , Simone I.L. , Lamberti P. , Samarelli V. , Tortelli R. , Serlenga L. , and Logroscino G. 2008. Elevated plasma homocysteine levels in patients with amyotrophic lateral sclerosis. Neurology. 70 (3): 222225.
Zylberstein, D.E. , Lissner L. , Bjorkelund C. , Mehlig K. , Thelle D.S. , Gustafson D. , Ostling S. , Waern M. , Guo X. , and Skoog I. 2011. Midlife homocysteine and late-life dementia in women. A prospective population study. Neurobiol Aging. 32 (3): 380386.

The Role of Cobalamin in the Central and Peripheral Nervous Systems: Mechanistic Insights

Agamanolis, D. P. , Victor M. , Harris J.W. , Hines J.D. , Chester E.M. , and Kark J.A. 1978. An ultrastructural study of subacute combined degeneration of the spinal cord in vitamin B12-deficient rhesus monkeys. J Neuropathol Exp Neurol. 37 (3): 273299.

Beck, W. S. 1991. Neuropsychiatric consequences of cobalamin deficiency. Adv Int Med. 36: 3356.

186 Birch, C. S. , Brasch N.E. , McCaddon A. , and Williams J.H. 2009. A novel role for vitamin B12: Cobalamins are intracellular antioxidants in vitro . Free Radical Biol Med. 47: 184188.

Bolander-Gouaille C. and Bottiglieri T. 2007. How can Homocysteine be Neurotoxic? In: Homocysteine. Related Vitamins and Neuropsychiatric Disorders. Springer-Verlag Paris.

Bottiglieri, T. 1996. Folate, vitamin B12, and neuropsychiatric disorders. Nutr Rev. 54 (12): 38290.

Briani, C. , Dalla Torre C. , Citton V. , Manara R. , Pompanin S. , Binotto G. , and Adami F. 2013. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 5 (11): 452139.

Buccellato, F. R. , Miloso M. , Braga M. , Nicolini G. , Morabito A. , Pravettoni G. , Tredici G. , and Scalabrino G. 1999. Myelinolytic lesions in spinal cord of cobalamin-deficient rats are TNF-alpha- mediated. FASEB J. 13 (2): 297304.

Carmel, R. , Karnaze D.S. , and Weiner J.M. 1988. Neurologic abnormalities in cobalamin deficiency are associated with higher cobalamin analogue values than are hematologic abnormalities. J Lab Clin Med. 111 (1): 5762.

Chatterjee, A. , Yapundich R. , Palmer C.A. , Marson D.C. , and Mitchell G.W. 1996. Leukoencephalopathy associated with cobalamin deficiency. Neurology. 46 (3): 832834.

Diaz-Arrastia, R. , and, 2000. Homocysteine and neurologic disease. Arch Neurol. 57 (10): 14227.

Douaud, G. , Refsum H. , de Jager C.A. , Jacoby R. , Nichols T.E. , Smith S.M. , and Smith A.D. 2013. Preventing Alzheimers disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci U S A. 110 (23): 95238.

Duffield, M. S. , Phillips J.I. , Vieira-Makings E. , Van der Westhuyzen J. , and Metz J. 1990. Demyelinisation in the spinal cord of vitamin B12 deficient fruit bats. Comp Biochem Physiol C. 96 (2): 291297.

Fine, E. J. , Soria E. , Paroski M.W. , Petryk D. , and Thomasula L. 1990. The neurophysiological profile of vitamin B12 deficiency. Muscle Nerve. 13 (2): 158164.

Kim, S. , Lim I.K. , Park G.H. , and Paik W.K. 1997. Biological methylation of myelin basic protein: enzymology and biological significance. Int J Biochem Cell Biol. 29 (5): 74351.

Kolhouse, J. F. , Kondo H. , Allen N.C. , Podell E. , and Allen R.H. 1978. Cobalamin analogues are present in human plasma and can mask cobalamin deficiency because current radioisotope dilution assays are not specific for true cobalamin. N Engl J Med. 12: 785792.

Kumar, N. 2007. Nutritional neuropathies. Neurol Clin. 25 (1): 209255.

Lipton, S. A. , Kim W.K. , Choi Y.B. , Kumar S. , and D Emilia DM, Rayudu PV, Arnelle DR and Stamler JS. 1997. Neurotoxicity associated with dual actions of homocysteine at the N-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A. 94 (11): 59238.

Lopes da Silva, S. , Vellas B. , Elemans S. , Luchsinger J. , Kamphuis P. , Yaffe K. , Sijben J. , Groenendijk M. , and Stijnen T. 2014. Plasma nutrient status of patients with Alzheimers disease: Systematic review and meta-analysis. Alzheimers Dement. 10 (4): 485502.

Manzanares, W. , and Hardy G. 2010. Vitamin B12: the forgotten micronutrient for critical care. Curr Opin Clin Nutr Metab Care. 13 (6): 6628.

McCaddon, A. , Hudson P. , Abrahamsson L. , Olofsson H. , and Regland B. 2001. Analogues, ageing and aberrant assimilation of vitamin B12 in Alzheimers disease. Dement Geriatr Cogn Disord. 12 (2): 1337.

McCaddon, A. 2013. Vitamin B12 in neurology and ageing; clinical and genetic aspects. Biochimie. 95 (5): 106676.

Morell, P. , and Quarles R.H. 1999. The Myelin Sheath. In Basic Neurochemistry: Molecular, Cellular and Medical. 6th ed, edited by George J. Siegel . Philadelphia, PA: Lippincott-Raven.

Mutti, E. , Lildballe D.L. , Kristensen L. , Birn H. , and Nexo E. 2013. Vitamin B12 dependent changes in mouse spinal cord expression of vitamin B12 related proteins and the epidermal growth factor system. Brain Res. 1503: 16.

Naidich, M. J. , and Ho S.U. 2005. Case 87: Subacute combined degeneration. Radiology. 237 (1): 1015.

Najafi, M. R. , Shaygannajad V. , Mirpourian M. , and Gholamrezaei A. 2012. Vitamin B12 deficiency and multiple sclerosis; is there any association? Int J Prev Med. 3 (4): 2869.

Peracchi, M. , Bamonti Catena F. , Pomati M. , De Franceschi M. , and Scalabrino G. 2001. Human cobalamin deficiency: alterations in serum tumour necrosis factor-alpha and epidermal growth factor. Eur J Haematol. 67 (2): 1237.

Qureshi, G. A. , Qureshi A.A. , Devrajani B.R. , Chippa M.A. , and Syed S.A. 2008. Is the deficiency of vitamin B12 related to oxidative stress and neurotoxicity in Parkinsons patients? CNS Neurol Disord Drug Targets. 7 (1): 207.

187 Roos, D. 1978. Neurological complications in patients with impaired vitamin B12 absorption following partial gastrectomy. Acta Neurol Scand. 59 (suppl 69): 177.

Sampaio A.L. , Dalli J. , Brancaleone V. , DAcquisto F. , Perretti M. and Wheatley C. 2013. Biphasic modulation of NOS expression, protein and nitrite products by hydroxocobalamin underlies its protective effect in endotoxemic shock: downstream regulation of COX-2, IL-1 p, TNF-a, IL-6, and HMGB1 expression. Mediators Inflamm. 741804.

Saperstein, D. S. , and Barohn R.J. 2002. Peripheral neuropathy due to cobalamin deficiency. Curr Treat Options Neurol. 4: 197201.

Scalabrino, G. 2001. Subacute combined degeneration one century later. The neurotrophic action of cobalamin (vitamin B12) revisited. J Neuropathol Exp Neurol. 60 (2): 109120.

Scalabrino, G. 2005. Cobalamin (vitamin B12) in subacute combined degeneration and beyond: traditional interpretations and novel theories. Exp Neurol. 192 (2): 46379.

Scalabrino, G. 2009. The multi-faceted basis of vitamin B12 (cobalamin) neurotrophism in adult central nervous system: Lessons learned from its deficiency. Prog Neurobiol. 88 (3): 20320.

Scalabrino, G. , Monzio-Compagnoni B. , Ferioli M.E. , Lorenzini E.C. , Chiodini E. , and Candiani R. 1990. Subacute combined degeneration and induction of ornithine decarboxylase in spinal cords of totally gastrectomized rats. Lab Invest. 62 (3): 297304.

Scalabrino, G. , Lorenzini E.C. , Monzio-Compagnoni B. , Colombi R.P. , Chiodini E. , and Buccellato F.R. 1995. Subacute combined degeneration in the spinal cords of totally gastrectomized rats. Ornithine decarboxylase induction, cobalamin status, and astroglial reaction. Lab Invest. 72 (1): 11423.

Scalabrino, G. , Nicolini G. , Buccellato F.R. , Peracchi M. , Tredici G. , Manfridi A. , and Pravettoni G. 1999. Epidermal growth factor as a local mediator of the neurotrophic action of vitamin B12 (cobalamin) in the rat central nervous system. FASEB J. 13 (14): 208390.

Scalabrino, G. , Tredici G. , Buccellato F.R. , and Manfridi A. 2000. Further evidence for the involvement of epidermal growth factor in the signaling pathway of vitamin B12 (cobalamin) in the rat central nervous system. J Neuropathol Exp Neurol. 59 (9): 80814.

Scalabrino, G. , Corsi M.M. , Veber D. , Buccellato F.R. , Pravettoni G. , Manfridi A. , and Magni P. 2002. Cobalamin (vitamin B12) positively regulates interleukin-6 levels in rat cerebrospinal fluid. J Neuroimmunol. 127 (12): 3743.

Scalabrino, G. , Carpo M. , Bamonti F. , Pizzinelli S. , DAvino C. , Bresolin N. , Meucci G. , Martinelli V. , Comi G.C. , and Peracchi M. 2004. High tumor necrosis factor-alpha levels in cerebrospinal fluid of cobalamin-deficient patients. Ann Neurol. 56 (6): 88690.

Scalabrino, G. , Mutti E. , Veber D. , Aloe L. , Corsi M.M. , Galbiati S. , and Tredici G. 2006. Increased spinal cord NGF levels in rats with cobalamin (vitamin B12) deficiency. Neurosci Lett. 396 (2): 1538.

Scalabrino, G. , Veber D. , and Mutti E. 2008. Experimental and clinical evidence of the role of cytokines and growth factors in the pathogenesis of acquired cobalamin-deficient leukoneuropathy. Brain Res Rev. 59: 4254.
Scalabrino, G. , Galimberti D. , Mutti E. , Scalabrini D. , Veber D. , De Riz M. , Bamonti F. , Capello E. , Mancardi G.L. , and Scarpini E. 2010. Loss of epidermal growth factor regulation by cobalamin in multiple sclerosis. Brain Res. 1333: 6471.
Scalabrino, G. , Mutti E. , Veber D. , Rodriguez Menendez V. , Novembrino C. , Calligaro A. , and Tredici G. 2011. The octapeptide repeat PrPC region and cobalamin-deficient polyneuropathy of the rat. Muscle Nerve. 44 (6): 95767.
Scalabrino, G. , Veber D. , Mutti E. , Calligaro A. , Milani S. , and Tredici G. 2012. Cobalamin (vitamin B12) regulation of PrPC, PrPC-mRNA and copper levels in rat central nervous system. Exp Neurol. 233 (1): 38090.
Scherer, K. 2003. Images in clinical medicine. Neurologic manifestations of vitamin B12 deficiency. N Engl J Med. 348 (22): 2208.
Song, Z. , Uriarte S. , Sahoo R. , Chen T. , Barve S. , Hill D. , and McClain C. 2005. S-adenosylmethionine (SAMe) modulates interleukin-10 and interleukin-6, but not TNF, production via the adenosine (A2) receptor. Biochim Biophys Acta. 1743 (3): 20513.
Suarez-Moreira, E. , Yun J. , Birch C.S. , Williams J.H. , McCaddon A. , and Brasch N.E. 2009. Vitamin B12 and redox homeostasis: cob(II)alamin reacts with superoxide at rates approaching superoxide dismutase (SOD). J Am Chem Soc. 131: 1507815079.
188 Surtees, R. 1993. Biochemical pathogenesis of subacute combined degeneration of the spinal cord and brain. J Inherit Metab Dis. 16 (4): 76270.
Tefferi, A. , and Pruthi R.K. 1994. The biochemical basis of cobalamin deficiency. Mayo Clin Proc. 69 (2): 1816.
Tredici, G. , Buccellato F.R. , Cavaletti G. , and Scalabrino G. 1998. Subacute combined degeneration in totally gastrectomized rats: an ultrastructural study. J Submicrosc Cytol Pathol. 30 (1): 165173.
Veber, D. , Mutti E. , Galmozzi E. , Cedrola S. , Galbiati S. , Morabito A. , Tredici G. , La Porta C.A. , and Scalabrino G. 2006. Increased levels of the CD40:CD40 ligand dyad in the cerebrospinal fluid of rats with vitamin B12 (cobalamin)-deficient central neuropathy. J Neuroimmunol. 176 (12): 2433.
Watson, W.H. , Zhao Y. , and Chawla R.K. 1999. S-adenosylmethionine attenuates the lipopolysaccharide- induced expression of the gene for tumour necrosis factor alpha. Biochem J. 342 (Pt 1): 215.
Weir, D.G. , and J.M. Scott . 1995. The biochemical basis of the neuropathy in cobalamin deficiency. Baillieres Clin Haematol. 8 (3): 47997.
Wheatley, C. 2006. A scarlet pimpernel for the resolution of inflammation? The role of supra- therapeutic doses of cobalamin, in the treatment of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic or traumatic shock. Med Hypotheses. 67 (1): 124142.
Wheatley, C. 2007a. The return of the Scarlet Pimpernel: cobalamin in inflammation II - cobalamins can both selectively promote all three nitric oxide synthases (NOS), particularly iNOS and eNOS, and as needed, selectively inhibit iNOS and nNOS. J Nutr Environ Med. 16 (34): 181211.
Wheatley, C. 2007b. Cobalamin in inflammation IIIglutathionylcobalamin and thylcobalamin/ adenosylcobalamin coenzymes: the sword in the stone? How cobalamin may directly regulate the nitric oxide synthases. J Nutr Environ Med. 16 (34): 212226.
Zhao, H. , Li H. , Ruberu K. , and Garner B. . 2015. Impaired lysosomal cobalamin transport in Alzheimers disease. J Alzheimers Dis. 43 (3): 101730.
Zhu, Y. , He Z.Y. , and Liu H.N. 2011. Meta-analysis of the relationship between homocysteine, vitamin B12, folate, and multiple sclerosis. J Clin Neurosci. 18 (7): 9338.

Laboratory Markers and Diagnosis of Cobalamin Deficiency

Abuyaman, O. , Andreasen B.H. , Kronborg C. , Vittinghus E. , and Nexo E. 2013. The soluble receptor for vitamin B12 uptake (sCD320) increases during pregnancy and occurs in higher concentration in urine than in serum. PLoS One. 8: e73110.
Abuyaman, O. , and Nexo E. 2015. The soluble transcobalamin receptor (sCD320) is present in cerebrospinal fluid and correlates to dementia-related biomarkers tau proteins and amyloidbeta. Scand J Clin Lab Invest. 75: 514518.
Adjalla c. , Lambert D. , Benhayoun S. , Berthelsen J.G. , Nicolas J.P. , Gueant J.L. and Nexo E. 1994. Forms of cobalamin and vitamin B12 analogs in maternal plasma, milk, and cord plasma. In: p 406-410.
Agreus, L. , Kuipers E.J. , Kupcinskas L. , Malfertheiner P. , Di M.F. , Leja M. , Mahachai V. , Yaron N. , van O.M. , Perez P.G. , Rugge M. , Ronkainen J. , Salaspuro M. , Sipponen P. , Sugano K. and Sung J. 2012. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand J Gastroenterol. 47: 136147.
Areekul, S. , Churdchu K. , Cheeramakara C. , Wilairatana P. , and Charoenlarp P. 1995. Serum transcobalamin II levels in patients with acute and chronic renal failure. J Med Assoc Thai. 78: 191196.
Arnaud, J. , Cotisson A. , Meffre G. , Bourgeay-Causse M. , Augert C. , Favier A. , Vuillez J.P. , and Ville G. 1994. Comparison of three commercial kits and a microbiological assay for the determination of vitamin B12 in serum. Scand J Clin Lab Invest. 54: 235240.
Aslinia, F. , Mazza J.J. , and Yale S.H. 2006. Megaloblastic anemia and other causes of macrocytosis. Clin Med Res. 4: 236241.
Bailey, R.L. , Carmel R. , Green R. , Pfeiffer C.M. , Cogswell M.E. , Osterloh J.D. , Sempos C.T. , and Yetley E.A. 2011. Monitoring of vitamin B12 nutritional status in the United States by using plasma methylmalonic acid and serum vitamin B12. Am J Clin Nutr. 94: 552561.
Bailey, R.L. , Durazo-Arvizu R.A. , Carmel R. , Green R. , Pfeiffer C.M. , Sempos C.T. , Carriquiry A. , and Yetley E.A. 2013. Modeling a methylmalonic acid-derived change point for serum vitamin B12 for adults in NHANES. Am J Clin Nutr. 98: 460467.
Baker, H. , Leevy C.B. , DeAngelis B. , Frank O. , and Baker E.R. 1998. Cobalamin (vitamin B12) and holotranscobalamin changes in plasma and liver tissue in alcoholics with liver disease. J Am Coll Nutr. 17: 235238.
Bamonti, F. , Moscato G.A. , Novembrino C. , Gregori D. , Novi C. , De G.R. , Galli C. , Uva V. , Lonati S. , and Maiavacca R. 2010. Determination of serum holotranscobalamin concentrations with the AxSYM active B(12) assay: cut-off point evaluation in the clinical laboratory. Clin Chem Lab Med. 48: 249253.
Bhat, D.S. , Thuse N.V. , Lubree H.G. , Joglekar C.V. , Naik S.S. , Ramdas L.V. , Johnston C. , Refsum H. , Fall C.H. , and Yajnik C.S. 2009. Increases in plasma holotranscobalamin can be used to assess vitamin B12 absorption in individuals with low plasma vitamin B12. J Nutr. 139: 21192123.
Birn, H. 2006. The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins. Am J Physiol Renal Physiol. 291: F22F36.
Birn, H. , Nexo E. , Christensen E.I. , and Nielsen R. 2003. Diversity in rat tissue accumulation of vitamin B12 supports a distinct role for the kidney in vitamin B12 homeostasis. Nephrol Dial Transplant. 18: 10951100.
Bizzaro, N. , and Antico A. 2014. Diagnosis and classification of pernicious anemia. Autoimmun Rev. 13: 565568.
Bor, M.V. , Cetin M. , Aytac S. , Altay C. , and Nexo E. 2005. Nonradioactive vitamin B12 absorption test evaluated in controls and in patients with inherited malabsorption of vitamin B12. Clin Chem. 51: 21512155.

Bor, M.V. , Lydeking-Olsen E. , Moller J. , and Nexo E. 2006. A daily intake of approximately 6 microg vitamin B12 appears to saturate all the vitamin B12-related variables in Danish postmenopausal women. Am J Clin Nutr. 83: 5258.
Bor, M.V. , von Castel-Roberts K.M. , Kauwell G.P. , Stabler S.P. , Allen R.H. , Maneval D.R. , Bailey L.B. , and Nexo E. 2010. Daily intake of 4 to 7 microg dietary vitamin B12 is associated with steady concentrations of vitamin B12-related biomarkers in a healthy young population. Am J Clin Nutr. 91: 571577.
233 Brady, J. , Wilson L. , McGregor L. , Valente E. , and Orning L. 2008. Active B12: a rapid, automated assay for holotranscobalamin on the Abbott AxSYM analyzer. Clin Chem. 54: 567573.
Brito, A. , Verdugo R. , Hertrampf E. , Miller J.W. , Green R. , Fedosov S.N. , Shahab-Ferdows S. , Sanchez H. , Albala C. , Castillo J.L. , Matamala J.M. , Uauy R. , and Allen L.H. 2016. Vitamin B12 treatment of asymptomatic, deficient, elderly Chileans improves conductivity in myelinated peripheral nerves, but high serum folate impairs vitamin B12 status response assessed by the combined indicator of vitamin B12 status. Am J Clin Nutr. 103: 250257.
Bystrom, P. , Bjorkegren K. , Larsson A. , Johansson L. , and Berglund A. 2009. Serum vitamin B12 and folate status among patients with chemotherapy treatment for advanced colorectal cancer. Ups J Med Sci. 114: 160164.
Carmel, R. 1996. Prevalence of undiagnosed pernicious anemia in the elderly. Arch Intern Med. 156: 10971100.
Carmel, R. 2003. Mild transcobalamin I (haptocorrin) deficiency and low serum cobalamin concentrations. Clin Chem. 49: 13671374.
Carmel, R. , Aurangzeb I. , and Qian D. 2001a. Associations of food-cobalamin malabsorption with ethnic origin, age, Helicobacter pylori infection, and serum markers of gastritis. Am J Gastroenterol. 96: 6370.
Carmel, R. , Brar S. , and Frouhar Z. 2001b. Plasma total transcobalamin I. Ethnic/racial patterns and comparison with lactoferrin. Am J Clin Pathol. 116: 576580.
Carmel, R. , and Eisenberg L. 1977. Serum vitamin B12 and transcobalamin abnormalities in patients with cancer. Cancer. 40: 13481353.
Carmel, R. , and Hollander D. 1978. Extreme elevation of transcobalamin II levels in multiple myeloma and other disorders. Blood. 51: 10571063.
Carmel, R. , Vasireddy H. , Aurangzeb I. , and George K. 2001c. High serum cobalamin levels in the clinical settingclinical associations and holo-transcobalamin changes. Clin Lab Haematol. 23: 365371.
Collins, R.A. , Harper A.E. , Scheiber M. , and Elvehjem C. 1951. The folic acid and vitamin B12 content of the milk of various species. J Nutr. 43: 313321.
Deegan, K.L. , Jones K.M. , Zuleta C. , Ramirez-Zea M. , Lildballe D.L. , Nexo E. , and Allen L.H. 2012. Breast milk vitamin B12 concentrations in guatemalan women are correlated with maternal but not infant vitamin B12 status at 12 months postpartum. J Nutr. 142: 112116.
Dierkes, J. , Domrose U. , Ambrosch A. , Schneede J. , Guttormsen A.B. , Neumann K.H. , and Luley C. 1999. Supplementation with vitamin B12 decreases homocysteine and methylmalonic acid but also serum folate in patients with end-stage renal disease. Metabolism. 48: 631635.
Dominguez-Salas, P. , Moore S.E. , Cole D. , da Costa K.A. , Cox S.E. , Dyer R.A. , Fulford A.J. , Innis S.M. , Waterland R.A. , Zeisel S.H. , Prentice A.M. , and Hennig B.J. 2013. DNA methylation potential: dietary intake and blood concentrations of one-carbon metabolites and cofactors in rural African women. Am J Clin Nutr. 97: 12171227.
Doscherholmen, A. , and Swaim W.R. 1973. Impaired assimilation of egg Co 57 vitamin B12 in patients with hypochlorhydria and achlorhydria and after gastric resection. Gastroenterology. 64: 913919.
Ducros, V. , Demuth K. , Sauvant M.P. , Quillard M. , Causse E. , Candito M. , Read M.H. , Drai J. , Garcia I. , and Gerhardt M.F. 2002. Methods for homocysteine analysis and biological relevance of the results. J Chromatogr B Analyt Technol Biomed Life Sci. 781: 207226.
Duggan, C. , Srinivasan K. , Thomas T. , Samuel T. , Rajendran R. , Muthayya S. , Finkelstein J.L. , Lukose A. , Fawzi W. , Allen L.H. , Bosch R.J. , and Kurpad A.V. 2014. Vitamin B12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B12 status. J Nutr. 144: 758764.
Dullemeijer, C. , Souverein O.W. , Doets E.L. , van der Voet H. , van Wijngaarden J.P. , de Boer W.J. , Plada M. , Dhonukshe-Rutten R.A. , In t Veld P.H. , Cavelaars A.E. , de Groot L.C. , van t Veer P. , 2013. Systematic review with dose-response meta-analyses between vitamin B12 intake and European Micronutrient Recommendations Aligneds prioritized biomarkers of vitamin B12 including randomized controlled trials and observational studies in adults and elderly persons. Am J Clin Nutr. 97: 390402.
Elian, K.M. , and Hoffer L.J. 2002. Hydroxocobalamin reduces hyperhomocysteinemia in end-stage renal disease. Metabolism. 51: 881886.
234 Eussen, S.J. , Nilsen R.M. , Midttun O. , Hustad S. , Ijssennagger N. , Meyer K. , Fredriksen A. , Ulvik A. , Ueland P.M. , Brennan P. , Johansson M. , Bueno-de-Mesquita B. , Vineis P. , Chuang S.C. , Boutron- Ruault M.C. , Dossus L. , Perquier F. , Overvad K. , Teucher B. , Grote V.A. , Trichopoulou A. , Adarakis G. , Plada M. , Sieri S. , Tumino R. , de Magistris M.S. , Ros M.M. , Peeters P.H. , Redondo M.L. , Zamora-Ros R. , Chirlaque M.D. , Ardanaz E. , Sonestedt E. , Ericson U. , Schneede J. , Van G.B. , Wark P.A. , Gallo V. , Norat T. , Riboli E. , and Vollset S.E. 2012. North-south gradients in plasma concentrations of B-vitamins and other components of one-carbon metabolism in Western Europe: results from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Br J Nutr. 112.
Fedosov, S.N. , Brito A. , Miller J.W. , Green R. , and Allen L.H. 2015. Combined indicator of vitamin B12 status: modification for missing biomarkers and folate status and recommendations for revised cut-points. Clin Chem Lab Med. 53: 12151225.
Fernandes-Costa, F. , and van T.S. and Metz J. 1985. A sex difference in serum cobalamin and transcobalamin levels. Am J Clin Nutr. 41: 784786.
Festen, H.P. 1991. Intrinsic factor secretion and cobalamin absorption. Physiology and pathophysiology in the gastrointestinal tract. Scand J Gastroenterol Suppl. 188: 17.
Flatley, J.E. , Garner C.M. , Al-Turki M. , Manning N.J. , Olpin S.E. , Barker M.E. , and Powers H.J. 2012. Determinants of urinary methylmalonic acid concentration in an elderly population in the United Kingdom. Am J Clin Nutr. 95: 686693.
Garcia, A. , Paris-Pombo A. , Evans L. , Day A. , and Freedman M. 2002. Is low-dose oral cobalamin enough to normalize cobalamin function in older people? J Am Geriatr Soc. 50: 14011404.
Gilsing, A.M. , Crowe F.L. , Lloyd-Wright Z. , Sanders T.A. , Appleby P.N. , Allen N.E. , and Key T.J. 2010. Serum concentrations of vitamin B12 and folate in British male omnivores, vegetarians and vegans: results from a cross-sectional analysis of the EPIC-Oxford cohort study. Eur J Clin Nutr. 64: 933939.
Gimsing, P. , and Nexo E. 1989. Cobalamin-binding capacity of haptocorrin and transcobalamin: age-correlated reference intervals and values from patients. Clin Chem. 35: 14471451.
Gonzalez-Gross, M. , Benser J. , Breidenassel C. , Albers U. , Huybrechts I. , Valtuena J. , Spinneker A. , Segoviano M. , Widhalm K. , Molnar D. , Moreno L.A. , Stehle P. , and Pietrzik K. 2012. Gender and age influence blood folate, vitamin B12, vitamin B6, and homocysteine levels in European adolescents: the Helena Study. Nutr Res. 32: 817826.
Gulati, S. , Baker P. , Li Y.N. , Fowler B. , Kruger W. , Brody L.C. , and Banerjee R. 1996. Defects in human methionine synthase in cblG patients. Hum Mol Genet. 5: 18591865.
Gultepe, M. , Ozcan O. , Avsar K. , Cetin M. , Ozdemir A.S. , and Gok M. 2003. Urine methylmalonic acid measurements for the assessment of cobalamin deficiency related to neuropsychiatric disorders. Clin Biochem. 36: 275282.

Hampel, D. , Shahab-Ferdows S. , Domek J.M. , Siddiqua T. , Raqib R. , and Allen L.H. 2014. Competitive chemiluminescent enzyme immunoassay for vitamin B12 analysis in human milk. Food Chem. 153: 6065.
Hardlei, T.F. , Morkbak A.L. , Bor M.V. , Bailey L.B. , Hvas A.M. , and Nexo E. 2010. Assessment of vitamin B(12) absorption based on the accumulation of orally administered cyanocobalamin on transcobalamin. Clin Chem. 56: 432436.
Herrmann, W. , and Obeid R. 2009. Holotranscobalaminan early marker for laboratory diagnosis of vitamin B12 deficiency. European Haematology. 2: 26.
Herrmann, W. , and Obeid R. 2013. Utility and limitations of biochemical markers of vitamin B12 deficiency. Eur J Clin Invest. 43: 231237.
Herrmann, W. , Obeid R. , Schorr H. , and Geisel J. 2005. The usefulness of holotranscobalamin in predicting vitamin B12 status in different clinical settings. Curr Drug Metab. 6: 4753.
Herrmann, W. , Schorr H. , Obeid R. , and Geisel J. 2003. Vitamin B12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr. 78: 131136.
Hill, M.H. , Flatley J.E. , Barker M.E. , Garner C.M. , Manning N.J. , Olpin S.E. , Moat S.J. , Russell J. , and Powers H.J. 2013. A vitamin B12 supplement of 500 mug/d for eight weeks does not normalize urinary methylmalonic acid or other biomarkers of vitamin B12 status in elderly people with moderately poor vitamin B12 status. J Nutr. 143: 142147.
235 Hirschowitz, B.I. , Worthington J. , and Mohnen J. 2008. Vitamin B12 deficiency in hypersecretors during long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther. 27: 11101121.
Hubner, U. , Schorr H. , Eckert R. , Geisel J. , and Herrmann W. 2007a. Stability of plasma homocysteine, S-adenosylmethionine, and S-adenosylhomocysteine in EDTA, acidic citrate, and Primavette collection tubes. Clin Chem. 53: 22172218.
Hubner, U. , Schorr H. , Eckert R. , Geisel J. , and Herrmann W. 2007b. Stability of plasma homocysteine, S-adenosylmethionine, and S-adenosylhomocysteine in EDTA, acidic citrate, and Primavette collection tubes. Clin Chem. 53: 22172218.
Hurwitz, A. , Brady D.A. , Schaal S.E. , Samloff I.M. , Dedon J. , and Ruhl C.E. 1997. Gastric acidity in older adults 1. JAMA. 278: 659662.
Hyndman, M.E. , Manns B.J. , Snyder F.F. , Bridge P.J. , Scott-Douglas N.W. , Fung E. , and Parsons H.G. 2003. Vitamin B12 decreases, but does not normalize, homocysteine and methylmalonic acid in end-stage renal disease: a link with glycine metabolism and possible explanation of hyperhomocysteinemia in end-stage renal disease. Metabolism. 52: 168172.
Ikeda, T. , Furukawa Y. , Mashimoto S. , Takahashi K. , and Yamada M. 1990. Vitamin B12 levels in serum and cerebrospinal fluid of people with Alzheimers disease. Acta Psychiatr Scand. 82: 327329.
Ispir, E. , Serdar M.A. , Ozgurtas T. , Gulbahar O. , Akin K.O. , Yesildal F. , and Kurt I. 2015. Comparison of four automated serum vitamin B12 assays. Clin Chem Lab Med. 53: 12051213.
Israel-Ballard, K.A. , Abrams B.F. , Coutsoudis A. , Sibeko L.N. , Cheryk L.A. , and Chantry C.J. 2008. Vitamin content of breast milk from HIV-1-infected mothers before and after flash-heat treatment. J Acquir Immune Defic Syndr. 48: 444449.
Jathar, V.S. , Kamath S.A. , Parikh M.N. , Rege D.V. , and Satoskar R.S. 1970. Maternal milk and serum vitamin B12, folic acid, and protein levels in Indian subjects. Arch Dis Child. 45: 236241.
Joosten, E. , van den Berg A. , Riezler R. , Naurath H.J. , Lindenbaum J. , Stabler S.P. , and Allen R.H. 1993. Metabolic evidence that deficiencies of vitamin B12 (cobalamin), folate, and vitamin B-6 occur commonly in elderly people. Am J Clin Nutr. 58: 468476.
Kaptan, K. , Beyan C. , Ural A.U. , Cetin T. , Avcu F. , Gulsen M. , Finci R. , and Yalcin A. 2000. Helicobacter pyloriis it a novel causative agent in Vitamin B12 deficiency? Arch Intern Med. 160: 13491353.
kidd H.M. , Gould C.E. and Thomas J.W. 1963. Free and total vitamin B12 in cerebrospinal fluid. Can Med Assoc J. 88: 876881.
Krasinski, S.D. , Russell R.M. , Samloff I.M. , Jacob R.A. , Dallal G.E. , McGandy R.B. , and Hartz S.C. 1986. Fundic atrophic gastritis in an elderly population. Effect on hemoglobin and several serum nutritional indicators. J Am Geriatr Soc. 34: 800806.
Kurnat-Thoma, E.L. , Pangilinan F. , Matteini A.M. , Wong B. , Pepper G.A. , Stabler S.P. , Guralnik J.M. , and Brody L.C. 2015. Association of transcobalamin II (TCN2) and transcobalamin II-receptor (TCblR) genetic variations with cobalamin deficiency parameters in elderly women. Biol Res Nurs. 17: 444454.
Kvestad, I. , Taneja S. , Kumar T. , Hysing M. , Refsum H. , Yajnik C.S. , Bhandari N. , and Strand T.A. 2015. Vitamin B12 and folic acid improve gross motor and problem-solving skills in young North Indian children: A randomized placebo-controlled trial. PLoS One. 10: e0129915.
Kwok, T. , Cheng G. , Lai W.K. , Poon P. , Woo J. , and Pang C.P. 2004. Use of fasting urinary methylmalonic acid to screen for metabolic vitamin B12 deficiency in older persons. Nutrition. 20: 764768.
Lahner, E. , Norman G.L. , Severi C. , Encabo S. , Shums Z. , Vannella L. , Fave G.D. , and Annibale B. 2009. Reassessment of intrinsic factor and parietal cell autoantibodies in atrophic gastritis with respect to cobalamin deficiency. Am J Gastroenterol. 104: 20712079.
Lam, J.R. , Schneider J.L. , Zhao W. , and Corley D.A. 2013. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 310: 24352442.
Lazar, G.S. , and Carmel R. 1981. Cobalamin binding and uptake in vitro in the human central nervous system. J Lab Clin Med. 97: 123133.
Lildballe, D.L. , Hardlei T.F. , Allen L.H. , and Nexo E. 2009. High concentrations of haptocorrin interfere with routine measurement of cobalamins in human serum and milk. A problem and its solution. Clin Chem Lab Med. 47: 182187.
236 Lindemans, J. , Schoester M. , and van Kapel J. 1983. Application of a simple immunoadsorption assay for the measurement of saturated and unsaturated transcobalamin II and R-binders. Clin Chim Acta. 132: 5361.
Lindgren, A. , Kilander A. , Bagge E. , and Nexo E. 1999. Holotranscobalamina sensitive marker of cobalamin malabsorption. Eur J Clin Invest. 29: 321329.
Lloyd-Wright, Z. , Hvas A.M. , Moller J. , Sanders T.A. , and Nexo E. 2003. Holotranscobalamin as an indicator of dietary vitamin B12 deficiency. Clin Chem. 49: 20762078.
Loikas, S. , Lopponen M. , Suominen P. , Moller J. , Irjala K. , Isoaho R. , Kivela S.L. , Koskinen P. , and Pelliniemi T.T. 2003. RIA for serum holo-transcobalamin: method evaluation in the clinical laboratory and reference interval. Clin Chem. 49: 455462.
Mansoor, M.A. , Stea T.H. , Schneede J. , and Reine A. 2013. Early biochemical and hematological response to intramuscular cyanocobalamin therapy in vitamin B(12)-deficient patients. Ann Nutr Metab. 62: 347353.
Marcell, P.D. , Stabler S.P. , Podell E.R. , and Allen R.H. 1985. Quantitation of methylmalonic acid and other dicarboxylic acids in normal serum and urine using capillary gas chromatography- mass spectrometry. Anal Biochem. 150: 5866.
McPhee, A.J. , Davidson G.P. , Leahy M. , and Beare T. 1988. Vitamin B12 deficiency in a breast fed infant. Arch Dis Child. 63: 921923.
Mendelsohn, R.S. , Watkin D.M. , Horbett A.P. , and Fahey J.L. 1958. Identification of the vitamin B12- binding protein in the serum of normals and of patients with chronic myelocytic leukemia. Blood. 13: 740747.
Mineva, E.M. , Zhang M. , Rabinowitz D.J. , Phinney K.W. , and Pfeiffer C.M. 2015. An LC-MS/MS method for serum methylmalonic acid suitable for monitoring vitamin B12 status in population surveys. Anal Bioanal Chem. 407: 29552964.
Moelby, L. , Rasmussen K. , Ring T. , and Nielsen G. 2000. Relationship between methylmalonic acid and cobalamin in uremia. Kidney Int. 57: 265273.
Moestrup, S.K. , Birn H. , Fischer P.B. , Petersen C.M. , Verroust P.J. , Sim R.B. , Christensen E.I. , and Nexo E. 1996. Megalin-mediated endocytosis of transcobalamin-vitamin-B12 complexes suggests a role of the receptor in vitamin-B12 homeostasis. Proc Natl Acad Sci U S A. 93: 86128617.

Molloy, A.M. , Mills J.L. , McPartlin J. , Kirke P.N. , Scott J.M. , and Daly S. 2002. Maternal and fetal plasma homocysteine concentrations at birth: the influence of folate, vitamin B12, and the 5,10-methylenetetrahydrofolate reductase 677C>T variant. Am J Obstet Gynecol. 186: 499503.
Morkbak, A.L. , Hvas A.M. , Milman N. , and Nexo E. 2007. Holotranscobalamin remains unchanged during pregnancy. Longitudinal changes of cobalamins and their binding proteins during pregnancy and postpartum. Haematologica. 92: 17111712.
Morkbak, A.L. , Pedersen J.F. , and Nexo E. 2005. Glycosylation independent measurement of the cobalamin binding protein haptocorrin. Clin Chim Acta. 356: 184190.
Murphy, M.M. , Molloy A.M. , Ueland P.M. , Fernandez-Ballart J.D. , Schneede J. , Arija V. , and Scott J.M. 2007. Longitudinal study of the effect of pregnancy on maternal and fetal cobalamin status in healthy women and their offspring. J Nutr. 137: 18631867.
Naurath, H.J. , Joosten E. , Riezler R. , Stabler S.P. , Allen R.H. , and Lindenbaum J. 1995. Effects of vitamin B12, folate, and vitamin B6 supplements in elderly people with normal serum vitamin concentrations. Lancet. 346: 8589.
Nexo, E. , Christensen A.L. , Hvas A.M. , Petersen T.E. , and Fedosov S.N. 2002a. Quantification of holotranscobalamin, a marker of vitamin B12 deficiency. Clin Chem. 48: 561562.
Nexo, E. , Christensen A.L. , Petersen T.E. , and Fedosov S.N. 2000. Measurement of transcobalamin by ELISA. Clin Chem. 46: 16431649.
Nexo, E. , and Hoffmann-Lucke E. 2011. Holotranscobalamin, a marker of vitamin B12 status: analytical aspects and clinical utility. Am J Clin Nutr. 94: 359S365S.
Nexo, E. , Hvas A.M. , Bleie O. , Refsum H. , Fedosov S.N. , Vollset S.E. , Schneede J. , Nordrehaug J.E. , Ueland P.M. , and Nygard O.K. 2002b. Holo-transcobalamin is an early marker of changes in cobalamin homeostasis. A randomized placebo-controlled study. Clin Chem. 48: 17681771.
Niafar, M. , Hai F. , Porhomayon J. , and Nader N.D. 2015. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med. 10: 93102.
237 Nickoloff, E. 1988. Schilling test: physiologic basis for and use as a diagnostic test. Crit Rev Clin Lab Sci. 26: 263276.
Nilsson-Ehle, H. , Landahl S. , Lindstedt G. , Netterblad L. , Stockbruegger R. , Westin J. , and Ahren C. 1989. Low serum cobalamin levels in a population study of 70- and 75-year-old subjects. Gastrointestinal causes and hematological effects. Dig Dis Sci. 34: 716723.
Niyikiza, C. , Baker S.D. , Seitz D.E. , Walling J.M. , Nelson K. , Rusthoven J.J. , Stabler S.P. , Paoletti P. , Calvert A.H. , and Allen R.H. 2002. Homocysteine and methylmalonic acid: markers to predict and avoid toxicity from pemetrexed therapy. Mol Cancer Ther. 1: 545552.
Norman, E.J. , and Morrison J.A. 1993. Screening elderly populations for cobalamin (vitamin B12) deficiency using the urinary methylmalonic acid assay by gas chromatography mass spectrometry [see comments]. Am J Med. 94: 589594.
Obeid R. , Geisel J. and Herrmann W. 2015. Comparison of two methods for measuring methylmalonic acid as a marker for vitamin B12 deficiency. In: Diagnosis: Walter de Gruyter. pp. 67-72.
Obeid, R. , Jung J. , Falk J. , Herrmann W. , Geisel J. , Friesenhahn-Ochs B. , Lammert F. , Fassbender K. , and Kostopoulos P. 2013. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. Biochimie. 95: 10561061.
Obeid, R. , Kasoha M. , Knapp J.P. , Kostopoulos P. , Becker G. , Fassbender K. , and Herrmann W. 2007a. Folate and methylation status in relation to phosphorylated tau protein(181P) and beta- amyloid(1-42) in cerebrospinal fluid. Clin Chem. 53: 11291136.
Obeid, R. , Kostopoulos P. , Knapp J.P. , Kasoha M. , Becker G. , Fassbender K. , and Herrmann W. 2007b. Biomarkers of folate and vitamin B12 are related in blood and cerebrospinal fluid. Clin Chem. 53: 326333.
Obeid, R. , Kuhlmann M.K. , Kohler H. , and Herrmann W. 2005a. Response of homocysteine, cystathionine, and methylmalonic acid to vitamin treatment in dialysis patients. Clin Chem. 51: 196201.
Obeid, R. , Morkbak A.L. , Munz W. , Nexo E. , and Herrmann W. 2006. The cobalamin-binding proteins transcobalamin and haptocorrin in maternal and cord blood sera at birth. Clin Chem. 52: 263269.
Obeid, R. , Munz W. , Jager M. , Schmidt W. , and Herrmann W. 2005b. Biochemical indexes of the B vitamins in cord serum are predicted by maternal B vitamin status. Am J Clin Nutr. 82: 133139.
Obeid, R. , Schorr H. , Eckert R. , and Herrmann W. 2004. Vitamin B12 status in the elderly as judged by available biochemical markers. Clin Chem. 50: 238241.
Okuma, Y. , Hosomi Y. , Watanabe K. , Takahashi S. , Okamura T. , and Hishima T. 2015. Gemcitabine in patients previously treated with platinum-containing chemotherapy for refractory thymic carcinoma: radiographic assessment using the RECIST criteria and the ITMIG recommendations. Int J Clin Oncol. 21: 531538.
Orning, L. , Rian A. , Campbell A. , Brady J. , Fedosov S.N. , Bramlage B. , Thompson K. , and Quadros E.V. 2006. Characterization of a monoclonal antibody with specificity for holo-transcobalamin. Nutr Metab (Lond). 3: 3.
Pedersen, T.L. , Keyes W.R. , Shahab-Ferdows S. , Allen L.H. , and Newman J.W. 2011. Methylmalonic acid quantification in low serum volumes by UPLC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 879: 15021506.
Quadros, E.V. 2010. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol. 148: 195204.
Rajan, S. , Wallace J.I. , Brodkin K.I. , Beresford S.A. , Allen R.H. , and Stabler S.P. 2002. Response of elevated methylmalonic acid to three dose levels of oral cobalamin in older adults. J Am Geriatr Soc. 50: 17891795.
Rasmussen, K. 1989. Studies on methylmalonic acid in humans. I. Concentrations in serum and urinary excretion in normal subjects after feeding and during fasting, and after loading with protein, fat, sugar, isoleucine, and valine. Clin Chem. 35: 22712276.
Refsum, H. , Johnston C. , Guttormsen A.B. , and Nexo E. 2006. Holotranscobalamin and total transcobalamin in human plasma: determination, determinants, and reference values in healthy adults. Clin Chem. 52: 129137.
238 Rogers, L.M. , Boy E. , Miller J.W. , Green R. , Rodriguez M. , Chew F. , and Allen L.H. 2003a. Predictors of cobalamin deficiency in Guatemalan school children: diet, Helicobacter pylori, or bacterial overgrowth? J Pediatr Gastroenterol Nutr. 36: 2736.
Rogers, L.M. , Boy E. , Miller J.W. , Green R. , Sabel J.C. , and Allen L.H. 2003b. High prevalence of cobalamin deficiency in Guatemalan school children: associations with low plasma holotranscobalamin II and elevated serum methylmalonic acid and plasma homocysteine concentrations. Am J Clin Nutr. 77: 433440.
Savage, D.G. , Lindenbaum J. , Stabler S.P. , and Allen R.H. 1994. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med. 96: 239246.
Schloss, J.M. , Colosimo M. , Airey C. , and Vitetta L. 2015. Chemotherapy-induced peripheral neuropathy (CIPN) and vitamin B12 deficiency. Support Care Cancer. 23: 18431850.
Serin, E. , Gumurdulu Y. , Ozer B. , Kayaselcuk F. , Yilmaz U. , and Kocak R. 2002. Impact of Helicobacter pylori on the development of vitamin B12 deficiency in the absence of gastric atrophy. Helicobacter. 7: 337341.
Sharabi, A. , Cohen E. , Sulkes J. , and Garty M. 2003. Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. Br J Clin Pharmacol. 56: 635638.
Siekmann, J.H. , Allen L.H. , Bwibo N.O. , Demment M.W. , Murphy S.P. , and Neumann C.G. 2003. Kenyan school children have multiple micronutrient deficiencies, but increased plasma vitamin B12 is the only detectable micronutrient response to meat or milk supplementation. J Nutr. 133: 3972S3980S.
Sipponen, P. , Laxen F. , Huotari K. , and Harkonen M. 2003. Prevalence of low vitamin B12 and high homocysteine in serum in an elderly male population: association with atrophic gastritis and Helicobacter pylori infection. Scand J Gastroenterol. 38: 12091216.

Snow, C.F. 1999. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician [see comments]. Arch Intern Med. 159: 12891298.
Sobczynska-Malefora, A. , Gorska R. , Pelisser M. , Ruwona P. , Witchlow B. , and Harrington D.J. 2014. An audit of holotranscobalamin (Active B12) and methylmalonic acid assays for the assessment of vitamin B12 status: application in a mixed patient population. Clin Biochem. 47: 8286.
Specker, B.L. , Black A. , Allen L. , and Morrow F. 1990. Vitamin B12: low milk concentrations are related to low serum concentrations in vegetarian women and to methylmalonic aciduria in their infants. Am J Clin Nutr. 52: 10731076.
Stabler, S.P. , Marcell P.D. , Podell E.R. , Allen R.H. , and Lindenbaum J. 1986. Assay of methylmalonic acid in the serum of patients with cobalamin deficiency using capillary gas chromatography- mass spectrometry. J Clin Invest. 77: 16061612.
Strand, T.A. , Taneja S. , Kumar T. , Manger M.S. , Refsum H. , Yajnik C.S. , and Bhandari N. 2015. Vitamin B12, folic acid, and growth in 6- to 30-month-old children: a randomized controlled trial. Pediatrics. 135: e918e926.
Stucki, M. , Coelho D. , Suormala T. , Burda P. , Fowler B. , and Baumgartner M.R. 2012. Molecular mechanisms leading to three different phenotypes in the cblD defect of intracellular cobalamin metabolism. Hum Mol Genet. 21: 14101418.
Tamura, T. , and Baggott J.E. 2008. In vitro formation of homocysteine in whole blood in the presence of anticoagulants. Clin Chem. 54: 14021403.
Thompson, G.N. , Chalmers R.A. , Walter J.H. , Bresson J.L. , Lyonnet S.L. , Reed P.J. , Saudubray J.M. , Leonard J.V. , and Halliday D. 1990. The use of metronidazole in management of methylmalonic and propionic acidaemias. Eur J Pediatr. 149: 792796.
Ubbink, J.B. , Hayward Vermaak W.J. , and Bissbort S. 1991. Rapid high-performance liquid chromatographic assay for total homocysteine levels in human serum. J Chromatogr. 565: 441446.
Ulleland, M. , Eilertsen I. , Quadros E.V. , Rothenberg S.P. , Fedosov S.N. , Sundrehagen E. , and Orning L. 2002. Direct assay for cobalamin bound to transcobalamin (holo-transcobalamin) in serum. Clin Chem. 48: 526532.
Valente, E. , Scott J.M. , Ueland P.M. , Cunningham C. , Casey M. , and Molloy A.M. 2011. Diagnostic accuracy of holotranscobalamin, methylmalonic acid, serum cobalamin, and other indicators of tissue vitamin B status in the elderly. Clin Chem. 57: 856863.
van Walraven, C. , Austin P. , and Naylor C.D. 2001. Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills? Can Fam Physician. 47: 7986.
239 Vashi, P. , Edwin P. , Popiel B. , Lammersfeld C. , and Gupta D. 2016. Methylmalonic acid and homocysteine as indicators of vitamin B12 deficiency in cancer. PLoS One. 11: e0147843.
von Castel-Roberts, K.M. , Morkbak A.L. , Nexo E. , Edgemon C.A. , Maneval D.R. , Shuster J.J. , Valentine J.F. , Kauwell G.P. , and Bailey L.B. 2007. Holo-transcobalamin is an indicator of vitamin B12 absorption in healthy adults with adequate vitamin B12 status. Am J Clin Nutr. 85: 10571061.
Waldmann, A. , Koschizke J.W. , Leitzmann C. , and Hahn A. 2004. Homocysteine and cobalamin status in German vegans. Public Health Nutr. 7: 467472.
Windelberg, A. , Arseth O. , Kvalheim G. , and Ueland P.M. 2005. Automated assay for the determination of methylmalonic acid, total homocysteine, and related amino acids in human serum or plasma by means of methylchloroformate derivatization and gas chromatography-mass spectrometry. Clin Chem. 51: 21032109.
Winkels, R.M. , Brouwer I.A. , Clarke R. , Katan M.B. , and Verhoef P. 2008. Bread cofortified with folic acid and vitamin B-12 improves the folate and vitamin B-12 status of healthy older people: a randomized controlled trial. Am J Clin Nutr. 88: 348355.
Yakut, M. , Ustun Y. , Kabacam G. , and Soykan I. 2010. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. Eur J Intern Med. 21: 320323.
Yetley, E.A. , Pfeiffer C.M. , Phinney K.W. , Bailey R.L. , Blackmore S. , Bock J.L. , Brody L.C. , Carmel R. , Curtin L.R. , Durazo-Arvizu R.A. , Eckfeldt J.H. , Green R. , Gregory J.F. III , Hoofnagle A.N. , Jacobsen D.W. , Jacques P.F. , Lacher D.A. , Molloy A.M. , Massaro J. , Mills J.L. , Nexo E. , Rader J.I. , Selhub J. , Sempos C. , Shane B. , Stabler S. , Stover P. , Tamura T. , Tedstone A. , Thorpe S.J. , Coates P.M. , Johnson C.L. , and Picciano M.F. 2011. Biomarkers of vitamin B12 status in NHANES: a roundtable summary. Am J Clin Nutr. 94: 313S321S.
Yu, H.H. , Joubran R. , Asmi M. , Law T. , Spencer A. , Jouma M. , and Rifai N. 2000. Agreement among four homocysteine assays and results in patients with coronary atherosclerosis and controls. Clin Chem. 46: 258264.
Zetterberg, H. , Nexo E. , Regland B. , Minthon L. , Boson R. , Palmer M. , Rymo L. , and Blennow K. 2003. The transcobalamin (TC) codon 259 genetic polymorphism influences holo-TC concentration in cerebrospinal fluid from patients with Alzheimer disease. Clin Chem. 49: 11951198.

Cobalamin During Pregnancy and Lactation

Adjalla, c. , Lambert D. , Benhayoun S. , Berthelsen J.G. , Nicolas J.P. , Gueant J.L. , and Nexo E. 1994. Forms of cobalamin and vitamin B12 analogs in maternal plasma, milk, and cord plasma. J Nutr Biochem. 8: 406410.
Antony, A.C. 2003. Vegetarianism and vitamin B12 (cobalamin) deficiency. Am J Clin Nutr. 78: 36.
Bae, S. , West A.A. , Yan J. , Jiang X. , Perry C.A. , Malysheva O. , Stabler S.P. , Allen R.H. , and Caudill M.A. 2015. Vitamin B12 status differs among pregnant, lactating, and control women with equivalent nutrient intakes. J Nutr. 145: 15071514.
Berry, C.G. 1955. Anaemia of pregnancy in Africans of Lagos. Br Med J. 2: 819823.
Black, A.K. , Allen L.H. , Pelto G.H. , de Mata M.P. , and Chavez A. 1994. Iron, vitamin B12 and folate status in Mexico: associated factors in men and women and during pregnancy and lactation. J Nutr. 124: 11791188.
Brown, J. , Robertson J. , and Gallagher N. 1977. Humoral regulation of vitamin B12 absorption by pregnant mouse small intestine. Gastroenterology. 72: 881888.
Candito, M. , Magnaldo S. , Bayle J. , Dor J.F. , Gillet Y. , Bongain A. , and Van O.E. 2003. Clinical B12 deficiency in one case of recurrent spontaneous pregnancy loss. Clin Chem Lab Med. 41: 10261027.
Casterline, J.E. , Allen L.H. , and Ruel M.T. 1997. Vitamin B12 deficiency is very prevalent in lactating Guatemalan women and their infants at three months postpartum. J Nutr. 127: 19661972.
Chen, L.T. , and Rivera M.A. 2004. The Costa Rican experience: reduction of neural tube defects following food fortification programs. Nutr Rev. 62: S40S43.
Cherian, A. , Seena S. , Bullock R.K. , and Antony A.C. 2005. Incidence of neural tube defects in the least-developed area of India: a population-based study. Lancet. 366: 930931.
Collins, R.A. , Harper A.E. , Scheiber M. , and Elvehjem C. 1951. The folic acid and vitamin B12 content of the milk of various species. J Nutr. 43: 313321.
Crider, K.S. , Devine O. , Hao L. , Dowling N.F. , Li S. , Molloy A.M. , Li Z. , Zhu J. , and Berry R.J. 2014. Population red blood cell folate concentrations for prevention of neural tube defects: bayesian model. BMJ. 349: g4554.

Daly, L.E. , Kirke P.N. , Molloy A. , Weir D.G. , and Scott J.M. 1995. Folate levels and neural tube defects. Implications for prevention. JAMA. 274: 16981702.
Dominguez-Salas, P. , Moore S.E. , Cole D. , da Costa K.A. , Cox S.E. , Dyer R.A. , Fulford A.J. , Innis S.M. , Waterland R.A. , Zeisel S.H. , Prentice A.M. , and Hennig B.J. 2013. DNA methylation potential: dietary intake and blood concentrations of one-carbon metabolites and cofactors in rural African women. Am J Clin Nutr. 97: 12171227.
Duggan, C. , Srinivasan K. , Thomas T. , Samuel T. , Rajendran R. , Muthayya S. , Finkelstein J.L. , Lukose A. , Fawzi W. , Allen L.H. , Bosch R.J. , and Kurpad A.V. 2014. Vitamin B12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B12 status. J Nutr. 144: 758764.
Dwarkanath, P. , Barzilay J.R. , Thomas T. , Thomas A. , Bhat S. , and Kurpad A.V. 2013. High folate and low vitamin B12 intakes during pregnancy are associated with small-for-gestational age infants in South Indian women: a prospective observational cohort study. Am J Clin Nutr. 98: 14501458.
Faupel-Badger, J.M. , Hsieh C.C. , Troisi R. , Lagiou P. , and Potischman N. 2007. Plasma volume expansion in pregnancy: implications for biomarkers in population studies. Cancer Epidemiol Biomarkers Prev. 16: 17201723.
Fernandes-Costa, F. , and Metz J. 1982. Levels of transcobalamins I, II, and III during pregnancy and in cord blood. Am J Clin Nutr. 35: 8794.
Fernandez-Roig, S. , Cavalle-Busquets P. , Fernandez-Ballart J.D. , Ballesteros M. , Berrocal-Zaragoza M.I. , Salat-Batlle J. , Ueland P.M. , and Murphy M.M. 2013. Low folate status enhances pregnancy changes in plasma betaine and dimethylglycine concentrations and the association between betaine and homocysteine. Am J Clin Nutr. 97: 12521259.
Food and Drug Administration, and Department of health and human services 1996. Food standards: Amendment of standards of identity for enriched grain products to require addition of folic acid. Federal Register. 61: 87818797.
262 Frery, N. , Huel G. , Leroy M. , Moreau T. , Savard R. , Blot P. , and Lellouch J. 1992. Vitamin B12 among parturients and their newborns and its relationship with birthweight. Eur J Obstet Gynecol Reprod Biol. 45: 155163.
Giles, C. 1966. An account of 335 cases of megaloblastic anaemia of pregnancy and the puerperium. J Clin Pathol. 19: 111.
Giugliani, E.R. , Jorge S.M. , and Goncalves A.L. 1985. Serum vitamin B12 levels in parturients, in the intervillous space of the placenta and in full-term newborns and their interrelationships with folate levels. Am J Clin Nutr. 41: 330335.
Gomes, T.S. , Lindner U. , Tennekoon K.H. , Karandagoda W. , Gortner L. , and Obeid R. 2010. Homocysteine in small-for-gestational age and appropriate-for-gestational age preterm neonates from mothers receiving folic acid supplementation. Clin Chem Lab Med. 48: 11571161.
Graber, S.E. , Scheffel U. , Hodkinson B. , and McIntyre P.A. 1971. Placental transport of vitamin B12 in the pregnant rat. J Clin Invest. 50: 10001004.
Greibe, E. , Andreasen B.H. , Lildballe D.L. , Morkbak A.L. , Hvas A.M. , and Nexo E. 2011. Uptake of cobalamin and markers of cobalamin status: a longitudinal study of healthy pregnant women. Clin Chem Lab Med. 49: 18771882.
Greibe, E. , Lildballe D.L. , Streym S. , Vestergaard P. , Rejnmark L. , Mosekilde L. , and Nexo E. 2013. Cobalamin and haptocorrin in human milk and cobalamin-related variables in mother and child: a 9-mo longitudinal study. Am J Clin Nutr. 98: 389395.
Guerra-Shinohara, E.M. , Morita O.E. , Peres S. , Pagliusi R.A. , Sampaio Neto L.F. , DAlmeida V. , Irazusta S.P. , Allen R.H. , and Stabler S.P. 2004. Low ratio of S-adenosylmethionine to S-adenosylhomocysteine is associated with vitamin deficiency in Brazilian pregnant women and newborns. Am J Clin Nutr. 80: 13121321.
Hampel, D. , Shahab-Ferdows S. , Domek J.M. , Siddiqua T. , Raqib R. , and Allen L.H. 2014. Competitive chemiluminescent enzyme immunoassay for vitamin B12 analysis in human milk. Food Chem. 153: 6065.
Hay, G. , Clausen T. , Whitelaw A. , Trygg K. , Johnston C. , Henriksen T. , and Refsum H. 2010. Maternal folate and cobalamin status predicts vitamin status in newborns and 6-month-old infants. J Nutr. 140: 557564.
Heinrich, H.C. 1954. Biochemical principles of diagnosis and therapy of vitamin B12 deficiency in man and in domestic animals. II. Studies on vitamin B12 metabolism in man during pregnancy and lactation. Klin Wochenschr. 32: 205209.
Hellegers, A. , Okuda K. , Nesbitt R.E. Jr , Smith D.W. , and Chow B.F. 1957. Vitamin B12 absorption in pregnancy and in the newborn. Am J Clin Nutr. 5: 327331.
Hertrampf, E. , and Cortes F. 2004. Folic acid fortification of wheat flour: Chile. Nutr Rev. 62: S44S48.
Hubner, U. , Alwan A. , Jouma M. , Tabbaa M. , Schorr H. , and Herrmann W. 2008. Low serum vitamin B12 is associated with recurrent pregnancy loss in Syrian women. Clin Chem Lab Med. 46: 12651269.
Institute of Medicine 1998. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. In: USA: Washington, DC, National Academy Press. 390422.
Izak, G. , Rachmilewitz M. , Stein Y. , Berkovici B. , Sadovsky A. , Aronovitch Y. , and Grossowicz N. 1957. Vitamin B12 and iron deficiencies in anemia of pregnancy and puerperium. AMA Arch Intern Med. 99: 346355.
Jathar, V.S. , Kamath S.A. , Parikh M.N. , Rege D.V. , and Satoskar R.S. 1970. Maternal milk and serum vitamin B12, folic acid, and protein levels in Indian subjects. Arch Dis Child. 45: 236241.
Kaikov, Y. , Wadsworth L.D. , Hall C.A. , and Rogers P.C. 1991. Transcobalamin II deficiency: case report and review of the literature. Eur J Pediatr. 150: 841843.
Knight, B.A. , Shields B.M. , Brook A. , Hill A. , Bhat D.S. , Hattersley A.T. , and Yajnik C.S. 2015. Lower Circulating B12 Is Associated with Higher Obesity and Insulin Resistance during Pregnancy in a Non-Diabetic White British Population. PLoS One. 10: e0135268.
Koc, A. , Kocyigit A. , Soran M. , Demir N. , Sevinc E. , Erel O. , and Mil Z. 2006. High frequency of maternal vitamin B12 deficiency as an important cause of infantile vitamin B12 deficiency in Sanliurfa province of Turkey. Eur J Nutr. 45: 291297.
263 Koebnick, C. , Heins U.A. , Dagnelie P.C. , Wickramasinghe S.N. , Ratnayaka I.D. , Hothorn T. , Pfahlberg A.B. , Hoffmann I. , Lindemans J. , and Leitzmann C. 2002. Longitudinal concentrations of vitamin B(12) and vitamin B(12)-binding proteins during uncomplicated pregnancy. Clin Chem. 48: 928933.
Koebnick, C. , Hoffmann I. , Dagnelie P.C. , Heins U.A. , Wickramasinghe S.N. , Ratnayaka I.D. , Gruendel S. , Lindemans J. , and Leitzmann C. 2004. Long-term ovo-lacto vegetarian diet impairs vitamin B12 status in pregnant women. J Nutr. 134: 33193326.
Krishnaveni, G.V. , Veena S.R. , Karat S.C. , Yajnik C.S. , and Fall C.H. 2014. Association between maternal folate concentrations during pregnancy and insulin resistance in Indian children. Diabetologia. 57: 110121.
Lildballe, D.L. , Hardlei T.F. , Allen L.H. , and Nexo E. 2009. High concentrations of haptocorrin interfere with routine measurement of cobalamins in human serum and milk. A problem and its solution. Clin Chem Lab Med. 47: 182187.
Marchetta, C.M. , Devine O.J. , Crider K.S. , Tsang B.L. , Cordero A.M. , Qi Y.P. , Guo J. , Berry R.J. , Rosenthal J. , Mulinare J. , Mersereau P. , and Hamner H.C. 2015. Assessing the association between natural food folate intake and blood folate concentrations: a systematic review and Bayesian metaanalysis of trials and observational studies. Nutrients. 7: 26632686.
Milman, N. , Byg K.E. , Bergholt T. , Eriksen L. , and Hvas A.M. 2006. Cobalamin status during normal pregnancy and postpartum: a longitudinal study comprising 406 Danish women. Eur J Haematol. 76: 521525.
Molloy, A.M. , Kirke P.N. , Troendle J.F. , Burke H. , Sutton M. , Brody L.C. , Scott J.M. , and Mills J.L. 2009. Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic Acid fortification. Pediatrics. 123: 917923.

Moore, H.C. , Lillie E.W. , and Gatenby P.B. 1955. The response of megaloblastic anaemia of pregnancy to vitamin B12. Ir J Med Sci. 106116.
Morkbak, A.L. , Hvas A.M. , Milman N. , and Nexo E. 2007. Holotranscobalamin remains unchanged during pregnancy. Longitudinal changes of cobalamins and their binding proteins during pregnancy and postpartum. Haematologica. 92: 17111712.
Morris, M.S. , Jacques P.F. , Rosenberg I.H. , and Selhub J. 2007. Folate and vitamin B12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 85: 193200.
Murphy, M.M. , Molloy A.M. , Ueland P.M. , Fernandez-Ballart J.D. , Schneede J. , Arija V. , and Scott J.M. 2007. Longitudinal study of the effect of pregnancy on maternal and fetal cobalamin status in healthy women and their offspring. J Nutr. 137: 18631867.
Obeid, R. , Morkbak A.L. , Munz W. , Nexo E. , and Herrmann W. 2006. The cobalamin-binding proteins transcobalamin and haptocorrin in maternal and cord blood sera at birth. Clin Chem. 52: 263269.
Patel, K.D. , and Lovelady C.A. 1998. Vitamin B12 status of east indian vegetarian lactating women living in the united states. Nutr Res. 18: 18391946.
Qi, Y.P. , Do A.N. , Hamner H.C. , Pfeiffer C.M. , and Berry R.J. 2014. The prevalence of low serum vitamin B12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. J Nutr. 144: 170176.
Ray, J.G. 2004. Folic acid food fortification in Canada. Nutr Rev. 62: S35S39.
Relton, C.L. , Pearce M.S. , and Parker L. 2005. The influence of erythrocyte folate and serum vitamin B12 status on birth weight. Br J Nutr. 93: 593599.
Robertson, J.A. , and Gallagher N.D. 1983. Increased intestinal uptake of cobalamin in pregnancy does not require synthesis of new receptors. Biochim Biophys Acta. 757: 145150.
Ronnenberg, A.G. , Goldman M.B. , Chen D. , Aitken I.W. , Willett W.C. , Selhub J. , and Xu X. 2002. Preconception homocysteine and B vitamin status and birth outcomes in Chinese women. Am J Clin Nutr. 76: 13851391.
Rosenthal, J. , Lopez-Pazos E. , Dowling N.F. , Pfeiffer C.M. , Mulinare J. , Vellozzi C. , Zhang M. , Lavoie D.J. , Molina R. , Ramirez N. , and Reeve M.E. 2015. Folate and Vitamin B12 Deficiency Among Nonpregnant Women of Childbearing-Age in Guatemala 2009-2010: Prevalence and Identification of Vulnerable Populations. Matern Child Health J. 19: 22722285.
264 Samuel, T.M. , Duggan C. , Thomas T. , Bosch R. , Rajendran R. , Virtanen S.M. , Srinivasan K. , and Kurpad A.V. 2013. Vitamin B(12) intake and status in early pregnancy among urban South Indian women. Ann Nutr Metab. 62: 113122.
Sandberg, D.P. , Begley J.A. , and Hall C.A. 1981. The content, binding, and forms of vitamin B12 in milk. Am J Clin Nutr. 34: 17171724.
Selhub, J. , Morris M.S. , and Jacques P.F. 2007. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci U S A. 104: 1999520000.
Shapiro, J. , Alberts H.W. , Welch P. , and Metz J. 1965. Folate and vitamin B12 deficiency associated with lactation. Br J Haematol. 11: 498504.
Specker, B.L. , Black A. , Allen L. , and Morrow F. 1990. Vitamin B12: low milk concentrations are related to low serum concentrations in vegetarian women and to methylmalonic aciduria in their infants. Am J Clin Nutr. 52: 10731076.
Specker, B.L. , Miller D. , Norman E.J. , Greene H. , and Hayes K.C. 1988. Increased urinary methylmalonic acid excretion in breast-fed infants of vegetarian mothers and identification of an acceptable dietary source of vitamin B12. Am J Clin Nutr. 47: 8992.
Srikantia, S.G. , and Reddy V. 1967. Megaloblastic anaemia of infancy and vitamin B12. Br J Haematol. 13: 949953.
Tasker, P.W. 1955. Correlation of serum-vitamin B12 levels and urinary folic acid in nutritional megaloblastic anaemia. Lancet. 269: 6163.
Trugo N.M. and Sardinha F. 1994. Cobalamin and cobalamin binding capacity in human milk. pp. 2333.
Ullberg, S. , Kristoffersson H. , Flodh H. , and Hanngren A. 1967. Placental passage and fetal accumulation of labelled vitamin B12 in the mouse. Arch Int Pharmacodyn Ther. 167: 431449.
Vaz, P.A. , Torras V. , Sandoval J.F. , Dillman E. , Mateos C.R. , and Cordova M.S. 1975. Folic acid and vitamin B12 determination in fetal liver. Am J Clin Nutr. 28: 10851086.
Wills, L. 1931. Treatment of pernicious anaemia of pregnancy and tropical anaemia with special reference to yeast extract as a curative agent. Nutrition. 7: 323327.
World Health Organization 2015. Guidelines: Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects. In: World Health Organization, editor.
Wu, B.T. , Innis S.M. , Mulder K.A. , Dyer R.A. , and King D.J. 2013. Low plasma vitamin B12 is associated with a lower pregnancy-associated rise in plasma free choline in Canadian pregnant women and lower postnatal growth rates in their male infants. Am J Clin Nutr. 98: 12091217.
Yajnik, C.S. , Deshpande S.S. , Jackson A.A. , Refsum H. , Rao S. , Fisher D.J. , Bhat D.S. , Naik S.S. , Coyaji K.J. , Joglekar C.V. , Joshi N. , Lubree H.G. , Deshpande V.U. , Rege S.S. , and Fall C.H. 2008. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia. 51: 2938.

Vitamin B12 After Birth and During Early Life

Allen, L.H. 1993. The nutrition CRSP: what is marginal malnutrition, and does it affect human function? Nutr Rev. 51: 255267.
Andersson, H.C. and Shapira E. 1998. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (cblC). J Pediatr. 132: 121124.
Arsenault, J.E. , Mora-Plazas M. , Forero Y. , Lopez-Arana S. , Marin C. , Baylin A. and Villamor E. 2009. Provision of a school snack is associated with vitamin B12 status, linear growth and morbidity in children from Bogota. Colombia. J Nutr. 139: 17441750.
Banerjee, R. 2006. B12 trafficking in mammals: A for coenzyme escort service. ACS Chem Biol. 1: 149159.
Berry, C.G. 1955. Anaemia of pregnancy in Africans of Lagos. Br Med J. 2: 819823.
Bhate, V. , Deshpande S. , Bhat D. , Joshi N. , Ladkat R. , Watve S. , Fall C. , de Jager C.A. , Refsum H. and Yajnik C. 2008. Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children. Food Nutr Bull. 29: 249254.
Bijur, A.M. and Desai A.G. 1985. Composition of breast milk with reference to vitamin B12 and folic acid in Indian mothers. Indian J Pediatr. 52: 147150.
Bjorke Monsen, A.L. , Ueland P.M. , Vollset S.E. , Guttormsen A.B. , Markestad T. , Solheim E. and Refsum H. 2001. Determinants of cobalamin status in newborns. Pediatrics. 108: 624630.
Bjorke-Monsen, A.L. , Torsvik I. , Saetran H. , Markestad T. and Ueland P.M. 2008. Common metabolic profile in infants indicating impaired cobalamin status responds to cobalamin supplementation. Pediatrics. 122: 8391.
Black, A.K. , Allen L.H. , Pelto G.H. , de Mata M.P. and Chavez A. 1994. Iron, vitamin B12 and folate status in Mexico: associated factors in men and women and during pregnancy and lactation. J Nutr. 124: 11791188.

Bondevik, G.T. , Schneede J. , Refsum H. , Lie R.T. , Ulstein M. and Kvale G. 2001. Homocysteine and methylmalonic acid levels in pregnant Nepali women. Should cobalamin supplementation be considered? Eur J Clin Nutr. 55: 856864.
Bor, M.V. , Cetin M. , Aytac S. , Altay C. , Ueland P.M. and Nexo E. 2008. Long term biweekly 1 mg oral vitamin B12 ensures normal hematological parameters, but does not correct all other markers of vitamin B12 deficiency. A study in patients with inherited vitamin B12 deficiency. Haematologica. 93: 17551758.
Carmel, R. , Mallidi P.V. , Vinarskiy S. , Brar S. and Frouhar Z. 2002. Hyperhomocysteinemia and cobalamin deficiency in young Asian Indians in the United States. Am J Hematol. 70: 107114.
Casterline, J.E. , Allen L.H. and Ruel M.T. 1997. Vitamin B12 deficiency is very prevalent in lactating Guatemalan women and their infants at three months postpartum. J Nutr. 127: 19661972.
292 Chambers, J.C. , Obeid O.A. , Refsum H. , Ueland P. , Hackett D. , Hooper J. , Turner R.M. , Thompson S.G. and Kooner J.S. 2000. Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men. Lancet. 355: 523527.
Chanarin, I. , Malkowska V. , OHea A.M. , Rinsler M.G. and Price A.B. 1985. Megaloblastic anaemia in a vegetarian Hindu community. Lancet. 2: 11681172.
Codazzi, D. , Sala F. , Parini R. and Langer M. 2005. Coma and respiratory failure in a child with severe vitamin B(12) deficiency. Pediatr Crit Care Med. 6: 483485.
Dagnelie, P.C. and van Staveren W.A. 1994. Macrobiotic nutrition and child health: results of a population-based, mixed-longitudinal cohort study in The Netherlands. Am J Clin Nutr. 59: 1187S1196S.
Dagnelie, P.C. , van Staveren W.A. , Vergote F.J. , Dingjan P.G. and van den BH and Hautvast JG. 1989. Increased risk of vitamin B12 and iron deficiency in infants on macrobiotic diets. Am J Clin Nutr. 50: 818824.
Deegan, K.L. , Jones K.M. , Zuleta C. , Ramirez-Zea M. , Lildballe D.L. , Nexo E. and Allen L.H. 2012. Breast milk vitamin B12 concentrations in guatemalan women are correlated with maternal but not infant vitamin B12 status at 12 months postpartum. J Nutr. 142: 112116.
Dhonukshe-Rutten, R.A. , van Dusseldorp M. , Schneede J. , de Groot L.C. and van Staveren W.A. 2005. Low bone mineral density and bone mineral content are associated with low cobalamin status in adolescents. Eur J Nutr. 44: 341347.
Donangelo, C.M. , Trugo N.M. , Koury J.C. , Barreto Silva M.I. , Freitas L.A. , Feldheim W. and Barth C. 1989. Iron, zinc, folate and vitamin B12 nutritional status and milk composition of low-income Brazilian mothers. Eur J Clin Nutr. 43: 253266.
Dror, D.K. and Allen L.H. 2008. Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms. Nutr Rev. 66: 250255.
Duggan, C. , Srinivasan K. , Thomas T. , Samuel T. , Rajendran R. , Muthayya S. , Finkelstein J.L. , Lukose A. , Fawzi W. , Allen L.H. , Bosch R.J. and Kurpad A.V. 2014. Vitamin B12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B12 status. J Nutr. 144: 758764.
Gimsing, P. , Hippe E. , Helleberg-Rasmussen I. , Moesgaard M. , Nielsen J.L. , Bastrup-Madsen P. , Berlin R. and Hansen T. 1982. Cobalamin forms in plasma and tissue during treatment of vitamin B12 deficiency. Scand J Haematol. 29: 311318.
Giugliani, E.R. , Jorge S.M. and Goncalves A.L. 1985. Serum vitamin B12 levels in parturients, in the intervillous space of the placenta and in full-term newborns and their interrelationships with folate levels. Am J Clin Nutr. 41: 330335.
Gomber, S. , Kumar S. , Rusia U. , Gupta P. , Agarwal K.N. and Sharma S. 1998. Prevalence & etiology of nutritional anaemias in early childhood in an urban slum. Indian J Med Res. 107: 269273.
Graber, S.E. , Scheffel U. , Hodkinson B. and McIntyre P.A. 1971. Placental transport of vitamin B12 in the pregnant rat. J Clin Invest. 50: 10001004.
Graham, S.M. , Arvela O.M. and Wise G.A. 1992. Long-term neurologic consequences of nutritional vitamin B12 deficiency in infants. J Pediatr. 121: 710714.
Grattan-Smith, P.J. , Wilcken B. , Procopis P.G. and Wise G.A. 1997. The neurological syndrome of infantile cobalamin deficiency: developmental regression and involuntary movements. Mov Disord. 12: 3946.
Greibe, E. , Lildballe D.L. , Streym S. , Vestergaard P. , Rejnmark L. , Mosekilde L. and Nexo E. 2013a. Cobalamin and haptocorrin in human milk and cobalamin-related variables in mother and child: a 9-mo longitudinal study. Am J Clin Nutr. 98: 389395.
Greibe, E. , Trolle B. , Bor M.V. , Lauszus F.F. and Nexo E. 2013b. Metformin lowers serum cobalamin without changing other markers of cobalamin status: A study on women with polycystic ovary syndrome. Nutrients. 5: 24752482.
Guerra-Shinohara, E.M. , Morita O.E. , Peres S. , Pagliusi R.A. , Sampaio Neto L.F. , DAlmeida V. , Irazusta S.P. , Allen R.H. and Stabler S.P. 2004. Low ratio of S-adenosylmethionine to S-adenosylhomocysteine is associated with vitamin deficiency in Brazilian pregnant women and newborns. Am J Clin Nutr. 80: 13121321.
Guez, S. , Chiarelli G. , Menni F. , Salera S. , Principi N. and Esposito S. 2012. Severe vitamin B12 deficiency in an exclusively breastfed 5-month-old Italian infant born to a mother receiving multivitamin supplementation during pregnancy. BMC Pediatr. 12: 85.
293 Hampel, D. and Allen L.H. 2016. Analyzing B-vitamins in human milk: Methodological approaches. Crit Rev Food Sci Nutr. 56: 494511.
Hay, G. , Clausen T. , Whitelaw A. , Trygg K. , Johnston C. , Henriksen T. and Refsum H. 2010. Maternal folate and cobalamin status predicts vitamin status in newborns and 6-month-old infants. J Nutr. 140: 557564.
Hay, G. , Johnston C. , Whitelaw A. , Trygg K. and Refsum H. 2008. Folate and cobalamin status in relation to breastfeeding and weaning in healthy infants. Am J Clin Nutr. 88: 105114.
Hellegers, A. , Okuda K. , Nesbitt R.E. Jr , Smith D.W. and Chow B.F. 1957. Vitamin B12 absorption in pregnancy and in the newborn. Am J Clin Nutr. 5: 327331.
Herrmann, W. , Isber S. , Obeid R. , Herrmann M. and Jouma M. 2005. Concentrations of homocysteine, related metabolites and asymmetric dimethylarginine in preeclamptic women with poor nutritional status [abstract]. Clin Chem Lab Med. 43: A7.
Hertz, H. , Kristensen H.P. and Hoff-Jorgensen E. 1964. Studies on vitamin B12 retention. Composition of retention following intramuscular injection of cyanocobalamin and hydroxocobalamin. Scand J Haematol. 1: 515.
Hoey, H. , Linnell J.C. , Oberholzer V.G. and Laurance B.M. 1982. Vitamin B12 deficiency in a breastfed infant of a mother with pernicious anaemia. J R Soc Med. 75: 656658.
Horstmann, M. , Neumaier-Probst E. , Lukacs Z. , Steinfeld R. , Ullrich K. and Kohlschutter A. 2003. Infantile cobalamin deficiency with cerebral lactate accumulation and sustained choline depletion. Neuropediatrics. 34: 261264.
Hyland, K. , Smith I. , Bottiglieri T. , Perry J. , Wendel U. , Clayton P.T. and Leonard J.V. 1988. Demyelination and decreased S-adenosylmethionine in 5,10-methylenetetrahydrofolate reductase deficiency. Neurology. 38: 459462.
Institute of Medicine 1998. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. In: USA: Washington, DC: National Academy Press. pp. 390422.
Institute of Medicine 2000. Vitamin B12. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline, . USA, Washington, DC: National Academy Press. pp. 306356.
Johnson Jr, P.R. and Roloff J.S. 1982. Vitamin B12 deficiency in an infant strictly breast-fed by a mother with latent pernicious anemia. J Pediatr. 100: 917919.

Karademir, F. , Suleymanoglu S. , Ersen A. , Aydinoz S. , Gultepe M. , Meral C. , Ozkaya H. and Gocmen I. 2007. Vitamin B12, folate, homocysteine and urinary methylmalonic acid levels in infants. J Int Med Res. 35: 384388.
Koc, A. , Kocyigit A. , Soran M. , Demir N. , Sevinc E. , Erel O. and Mil Z. 2006. High frequency of maternal vitamin B12 deficiency as an important cause of infantile vitamin B12 deficiency in Sanliurfa province of Turkey. Eur J Nutr. 45: 291297.
Kocaoglu, C. , Akin F. , Caksen H. , Boke S.B. , Arslan S. and Aygun S. 2014. Cerebral atrophy in a vitamin B12-deficient infant of a vegetarian mother. J Health Popul Nutr. 32: 367371.
Kvestad, I. , Taneja S. , Kumar T. , Hysing M. , Refsum H. , Yajnik C.S. , Bhandari N. and Strand T.A. 2015. Vitamin B12 and Folic Acid Improve Gross Motor and Problem-Solving Skills in Young North Indian Children: A Randomized Placebo-Controlled Trial. PLoS One. 10: e0129915.
Lildballe, D.L. , Hardlei T.F. , Allen L.H. and Nexo E. 2009. High concentrations of haptocorrin interfere with routine measurement of cobalamins in human serum and milk. A problem and its solution. Clin Chem Lab Med. 47: 182187.
Louwman, M.W. , Van D.M. and van d V, Thomas CM, Schneede J, Ueland PM, Refsum H and van Staveren WA. 2000. Signs of impaired cognitive function in adolescents with marginal cobalamin status. Am J Clin Nutr. 72: 762769.
McLean, E.D. , Allen L.H. , Neumann C.G. , Peerson J.M. , Siekmann J.H. , Murphy S.P. , Bwibo N.O. and Demment M.W. 2007. Low plasma vitamin B12 in Kenyan school children is highly prevalent and improved by supplemental animal source foods. J Nutr. 137: 676682.
Miller, A. , Korem M. , Almog R. and Galboiz Y. 2005. Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. J Neurol Sci. 233: 9397.
Miller, D.R. , Specker B.L. , Ho M.L. and Norman E.J. 1991. Vitamin B12 status in a macrobiotic community. Am J Clin Nutr. 53: 524529.
294 Monagle, P.T. and Tauro G.P. 1997. Infantile megaloblastosis secondary to maternal vitamin B12 deficiency. Clin Lab Haematol. 19: 2325.
Monsen, A.L. , Refsum H. , Markestad T. and Ueland P.M. 2003. Cobalamin status and its biochemical markers methylmalonic acid and homocysteine in different age groups from 4 days to 19 years. Clin Chem. 49: 20672075.
Murphy M.M. , Fernandez-Ballart J.D. , Molloy A.M. and Canals J. 2016. Moderately elevated maternal homocysteine at preconception is inversely associated with cognitive performance in children 4 months and 6 years after birth. Matern Child Nutr. in press. DOI: 10.1111/mcn.12289.
Murphy, M.M. , Molloy A.M. , Ueland P.M. , Fernandez-Ballart J.D. , Schneede J. , Arija V. and Scott J.M. 2007. Longitudinal study of the effect of pregnancy on maternal and fetal cobalamin status in healthy women and their offspring. J Nutr. 137: 18631867.
Nyaradi, A. , Li J. , Hickling S. , Foster J. and Oddy W.H. 2013. The role of nutrition in childrens neurocognitive development, from pregnancy through childhood. Front Hum Neurosci. 7: 97.
Obeid, R. , Fedosov S.N. and Nexo E. 2015. Cobalamin coenzyme forms are not likely to be superior to cyano- and hydroxyl-cobalamin in prevention or treatment of cobalamin deficiency. Mol Nutr Food Res. 59: 13641372.
Obeid, R. , Jouma M. and Herrmann W. 2002. Cobalamin status (holo-transcobalamin, methylmalonic acid) and folate as determinants of homocysteine concentration. Clin Chem. 48: 20642065.
Obeid, R. , Morkbak A.L. , Munz W. , Nexo E. , and Herrmann W. 2006. The cobalamin-binding proteins transcobalamin and haptocorrin in maternal and cord blood sera at birth. Clin Chem. 52: 263269.
Oladipo, O. , Rosenblatt D.S. , Watkins D. , Miousse I.R. , Sprietsma L. , Dietzen D.J. and Shinawi M. 2011. Cobalamin F disease detected by newborn screening and follow-up on a 14-year-old patient. Pediatrics. 128: e1636e1640.
Pasricha, S.R. , Shet A.S. , Black J.F. , Sudarshan H. , Prashanth N.S. and Biggs B.A. 2011. Vitamin B12, folate, iron, and vitamin A concentrations in rural Indian children are associated with continued breastfeeding, complementary diet, and maternal nutrition. Am J Clin Nutr. 94: 13581370.
Reghu, A. , Hosdurga S. , Sandhu B. and Spray C. 2005. Vitamin B12 deficiency presenting as oedema in infants of vegetarian mothers. Eur J Pediatr. 164: 257258.
Rogers, L.M. , Boy E. , Miller J.W. , Green R. , Rodriguez M. , Chew F. and Allen L.H. 2003a. Predictors of cobalamin deficiency in Guatemalan school children: diet, Helicobacter pylori, or bacterial overgrowth? J Pediatr Gastroenterol Nutr. 36: 2736.
Rogers, L.M. , Boy E. , Miller J.W. , Green R. , Sabel J.C. and Allen L.H. 2003b. High prevalence of cobalamin deficiency in Guatemalan school children: associations with low plasma holotranscobalamin II and elevated serum methylmalonic acid and plasma homocysteine concentrations. Am J Clin Nutr. 77: 433440.
Rosenthal, J. , Lopez-Pazos E. , Dowling N.F. , Pfeiffer C.M. , Mulinare J. , Vellozzi C. , Zhang M. , Lavoie D.J. , Molina R. , Ramirez N. and Reeve M.E. 2015. Folate and Vitamin B12 Deficiency Among Nonpregnant Women of Childbearing-Age in Guatemala 20092010: Prevalence and Identification of Vulnerable Populations. Matern Child Health J. 19: 22722285.
Sakurai, T. , Furukawa M. , Asoh M. , Kanno T. , Kojima T. and Yonekubo A. 2005. Fat-soluble and water-soluble vitamin contents of breast milk from Japanese women. J Nutr Sci Vitaminol (Tokyo). 51: 239247.
Sandberg, D.P. , Begley J.A. and Hall C.A. 1981. The content, binding, and forms of vitamin B12 in milk. Am J Clin Nutr. 34: 17171724.
Schneede, J. , Dagnelie P.C. , van Staveren W.A. , Vollset S.E. , Refsum H. and Ueland P.M. 1994. Methylmalonic acid and homocysteine in plasma as indicators of functional cobalamin deficiency in infants on macrobiotic diets. Pediatr Res. 36: 194201.
Siddiqua, T.J. , Ahmad S.M. , Ahsan K.B. , Rashid M. , Roy A. , Rahman S.M. , Shahab-Ferdows S. , Hampel D. , Ahmed T. , Allen L.H. and Raqib R. 2015. Vitamin B12 supplementation during pregnancy and postpartum improves B12 status of both mothers and infants but vaccine response in mothers only: a randomized clinical trial in Bangladesh. Eur J Nutr. 55: 281293.
Siekmann, J.H. , Allen L.H. , Bwibo N.O. , Demment M.W. , Murphy S.P. and Neumann C.G. 2003. Kenyan school children have multiple micronutrient deficiencies, but increased plasma vitamin B12 is the only detectable micronutrient response to meat or milk supplementation. J Nutr. 133: 3972S3980S.
295 Specker, B.L. 1994. Nutritional concerns of lactating women consuming vegetarian diets. Am J Clin Nutr. 59: 1182S1186S.
Specker, B.L. , Black A. , Allen L. and Morrow F. 1990. Vitamin B12: low milk concentrations are related to low serum concentrations in vegetarian women and to methylmalonic aciduria in their infants. Am J Clin Nutr. 52: 10731076.
Specker, B.L. , Miller D. , Norman E.J. , Greene H. and Hayes K.C. 1988a. Increased urinary methylmalonic acid excretion in breast-fed infants of vegetarian mothers and identification of an acceptable dietary source of vitamin B12. Am J Clin Nutr. 47: 8992.
Specker, B.L. , Miller D. , Norman E.J. , Greene H. and Hayes K.C. 1988b. Increased urinary methylmalonic acid excretion in breast-fed infants of vegetarian mothers and identification of an acceptable dietary source of vitamin B12. Am J Clin Nutr. 47: 8992.
Srikantia, S.G. and Reddy V. 1967. Megaloblastic anaemia of infancy and vitamin B12. Br J Haematol. 13: 949953.
Strand, T.A. , Taneja S. , Kumar T. , Manger M.S. , Refsum H. , Yajnik C.S. and Bhandari N. 2015. Vitamin B12, folic acid, and growth in 6- to 30-month-old children: a randomized controlled trial. Pediatrics. 135: e918e926.
Strand, T.A. , Taneja S. , Ueland P.M. , Refsum H. , Bahl R. , Schneede J. , Sommerfelt H. and Bhandari N. 2013. Cobalamin and folate status predicts mental development scores in North Indian children 12-18 mo of age. Am J Clin Nutr. 97: 310317.
Taneja, S. , Bhandari N. , Strand T.A. , Sommerfelt H. , Refsum H. , Ueland P.M. , Schneede J. , Bahl R. and Bhan M.K. 2007. Cobalamin and folate status in infants and young children in a low-to-middle income community in India. Am J Clin Nutr. 86: 13021309.

Thompson, G.N. , Chalmers R.A. , Walter J.H. , Bresson J.L. , Lyonnet S.L. , Reed P.J. , Saudubray J.M. , Leonard J.V. and Halliday D. 1990. The use of metronidazole in management of methylmalonic and propionic acidaemias. Eur J Pediatr. 149: 792796.
Torsvik, I. , Ueland P.M. , Markestad T. and Bjorke-Monsen A.L. 2013. Cobalamin supplementation improves motor development and regurgitations in infants: results from a randomized intervention study. Am J Clin Nutr. 98: 12331240.
Trugo N.M. and Sardinha F. 1994. Cobalamin and cobalamin binding capacity in human milk. In: p. 2333.
Ueland, P.M. and Monsen A.L. 2003. Hyperhomocysteinemia and B-vitamin deficiencies in infants and children. Clin Chem Lab Med. 41: 14181426.
Ulak, M. , Chandyo R.K. , Adhikari R.K. , Sharma P.R. , Sommerfelt H. , Refsum H. and Strand T.A. 2014. Cobalamin and folate status in 6 to 35 months old children presenting with acute diarrhea in Bhaktapur. Nepal. PLoS One. 9: e90079.
Ullberg, S. , Kristoffersson H. , Flodh H. and Hanngren A. 1967. Placental passage and fetal accumulation of labelled vitamin B12 in the mouse. Arch Int Pharmacodyn Ther. 167: 431449.
van Beynum, I. , den Heijer M. , Thomas C.M. , Afman L. , Oppenraay-van E.D. and Blom H.J. 2005. Total homocysteine and its predictors in Dutch children. Am J Clin Nutr. 81: 11101116.
Van, D.M. , Schneede J. , Refsum H. , Ueland P.M. , Thomas C.M. and de BE and van Staveren W.A. 1999. Risk of persistent cobalamin deficiency in adolescents fed a macrobiotic diet in early life. Am J Clin Nutr. 69: 664671.
Waggoner, D.J. , Ueda K. , Mantia C. and Dowton S.B. 1998. Methylmalonic aciduria (cblF): case report and response to therapy. Am J Med Genet. 79: 373375.
Wardinsky, T.D. , Montes R.G. , Friederich R.L. , Broadhurst R.B. , Sinnhuber V. and Bartholomew D. 1995. Vitamin B12 deficiency associated with low breast-milk vitamin B12 concentration in an infant following maternal gastric bypass surgery. Arch Pediatr Adolesc Med. 149: 12811284.
Weiss, R. , Fogelman Y. and Bennett M. 2004. Severe vitamin B12 deficiency in an infant associated with a maternal deficiency and a strict vegetarian diet. J Pediatr Hematol Oncol. 26: 270271.

CobalaminFolate Interactions

Allen, R.H. , Stabler S.P. , Savage D.G. , and Lindenbaum J. 1993. Metabolic abnormalities in cobalamin (vitamin B12) and folate deficiency. Faseb J. 7: 134453.
Bailey, L.B. , Stover P.J. , McNulty H. , Fenech M.F. , Gregory J.F. III , Mills J.L. , Pfeiffer C.M. , Fazili Z. , Zhang M. , Ueland P.M. , Molloy A.M. , Caudill M.A. , Shane B. , Berry R.J. , Bailey R.l. , Hausman D.B. , Raghavan R. , and Raiten D. 2015. Biomarkers of nutrition for developmentfolate review. J Nutr. 145: 1636S80S.
Bailey, S.W. , and Ayling J.E. 2009. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc Natl Acad Sci U S A. 106: 154249.
Battaglia-Hsu S. , Akchiche N. , Noel N. , Alberto J.-M. , Jeannesson E. , Orozco-Barrios C.E. , Martinez- Fong D. , Daval J.-L. and Guant J.-L. 2009. Vitamin B12 deficiency reduces proliferation and promotes differentiation of neuroblastoma cells and up-regulates PP2A, proNGF, and TACE. Proc Natl Acad Sci U S A. 106: 21930-5.
312 Bentley, T. G. K. , Willett W.C. , Weinstein M.C. , and Kuntz K.M. 2006. Population-level changes in folate intake by age, gender, and race/ethnicity after folic acid fortification. Am J Public Health. 96: 20407.
Berry, R.J. , Carter H.K. , and Yang Q. 2007. Cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 86: 2657; author reply 2679.
Boilson, A. , Staines A. , Kelleher C.C. , Daly L. , Shirley I. , Shrivastava A. , Bailey S.W. , Alverson P.B. , Ayling J.E. , Parle-McDermott A. , MacCooey A. , Scott J.M. , and Sweeney M.R. 2012. Unmetabolized folic acid prevalence is widespread in the older Irish population despite the lack of a mandatory fortification program. Am J Clin Nutr. 96: 61321.
Brito, A. , Verdugo R. , Hertrampf E. , Miller J.W. , Green R. , Fedosov S.N. , Shahab-Ferdows S. , Sanchez H. , Albala C. , Castillo J.L. , Matamala J.M. , Uauy R. , and Allen L.H. 2016. Vitamin B12 treatment of asymptomatic, deficient, elderly Chileans improves conductivity in myelinated peripheral nerves, but high serum folate impairs vitamin B12 status response assessed by the combined indicator of vitamin B12 status. Am J Clin Nutr. 103: 2507.
Bueno, O. , Molloy A.M. , Fernandez-Ballart J.D. , Garca- Minguillan C.J. , Ceruelo S. , Rios L. , Ueland P.M. , Meyer K. , and Murphy M.M. 2016. Common polymorphisms that affect folate transport or metabolism modify the effect of the MTHFR 677C > T polymorphism on folate status. J Nutr. 146: 18.
Carmel, R. 2009. Does high folic acid intake affect unrecognized cobalamin deficiency, and how will we know it if we see it? Am J Clin Nutr. 90: 144950.
Cherian A. , Seena S. , Bullock R.K. and Antony A.C. 2005. Incidence of neural tube defects in the leastdeveloped area of India: a population-based study. Lancet (London, England). 366: 930-1.
Chodos, R. , and Ross J. 1951. The effects of combined folic acid and liver extract therapy. Blood. 6: 121333.
Christensen, K.E. , Mikael L.G. , K.-Y. Leung , Lvesque N. , Deng L. , Wu Q. , Malysheva O.V. , Best A. , Caudill M.A. , Greene N.D.E. , and Rozen R. 2015. High folic acid consumption leads to pseudo-MTHFR deficiency, altered lipid metabolism, and liver injury in mice. Am J Clin Nutr. 101: 64658.
Clarke, R. , Sherliker P. , Hin H. , Molloy A.M. , Nexo E. , Ueland P.M. , Emmens K. , Scott J.M. , and Evans J.G. 2008. Folate and vitamin B12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK. Br J Nutr. 100: 10549.
Cook, J.D. , Cichowicz D.J. , George S. , Lawler A. , and Shane B. 1987. Mammalian folylpolyl-gamma- glutamate-synthetase. 4. In vitro and in vivo metabolism of folates and analogues and regulation of folate homeostasis. Biochemistry. 26: 5309.
Crider, K.S. , Devine O. , Hao L. , Dowling N.F. , Li S. , Molloy A.M. , Li Z. , Zhu J. , and Berry R.J. 2014. Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. BMJ. 349: g4554.
Cuskelly, G.C. , McNulty H. , and Scott J.M. 1996. Effects of increasing dietary folate on red cell faolte. Implications for the prevention of neural tube defects. Lancet. 347: 6579.
Daly, L.E. , Kirke P.N. , Molloy A. , Weir D.G. , and Scott J.M. 1995. Folate levels and neural tube defects. Implications for prevention. JAMA. 274: 1698702.
Deacon, R. , Lumb M. , Perry J. , Chanarin I. , Minty B. , Halsey M.J. , and Nunn J.F. 1978. Selective inactivation of vitamin B12 in rats by nitrous oxide. Lancet (London, England). 2: 10234.
Deshmukh, U.S. , Joglekar C.V. , Lubree H.G. , Ramdas L.V. , Bhat D.S. , Naik S.S. , Hardikar P.S. , Raut D.A. , Konde T.B. , Wills A.K. , Jackson A.A. , Refsum H. , Nanivadekar A.S. , Fall C.H. , and Yajnik C.S. 2010. Effect of physiological doses of oral vitamin B12 on plasma homocysteine: a randomized, placebo-controlled, double-blind trial in India. Eur J Clin Nutr. 64: 495502.
Doets, E.L. , Ueland P.M. , Tell G.S. , Vollset S.E. , Nygrd O.K. , Vant Veer P. , de Groot L.C.P.G.M. , Nurk E. , Dolnick B.J. , and Cheng Y.C. 1978. Human thymidylate synthetase. II. Derivatives of pteroylmono and -polyglutamates as substrates and inhibitors. J Biol Chem.

253: 35637.
Dominguez-Salas, P. , Moore S.E. , Cole D. , da Costa K.A. , Cox S.E. , Dyer R.A. , Fulford A.J. , Innis S.M. , Waterland R.A. , Zeisel S.H. , Prentice A.M. , and Hennig B.J. 2013. DNA methylation potential: dietary intake and blood concentrations of one-carbon metabolites and cofactors in rural African women. Am J Clin Nutr. 97: 121727.
313 Fernandez-Roig, S. , Cavall-Busquets P. , Fernandez-Ballart J.D. , Ballesteros M. , Berrocal Zaragoza M.I. , Salat-Batlle J. , and Murphy M.M. 2013. Low folate status enhances pregnancy changes in plasma betaine and dimethylglycine concentrations and the association between betaine and homocysteine. Am J Clin Nutr. 97: 12529.
Flour Fortification Initiative 2015. Flour Fortification Initiative home page. Available from: http://www.ffinetwork.org/about/stay_informed/releases/2014 Review.html.
Food and Drug Administration 1996. Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid.
Food Safety Authority of Ireland 2008. Report of the National Committee on Folic Acid Food Fortification.
Frenkel, E.P. 1973. Abnormal fatty acid metabolism in peripheral nerves of patiens with pernicious anemia. J Clin Invest. 52: 123745.
Fridman, S. 2005. High folic acid intake is not a risk factor for cognitive decline: misinterpretation of results. Arch Neurol. 62: 17856; author reply 1786.
Garca-Minguilln, C.J. , Fernandez-Ballart J.D. , Ceruelo S. , Ros L. , Bueno O. , Berrocal-Zaragoza M.I. , Molloy A.M. , Ueland P.M. , Meyer K. , and Murphy M.M. 2014. Riboflavin status modifies the effects of methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) polymorphisms on homocysteine. Genes Nutr. 9: 435.
Hannon-Fletcher, M.P. , Armstrong N.P. , Scott J.M. , Pentieva K. , Bradbury I. , Ward M. , Strain J.J. , Dunn A.A. , Molloy A.M. , Kerr M.A. , and McNulty H. 2004. Determining bioavailability of food folates in a controlled intervention study. Am J Clin Nutr. 80: 9118.
Healton, E.B. , Savage D.G. , Brust J.C. , Garrett T.J. , and Lindenbaum J. 1991. Neurologic aspects of vitamin B12 deficiency. Medicine (Baltimore). 70: 22945.
Hemmer, B. , Glocker F.X. , Schumacher M. , Deuschl G. , and Lcking C.H. 1998. Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. J Neurol Neurosurg Psychiatry. 65: 8227.
Herbert, V. , and Zalusky R. 1962. Interrelations of vitamin B12 and folic acid metabolism: folic acid clearance studies. J Clin Invest. 41: 126376.
Herrmann, W. , Obeid R. , Schorr H. , Hubner U. , Geisel J. , Sand-Hill M. , Ali N. , and Herrmann M. 2009. Enhanced bone metabolism in vegetariansthe role of vitamin B12 deficiency. Clin Chem Lab Med. 47: 13811387.
Hertrampf, E. , Corts F. , Erickson J.D. , Cayazzo M. , Freire W. , Bailey L.B. , Howson C. , Kauwell G.P.A. , and Pfeiffer C. 2003. Consumption of folic acid-fortified bread improves folate status in women of reproductive age in Chile. J Nutr. 133: 31669.
Hertrampf E. and Corts F. 2004. Folic acid fortification of wheat flour: Chile. Nutr Rev. 62: S44-8; discussion S49.
Hoey, L. , McNulty H. , Askin N. , Dunne A. , Ward M. , Pentieva K. , Strain J. , Molloy A.M. , Flynn C.A. , and Scott J.M. 2007. Effect of a voluntary food fortification policy on folate, related B vitamin status, and homocysteine in healthy adults. Am J Clin Nutr. 86: 140513.
Holm, P.I. , Bleie O. , Ueland P.M. , Lien E.A. , Refsum H. , Nordrehaug J.E. and Nygrd O. 2004. Betaine as a determinant of postmethionine load total plasma homocysteine before and after B-vitamin supplementation. Arterioscler Thromb Vasc Biol. 24: 3017.
Hopkins, S.M. , Gibney M.J. , Nugent A.P. , McNulty H. , Molloy A.M. , Scott J.M. , Flynn A. , Strain J.J. , Ward M. , Walton J. , and McNulty B.A. 2015. Impact of voluntary fortification and supplement use on dietary intakes and biomarker status of folate and vitamin B12 in Irish adults. Am J Clin Nutr. 101: 116372.
Horne, D.W. , Cook R.J. , and Wagner C. 1989. Effect of dietary methyl group deficiency on folate metabolism in rats. J Nutr. 19: 61821.
Houghton, L.A. , Yang J. , and OConnor D.L. 2009. Unmetabolized folic acid and folate concentrations in breast milk are unaffected by low-dose folate supplements. Am J Clin Nutr. 89: 21620.
Jacques, P.F. , Bostom A.G. , Wilson P.W. , Rich S. , Rosenberg I.H. , and Selhub J. 2001. Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. Am J Clin Nutr. 73: 61321.
Jaikrishan, G. , Sudheer K.R. , Andrews V.J. , Koya P.K.M. , Madhusoodhanan M. , Jagadeesan C.K. , and Seshadri M. 2013. Study of stillbirth and major congenital anomaly among newborns in the high-level natural radiation areas of Kerala. India. J Community Genet. 4: 2131.
314 Kelly, P. , McPartlin J. , Goggins M. , Weir D.G. , and Scott J.M. 1997. Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr. 65: 17905.
Kim, Y.I. , Miller J.W. , da Costa K.A. , Nadeau M. , Smith D. , Selhub J. , Zeisel S.H. , and Mason J.B. 1994. Severe folate deficiency causes secondary depletion of choline and phosphocholine in rat liver. J Nutr. 124: 2197203.
Liaugaudas, G. , Jacques P.F. , Selhub J. , Rosenberg I.H. , and Bostom A.G. 2001. Renal insufficiency, Vitamin B12 status, and population attributable risk for mild hyperhomocysteinemia among coronary artery disease patients in the era of folic acid-fortified cereal grain flour. Arterioscler Thromb Vasc Biol. 21: 849851.
Marchetta, C.M. , Devine O.J. , Crider K.S. , Tsang B.L. , Cordero A.M. , Qi Y.P. , Guo J. , Berry R.J. , Rosenthal J. , Mulinare J. , Mersereau P. , and Hamner H.C. 2015. Assessing the association between natural food folate intake and blood folate concentrations: a systematic review and Bayesian metaanalysis of trials and observational studies. Nutrients. 7: 266386.
McGregor, D.O. , Dellow W.J. , Robson R.A. , Lever M. , George P.M. , and Chambers S.T. 2002. Betaine supplementation decreases post-methionine hyperhomocysteinemia in chronic renal failure. Kidney Int. 61: 10406.
Miller, J.W. , Garrod M.G. , Allen L.H. , Haan M.N. , and Green R. 2009. Metabolic evidence of vitamin B12 deficiency, including high homocysteine and methylmalonic acid and low holotransvitamin B12, is more pronounced in older adults with elevated plasma folate. Am J Clin Nutr. 90: 158692.
Mills, J.L. , Carter T.C. , Scott J.M. , Troendle J.F. , Gibney E.R. , Shane B. , Kirke P.N. , Ueland P.M. , Brody L.C. , and Molloy A.M. 2011. Do high blood folate concentrations exacerbate metabolic abnormalities in people with low vitamin B12 status? Am J Clin Nutr. 94: 495500.
Molloy, A.M. , Kirke P.N. , Troendle J.F. , Burke H. , Sutton M. , Brody L.C. , Scott J.M. , and Mills J.L. 2009. Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic Acid fortification. Pediatrics. 123: 91723.
Morris, M.C. , Evans D.A. , Bienias J.L. , Tangney C.C. , Hebert L.E. , Scherr P.A. , and Schneider J.A. 2005. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. Arch Neurol. 62: 6415.
Morris, M.S. , Jacques P.F. , Rosenberg I.H. , and Selhub J. 2007. Folate and vitamin B12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr. 85: 193200.
Morris, M.S. , Jacques P.F. , Rosenberg I.H. , and Selhub J. 2010. Circulating unmetabolized folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. Am J Clin Nutr. 91: 173344.
Morris, M.S. , Selhub J. , and Jacques P.F. 2012. Vitamin B12 and folate status in relation to decline in scores on the mini-mental state examination in the framingham heart study. J Am Geriatr Soc. 60: 145764.
Obeid, R. , Kasoha M. , Kirsch S.H. , Munz W. , and Herrmann W. 2010. Concentrations of unmetabolized folic acid and primary folate forms in pregnant women at delivery and in umbilical cord blood. Am J Clin Nutr. 92: 141622.

Obeid, R. , Kirsch S.H. , Kasoha M. , Eckert R. , and Herrmann W. 2011. Concentrations of unmetabolized folic acid and primary folate forms in plasma after folic acid treatment in older adults. Metabolism. 60: 67380.
Obeid, R. , Kirsch S.H. , Dilmann S. , Klein C. , Eckert R. , Geisel J. , and Herrmann W. 2016. Folic acid causes higher prevalence of detectable unmetabolized folic acid in serum than B-complex: a randomized trial. Eur J Nutr. 55: 10211028.
Olteanu, H. , Munson T. , and Banerjee R. 2002. Differences in the efficiency of reductive activation of methionine synthase and exogenous electron acceptors between the common polymorphic variants of human methionine synthase reductase. Biochem. 41: 1337813385.
Papathakis, P.C. , and Pearson K.E. 2012. Food fortification improves the intake of all fortified nutrients, but fails to meet the estimated dietary requirements for vitamins A and B6, riboflavin and zinc, in lactating South African women. Public Health Nutr. 15: 18107.
Pentieva, K. , Selhub J. , Paul L. , Molloy A.M. , McNulty B. , Ward M. , Marshall B. , Dornan J. , Reilly R. , Parle-McDermott A. , Bradbury I. , Ozaki M. , Scott J.M. , and McNulty H. 2016. Evidence from a randomized trial that exposure to supplemental folic acid at recommended levels during pregnancy does not lead increased unmetabolized folic acid concentrations in maternal or cord blood. J Nutr. 146: 494500.
315 Pfeiffer, C.M. , Osterloh J.D. , Kennedy-Stephenson J. , Picciano M.F. , Yetley E.A. , Rader J.I. , and Johnson C.L. 2008. Trends in circulating concentrations of total homocysteine among US adolescents and adults: findings from the 1991-1994 and 1999-2004 National Health and Nutrition Examination Surveys. Clin Chem. 54: 80113.
Pfeiffer, C.M. , Hughes J.P. , Lacher D.A. , Bailey R.L. , Berry R.J. , Zhang M. , Yetley E.A. , Rader J.I. , Sempos C.T. , and Johnson C.L. 2012. Estimation of trends in serum and RBC folate in the U.S. population from pre- to postfortification using assay-adjusted data from the NHANES 1988-2010. J Nutr. 142: 88693.
Pfeiffer, C.M. , Sternberg M.R. , Fazili Z. , Lacher D.A. , and Johnson C.L. 2015. Unmetabolized folic acid is detected in nearly all serum samples from US children, adolescents and adults. J Nutr. 145: 52031.
Qi, Y.P. , Do A.N. , Hamner H.C. , Pfeiffer C.M. , and Berry R.J. 2014. The prevalence of low serum vitamin B12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. J Nutr. 144: 1706.
Quinlivan, E.P. 2008. In vitamin B12 deficiency, higher serum folate is associated with increased homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci U S A. 105: E7; author reply E8.
Quinlivan, E.P. , McPartlin J. , McNulty H. , Ward M. , Strain J.J. , Weir D.G. , and Scott J.M. 2002. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. Lancet (London, England). 359: 2278.
Ray, J.G. 2004. Folic acid food fortification in Canada. Nutr Rev. 62: S359.
Refsum, H. , Yajnik C.S. , Gadkari M. , Schneede J. , Vollset S.E. , Orning L. , Guttormsen A.B. , Joglekar A. , Sayyad M.G. , Ulvik A. , and Ueland P.M. 2001. Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of vitamin B12 deficiency in Asian Indians. Am J Clin Nutr. 74: 23341.
Refsum, H. , Smith A.D. , and S. J. P. M. Eussen 2014. Interactions between plasma concentrations of folate and markers of vitamin B(12) status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. Br J Nutr. 111: 108595.
Reynolds, E. 2006. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 5: 949-960. Samaniego-Vaesken ML, Alonso-Aperte E and Varela-Moreiras G. 2016. Voluntary fortification with folic acid in Spain: An updated food composition database. Food Chem. 193: 14853.
Savage, D.G. , Lindenbaum J. , Stabler S.P. , and Allen R.H. 1994. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing vitamin B12 and folate deficiencies. Am J Med. 96: 23946.
Savage D.G. and Lindenbaum J. 1995. Folate-cobalamin interactions. pp. 237-85. In: L.B. Bailey (ed.). Folate in Health and Disease. 1st ed. Marcel Dekker Inc NY.
Savage, D.G. , and Lindenbaum J. 1995. Neurological complications of acquired vitamin B12 deficiency: clinical aspects. Baillieres Clin Haematol. 8: 65778.
Scott, J.M. , Dinn J.J. , Wilson P. , and Weir D.G. 1981. Pathogenesis of subacute combined degeneration: a result of methyl group deficiency. Lancet (London, England). 2: 3347.
Scott, J.M. , and Weir D.G. 1981. The methyl folate trap. A physiological response in man to prevent methyl group deficiency in kwashiorkor (methionine deficiency) and an explanation for folic-acid induced exacerbation of subacute combined degeneration in pernicious anaemia. Lancet. 2: 33740.
Selhub, J. , Morris M.S. , and Jacques P.F. 2007. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci U S A. 104: 1999520000.
Shorvon, S.D. , Carney M.W. , Chanarin I. , and Reynolds E.H. 1980. The neuropsychiatry of megaloblastic anaemia. Br Med J. 281: 10368.
Smith, A.D. , Y.-I. Kim , and Refsum H. 2008. Is folic acid good for everyone? Am J Clin Nutr. 87: 51733.
Smulders, Y.M. , Smith D.E.C. , Kok R.M. , Teerlink T. , Swinkels D.W. , Stehouwer C.D.A. , and Jakobs C. 2006. Cellular folate vitamer distribution during and after correction of vitamin B12 deficiency: a case for the methylfolate trap. Br J Haematol. 132: 6239.
316 Stokstad, E.L. , Reisenauer A. , Kusano G. , and Keating J.N. 1998. Effect of high levels of dietary folic acid on folate metabolism in vitamin B12 deficiency. Arch Biochem Biophys. 265: 40714.
Tighe, P. , Ward M. , McNulty H. , Finnegan O. , Dunne A. , Strain J. , Molloy A.M. , Duffy M. , Pentieva K. , and Scott J.M. 2011. A dose-finding trial of the effect of long-term folic acid intervention: implications for food fortification policy. Am J Clin Nutr. 93: 118.
Tinker, S.C. , Hamner H.C. , Qi Y.P. , and Crider K.S. 2015. U.S. women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. Birth Defects Res A Clin Mol Teratol. 103: 51726.
US Food and Drug Administration 1996. Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid. Fed. Regist. 61: 87818797.
UK Standing Advisory Committee on Nutrition 2006. Folate and Disease Prevention Report. London.
World Health Organization 2015. Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects.
Wyckoff, K.F. , and Ganji V. 2007. Proportion of individuals with low serum vitamin B12 concentrations without macrocytosis is higher in the post folic acid fortification period than in the pre folic acid fortification period. Am J Clin Nutr. 86: 118792.
Yajnik, C.S. , Deshpande S.S. , Lubree H.G. , Naik S.S. , Bhat D.S. , Uradey B.S. , Deshpande J.A. , Rege S.S. , Refsum H. , and Yudkin J.S. 2006. Vitamin B12 deficiency and hyperhomocysteinemia in rural and urban Indians. J Assoc Physicians India. 54: 77582.
Zeisel, S.H. , Zola T. , daCosta K.A. , and Pomfret E.A. 1989. Effect of choline deficiency on S-adenosylmethionine and methionine concentrations in rat liver. Biochem J. 259: 725729.

Extreme Vitamin B12 Concentrations in Clinical Practice in the Absence of Symptoms or B12 Treatment

Aminoff, M. , Carter J.E. , Chadwick R.B. , Johnson C. , Grasbeck R. , Abdelaal M.A. , Broch H. , Jenner L.B. , Verroust P.J. , Moestrup S.K. , de la C.A. and Krahe R. 1999. Mutations in CUBN, encoding the intrinsic factor-vitamin B12 receptor, cubilin, cause hereditary megaloblastic anaemia 1. Nat Genet. 21: 309313.

Arendt, J.F. , Farkas D.K. , Pedersen L. , Nexo E. , and Sorensen H.T. 2015. Elevated plasma vitamin B12 levels and cancer prognosis: A population-based cohort study. Cancer Epidemiol. 40: 158165.

Arlet, J.B. , Rachas A. , Colombet I. , Pouchot J. , and Chiche L. 2015. Is cobalamin measurement overprescribed by physicians? Results of an eight-year single academic centre survey. Rev Med Interne. 36: 495497.

Aronovitch, J. , Grossowicz N. , and Rachmilewitz M. 1956. Serum concentrations of vitamin B12 in acute and chronic liver disease. J Lab Clin Med. 48: 339344.

Baker, H. , Frank O. , and DeAngelis B. 1987. Plasma vitamin B12 titres as indicators of disease severity and mortality of patients with alcoholic hepatitis. Alcohol Alcohol. 22: 15.

Baker, H. , Leevy C.B. , DeAngelis B. , Frank O. , and Baker E.R. 1998. Cobalamin (vitamin B12) and holotranscobalamin changes in plasma and liver tissue in alcoholics with liver disease. J Am Coll Nutr. 17: 235238.

Beckett, A.G. , and Matthews D.M. 1962. Vitamin B12 in diabetes mellitus. Clin Sci. 23: 361370.

Boger, C.A. , Chen M.H. , Tin A. , Olden M. , Kottgen A. , de Boer I.H. , Fuchsberger C. , OSeaghdha C.M. , Pattaro C. , Teumer A. , Liu C.T. , Glazer N.L. , Li M. , OConnell J.R. , Tanaka T. , Peralta C.A. , Kutalik Z. , Luan J. , Zhao J.H. , Hwang S.J. , Akylbekova E. , Kramer H. , van der Harst P. , Smith A.V. , Lohman K. , de A.M. , Hayward C. , Kollerits B. , Tonjes A. , Aspelund T. , Ingelsson E. , Eiriksdottir G. , Launer L.J. , Harris T.B. , Shuldiner A.R. , Mitchell B.D. , Arking D.E. , Franceschini N. , Boerwinkle E. , Egan J., Hernandez D. , Reilly M. , Townsend R.R. , Lumley T. , Siscovick D.S. , Psaty B.M. , Kestenbaum B. , Haritunians T. , Bergmann S. , Vollenweider P. , Waeber G. , Mooser V. , Waterworth D. , Johnson A.D. , Florez J.C. , Meigs J.B. , Lu X. , Turner S. T. , Atkinson E.J. , Leak T. S. , Aasarod K. , Skorpen F. , Syvanen A.C. , Illig T. , Baumert J. , Koenig W. , Kramer B.K. , Devuyst O. , Mychaleckyj J.C. , Minelli C. , Bakker S.J. , Kedenko L. , Paulweber B. , Coassin S. , Endlich K. , Kroemer H.K. , Biffar R. , Stracke S. , Volzke H. , Stumvoll M. , Magi R. , Campbell H., Vitart V., Hastie N. D., Gudnason V. , Kardia S.L. , Liu Y. , Polasek O. , Curhan G. , Kronenberg F. , Prokopenko I. , Rudan I. , Arnlov J. , Hallan S. , Navis G. , Parsa A. , Ferrucci L. , Coresh J. , Shlipak M.G. , Bull S.B. , Paterson N.J. , Wichmann H. E. , Wareham N.J. , Loos R.J. , Rotter J.I. , Pramstaller P.P. , Cupples L.A. , Beckmann J.S. , Yang Q. , Heid I.M. , Rettig R. , Dreisbach A.W. , Bochud M. , Fox C.S. and Kao W.H. 2011. CUBN is a gene locus for albuminuria. J Am Soc Nephrol. 22: 555570.

335 Boger, W.P. , Strickland S.C. , Wright L.D. , and Ciminera J.L. 1957. Diabetes mellitus and serum vitamin B12 concentrations: 333 patients. Proc Soc Exp Biol Med. 96: 316319.

Bowen, R.A. , Drake S.K. , Vanjani R. , Huey E.D. , Grafman J. , and Horne M.K. III 2006. Markedly increased vitamin B12 concentrations attributable to IgG-IgM-vitamin B12 immune complexes. Clin Chem. 52: 21072114.

Brah, S. , Chiche L. , Mancini J. , Meunier B. , and Arlet J.B. 2014. Characteristics of patients admitted to internal medicine departments with high serum cobalamin levels: results from a prospective cohort study. Eur J Intern Med. 25: e57e58.

Burger, R.L. , Waxman S. , Gilbert H.S. , Mehlman C.S. , and Allen R.H. 1975. Isolation and characterization of a novel vitamin B12-binding protein associated with hepatocellular carcinoma. J Clin Invest. 56: 12621270.

Carmel, R. 1982. A new case of deficiency of the R binder for cobalamin, with observations on minor cobalamin-binding proteins in serum and saliva. Blood. 59: 152156.

Carmel, R. , and Eisenberg L. 1977. Serum vitamin B12 and transcobalamin abnormalities in patients with cancer. Cancer. 40: 13481353.

Carmel, R. , and Herbert V. 1969. Deficiency of vitamin B12-binding alpha globulin in two brothers. Blood. 33: 112.

Carmel, R. , and Hollander D. 1978. Extreme elevation of transcobalamin II levels in multiple myeloma and other disorders. Blood. 51: 10571063.

Carmel, R. , Vasireddy H. , Aurangzeb I. , and George K. 2001. High serum cobalamin levels in the clinical settingclinical associations and holo-transcobalamin changes. Clin Lab Haematol. 23: 365371.

Chang, S.C. , Goldstein B.Y. , Mu L. , Cai L. , You N.C. , He N. , Ding B.G. , Zhao J.K. , Yu S.Z. , Heber D. , Zhang Z.F. , and Lu Q.Y. 2015. Plasma folate, vitamin B12, and homocysteine and cancers of the esophagus, stomach, and liver in a Chinese population. Nutr Cancer. 67: 212223.

Chiche, L. , Mancini J. , and Arlet J.B. 2013. Indications for cobalamin level assessment in departments of internal medicine: a prospective practice survey. Postgrad Med J. 89: 560565.

Chow, B.F. , Rosen D.A. , and Lang C.A. 1954. Vitamin B12 serum levels and diabetic retinopathy. Proc Soc Exp Biol Med. 87: 3839.

Cinemre, H. , Serinkan Cinemre B.F. , Cekdemir D. , Aydemir B. , Tamer A. , and Yazar H. 2015. Diagnosis of vitamin B12 deficiency in patients with myeloproliferative disorders. J Investig Med. 63: 636640.

Collin, S.M. , Metcalfe C. , Refsum H. , Lewis S.J. , Zuccolo L. , Smith G.D. , Chen L. , Harris R. , Davis M. , Marsden G. , Johnston C. , Lane J.A. , Ebbing M. , Bonaa K.H. , Nygard O. , Ueland P.M. , Grau M.V. , Baron J.A. , Donovan J.L. , Neal D.E. , Hamdy F.C. , Smith A.D. , and Martin R.M. 2010. Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev. 19: 16321642.

Corbus, H.F. , Miller A. , and Sullivan J.F. 1957. The plasma disappearance, excretion, and tissue distribution of cobalt 60 labelled vitamin B12 in normal subjects and patients with chronic myelogenous leukemia. J Clin Invest. 36: 1824.

Elian, K.M. , and Hoffer L.J. 2002. Hydroxocobalamin reduces hyperhomocysteinemia in end-stage renal disease. Metabolism. 51: 881886.

336 Ferre, N. , Gomez F. , Camps J. , Simo J.M. , Murphy M.M. , Fernandez-Ballart J. , and Joven J. 2002. Plasma homocysteine concentrations in patients with liver cirrhosis. Clin Chem. 48: 183185.

Fremont, S. , Champigneulle B. , Gerard P. , Felden F. , Lambert D. , Gueant J.L. , and Nicolas J.P. 1991. Blood transcobalamin levels in malignant hepatoma. Tumour Biol. 12: 353359.

Garcia-Tevijano, E.R. , Berasain C. , Rodriguez J.A. , Corrales F.J. , Arias R. , Martin-Duce A. , Caballeria J. , Mato J.M. , and Avila M.A. 2001. Hyperhomocysteinemia in liver cirrhosis: mechanisms and role in vascular and hepatic fibrosis. Hypertension. 38: 12171221.

Gauchan, D. , Joshi N. , Gill A.S. , Patel V. , Debari V.A. , Guron G. , and Maroules M. 2012. Does an elevated serum vitamin B(12) level mask actual vitamin B(12) deficiency in myeloproliferative disorders? Clin Lymphoma Myeloma Leuk. 12: 269273.

Geissbuhler, P. , Mermillod B. , and Rapin C.H. 2000. Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: a prospective study over five years. J Pain Symptom Manage. 20: 93103.

Hall, C.A. , and Begley J.A. 1977. Congenital deficiency of human R-type binding proteins of cobalamin. Am J Hum Genet. 29: 619626.

Halsted, C.H. , and Medici V. 2012. Aberrant hepatic methionine metabolism and gene methylation in the pathogenesis and treatment of alcoholic steatohepatitis. Int J Hepatol. 2012: 959746.

Halsted, J.A. , Carroll J. , and Rubert S. 1959. Serum and tissue concentration of vitamin B12 in certain pathologic states. N Engl J Med. 260: 575580.
Hauck, F.H. , Tanner S.M. , Henker J. , and Laass M.W. 2008. Imerslund-Grasbeck syndrome in a 15-yearold German girl caused by compound heterozygous mutations in CUBN. Eur J Pediatr. 167: 671675.
Heinrich H.C. and Erdmann-Oehlecker S. 1956. Der Vitamin B12-Stoffwechsel bei Haemolastosen. III. Resorption, blutverteilung, serumproteinbindung, etention und Exkretion der B12- Vitamine bei Haemoblastosen nach oraler und parenteraler B12-Applikation. In: p 326.
Herrmann, W. , and Obeid R. 2013. Utility and limitations of biochemical markers of vitamin B12 deficiency. Eur J Clin Invest. 43: 231237.
Herrmann, W. , Obeid R. , Schorr H. , and Geisel J. 2005. The usefulness of holotranscobalamin in predicting vitamin B12 status in different clinical settings. Curr Drug Metab. 6: 4753.
Holdsworth, C.D. , Atkinson M. , Dossett J.A. , and Hall R. 1964. An assessment of the diagnostic and prognostic value of serum vitamin B12 levels in liver disease. Gut. 5: 601606.
House, A.A. , Eliasziw M. , Cattran D.C. , Churchill D.N. , Oliver M.J. , Fine A. , Dresser G.K. , and Spence J.D. 2010. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. JAMA. 303: 16031609.
Hultdin, J. , Van G.B. , Bergh A. , Hallmans G. , and Stattin P. 2005. Plasma folate, vitamin B12, andhomocysteine and prostate cancer risk: a prospective study. Int J Cancer. 113: 819824.
Hyndman, M.E. , Manns B.J. , Snyder F.F. , Bridge P.J. , Scott-Douglas N.W. , Fung E. , and Parsons H.G. 2003. Vitamin B12 decreases, but does not normalize, homocysteine and methylmalonic acid in end-stage renal disease: a link with glycine metabolism and possible explanation of hyperhomocysteinemia in end-stage renal disease. Metabolism. 52: 168172.
Jeffery, J. , Millar H. , Mackenzie P. , Fahie-Wilson M. , Hamilton M. , and Ayling R.M. 2010. An IgG complexed form of vitamin B12 is a common cause of elevated serum concentrations. Clin Biochem. 43: 8288.
Mackay, I.R. , Cowling D.C. , and Gray A. 1957. Highly raised serum vitamin B12 levels in obstructive hepatic necrosis. Br Med J. 2: 800801.
McMahon, G.M. , Hwang S.J. , Tanner R.M. , Jacques P.F. , Selhub J. , Muntner P. , and Fox C.S. 2015. The association between vitamin B12, albuminuria and reduced kidney function: an observational cohort study. BMC Nephrol. 16: 7.
Medici, V. , Peerson J.M. , Stabler S.P. , French S.W. , Gregory J.F. III , Virata M.C. , Albanese A. , Bowlus C.L. , Devaraj S. , Panacek E.A. , Rahim N. , Richards J.R. , Rossaro L. , and Halsted C.H. 2010. Impaired homocysteine transsulfuration is an indicator of alcoholic liver disease. J Hepatol. 53: 551557.
Mendelsohn, R.S. , Watkin D.M. , Horbett A.P. , and Fahey J.L. 1958. Identification of the vitamin B12- binding protein in the serum of normals and of patients with chronic myelocytic leukemia. Blood. 13: 740747.
Miller, A. 1958. The in vitro binding of cobalt 60 labeled vitamin B12 by normal and leukemic sera. J Clin Invest. 37: 556566.
337 Moelby, L. , Rasmussen K. , Ring T. , and Nielsen G. 2000. Relationship between methylmalonic acid and cobalamin in uremia. Kidney Int. 57: 265273.
Mollin, D.L. , and PITNEY WR, Baker SJ and BRADLEY JE. 1956. The plasma clearance and urinary excretion of parenterally administered 58Co B12. Blood. 11: 3143.
Nexo, E. , Olesen H. , Norredam K. , and Schwartz M. 1975. A rare case of megaloblastic anaemia caused by disturbances in the plasma cobalamin binding proteins in a patient with hepatocellular carcinoma. Scand J Haematol. 14: 320327.
Obeid, R. , Kuhlmann M. , Kirsch C.M. , and Herrmann W. 2005a. Cellular uptake of vitamin B12 in patients with chronic renal failure. Nephron Clin Pract. 99: c42c48.
Obeid, R. , Kuhlmann M.K. , Kohler H. , and Herrmann W. 2005b. Response of homocysteine, cystathionine, and methylmalonic acid to vitamin treatment in dialysis patients. Clin Chem. 51: 196201.
Polyzos, S.A. , Kountouras J. , Patsiaoura K. , Katsiki E. , Zafeiriadou E. , Deretzi G. , Zavos C. , Gavalas E. , Katsinelos P. , Mane V. , and Slavakis A. 2012. Serum homocysteine levels in patients with nonalcoholic fatty liver disease. Ann Hepatol. 11: 6876.
Portugal, V. , Garcia-Alonso I. , Barcelo P. , and Mendez J. 1995. Effect of allopurinol, folinic acid, SOD and cyclosporine A on ischemic liver regeneration. Eur Surg Res. 27: 6976.
Portugal, V. , Garcia-Alonso I. , and Mendez J. 1996. Hepatotrophic effect of folinic acid in rats. J Surg Res. 61: 527530.
Powell, C.L. , Bradford B.U. , Craig C.P. , Tsuchiya M. , Uehara T. , OConnell T.M. , Pogribny I.P. , Melnyk S. , Koop D.R. , Bleyle L. , Threadgill D.W. , and Rusyn I. 2010. Mechanism for prevention of alcohol- induced liver injury by dietary methyl donors. Toxicol Sci. 115: 131139.
Price, A.J. , Travis R.C. , Appleby P.N. , Albanes D. , Barricarte G.A. , Bjorge T. , Bueno-de-Mesquita H.B. , Chen C. , Donovan J. , Gislefoss R. , Goodman G. , Gunter M. , Hamdy F.C. , Johansson M. , King I.B. , Kuhn T. , Mannisto S. , Martin R.M. , Meyer K. , Neal D.E. , Neuhouser M.L. , Nygard O. , Stattin P. , Tell G.S. , Trichopoulou A. , Tumino R. , Ueland P.M. , Ulvik A. , de V.S. , Vollset S. E., Weinstein S.J. , Key T.J. and Allen N.E. 2016. Circulating Folate and Vitamin B and Risk of Prostate Cancer: A Collaborative Analysis of Individual Participant Data from Six Cohorts Including 6875 Cases and 8104 Controls. Eur Urol. doi:(10.1016/j.eururo.2016.03.029).
Rachmilewitz, M. , Stein Y. , Aronovitch J. , and Grossowicz N. 1959. Serum cyanocobalamin (vitamin B12) as an index of hepatic damage in chronic congestive heart failure. Arch Intern Med. 104: 406410.
Rachmilewitz, M. , Stein Y. , Aronovitch J. , and Grossowicz N. 1958. The clinical significance of serum cyanocobalamin (vitamin B12) in liver disease. AMA Arch Intern Med. 101: 11181125.
Rasmussen, K. , Vyberg B. , Pedersen K.O. , and Brochner-Mortensen J. 1990. Methylmalonic acid in renal insufficiency: evidence of accumulation and implications for diagnosis of cobalamin deficiency. Clin Chem. 36: 15231524.
Salles, N. , Herrmann F. , Sieber C. , and Rapin C. 2008. High vitamin B12 level and mortality in elderly inpatients. J Nutr Health Aging. 12: 219221.
Simonsen, K. , Rode A. , Nicoll A. , Villadsen G. , Espelund U. , Lim L. , Angus P. , Arachchi N. , Vilstrup H. , Nexo E. , and Gronbaek H. 2014. Vitamin B(1)(2) and its binding proteins in hepatocellular carcinoma and chronic liver diseases. Scand J Gastroenterol. 49: 10961102.
Stevenson, T.D. , and Beard M.F. 1959. Serum vitamin B12 content in liver disease. N Engl J Med. 260: 206210.
Vashi, P. , Edwin P. , Popiel B. , Lammersfeld C. , and Gupta D. 2016. Methylmalonic Acid and Homocysteine as Indicators of Vitamin B12 Deficiency in Cancer. PLoS One. 11: e0147843.
Vollset, S.E. , Clarke R. , Lewington S. , Ebbing M. , Halsey J. , Lonn E. , Armitage J. , Manson J.E. , Hankey G.J. , Spence J.D. , Galan P. , Bonaa K.H. , Jamison R. , Gaziano J.M. , Guarino P. , Baron J.A. , Logan R.F. , Giovannucci E.L. , and den HM, Ueland PM, Bennett D, Collins R and Peto R. 2013. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50000 individuals. Lancet. 381: 10291036.
Waters, W.E. , Withey J.L. , Kilpatrick G.S. , and Wood P.H. 1971. Serum vitamin B 12 concentrations in the general population: a ten-year follow-up. Br J Haematol. 20: 521526.
Weinstein, I.B. , and Watkin D.M. 1960. Co58B12 absorption, plasma transport and excretion in patients with myeloproliferative disorders, solid tumors and non-neoplastic diseases. J Clin Invest. 39: 16671674.

Vitamin B12 and Drug Development

Ahrenstedt S. Stefan and Jan I. Thorell. 1979. The production of antibodies to vitamin B12. Clinica Chimica Acta. 95 (3): 419423.

Alsenz J, Russell-Jones GJ, Westwood S, Levet-Trafit B and de Smidt PC. 2000. Oral absorption of peptides through the cobalamin (vitamin B12) pathway in the rat intestine. Pharmaceutical Research. 17 (7): 825832.

Andersen Christian Brix Folsted, Mette Madsen, Tina Storm, Soren K Moestrup and Gregers R Andersen. 2010. Structural basis for receptor recognition of vitamin-B12-intrinsic factor complexes. Nature. 464 (7287): 445448.

Bagnato Joshua D, Alanna L Eilers, Robert A Horton and Charles B Grissom. 2004. Synthesis and characterization of a cobalamin-colchicine conjugate as a novel tumor-targeted cytotoxin. The Journal of Organic Chemistry. 69 (26): 89878996.

Bauer Joseph A, Bei H Morrison, Ronald W Grane et al. 2002. Effects of interferon beta on transcobalamin II-receptor expression and antitumor activity of nitrosylcobalamin. Journal of the National Cancer Institute. 94 (13): 10101019.

Beedholm-Ebsen Rasmus, Koen van de Wetering, Tore Hardlei et al. 2010. Identification of multidrug resistance protein 1 (MRP1/ABCC1) as a molecular gate for cellular export of cobalamin. Blood. 115 (8): 16321639.

Bonaccorso Ron L, Oleg G Chepurny, Christoph Becker-Pauly, George G Holz and Robert P Doyle. 2015. Enhanced peptide stability against protease digestion induced by intrinsic factor binding of a vitamin B12 conjugate of exendin-4. Molecular Pharmaceutics. 12 (9): 35023506.

Carmel Ralph. 1975. Extreme elevation of serum transcobalamin I in patients with metastatic cancer. New England Journal of Medicine. 292 (6): 282284.

Chalasani Kishore B, Gregory J Russell-Jones, Akhlesh K Jain, Prakash V Diwan and Sanjay K Jain. 2007. Effective oral delivery of insulin in animal models using vitamin B12-coated dextran nanoparticles. Journal of Controlled Release. 122 (2): 141150.

Christensen Erik I, Rikke Nielsen and Henrik Birn. 2013. From bowel to kidneys: The role of cubilin in physiology and disease. Nephrology Dialysis Transplantation. 28 (2): 274281.

Chrominski Mikotaj and Dorota Gryko. 2013. Clickable vitamin B12 derivative. ChemistryA. European Journal. 19 (16): 51415148.

Chrominski Mikotaj, Agnieszka Lewalska and Dorota Gryko. 2013. Reduction-free synthesis of stable acetylide cobalamins. Chemical Communications. 49 (97): 1140611408.

Clardy-James Susan, Jaime Bernstein, Deborah Kerwood and Robert Doyle. 2012. Site-selective oxidation of vitamin B12 using 2-iodoxybenzoic acid. Synlett. 23 (16): 23632366.

Clardy Susan M, Damian G Allis, Timothy J Fairchild and Robert P Doyle. 2011. Vitamin B12 in drug delivery: Breaking through the barriers to a B12 bioconjugate pharmaceutical. Expert Opinion on Drug Delivery. 8 (1): 127140.

361 Collins Douglas A, Harry PC Hogenkamp and Mark W Gebhard. 1999. Tumor imaging via indium 111-labeled DTPA-adenosylcobalamin. Mayo Clinic Proceedings. 74 (7): 687691.

Collins Douglas A and Hogenkamp H.P.C. 1997. Transcobalamin II receptor imaging via radiolabeled diethylene-triaminepentaacetate cobalamin analogs. Journal of Nuclear Medicine. 38 (5): 717723.

Dix CJ, Hassan IF, Obray HY, Shah R and Wilson G. 1990. The transport of vitamin B12 through polarized monolayers of Caco-2 cells. Gastroenterology 98(5 PART 1). Scopus. 12721279.

Doxey Andrew C, Daniel A Kurtz, Michael DJ Lynch, Laura A Sauder and Josh D Neufeld. 2015. Aquatic metagenomes implicate thaumarchaeota in global cobalamin production. The ISME Journal. 9 (2): 461471.

Fazen Christopher H, Debbie Valentin, Timothy J Fairchild and Robert P Doyle. 2011. Oral delivery of the appetite suppressing peptide hPYY(336) through the vitamin B12 uptake pathway. Journal of Medicinal Chemistry. 54 (24): 87078711.

Fedosov Sergey N, Lars Berglund, Natalya U Fedosova, Ebba Nexo and Torben E Petersen. 2002. Comparative analysis of cobalamin binding kinetics and ligand protection for intrinsic factor, transcobalamin, and haptocorrin. Journal of Biological Chemistry. 277 (12): 99899996.

Fedosov Sergey N, Natalya U Fedosova, Bernhard Krutler, Ebba Nexo and Torben E Petersen. 2007. Mechanisms of discrimination between cobalamins and their natural analogues during their binding to the specific B12-transporting proteins. Biochemistry. 46 (21): 64466458.

Fowler Robyn, Driton Vllasaliu, Franco H Falcone et al. 2013. Uptake and transport of B12- conjugated nanoparticles in airway epithelium. Journal of Controlled Release. 172 (1): 374381.

Furger Evelyne, Dominik C Frei, Roger Schibli, Eliane Fischer and Andrea E Prota. 2013. Structural basis for Universal corrinoid recognition by the cobalamin transport protein haptocorrin. Journal of Biological Chemistry. 288 (35): 2546625476.

Fyfe John C, Mette Madsen, Peter Hojrup et al. 2004. The functional cobalamin (vitamin B12)- intrinsic factor receptor is a novel complex of Cubilin and Amnionless. Blood. 103 (5): 15731579.

Gherasim Carmen, Michael Lofgren and Ruma Banerjee. 2013. Navigating the B12 road: Assimilation, delivery, and disorders of cobalamin. Journal of Biological Chemistry. 288 (19): 1318613193.

Glass GBJ. 1963. Gastric intrinsic factor and its function in the metabolism of vitamin B12. Physiological Reviews 43. CAB Direct. 2: 529849.

Habberfield Alan David, Olaf Boris Kinstler and Colin Geoffrey Pitt. 1996. Conjugates of vitamin b12 and proteins. http://www.google.com/patents/WO1996004016A1, accessed April 17, 2016.

Henry Kelly E, Clinton T Elfers, Rachael M Burke et al. 2015. Vitamin B12 conjugation of peptide- YY336 decreases food intake compared to native peptide-YY336 upon subcutaneous administration in male rats. Endocrinology. 156 (5): 17391749.

Henry Kelly E, Deborah J Kerwood, Damian G Allis et al. 2016. Solution structure and constrained molecular dynamics study of Vitamin B12 conjugates of the anorectic peptide PYY(336). Chem Med Chem. doi:10.1002/cmdc.201600073.

Hippe Erik, Edgar Haber and Henrik Olesen. 1971. Nature of vitamin B12 binding. Biochimica et Biophysica Acta (BBA)Protein. Structure. 243 (1): 7582.

Hodgkin Dorothy Crowfoot, Jenny Pickworth, John H Robertson et al. 1955. Structure of vitamin B12: The crystal structure of the hexacarboxylic acid derived from B12 and the molecular structure of the vitamin. Nature. 176 (4477): 325328.

Hogenkamp HP, Collins DA, Live D, Benson LM and Naylor S. 2000. Synthesis and characterization of Nido-Carborane-Cobalamin conjugates. Nuclear Medicine and Biology. 27 (1): 8992.

Hygum Katrine, Dorte L Lildballe, Eva H Greibe et al. 2011. Mouse Transcobalamin Has Features Resembling Both Human Transcobalamin and Haptocorrin. PLOS ONe. 6 (5): e20638.

Ikotun Oluwatayo F, Bernadette V Marquez, Christopher H Fazen et al. 2014. Investigation of a vitamin B12 conjugate as a PET imaging probe. Chem Med Chem. 9 (6): 12441251.

Krutler B. 2005. Vitamin B12: Chemistry and biochemistry. Biochemical Society Transactions. 33 (4): 806810.

Krutler B. 2015. Antivitamins B12A structure- and reactivity-based concept. ChemistryA. European Journal. 21 (32): 1128011287.

362 Kunze Susanne, Fabio Zobi, Philipp Kurz, Bernhard Spingler and Roger Alberto. 2004. Vitamin B12 as a Ligand for Technetium and Rhenium Complexes. Angewandte Chemie (International Ed. in English) 43 (38): 50255029.

Lee Manfai and Charles B Grissom. 2009. Design, synthesis, and characterization of fluorescent cobalamin analogues with high quantum efficiencies. Organic Letters. 11 (12): 24992502.

Lildballe Dorte L, Elena Mutti, Henrik Birn and Ebba Nexo. 2012. Maximal load of the vitamin B12 transport system: A study on mice treated for four weeks with high-dose vitamin B12 or cobinamide. PLOS ONE. 7 (10): e46657.
Martens J-H, Barg H, Warren M and Jahn D. 2002. Microbial production of vitamin B12. Applied Microbiology and Biotechnology. 58 (3): 275285.
Mathews FS, Gordon MM, Chen Z et al. 2007. Crystal structure of human intrinsic factor: Cobalamin complex at 2.6- resolution. Proceedings of the National Academy of Sciences. 104 (44): 1731117316.
McEwan JF, Veitch HS and Russell-Jones GJ. 1999. Synthesis and biological activity of ribose-5- carbamate derivatives of vitamin B12. Bioconjugate Chemistry. 10 (6): 11311136.
McGreevy James M, Michelle J Cannon and Charles B Grissom. 2003. Minimally invasive lymphatic mapping using fluorescently labeled vitamin B12. The Journal of Surgical Research. 111 (1): 3844.
Moestrup SK, Birn H, Fischer PB et al. 1996. Megalin-mediated endocytosis of transcobalamin- vitamin-B12 complexes suggests a role of the receptor in vitamin-B12 homeostasis. Proceedings of the National Academy of Sciences. 93 (16): 86128617.
Mukherjee Riya, Edward G Donnay, Michal A Radomski et al. 2008. Vanadium-vitamin B12 bioconjugates as potential therapeutics for treating diabetes. Chemical Communications (Cambridge, England). 32: 37833785.
Mundwiler Stefan, Bernhard Spingler, Philipp Kurz, Susanne Kunze and Roger Alberto. 2005. Cyanide-bridged vitamin B12-cisplatin conjugates. Chemistry (Weinheim an Der Bergstrasse, Germany). 11 (14): 40894095.
Mundwiler Stefan, Robert Waibel, Bernhard Spingler, Susanne Kunze and Roger Alberto. 2005. Picolylamine-methylphosphonic acid esters as tridentate ligands for the labeling of alcohols with the Fac-[M(CO)3]+ core (M=99mTc, Re): Synthesis and biodistribution of model compounds and of a 99mTc-Labeled cobinamide. Nuclear Medicine and Biology. 32 (5): 473484.
Mutti Elena, Markus Ruetz, Henrik Birn, Bernhard Krutler and Ebba Nexo. 2013. 4-Ethylphenyl- cobalamin impairs tissue uptake of vitamin B 12 and causes vitamin B 12 deficiency in mice. PLOS ONE. 8 (9): e75312.
Nexo Ebba and Jorgen Andersen. 1977. Unsaturated and cobalamin saturated transcobalamin I and II in normal human plasma. Scandinavian Journal of Clinical and Laboratory Investigation. 37 (8): 723728.
Nexo Ebba and Henrik Olesen. 1981. Purification and characterization of rabbit haptocorrin. Biochimica et Biophysica Acta (BBA)Protein. Structure. 667 (2): 370376.
Nexo Ebba, Mads Hansen, Steen Seier Poulsen and Peter Skov Olsen. 1985. Characterization and immunohistochemical localization of rat salivary cobalamin-binding protein and comparison with human salivary haptocorrin. Biochimica et Biophysica Acta (BBA)General Subjects. 838 (2): 264269.
Nielsen Marianne J, Mie R Rasmussen, Christian BF Andersen, Ebba Nexo and Soren K Moestrup. 2012. Vitamin B12 transport from food to the bodys cellsa sophisticated, multistep pathway. Nature Reviews Gastroenterology and Hepatology. 9 (6): 345354.
Pathare Pradip M, D Scott Wilbur, Shannon Heusser et al. 1996. Synthesis of cobalamin-Botin conjugates that vary in the position of cobalamin coupling. Evaluation of cobalamin derivative binding to transcobalamin II. Bioconjugate Chemistry. 7 (2): 217232.
Petrus Amanda K, Timothy J Fairchild and Robert P Doyle. 2009. Traveling the vitamin B12 pathway: Oral delivery of protein and peptide drugs. Angewandte Chemie International Edition. 48 (6): 10221028.
Petrus Amanda K, Anthony R Vortherms, Timothy J Fairchild and Robert P Doyle. 2007. Vitamin B12 as a carrier for the oral delivery of insulin. Chem Med Chem. 2 (12): 17171721.
363 Polak DM, Elliot JM and Haluska M. 1979. Vitamin B12 binding proteins in bovine seruml. Journal of Dairy Science. 62 (5): 697701.
Proinsias Keith o, Maciej Giedyk and Dorota Gryko. 2013. Vitamin B12: Chemical modifications. Chemical Society Reviews. 42 (16): 66056619.
Proinsias Keith o, Michal Ociepa, Katarzyna Pluta, Mikolaj Chrominski, Ebba Nexo and Dorota Gryko. 2016. Vitamin B12 phosphate conjugation and its effect on binding to the human B12 binding proteins intrinsic factor and haptocorrin. ChemistryA European Journal. IN PRESS.
Ruetz Markus, Carmen Gherasim, Karl Gruber et al. 2013. Access to organometallic arylcobaltcorrins through radical synthesis: 4-Ethylphenylcobalamin, a potential Antivitamin B12. Angewandte Chemie International Edition. 52 (9): 26062610.
Ruetz Markus, Robert Salchner, Klaus Wurst, Sergey Fedosov and Bernhard Krutler. 2013. Phenylethynylcobalamin: A light-stable and thermolysis-resistant organometallic vitamin B12 derivative prepared by radical synthesis. Angewandte Chemie International Edition. 52 (43): 1140611409.
Ruiz-Sanchez Pilar, Stefan Mundwiler, Alfredo Medina-Molner, Bernhard Spingler and Roger Alberto. 2007. Iodination of Cisplatin adduct of vitamin B12 [{B12)-CN-{cis- PtCl(NH3)2)]+. Journal of Organometallic Chemistry 692(6). Third International Symposium on Bioorganometallic Chemistry(ISBOMC06)Third International Symposium on Bioorganometallic. Chemistry. 13581362.
Ruiz-Snchez Pilar, Stefan Mundwiler, Bernhard Spingler et al. 2007. Syntheses and characterization of vitamin B12-Pt(II) conjugates and their Adenosylation in an enzymatic assay. JBIC Journal of Biological Inorganic Chemistry. 13 (3): 335347.
Russell-Jones GJ, Westwood SW and Habberfield AD. 1995. Vitamin B12 mediated oral delivery systems for granulocyte-colony stimulating factor and erythropoietin. Bioconjugate Chemistry. 6 (4): 459465.
Russell-Jones Gregory, Kirsten McTavish and John McEwan. 2011. Preliminary studies on the selective accumulation of vitamin-targeted polymers within tumors. Journal of Drug Targeting. 19 (2): 133139.
Russell-Jones G, Westwood S, Farnworth P, Findlay J and Burger H. 1995. Synthesis of LHRH antagonists suitable for oral administration via the vitamin B12 uptake system. Bioconjugate Chemistry. 6 (1): 3442.
Sah Bert-Ram, Roger Schibli, Robert Waibel et al. 2014. Tumor imaging in patients with advanced tumors using a new 99mTc-radiolabeled vitamin B12 derivative. Journal of Nuclear Medicine. 55 (1): 4349.
Schjonsby H and Andersen KJ. 1974. The intestinal absorption of vitamin B12. Scan J Gastro Suppl. 29: 711.
Seetharam Bellur and David H Alpers. 1994. Cobalamin binding proteins and their receptors. In Vitamin Receptors: Intercellular and Intracellular Communication. Cambridge University Press. dx. doi:doi.org/10.1017/CBO9780511525391.006.
Shell Thomas A, Jennifer R Shell, Zachary L Rodgers and David S Lawrence. 2014. Tunable visible and near-IR photoactivation of light-responsive compounds by using fluorophores as lightcapturing antennas. Angewandte Chemie International Edition. 53 (3): 875878.
Sheppard K, Bradbury DA, Davies JM and Ryrie DR. 1984. Cobalamin and folate binding proteins in human tumour tissue. Journal of Clinical Pathology. 37 (12): 13361338.
Siega Patrizia, Jochen Wuerges, Francesca Arena et al. 2009. Release of toxic Gd3+ ions to tumour cells by vitamin B12 bioconjugates. Chemistry (Weinheim an Der Bergstrasse, Germany). 15 (32): 79807989.
Smith Weston J, Nathan P Oien, Robert M Hughes et al. 2014. Cell-mediated assembly of phototherapeutics. Angewandte Chemie International Edition. 53 (41): 1094510948.
Takahashi-Iniguez Toshiko, Enrique Garcia-Hernandez, Roberto Arreguin-Espinosa and Mara Elena Flores. 2012. Role of vitamin B12 on methylmalonyl-CoA mutase activity. Journal of Zhejiang University. Science. B. 13 (6): 423437.
364 Tran Mai Thanh Quynh, Evelyne Furger and Roger Alberto. 2013. Two-step activation prodrugs: Transplatin mediated binding of chemotherapeutic agents to vitamin B12. Organic & Biomolecular Chemistry. 11 (19): 32473254.
Tran Mai Thanh Quynh, Stefan Strup, Ian Henry Lambert et al. 2016. Cellular uptake of metallated cobalamins. Metallomics. 8 (3): 298304.

Verma Ashwni, Shweta Sharma, Pramod Kumar Gupta et al. 2016. Vitamin B12 functionalized layer by layer calcium phosphate nanoparticles: A mucoadhesive and pH responsive carrier for improved oral delivery of insulin. Acta Biomaterialia. 31: 288300.
Vortherms Anthony R, Anna R Kahkoska, Amy E Rabideau et al. 2011. A water soluble vitamin B12-Re(I) fluorescent conjugate for cell uptake screens: Use in the confirmation of Cubilin in the lung cancer line A549. Chemical Communications. 47 (35): 97929794.
Waibel Robert, Hansjorg Treichler, Niklaus G Schaefer et al. 2008. New derivatives of vitamin B12 show preferential targeting of tumors. Cancer Research. 68 (8): 29042911.
Wang Xiaoyang, Lianhu Wei and Lakshmi P Kotra. 2007. Cyanocobalamin (vitamin B12) conjugates with enhanced solubility. Bioorganic & Medicinal Chemistry. 15 (4): 17801787.
Wierzba Aleksandra, Monika Wojciechowska, Joanna Trylska and Dorota Gryko. 2016. Vitamin B12 suitably tailored for disulfide-based conjugation. Bioconjugate Chemistry. 27 (1): 189197.
Wuerges, Jochen, Gianpiero Garau, Silvano Geremia et al. 2006. Structural basis for mammalian vitamin B12 transport by transcobalamin. Proceedings of the National Academy of Sciences of the United States of America. 103 (12): 43864391.
Wuerges Jochen, Silvano Geremia, Sergey N Fedosov and Lucio Randaccio. 2007. Vitamin B12 transport proteins: Crystallographic analysis of p-axial ligand substitutions in cobalamin bound to transcobalamin. IUBMB Life. 59 (11): 722729.
Zelder Felix. 2015. Recent trends in the development of vitamin B12 derivatives for medicinal applications. Chemical Communications. 51 (74): 1400414017.
Zelder Felix, Marjorie Sonnay and Lucas Prieto. 2015. Antivitamins for medicinal applications. Chem Bio Chem. 16 (9): 12641278.
Zhou Kai, Ren M Oetterli, Helmut Brandl et al. 2012. Chemistry and bioactivity of an artificial adenosylpeptide B12 cofactor. Chem Bio Chem. 13 (14): 20522055.
Zhou Kai and Felix Zelder. 2010. Vitamin B12 mimics having a peptide backbone and tuneable coordination and redox properties. Angewandte Chemie International Edition. 49 (30): 51785180.