

HERE IS SOMETHING LEFT OF FIELD, VERY SAFE, AND AVAILABLE , THAT COULD BE USED TO HELP CHARLIE GARD, WITH NO DOWNSIDE, *RIGHT WHERE HE IS NOW.*

SOME NOTES ON THE SAFETY & CLINICAL USES/ UNTAPPED POTENTIAL OF HIGH DOSE INJECTABLE VITAMIN B12: [WHICH IS ESSENTIAL FOR DNA SYNTHESIS & MITOCHONDRIAL REGENERATION OR BIOGENESIS].

[COMMENTARY, POSSIBLE APPLICATION TO CHARLIE, AND REFERENCES PROVIDED BY DR CARMEN WHEATLEY D PHIL OXON, St Catherine's College, Oxford].

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VITAMIN B12 HAS A LONG HISTORY OF VERY SAFE USE IN THE CLINIC, FOR CONDITIONS OTHER THAN JUST THE TREATMENT OF ITS DEFICIENCY, OR PERNICIOUS ANAEMIA.

B12 , AS HYDROXOCOBALAMIN [HOCBL], IN SUPRA-PHYSIOLOGICAL DOSES, GIVEN BY IV, HAS BEEN USED FOR NEARLY 70 YEARS IN FRENCH AND OTHER INTENSIVE CARE UNITS ACROSS THE WORLD AS A TOTALLY SAFE AND EFFECTIVE TREATMENT FOR CYANIDE POISONING.

IN THE USA **THE FDA HAS GIVEN INJECTABLE B12 AS HOCBL ORPHAN DRUG STATUS**, FOR USE IN TERRORIST SCENARIOS, WHERE USE OF CYANIDE GAS MAY BE SUSPECTED AND A SAFE ANTIDOTE MAY BE NEEDED.

IN THE 1950S, '60S AND '70S, THE CELL ACTIVE FORMS OF VITAMIN B12, METHYLCOBALAMIN [MECBL] AND ADENOSYLCOBALAMIN [ADOCBL] WERE USED IN FRENCH, ITALIAN, PORTUGUESE, SPANISH AND RUSSIAN HOSPITALS FOR A VARIETY OF CONDITIONS.

B12 WAS CONSIDERED SO SAFE THAT EVEN PRE-TERM BABIES WERE TREATED WITH B12 INJECTIONS.

OVER HALF A CENTURY OR MORE THERE HAVE BEEN A NUMBER OF SMALL, BUT MOSTLY EFFECTIVE, CLINICAL TRIALS OF VARYING DOSES AND FORMS OF B12 FOR VARYING PROBLEMS, INCLUDING

A 10 YEAR TRIAL OF INJECTABLE VITAMIN B12, USED IN BABIES AND SMALL CHILDREN WITH NEUROBLASTOMA, IN GREAT ORMOND STREET HOSPITAL.

THE TRIAL WAS DESIGNED AND RUN BY A PAEDIATRIC PATHOLOGIST, DR MARTIN BODIAN, WHO, UNFORTUNATELY, DIED IN 1963, AFTER WHICH HIS SIGNIFICANT WORK AND POSITIVE RESULTS OF THIS TRIAL WERE GROSSLY MISREPRESENTED.

TODAY THERE IS STILL NO CURE FOR NEUROBLASTOMA.

IN THE LAST DECADE THERE HAVE BEEN **2 TRIALS OF METHYLCOBALAMIN FOR ALS,**

A RAPID DEATH SENTENCE, THAT BOTH SHOWED VERY SIGNIFICANTLY INCREASED SURVIVAL, EVEN THOUGH THE FULL POTENTIAL OF MECBL IN TERMS OF DOSE AND FREQUENCY OF ADMINISTRATION MAY NOT HAVE BEEN TAPPED.

IN THE LAST DECADE THERE HAVE BEEN 2 OXFORD LED TRIALS OF ORAL B12 COMBINED WITH B6 AND FOLATE AS **A TREATMENT TO PREVENT ALZHEIMERS. THE RESULTS WERE SO SUCCESSFUL THAT THEY MADE INTERNATIONAL HEADLINES.**

YET NOW **MOST DOCTORS ARE UNAWARE OF THIS SIMPLE PREVENTIVE STRATEGY,** AND IT IS STILL SAID THAT THERE IS NO SUCCESSFUL TREATMENT OF ALZHEIMERS WHEN PREVENTION WITH B12, B6 AND FOLATE HAS BEEN PROVEN.....

THE RUSSIANS HAVE USED B12 TO TREAT AND REVERSE HEART RHYTHM PROBLEMS.

THE JAPANESE HAVE USED B12 AS MECBL TO TREAT RHEUMATOID ARTHRITIS.

B12 AS ADENOSYLCOBALAMIN HAS BEEN SHOWN TO HAVE NOTABLE ANTI-MALARIAL ACTIVITY IN THE LAB.

WHILST CONVENTIONAL ANTI-MALARIALS SHOW INCREASING PROBLEMS WITH DRUG RESISTANCE, **THIS SAFE POSSIBLE TREATMENT IS IGNORED BY LARGE MALARIA FUNDING AGENCIES WHICH COULD TEST IT AND MAKE IT WIDELY AVAILABLE.**

A COUPLE OF LAB STUDIES ALSO INDICATE THAT B12 HAS STRONG ANTIVIRAL ACTION AGAINST HIV.

OTHER CONDITIONS FOR WHICH B₁₂ HAS BEEN USED IN THE CLINIC WITH POSITIVE OUTCOMES INCLUDE:

TRIGEMINAL NEURALGIA; BELL'S Palsy; FAILURE TO THRIVE; DIABETIC NEUROPATHY; PAIN CONTROL IN LATE STAGE CANCER; HEART RATE VARIABILITY; EYE PROBLEMS; HEPATITIS; MALE INFERTILITY; SLEEP DISTURBANCES; ANOREXIA; CANCER IN THE GERSON THERAPY -USED MOST SUCCESSFULLY FOR OVARIAN CANCER AND MELANOMA, AND IN DOGS WITH VARIOUS TUMOURS; REVERSAL OF PRE-CANCER -BRONCHIAL SQUAMOUS METAPLASIA- IN SMOKERS' LUNGS; **NORMALISATION OF ELEVATED LIVER ENZYMES;** **CHRONIC FATIGUE SYNDROME;** **CEREBRAL ATAXIA;** **DYSARTHRIA AND PARAESTHESIAS;** MIGRAINE; **INTRACTABLE SEIZURES;** NITROUS OXIDE GAS POISONING LEADING TO DYSARTHRIA AND **LIMB PARALYSIS;** ANAPHYLACTIC SHOCK; AUTISM; ECZEMA; MULTIPLE SCLEROSIS.....
YET, VERY FEW DOCTORS ARE AWARE OF THIS KNOWLEDGE AND RESEARCH, OR USE IT.

WHY SHOULD VITAMIN B12 IMPACT ON SUCH A VARIETY OF MEDICAL CONDITIONS?

BECAUSE VITAMIN B12 IS A CENTRAL REGULATOR OF INFLAMMATION AND OF THE IMMUNE SYSTEM. REFS -

INFLAMMATION AND DEREGULATIONS OF THE NORMAL IMMUNE RESPONSE ARE CENTRALLY IMPLICATED IN EVERYTHING FROM

AUTO-IMMUNE DISEASES TO CANCER, HEART DISEASES, SEPSIS, NEUROLOGICAL PROBLEMS, DIABETES, ALZHEIMERS....ETC. VITAMIN B12 IS ALSO KEY TO PROVISION OF METHYL GROUPS, WHICH ARE USED TO SWITCH GENES OFF AND ON.

WHY MIGHT HIGH DOSE IV B12 MAKE A DIFFERENCE TO CHARLIE GARD'S CONDITION?

IN BRIEF:

CHARLIE HAS NEUROLOGICAL PROBLEMS, SEIZURES:

HIGH DOSE B12 IS EFFECTIVE FOR A NUMBER OF NEUROLOGICAL PROBLEMS, INCLUDING SEIZURES & LIMB PARALYSIS, AND DYSARTHRIA/LOSS OF THE ABILITY TO SPEAK OR ARTICULATE.

CHARLIE HAS A MITOCHONDRIAL ENERGY DEFICIT PROBLEM:

B12 IS CRITICAL TO MITOCHONDRIAL ENERGY PRODUCTION, BECAUSE OF ITS KEY ROLE IN THE KREBS CYCLE.

B12 IS CRITICAL ALSO FOR MITOCHODRIAL REGENERATION.

CHARLIE HAS MUSCLE LOSS/ WASTING.

B12 HAS BEEN USED AS AN ANABOLIC TREATMENT IN INFANTS, AND AS A TREATMENT FOR ANOREXIA, AND MYELOPATHY.

CHARLIE HAS FAILED TO THRIVE.

B12 HAS BEEN USED IN PRE-TERM INFANTS WITH FAILURE TO THRIVE.

CHARLIE IS AT HIGHER RISK OF INFECTIONS AND SEPSIS.

B12 PROTECTS AGAINST & SIGNIFICANTLY DECREASES SEPSIS MORTALITY IN LAB ANIMALS, AND IMPROVES IMMUNE RESPONSES.

THE EXPERIMENTAL TREATMENT PROPOSED FOR CHARLIE GARD IN THE USA IS BASED ON NUCLEOSIDES, BECAUSE NUCLEOSIDES ARE USED IN DNA SYNTHESIS. [THE LOWER AXIAL LIGAND OF VITAMIN B12'S STRUCTURE FAMOUSLY CONTAINS A 5,6'DIMETHYLBENZIMIDAZOLE NUCLEOSIDE/ NUCLEOTIDE. ITS FUNCTION REMAINS MYSTERIOUS]. HOWEVER, IT IS WELL KNOWN THAT

VITAMIN B12 IS ABSOLUTELY ESSENTIAL FOR DNA SYNTHESIS.

THUS, IF YOU GIVE CHARLIE B12 IN HIGH DOSES BY IV, HE MAY IN EFFECT RECEIVE A FORM OF DEOXYRIBONUCLEOSIDE BYPASS TREATMENT.....OR SOMETHING WHICH WILL SUPPORT THAT.

IF DEATH IS THE ONLY ALTERNATIVE, WHAT DO CHARLIE & HIS PARENTS/DOCTORS HAVE TO LOSE BY A TRIAL OF THE ANTI-CYANIDE DOSE OF B12 AS METHYLCOBALAMIN, TITRATED FOR HIS WEIGHT? NOTHING AT ALL.....IT COULD BE DONE IN GOSH, DISCREETLY,

AND IT WOULD CUT RIGHT THROUGH THE CURRENT DEADLOCK OF TRAVEL AND JUDICIARY PROBLEMS, IF HIS DOCTORS ARE WILLING TO GIVE THIS A GO.

PLEASE DO NOT DISMISS THIS LIGHTLY.

JUST FOLLOW THE WEIGHT ADJUSTED B12 [AS METHYLCOBALAMIN] IV PROTOCOL USED BY LAOUTID ET AL., -CF BELOW- IN THE LAST YEAR WITH SUCH A SPECTACULAR AND LIFE SAVING RESULT.

AT A CONCENTRATION OF 25,000mcg per ml, B12 as MeCbl, Charlie would need about 1 gram of MeCbl IV per day, initially. If there were any response within a week or 2, this could then be possibly modified, tapered down.

HERE IS THE LINK AND A BRIEF DESCRIPTION OF WHAT HAPPENED TO THEIR PATIENT. REFERENCES TO ALL THE ABOVE NOTES FOLLOW THIS:

[PDF] Delayed neurologic sequelae following anoxic-anoxia related to nitrous oxide by pipeline mix-up during anesthesia

J Laoutid, N Jbili, L Bibiche, H Kechna, MA Hachimi

This recent paper above, describes a major surgical accident of a 36 yr old lady, who was over exposed to nitrous oxide, an anaesthetic gas known to inactivate B12 enzyme pathways, and which thus has the potential to cause a functional B12 deficiency, even in the absence of negative B12 deficiency tests. A similar accident in the USA in 2002 killed 2 people.

The lady ended up with alarming neurological symptoms within 48 hrs of the accident. She lost the use of all her limbs/ascending paraesthesia. She had dysarthria. She would have continued to deteriorate, but....

It seems, [cf their citation and protocol that they then used], that the doctors had read a paper I published back in 2006, advocating the use of supra-therapeutic doses of B12, for sepsis, septic shock and SIRS, [cf. below] -at the very same dose used for cyanide poisoning treatment, a massive dose, of a different order of magnitude to doses some doctors across the world now use on a regular basis.

I have to say that these doctors were adventurous. They appreciated there was no downside, -a life was at stake, as a similar accident in the US in 2002 killed 2 people- and that B12/HOCbl is supremely safe, after over half a century's experience of this dose in French and other ICUs.

Anyway, the doctors went for broke, and look what happened to this lady in a very short time scale: nothing short of miraculous:

"The duration of surgery was one hour. The awakening was restless and the patient was sedated for 24 hours by midazolam-fentanyl at the ICU. Non contrast cerebral scan was without anomalies. The patient was extubated the next day without neurological deficit. **At the night of the second postoperative day, the patient presented symmetrical paresthesia on the feet, ascending to the trunk, chest and both arms. This was followed by weakness and clumsiness of all limbs, loss of their use and dysarthria, mental status was normal.**

Before any specific therapy, vitamin B12 and homocysteine (HC) was tested. Methylmalonic acid (MMA) was not tested. Cerebrospinal MR Imaging was normal. Delayed neurologic sequelae due to the anoxic- anoxia were suspected and neuropathy secondary to N2O toxicity was evocated too.

Before receiving results of laboratory, we decided to begin a course of vitamin B12 (hydroxocobalamin) injections: 5 g/day.

Biological exams received, two days after, showed normal vitamin B12 at 785 pg/mL (normal 193–982 pg/mL) and normal HC level at 7 µmol/L (normal < 10 µmol/L) what

permitted us to eliminate the diagnosis of nitrous oxide myelopathy.

Amelioration was noted from the second injection, the numbness decreased, so we decided to maintain vitamin B12 therapy 5 grams/day for one week then 5 grams/week for two months. **The patient could walk within five days and she was discharged from the hospital after one week with a light dysarthria. She has fully recovered in two months.** One year later, the patient was healthy without any sequela."

See also:

A scarlet pimpernel for the resolution of inflammation? The role of ...

<https://www.ncbi.nlm.nih.gov/pubmed/16545917>

by C Wheatley - 2006 - Cited by 43 - Related articles

Vitamin B12: the forgotten micronutrient for critical care. - NCBI

<https://www.ncbi.nlm.nih.gov/pubmed/20717016>

by W Manzanares - 2010

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REFERENCES.

Organised in Section headings, thus:

1. HIGH DOSE B12 SAFETY DATA.
2. THE RIGHT FORM OF B12 NEEDED FOR DNA SYNTHESIS IS METHYLCOBALAMIN.
3. EFFECTS OF B12 ON MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION.
4. SAFETY/USE OF B12 IN PRETERM & INFANTS/ NEONATES.
5. MECHANISMS OF B12 IMPACT ON THE BRAIN & CNS.

6. B12 FOR EPILEPSY AND SEIZURES.
7. ANALGESIC POTENTIAL OF VITAMIN B12.
8. WORK DONE ON B12 & THE CNS/BRAIN BY THE ITALIAN NEUROLOGIST, PROFESSOR GIUSEPPE SCALABRINO.
9. B12 CLINICAL IMPACT ON SOME NEUROLOGICAL CONDITIONS.
10. THE RIGHT HIGH DOSE OF B12 IS CRITICAL.
11. B12 AND METHYLATION.
12. PIONEERING USE OF B12 IN GOSH IN THE 1950S.
13. SOME ASSORTED CLINICAL USES OF B12 DATING BACK TO THE EARLY 1950S.

1. HIGH DOSE B12 SAFETY DATA:

SUFFICIENT DATA EXISTS ON THE EXTRAORDINARY CLINICAL SAFETY OF COBALAMINS AT SUPRA-PHYSIOLOGICAL DOSES, AS IN IV HOCBL FOR CYANIDE POISONING, GIVEN ON CONSECUTIVE DAYS IN IV INFUSIONS OF 5 GRAMS. *SEE ALSO SECTION 2. ON USE IN INFANTS.*

Mushett CW, Kelly KL, Boxer GE, et al. Antidotal efficacy of vitamin B12 (hydroxocobalamin) in experimental cyanide poisoning. *Proc Soc Exp Biol Med*. 1952;81:234–7. [[PubMed](#)]

Posner MA, Rodkey FL, Tobey RE. Nitroprusside-induced cyanide poisoning: antidotal effect of hydroxocobalamin. *Anaesthesia*. 1976;44:330–5. [[PubMed](#)]

Yacoub M, Faure H, Morena M, et al. L'intoxication cyanhydrique aiguë. Données actuelles sur le métabolisme du cyanure et le traitement par hydroxocobalamine. *J Europ de Toxicol*. 1974;7:22–9. [[PubMed](#)]

Motin J, Bouletrean P, Rouzious JM. Intoxication cyanhydrique grave traitée avec succès par hydroxocobalamine. *J Med de Strasbourg*. 1970;I: 717–22.

Tassan H, Joyon D, Richard T, et al. Intoxication au cyanure de potassium traitée par l'hydroxocobalamine. *Ann Fr Anesth Reanim*. 1990;9:383–5. [[PubMed](#)]

Brouard A, Blaisot B, Bismuth C. Hydroxocobalamine in cyanide poisoning. *J Toxicol Clin Exp*. 1987;7:155–68. [[PubMed](#)]

Hall AH, Rumack BH. Hydroxocobalamin/sodium thiosulfate as a cyanide antidote. *J Emerg Med*. 1987;5:115–21. [[PubMed](#)]

Forsyth JC, Mueller PD, Becker CE, et al. Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. *Clin Toxicol*. 1993;31:277–94. [[PubMed](#)]

Riou B, Gérard JL, Drieu la Rochelle C, et al. Hemodynamic effects of hydroxocobalamin in conscious dogs. *Anaesthesia*. 1991;74:552–8. [[PubMed](#)]

Riou B, Berdeaux A, Pussard E, Giudicelli JF. Comparison of the hemo-dynamic effects of hydroxocobalamin and cobalt edetate at equipotent cyanide antidotal doses in conscious dogs. *Intensive Care Med*, 1993; 19:26–32.

Forsyth JC, Mueller PD, Becker CE, Osterloh J, Benowitz NL, Rumack BH, Hall AH. Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. *Clin Toxicol* 1993; 31:277–294.

De La Coussaye JE, Houeto P, Sandouk P, Levillain P, Sassine A, Riou B. Pharmacokinetics of hydroxocobalamin in dogs. *J Neurosurg Anesthesiol* 1994; 6:111–115.

Curry SC, Connor DA, Raschke RA. Effect of the cyanide antidote hydroxocobalamin on commonly ordered serum chemistry studies. *Ann Emerg Med* 1994; 24:65–67.

Sauer SW, Keim ME. Hydroxocobalamin: improved public health readiness for cyanide disasters. *Ann Emerg Med* 2001; 37:635–641.

Mégarbane B, Delahaye A, Goldgran-Tolédano D, Baud FJ. Antidotal treatment of cyanide poisoning. *J Chin Med Assoc* 2003; 66:193–203.

Fortin J-L, Ruttimann M, Domanski L, Kowalski JJ. Hydroxocobalamin: treatment for smoke inhalation-associated cyanide poisoning. Meeting the needs of fire victims. *JEMS* 2004; 29:suppl 18–21.

Borron S, Mégarbane B, Baud FJ. Hydroxocobalamin is an effective antidote in severe acute cyanide poisoning in man. Abstract. *Int J Toxicol* 2004; 23:399–400.

Borron SW, Barriot P, Imbert M, Baud FJ. Hydroxocobalamin for empiric treatment of smoke inhalation-associated cyanide poisoning: results of a prospective study in the pre-hospital setting. Abstract 275. *Ann Emerg Med* 2005; S77.

von Landenberg F, Stonerook M, Judge M, Borron SW. Efficacy of hydroxocobalamin in a canine model of cyanide poisoning: a pilot study. Abstract. *Clin Tox* 2005; 43:692.

Fortin J-L, Ruttimann M, Domanski L, Kowalski JJ. Hydroxocobalamin for smoke inhalation-associated cyanide poisoning: 8 years of experience in the Paris Fire Brigade. Abstract. *Prehosp Emerg Care* 2006; 10:142.

Borron WS, Stonerook M, Reid F. Efficacy of Hydroxocobalamin for the Treatment of Acute Cyanide Poisoning in Adult Beagle Dogs. *Clinical Toxicology*, 44:5–15.

Clinical Toxicology, 44:17–28, 2006

Georg Golor and Karl Ludwig Rost

Andreas Kovar

Safety of Hydroxocobalamin in Healthy Volunteers in a Randomized, Placebo-Controlled Study

Wolfgang Uhl and Arno Nolting

Merck KGaA, Darmstadt, Germany

Uhl W, Nolting A, Golor G, Rost KL, Kovar A. Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study. *Clin Toxicol (Phila)*. 2006;44(suppl 1): 17-28.

Dart RC. Hydroxocobalamin for acute cyanide poisoning: new data from preclinical and clinical studies; new results from the prehospital emergency setting. *Clin Toxicol (Phila)*. 2006; 44(suppl 1):1-3.

Shepherd G, Velez L. Role of hydroxocobalamin in acute cyanide poisoning. *Ann Pharmacother*. 2008; 42(5): 661-669.

Utility and outcomes of hydroxocobalamin use in smoke inhalation patients

L Nguyen, A Afshari, SA Kahn, S McGrane, B Summitt - Burns, 2016

... It directly chelates cyanide to form **cyanocobalamin** (Vitamin B12), which is renally excreted and nontoxic [8]. Several studies have demonstrated its safety for prehospital use in the management of acute cyanide poisoning caused by smoke inhalation [9] and [10]. ...

↑ (en) A. Chan, M. Balasubramanian, W. Blackledge, O.M. Mohammad, L. Alvarez, G.R. Boss et T.D. Bigby, « Cobinamide is superior to other treatments in a mouse model of cyanide poisoning », *Clin. Toxicol. (Phila.)*, vol. 48, no 7, août 2010, p. 709-917 ([lire en ligne \[archive\]](#)) [PMID 20704457 \[archive\]](#)

↑ (en) M. Brenner, S.B. Mahon, J. Lee, J. Kim, D. Mukai, S. Goodman, K.A. Kreuter, R. Ahdout, O. Mohammad, V.S. Sharma, W. Blackledge, G.R. Boss,

« Comparison of cobinamide to hydroxocobalamin in reversing cyanide physiologic effects in rabbits using diffuse optical spectroscopy monitoring », *J. Biomed. Opt.*, vol. 15, no 1, janvier-février 2010, p. 017001 ([lire en ligne \[archive\]](#)) PMID 20210475 [\[archive\]](#)

[PDF] [Delayed neurologic sequelae following anoxic-anoxia related to nitrous oxide by pipeline mix-up during anesthesia](#)

J Laoutid, N Jbili, L Bibiche, H Kechna, MA Hachimi

2. THE RIGHT FORM OF B12 NEEDED FOR DNA SYNTHESIS IS METHYLCOBALAMIN:

Defective DNA Synthesis in Human Megaloblastic Bone Marrow ...

www.bloodjournal.org/content/41/2/299

by MB Van Der Weyden - 1973

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3. EFFECTS OF B12 ON MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION:

Effect of vitamins C, P, B-12 and folic acid on respiration and oxidative phosphorylation of the mitochondria of the liver of rats in some forms of damage.

Foreign Title : Vlijanie vitaminov, C, P, B-12 i folievoj kisloty na dyhanie i okislitel'noe fosforilirovanie mitohondrij peceni krys pri nekotoryh ee povrezdenijah.

Author(s) : KOKAROVCEVA, M. G.

Journal article : [Vitaminy v eksperim. i klinike. Resp. mezved. sb.](#) 1970 No.2 pp.102-109

Abstract : Rats weighing between 180 and 200 g were given subcutaneous injections of CC14 for 7 days or had part of the liver removed; they were given daily 50 mg per kg galascorbin

subcutaneously, 5 or 50 μg per kg vitamin B12 intramuscularly or 1 mg per kg folic acid intramuscularly or all 3 for 7 days. Galascorbin increased the oxidizing and phosphorylating capacity of mitochondria of the liver damaged by CC14.

Vitamin B-12 had more effect on oxidative phosphorylation of the regenerating liver. A combination of vitamin B-12, folic acid and galascorbin increased oxidizing and phosphorylating capacity of the mitochondria in the regenerating liver and in that damaged by CC14. (From Referativ. Z.)-M. C.

Record Number : 19711404987

Language of text : Russian

Language of summary : Russian

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4. SAFETY/USE OF B12 IN PRETERM & INFANTS/NEONATES:

[New combination of amino acids and cobamamide/ AdoCbl. Therapeutic use in premature infants].

[Article in Italian]

Murialdo P, Tondo U.

PMID: 5037198

Lyon Med. 1966 Apr 3;215(14):995-8.

[Clinical trials of a non-steroid protein anabolic agent in premature infants].

[Article in French]

Nivelon JL, Badinand P.

PMID: 5948903

Kinderarztl Prax. 1965 Jul;33(7):299-302.

[On the effect of parentally and orally administered vitamin B 12 on body weight increase in premature infants].

[Article in German]

Sillanpää M.

Clin Ter. 1970 Dec 31;55(6):549-56.

[Clinical use of 5,6-dimethylbenzimidazolo-5-desoxyadenosylcobamide coenzyme (cobamide) in the premature infant].

[Article in Italian]
Gaioni L, Giraldi L, Bertelli R.
PMID: 5515937

Clin Pediatr (Bologna). 1967 Sep;49(9):489-95.

[Clinical remarks on a group of premature infants treated with a physiologic anabolizing agent: Corinoidasi].

[Article in Italian]
Gualtieri V.
PMID: 5615929

Lille Med. 1966 May;11(5):616-8.

[Clinical trial of a nonsteroid anabolic agent in pediatrics: Heraclene].

[Article in French]
Fontaine G, Farriaux JP.
PMID: 5940688

Bord Med. 1972 Sep;5(14):1751-6.

**[Use of Indusil T in pediatrics].
[Adenosylcobalamin for injection].**

[Article in French]
Battin J, Azanza X.
PMID: 5082535

Bord Med. 1972 Mar;5(6):725-6.

[Use of cobanzyme/AdoCbl in the newborn in a maternity hospital department (50 cases)].

[Article in French]
Peborde J, Kremer A.
PMID: 5054774

Przegl Lek. 1969;25(10):723-5.

[Xobalin--a new anabolic drug from the coenzyme group].

[Article in Polish]
Stopczyk K.
PMID: 5355720

5. MECHANISMS OF B12 IMPACT ON THE BRAIN & CNS:

Neurosci Lett. 2011 May 20;495(3):201-4. doi: 10.1016/j.neulet.

2011.03.065. Epub 2011 Mar 30. **Akt/mammalian target of**

rapamycin signaling pathway regulates neurite outgrowth in cerebellar granule neurons stimulated by methylcobalamin.

Okada K1, Tanaka H, Temporin K, Okamoto M, Kuroda Y, Moritomo H, Murase T, Yoshikawa H

[Akt/mammalian target of rapamycin signaling pathway ...](#)

www.ncbi.nlm.nih.gov/..

by K Okada - 2011

J Neurol Sci. 1994 Apr;122(2):140-3.

Ultra-high dose methylcobalamin promotes nerve regeneration in experimental acrylamide neuropathy.

Watanabe T1, Kaji R, Oka N, Bara W, Kimura J.

[Ultra-high dose methylcobalamin promotes nerve ...](#)

www.ncbi.nlm.nih.gov/...

by T Watanabe - 1994

Exp Neurol. 2010 Apr;222(2):191-203. doi: 10.1016/j.expneurol.

2009.12.017. Epub 2010 Jan 4. **Methylcobalamin**

increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat

sciatic nerve injury model.

Okada K1, Tanaka H, Temporin K, Okamoto M, Kuroda Y, Moritomo H, Murase T, Yoshikawa H.

Biochem Biophys Res Commun. 2014 Jan 17;443(3):871-5. doi: 10.1016/j.bbrc.2013.12.056. Epub 2013 Dec 14.

Methylcobalamin promotes proliferation and migration and inhibits apoptosis of C2C12 cells via the Erk1/2 signaling pathway.

Okamoto M1, Tanaka H2, Okada K1, Kuroda Y3, Nishimoto S1, Murase T1, Yoshikawa H1. Tanaka H1.

Brain Nerve. 2013 Sep;65(9):1077-82.

[Old or new medicine? Vitamin B12 and peripheral nerve neuropathy].
[Article in Japanese]

6. ANALGESIC POTENTIAL OF VITAMIN B12:

Neural Plast. 2013; 2013: 424651.

Published online 2013 Dec 26. doi: [10.1155/2013/424651](https://doi.org/10.1155/2013/424651)

PMCID: PMC3888748

Methylcobalamin: A Potential Vitamin of Pain Killer

Ming Zhang, Wenjuan Han, Sanjue Hu, and Hui Xu*

Methylcobalamin: A Potential Vitamin of Pain Killer

www.ncbi.nlm.nih.gov/..

by M Zhang - 2013 -

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7. WORK DONE ON B12 & THE CNS/BRAIN BY THE ITALIAN NEUROLOGIST, PROFESSOR GIUSEPPE SCALABRINO:

High **tumor necrosis factor**- α in levels in cerebrospinal fluid of **cobalamin**-deficient patients

G **Scalabrino**, M Carpo, F Bamonti... - Annals of ..., 2004 - Wiley Online Library

Abstract We studied 14 patients with neurological manifestations of subacute combined degeneration (SCD) and 40 control patients not cobalamin (Cbl)-deficient. The cerebrospinal fluid (CSF) markers of Cbl deficiency (Cbl and total homocysteine [tHCYS])

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Experimental and clinical evidence of the role of cytokines and growth **factors** in the pathogenesis of acquired **cobalamin**-deficient leukoneuropathy

G **Scalabrino**, D Veber, E Mutti - Brain research reviews, 2008 - Elsevier

Our experimental and clinical studies have highlighted the non-coenzyme functions of cobalamin (Cbl; vitamin B12). The neuropathy of the rat central nervous system (CNS) due to Cbl deficiency is associated with increases in CNS tissue and/or cerebrospinal fluid (CSF)

Cited by 52Related articlesAll 6 versionsCiteSave
[PDF] researchgate.net

Myelinolytic lesions in spinal cord
of **cobalamin**-deficient rats are TNF- α -
mediated

..., A Morabito, G Pravettoni, G Tredici, G **Scalabrino** - The FASEB journal, 1999 -
FASEB

Abstract Repeated intracerebroventricular (icv) microinjection of tumor necrosis
factor- α
(TNF- α) into normal rats causes intramyelin and interstitial edema in the white
matter of the
spinal cord (SC). This response is identical to that observed in the SC white matter
of rats

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[PDF] researchgate.net

Epidermal growth **factor** as a local mediator
of the neurotrophic action of vitamin B12
(**cobalamin**) in the rat central nervous
systemG **Scalabrino**, G Nicolini, FR
Buccellato, M Peracchi... - The FASEB
journal, 1999 - FASEB

Abstract We have recently demonstrated that
the myelinolytic lesions in the spinal cord
(SC) of rats made deficient in vitamin B 12
(cobalamin)(Cbl) through total gastrectomy
(TG) are tumor necrosis factor- α (TNF- α)-

mediated. We investigate whether or not permanent Cbl

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[HTML] Association between **tumor necrosis factor- α** and disease progression in patients with multiple sclerosis

MK Sharief, R Hentges - New England Journal of Medicine, 1991 - Mass Medical Soc

... 37. Hofman FM, Hinton **DR**, Johnson K, Merrill JE. regulation of inflammatory and immunologic

responses: the capacity of α -melanocyte-stimulating hormone to inhibit **tumor necrosis factor**

and IL ... (2016) Risk of multiple sclerosis during **tumour necrosis factor** inhibitor treatment ...

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Loss of epidermal growth **factor** regulation by **cobalamin** in multiple sclerosis

G **Scalabrino**, D Galimberti, E Mutti, D Scalabrini... - Brain research, 2010 - Elsevier

We investigated whether the physiological regulation of cerebrospinal fluid (CSF) levels of

tumor necrosis factor (TNF)- α , epidermal growth factor (EGF), and nerve growth factor (NGF)

by cobalamin (Cbl) that is observed in rat and human central nervous system (CNS) is

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[\[HTML\] Vitamin–regulated cytokines and growth factors in the CNS and elsewhere](#)

[G Scalabrino](#) - Journal of neurochemistry, 2009 - Wiley Online Library

Abstract There is a growing awareness that natural vitamins (with the only exception of pantothenic acid) positively or negatively modulate the synthesis of some cytokines and growth factors in the CNS, and various mammalian cells and organs. As natural vitamins are

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[The octapeptide repeat PrPC region and cobalamin–deficient polyneuropathy of the rat](#)

[G Scalabrino](#), [E Mutti](#), [D Veber...](#) - Muscle & ..., 2011 - Wiley Online Library

Abstract Introduction: Cobalamin (Cbl) deficiency affects the peripheral nervous system

(PNS) morphologically and functionally. We investigated whether the octapeptide repeat

(OR) region of prion protein (PrP C)(which is claimed to have myelinotrophic properties) is

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[Are PrP C s involved in some human myelin diseases? Relating experimental studies to human pathology](#)

[D Veber](#), [G Scalabrino](#) - Journal of the neurological sciences, 2015 - Elsevier

Abstract We have experimentally demonstrated that cobalamin (Cbl) deficiency increases

normal cellular prion (PrP C) levels in rat spinal cord (SC) and cerebrospinal fluid (CSF),
and decreases PrP C-mRNA levels in rat SC.

Cobalamin (vitamin B 12) regulation of PrP C, PrP C-mRNA and copper levels in rat central nervous system

G **Scalabrino**, D Veber, E Mutti, [A Calligaro...](#) - *Experimental ...*, 2012 - Elsevier

The pathogenesis of cobalamin (Cbl)-deficient (Cbl-D) neuropathy is not clear, nor is the

role of prions (PrPC) in myelin maintenance. However, as it is known that Cbl deficiency

damages myelin by increasing tumor necrosis factor (TNF)- α and decreasing epidermal

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Cobalamin deficiency-induced down-regulation of p75-immunoreactive cell levels in rat central nervous system

..., E Gammella, L Tacchini, L Aloe, G **Scalabrino** - *Brain research*, 2007 - Elsevier

We investigated immunoreactivity for p75 neurotrophin receptor (NTR) in the spinal cord

white matter and septum of rats made cobalamin-deficient (Cbl-D) by means of total

gastrectomy or a Cbl-D diet. Cbl deficiency down-regulates p75NTR-immunoreactive cell

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The octapeptide repeat PrPC region and cobalamin-deficient polyneuropathy of the rat

G **Scalabrino**, E Mutti, D Veber... - ... & **nerve**, 2011 - Wiley Online Library

Abstract Introduction: Cobalamin (Cbl) deficiency affects the peripheral nervous system

(PNS) morphologically and functionally. We investigated whether the octapeptide repeat

(OR) region of prion protein (PrP C)(which is claimed to have myelinotropic properties) is

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G **Scalabrino** - Journal of neurochemistry, 2009 - Wiley Online Library

Abstract There is a growing awareness that natural vitamins (with the only exception of

pantothenic acid) positively or negatively modulate the synthesis of some cytokines and

growth factors in the CNS, and various mammalian cells and organs. As natural vitamins are

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Increased levels of the CD40: CD40 ligand dyad in the cerebrospinal fluid of rats with vitamin B 12 (**cobalamin**)-deficient central neuropathy

..., G Tredici, CA La Porta, G **Scalabrino** - Journal of ..., 2006 - Elsevier

The levels of the soluble (s) CD40: sCD40 ligand (L) dyad, which belongs to the tumor

necrosis factor (TNF)- α : TNF- α -receptor superfamily, are significantly increased in the

cerebrospinal fluid (CSF), but not the serum of cobalamin (Cbl)-deficient (Cbl-D) rats. They

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Myelin damage due to local quantitative abnormalities in normal prion levels: evidence

from subacute combined degeneration and multiple sclerosis

G **Scalabrino**, D Veber - Journal of neurology, 2014 - Springer

Abstract Cobalamin (Cbl) deficiency causes an imbalance in some cytokines and growth

factors in the central nervous system and peripheral nervous system (PNS) of the rat, and in

the serum and cerebrospinal fluid (CSF) of adult Cbl-deficient (Cbl-D) patients. It is

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Regulation of the ferritin H subunit by vitamin B12 (**cobalamin**) in rat spinal cord

..., [P Santambrogio](#), G **Scalabrino** - Journal of ..., 2002 - Wiley Online Library

Abstract Cobalamin-deficient (Cbl-D) central neuropathy is a pure myelinolytic disease, in

which gliosis is also observed. Iron is abundant in the mammalian central nervous system,

where it is required for various essential functions including myelinogenesis. It is

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Neuropsychiatric disorders caused by **cobalamin** deficiency in the absence of anemia or macrocytosis

J Lindenbaum, EB Healton, DG Savage... - ... England Journal of ..., 1988 - Mass Medical Soc

... Address reprint requests to **Dr.** Lindenbaum at Columbia–Presbyterian Medical Center, New

York, NY ... The **nervous** symptoms in pernicious anemia: an analysis of one hundred and fifty ...

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Cobalamin deficiency-induced changes in magnetic resonance imaging of cerebrospinal fluid volume in the cervical tract in the rat

..., L Sironi, U Guerrini, E Gianazza, G **Scalabrino** - Neuroscience ..., 2008 - Elsevier

We wanted to verify the magnetic resonance imaging (MRI) abnormalities that occur in the

central nervous system (CNS) of cobalamin-deficient (Cbl-D) rats. The rats were made Cbl-D

by means of total gastrectomy or feeding a Cbl-D diet. MR images of the cervical tract of the

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Low levels of **cobalamin**, epidermal **growth factor**, and normal prions in multiple sclerosis spinal cord

G **Scalabrino**, D Veber, R De **Giuseppe**, F Roncaroli - Neuroscience, 2015 - Elsevier

Cobalamin deficiency-induced down-regulation of p75-immunoreactive cell levels in rat central nervous system

..., E Gammella, L Tacchini, L Aloe, G **Scalabrino** - Brain research, 2007 - Elsevier

We investigated immunoreactivity for p75 neurotrophin receptor (NTR) in the spinal cord

white matter and septum of rats made cobalamin-deficient (Cbl-D) by means of total

gastrectomy or a Cbl-D diet. Cbl deficiency down-regulates p75NTR-immunoreactive cell

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Cobalamin (vitamin B 12) regulation of PrP C, PrP C-mRNA and copper levels in rat central nervous system

G Scalabrino, D Veber, E Mutti, A Calligaro... - Experimental ..., 2012 - Elsevier

The pathogenesis of cobalamin (Cbl)-deficient (Cbl-D) neuropathy is not clear, nor is the

role of prions (PrPC) in myelin maintenance. However, as it is known that Cbl deficiency

damages myelin by increasing tumor necrosis factor (TNF)- α and decreasing epidermal

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Relationships between **cobalamin**, epidermal growth factor, and normal prions in the myelin maintenance of central nervous system

G Scalabrino, D Veber, G Tredici - ... journal of biochemistry & cell biology, 2014 - Elsevier

Abstract Cobalamin (Cbl), epidermal growth factor (EGF), and prions (PrPs) are key

molecules for myelin maintenance in the central and peripheral nervous systems.

Cbl and

EGF increase normal prion (PrP C) synthesis and PrP C levels in rat spinal cord (SC) and

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Cobalamin deficiency-induced changes in magnetic resonance imaging of cerebrospinal fluid volume in the cervical tract in the rat

..., L Sironi, U Guerrini, E Gianazza, G **Scalabrino** - Neuroscience ..., 2008 - Elsevier

We wanted to verify the magnetic resonance imaging (MRI) abnormalities that occur in the

central nervous system (CNS) of cobalamin-deficient (Cbl-D) rats. The rats were made Cbl-D

by means of total gastrectomy or feeding a Cbl-D diet. MR images of the cervical tract of the

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The octapeptide repeat PrPC region
and **cobalamin**-deficient polyneuropathy of
the rat

G **Scalabrino**, E Mutti, D Veber... - Muscle & ..., 2011 - Wiley Online Library

Abstract Introduction: Cobalamin (Cbl) deficiency affects the peripheral nervous system

(PNS) morphologically and functionally. We investigated whether the octapeptide repeat

(OR) region of prion protein (PrP C)(which is claimed to have myelinotrophic properties) is

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High tumor necrosis factor- α in levels in
cerebrospinal fluid of **cobalamin**-deficient
patients

G **Scalabrino**, M Carpo, F Bamonti... - Annals of ..., 2004 - Wiley Online Library

Abstract We studied 14 patients with neurological manifestations of subacute combined

degeneration (SCD) and 40 control patients not cobalamin (Cbl)-deficient. The cerebrospinal fluid (CSF) markers of Cbl deficiency (Cbl and total homocysteine [tHCYS])

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[HTML] Clarifying the Molecular Basis of **Cobalamin** (Vitamin B12) Neurotrophism

G **Scalabrino** - Journal of Headache & Pain Management, 2016 - headache.imedpub.com

I have spent more than twenty-five years clarifying the molecular basis of the well-known neurotrophic effect of cobalamin (Cbl), more commonly known as vitamin B12. My studies have mainly concentrated on rat spinal cord (SC), the part of the central nervous system

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Normal prions as a new target of **cobalamin** (vitamin B12) in rat central nervous system

G **Scalabrino**, D Veber - Clinical chemistry and laboratory medicine, 2013 - degruyter.com

Abstract The pathogenesis of cobalamin (Cbl)-deficient (Cbl-D) neuropathy and the role of normal prions (PrP^{cs}) in myelin maintenance are both subjects of debate. We have demonstrated that Cbl deficiency damages myelin by increasing tumor necrosis factor (TNF)-

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Neuroprotective functions of prion protein

X **Roucou**, M Gains, **AC LeBlanc** - Journal of neuroscience ..., 2004 - Wiley Online Library

... Borchelt **DR**, Rogers M, Stahl N, Telling G, Prusiner SB. 1993. Release of the cellular prion protein from cultured cells after loss of its glycoinositol phospholipid anchor. Glycobiology 3: 319–329. ...

Brown **DR**. 2001. Prion and prejudice: normal protein and the synapse. ...

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Low levels of **cobalamin**, epidermal growth factor, and normal prions in multiple sclerosis spinal cord

G Scalabrino, D Veber, R De Giuseppe, F Roncaroli - Neuroscience, 2015 - Elsevier

Abstract We have previously demonstrated that multiple sclerosis (MS) patients have

abnormal cerebrospinal fluid (CSF) levels of the key myelin-related molecules cobalamin

(Cbl), epidermal growth factor (EGF), and normal cellular prions (PrP C s), thus confirming

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8. B12 CLINICAL IMPACT ON SOME NEUROLOGICAL CONDITIONS:

April 23, 2015

- Poster Session VII

- Neuromuscular Disease: Clinical Trials and Treatment

Ultra-high dose methylcobalamin (E0302) prolongs survival of ALS: Report of 7 years' randomised double-blind, phase 3 clinical trial(ClinicalTrials.gov NCT00444613) (P7.060)

Ryuji Kaji⁵, Shigeki Kuzuhara⁶, Yasuo Iwasaki⁷, Koichi Okamoto², Masanori Nakagawa⁴, Takashi Imai⁸, Takao Takase¹, Hiroki Shimizu¹ and Kunio Tashiro³

ABSTRACT

OBJECTIVE: To investigate the efficacy and safety of ultra-high dose (25mg or 50mg i.m. twice weekly) of methylcobalamin compared with placebo for amyotrophic lateral sclerosis (ALS) patients. **BACKGROUD:** High-dose methylcobalamin showed neuroprotective effects in acrylamide neuropathy (Watanabe et al.1994) and the increase in compound muscle action potential in a trial for ALS (Kaji et al.1998). **DESIGN/METHODS:** Patients (373) who were diagnosed with definite, probable, or

probable-laboratory-supported ALS by revised El Escorial criteria were enrolled in this study. Those with [percent]FVC less than 60[percent] and the disease duration more than 3 years were excluded. Patients were randomly assigned to receive placebo, 25mg, or 50mg methylcobalamin i.m. twice weekly for 182weeks. Primary endpoints were event-free survival (time until death, TIPPV or all-day NIPPV) and ALS Functional Rating Scale-Revised (ALSFRS-R) changes. RESULTS: Of 373 patients, 370 (placebo 123, 25mg 124, 50mg 123) constituted the full analysis set. In both endpoints, there was no statistical significance in the comparison for the two dose response contrasts (linear and saturate hypothesis). For the patients who were given diagnosis of ALS within 12months after the onset (placebo 48, 25mg 54, 50mg 42), the event-free survival was prolonged in a dose-dependent manner (P=0.010, hazard ratio [95[percent]CI] vs 25mg, 50mg were 0.640 [0.377, 1.085], 0.498 [0.267, 0.929], respectively) and ALSFRS-R changes were smaller in active groups (P=0.003) than in placebo. No adverse events of particular concern were noted. DISCUSSION: The diagnosis of ALS with revised El Escorial criteria is often delayed but newly-devised Awaji criteria have enabled earlier diagnosis. Patients are less likely to benefit from ultra-high dose methylcobalamin treatment if more than 2 to 3 years have passed since the onset of ALS.

CONCLUSION: The present study demonstrated for the first time that ultra-high dose methylcobalamin can significantly prolong survival and retard progression in ALS *if administered early*. [MY ITALICS!]

SEE ALSO:

About Methyl B12 | ALS Worldwide

alsworldwide.org/care-and-support/article/about-methyl-b12

1

HERE'S ANOTHER TRIAL REPORT ON MECBL FOR ANOTHER NEUROLOGICAL PROBLEM, BELL'S PALSY.

NOTE HOW STEROIDS SIGNIFICANTLY INTERFERE WITH RECOVERY....

[Methods Find Exp Clin Pharmacol.](#) 1995 Oct;17(8):539-4

Methylcobalamin treatment of Bell's palsy.

[Jalaludin MA](#)¹.

Author information

Abstract

Sixty patients with Bell's palsy were included in an open randomized trial. Patients were assigned into three treatment groups: **steroid (group 1), methylcobalamin (group 2) and methylcobalamin + steroid (group 3)**. Comparison between the three groups was based on the number of days needed to attain full recovery, facial nerve scores, and improvement of concomitant symptoms. **The time required for complete recovery of facial nerve function was significantly shorter ($p < 0.001$) in the methylcobalamin (mean of 1.95 ± 0.51 weeks) and methylcobalamin plus steroid groups (mean of 2.05 ± 1.23 weeks) than in the steroid group (mean of 9.60 ± 7.79 weeks).** The facial nerve score after 1-3 weeks of treatment was significantly more severe ($p < 0.001$) in the steroid group compared to the methylcobalamin and methylcobalamin plus steroid groups. **The improvement of concomitant symptoms was better in the methylcobalamin treated groups than the group treated with steroid alone.**

HERE'S A REPORT ON EFFECTS OF MECBL COMBINED WITH ALA IN DIABETIC PERIPHERAL NEUROPATHY:

[Diabetes Res Clin Pract.](#) 2013 Aug;101(2):99-105. doi: 10.1016/j.diabres.2013.03.033. Epub 2013 May 9.

Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy.

[Xu Q](#)¹, [Pan J](#), [Yu J](#), [Liu X](#), [Liu L](#), [Zuo X](#), [Wu P](#), [Deng H](#), [Zhang J](#), [Ji A](#).

Author information

Abstract

AIMS:

To compare the efficacy and safety of daily lipoic acid (300-600 mg i.v.) plus methylcobalamin (500-1000 mg i.v. or im.) (LA-MC) with that of methylcobalamin alone (MC) on diabetic peripheral neuropathy (DPN).

METHODS:

Electronic database were searched for studies published up to November 1, 2012 and study quality was assessed in duplicate. A random or a fixed effect model was used to analyse outcomes which were expressed as risk ratios (RRs) or mean difference (MD). I(2) statistic was used to assess heterogeneity.

RESULTS:

Seventeen studies were included. Combined data from all studies showed that the LA-MC combination therapy was significantly superior to MC monotherapy (RR=1.47; 95% CI: 1.37-1.58). Superiority of the LA-MC combination was shown in nerve conduction velocity (NCV) with WMDs of 6.89 (95% CI: 4.24-9.73) for

median motor nerve conduction velocity (MNCV), 5.24 (4.14-6.34) for median sensory nerve conduction velocity (SNCV), 4.34 (3.03-5.64) for peroneal MNCV, and 4.53 (3.2-5.85) for peroneal SNCV. There were no serious adverse events associated with treatment.

CONCLUSIONS:

The results of the meta-analysis show that treatment with LA-MC for 2-4 weeks is associated with better outcomes in NCV and neuropathic symptoms relative to MC treatment. However larger well-designed studies are required to confirm this conclusion.

THESE 2 POP ARTICLE LINKS ARE OF RELATED INTEREST:

Methylcobalamin: A Potential Breakthrough in Neurological Disease

www.prohealth.com › Research Library › Latest News & Research

Methylcobalamin Protects the Brain from Glutamate Damage ...

www.naturalnews.com/029309_met

%%%

9. THE RIGHT HIGH DOSE OF B12 IS CRITICAL:

These 2 references below show the increased therapeutic effect of *increasing* doses of high-dose cobalamin/ methylcobalamin:

At a low high dose, MeCbl has no effect on peripheral neuropathy. However, at a *sixfold higher dose* MeCbl reverses peripheral neuropathy in rats:

J Neurol Sci. 1994 Apr;122(2):140-3.

Ultra-high dose methylcobalamin promotes nerve regeneration

in experimental acrylamide neuropathy.

Watanabe T1, Kaji R, Oka N, Bara W, Kimura J.

Ultra-high dose methylcobalamin promotes nerve ...

www.ncbi.nlm.nih.gov/...

by T Watanabe - 1994

Similarly, in a mouse model of sepsis, increasing the dose of cobalamin and using the active form, methylcobalamin, increases survival in sepsis:

Mediators Inflamm. 2013;2013:741804. doi: 10.1155/2013/741804. Epub 2013 May 28. **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 β , TNF- α , IL-6, and HMGB1 expression.

Sampaio AL1, Dalli J, Brancaleone V, D'Acquisto F, Perretti M, Wheatley C. **Follow this link:** Biphasic modulation of NOS expression, protein and nitrite ...

www.ncbi.nlm.nih.gov/...

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10. B12 FOR EPILEPSY TREATMENT:



July 2005
Pages 1147–1148

Intractable Epilepsy as the Presentation of Vitamin B₁₂ Deficiency in the Absence of Macrocytic Anemia

Authors Meng Lee, et al.

First published: 30 June 2005 [Full publication history](#)

DOI: 10.1111/j.1528-1167.2005.66204.x [View/save citation](#)

Address correspondence and reprint requests to Dr. C.-M. Chen at Second Department of Neurology, Chang Gung Memorial Hospital, 199, Tung Hwa North Road, Taipei, Taiwan. E-mail: cmchen@adm.cgmh.org.tw

Vitamin B₁₂ deficiency often produces hematologic and neurologic deficits including macrocytic anemia, myelopathy, neuropathy, or mental abnormalities, which may become irreversible if not promptly treated (1–3). The diagnosis of vitamin B₁₂ deficiency can be difficult when the typical macrocytic anemia is absent (1). A few cases with seizures as the manifestation of vitamin B₁₂ deficiency have been reported, and macrocytic anemia also was noted in these patients (4,5). We report a patient with vitamin B₁₂ deficiency presenting as intractable epilepsy in the absence of macrocytic anemia. **The seizure attacks and all other symptoms/signs of vitamin B₁₂ deficiency resolved after an intramuscular administration of cobalamin.**

CASE REPORT

A 76-year-old man began to experience frequent generalized tonic–clonic seizures 3 years before visiting our hospital. The frequency

was ~3–5 times monthly. The initial investigations in a local hospital were normal except for mild normocytic anemia. He was diagnosed with epilepsy of an unknown etiology, and phenytoin (PHT), 300 mg once daily, was given to prevent seizure recurrence. In spite of a plasma drug concentration of 15.4 µg/ml (target concentration, 10–20 µg/ml), the frequency of seizures was still ~3–5 times monthly. Valproate (VPA), 500 mg twice daily, was added, but without an improvement in seizure control. One year later, he felt numbness at the plantar area of both feet. The abnormal sensation ascended to the knees within a few months. Because of these problems, he was admitted to our hospital in March 2003.

The neurologic examination showed an alert consciousness. The Mini-Mental Status Examination (MMSE) revealed a mild cognitive impairment (score, 22 of 30; normal score, >24). The muscle strength was full. Deep tendon reflexes (DTRs) were absent at the knees and the ankles. Plantar responses were flexor bilaterally. Sensation to pinprick was decreased throughout the legs. Sensory ataxia was noted.

The laboratory survey showed a low cobalamin serum level of 55 pg/ml (normal, 160–970 pg/ml). Homocysteine was elevated to 175.5 µM (normal, <12 µM). Normocytic anemia was present, with a hemoglobin of 11.0 g/dl (normal, 13.5–17.5 g/dl), a hematocrit of 33% (normal, 41–53%), a mean corpuscular volume of 96.5 fl (normal, 80–100 fl), and a slightly decreased reticulocyte count of 0.6% (normal, 0.5–1.9%). The anti-gastric-parietal-cell antibody was positive. The gastric biopsy showed atrophic gastritis. The EEG showed generalized continuous slow waves (4–6 Hz) over bilateral hemispheres. The brain MRI was normal. The nerve-conduction study (NCS) showed sensory-predominant polyneuropathy with mixed demyelinating changes and axonal degeneration. This was compatible with polyneuropathy caused by a vitamin B₁₂ deficiency or PHT toxicity. The cervical and thoracic MRI demonstrated a hyperintensity signal at the bilateral fasciculus gracilis, which was compatible with subacute combined degeneration.

Initial treatment consisted of daily intramuscular injections of 1 mg of hydroxycobalamin in the first week, followed by weekly injections for 1 month. The maintenance schedule was a monthly injection of 1 mg. The cobalamin has been administered for 22 months. The

hemoglobin, hematocrit, reticulocyte count, and homocysteine after the cobalamin treatment have all returned to a normal level (13.3 g/dl, 42%, 0.8%, and 8.6 μ M, respectively).

The patient had the last seizure attack during the admission before the replacement therapy, and no further seizure was noted after the first dose of hydroxycobalamin. The numbness in the legs improved gradually, and the gait became normal by the end of 6 months of cobalamin treatment. The NCS 3 months later was normal, except for an absence of bilateral H-reflexes. The MMSE 1 year later was normal (score, 29/30). The EEG 1 year later was normal, and PHT and VPA were thereafter tapered and stopped 2 months after the EEG study. **Since then, he has been seizure free for 8 months.**

DISCUSSION

The patient presented herein displayed intractable seizures, polyneuropathy, myelopathy, and normocytic anemia, all of which resolved gradually after hydroxocobalamin replacement therapy. Although the possibility that the patient has a dual-pathology idiopathic epilepsy and vitamin B₁₂ deficiency could not be excluded, it is reasonable to assume a cause–effect relation between the documented vitamin B₁₂ deficiency and the intractable seizures, because the patient remained seizure free after starting cobalamin therapy and even after stopping the AEDs. Although the neurologic complications of vitamin B₁₂ deficiency are myriad (1–3), seizure is an uncommon manifestation of this deficiency in adult individuals (4,5). Whether the polyneuropathy in this patient was caused by a vitamin B₁₂ deficiency or the PHT administration could not be confirmed on the initial NCS. After cobalamin therapy, the symptoms of polyneuropathy resolved, and the NCS 3 months later was normal, except for an absence of bilateral H-reflexes. During this period, PHT was still administered; therefore the polyneuropathy was most likely caused by a vitamin B₁₂ deficiency, rather than the PHT administration.

The crucial metabolic events leading to seizures in cobalamin deficiency are still uncertain, but experimental studies have suggested that homocysteinemia might play a role. Vitamin B₁₂ is essential for remethylation of homocysteine to methionine (6). As

shown in our patient, the homocysteine level increased with the deficiency of vitamin B₁₂ and returned to a normal level after the cobalamin replacement therapy. Systemic administration of high doses of homocysteine in animals has produced convulsive seizures (7). Homocysteine and its product, homocysteic acid, have been proven to induce seizures in adult as well as immature rats, with some age-dependent differences in the seizure patterns (i.e., seizures are longer and more severe in immature rats than in adult rats) (7,8). These results showed that younger animals are more prone to homocysteine-induced seizures, which most likely reflects the immaturity of the blood–brain barrier (8). This may explain why epileptic seizures are common manifestations of congenital cobalamin deficiency in infants (9) but are rare in adult patients.

The failure to recognize vitamin B₁₂ deficiency as the etiology for epileptic seizures is complicated by the absence of macrocytic anemia, which is widely regarded as the cardinal feature of this disease (1). However, among 141 consecutive patients with neuropsychiatric abnormalities due to cobalamin deficiency in one study, 28% had no anemia or macrocytosis (2). Given that 31% of the patients with epilepsy having their first seizure after age 50 years had seizures of unknown origin (10), and an examination of the cobalamin level is seldom part of a routine seizure evaluation, seizures caused by cobalamin deficiency are probably misdiagnosed. Our report highlights the importance of placing vitamin B₁₂ deficiency in the list of etiologies of epilepsy, when adult patients are first seen with unexplained recurrent seizures, even when macrocytic anemia is absent.

Victor M, Lear AA. Subacute combined degeneration of the spinal cord: current concepts of the disease process. *Am J Med* 1956;**20**: 896–911.

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2

Lindenbaum J, Healton EB, Savage DG, *et al.* Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med* 1988;**318**: 1720–8.

[CrossRef](#) | [PubMed](#) | [CAS](#) | [Web of Science®](#)

3

Healton EB, Savage DG, Brust JCM, *et al.* Neurologic aspects of cobalamin deficiency. *Medicine* 1991;**70**: 229–45.

[CrossRef](#) | [PubMed](#) | [CAS](#) | [Web of Science®](#)

4

Aguglia U, Gambardella A, Oliveri RL, *et al.* De novo epileptic confusional status in a patient with cobalamin deficiency. *Metab Brain Dis* 1995;**10**: 233–8.

[CrossRef](#) | [PubMed](#) | [CAS](#) | [Web of Science®](#)

5

Kumar S. Recurrent seizures: an unusual manifestation of vitamin B₁₂ deficiency. *Neurol India* 2004;**52**: 122–3.

[PubMed](#) | [CAS](#) | [Web of Science®](#)

6

Tefferi A, Pruthi RK. The biochemical basis of cobalamin deficiency. *Mayo Clin Proc* 1994;**69**: 181–6.

[CrossRef](#) | [PubMed](#) | [CAS](#) | [Web of Science®](#)

7

Kubova H, Folbergrova J, Mares P. Seizures induced by homocysteine in rats during ontogenesis. *Epilepsia* 1995;**36**: 750–6.

[Wiley Online Library](#) | [PubMed](#) | [CAS](#) | [Web of Science®](#)

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Mares P, Folbergrova J, Langmeier M, *et al.* Convulsant action of D, L-homocysteic acid and its stereoisomers in immature rats. *Epilepsia* 1997;**38**: 767–76.

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9

Biancheri R, Cerone R, Rossi A, *et al.* Early-onset cobalamin C/D deficiency: epilepsy and electroencephalographic features. *Epilepsia* 2002;**43**: 616–22.

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10

Ruggles KH, Haessly SM, Berg RL. Prospective study of seizures in the elderly in the Marshfield epidemiologic study area (MESA). *Epilepsia* 2001;**42**: 1594–9.

[Wiley Online Library](#) | [PubMed](#) | [CAS](#) | [Web of Science®](#)

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[HTML] Recurrent **seizures**: An unusual manifestation of vitamin B12 deficiency

[S Kumar](#) - Neurology India, 2004 - Medknow

De novo **epileptic** confusional status in a patient with **cobalamin** deficiency.

Optic atrophy in association with **cobalamin**
C (cblC) disease

Neurologic and neurodevelopmental
phenotypes in young children with early-
treated combined methylmalonic acidemia
and homocystinuria, **cobalamin** C type

[HTML] Early-onset **Cobalamin** C/D Deficiency: **Epilepsy** and
Electroencephalographic Features

%%

11. **B12 AND METHYLATION:** Effect of
cobalamin derivatives on in vitro enzymic
DNA methylation:methylcobalamin can act as
a methyl donor.

Annie Pfohl-Leszkowicz , Guy Dirheimer.

Biochemistry, **1991**, 30 (32), pp 8045–8051 **DOI:** 10.1021/
bi00246a024

**REF SHOWING ADOCBL, TO WHICH SOME MECBL
IS CONVERTED INTRACELLULARLY, ALSO
REGULATES tRNA METHYLATION:**

Tarasiavichene et al. (1976) Tarasiavichene LE, Kanopkaite SI, and Martsishauskas RP [Participation of 5'-deoxyadenosyl-B12 in regulating methylation of tRNA]. (1976) *Biokhimiia*, 41 1614-1618.

12. PIONEERING USE OF B12 IN GOSH IN THE 1950S:

Bodian (1963) Bodian M Neuroblastoma: An Evaluation of Its Natural History and the Effects of Therapy, with Particular Reference to Treatment by Massive Doses of Vitamin B12. (1963) *Arch Dis Child*, 38 606-619.

Bodian (1959) Bodian M. Neuroblastoma. *Pediatr Clin North Am* 1959;6:449–72.

AND:

Reilly, et al. (1968) Reilly D, Nesbit ME, and Krivit W Cure of three patients who had skeletal metastases in disseminated neuroblastoma. (1968) *Pediatrics*, 41 47-51.

% %

13. SOME ASSORTED CLINICAL USES OF B12 DATING BACK TO THE EARLY 1950S.

[Lists by no means complete....]

[Personal experience in therapeutic use of massive doses of vitamin B12].
(PMID:13153626)

POZUELO ESCUDERO V
Medicina [1954 Jan;22(1-1):24-30]

[Treatment of neural diseases with a relatively large and massive doses of vitamin B12].

(PMID:13605133)
ROIZEN SH S, POEMNYI FA
Zhurnal nevropatologii i psikiatrii imeni S.S. Korsakova (Moscow, Russia : 1952)
[1958;58(2):212-3]

[Preliminary observations on the results of administration of massive doses of vitamin B12 in various neurological diseases].

(PMID:13172905)
REY ARDID R
Clinica y laboratorio [1954 Apr;57(337):291-8]

[The use of vitamin B12 in neurology; eighteen months' experience].

(PMID:14925890)
LEREBOULLET J, PLUVINAGE R
Bulletins et memoires de la Societe medicale des hopitaux de Paris [1951 Nov
9-16;67(29-30):1258-63]

[Vitamin B12 treatment in neurology, especially in states of pain].

(PMID:13250976)
HAMPP H
Deutsche medizinische Wochenschrift (1946) [1955 Aug 5;80(31-32):1139-40]

[Vitamin B 12 in high doses in neurology].

(PMID:13089752)
MONSUS J
La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des
hopitaux de Paris [1953 Jun 30;29(43):2232]

[Therapeutic results with vitamin B12 in some neurological conditions, with large doses intravenously and subarachnoid].

(PMID:13335771)
BRAGE D
Prensa medica argentina [1956 Feb 10;43(6):498-504]

[Two cases of herpes zoster treated by vitamin B12 in doses of 1000 gammas].

(PMID:14369110)
DASTE M
Maroc medical [1954 Aug;33(351):789]

[B12 in neurology].

(PMID:13348606)
SAKER G, GAIDA A
Munchener medizinische Wochenschrift (1950) [1956 Jun 29;98(26):906-8]

[\[Vitamin B12 in neurologic clinic\].](#)

(PMID:13177400)

BENBANASTE JV

Prensa medica argentina [1954 Jun 11;41(24):1666-8]

[\[One thousand gammas Vitamin B12 in rheumatology\].](#)

(PMID:13089801)

LANIER M

La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris [1953 Aug 26-30;29(52-53):Unknown]

[\[Massive doses of vitamin B12; experience in the field of dermatology\].](#)

(PMID:13207959)

SANTOJANNI G

Annali italiani di dermatologia e sifilografia [1954 Jul-Aug;9(4):300-5]

[\[First results obtained in the treatment of certain rheumatic syndromes with massive doses of vitamin B12\].](#)

(PMID:13156110)

BARCELO TORRENT P, ALEGRE MARCET C, CASADEMONT M, VERGES G

Revista espanola de reumatismo y enfermedades osteoarticulares [1953 Jul;5(3):119-22]

[\[Liver-protective effects of vitamin B12 in massive doses; clinical case reports\].](#)

(PMID:13639295)

RICCI G

La Clinica terapeutica [1959 Jan;16(1):33-41]

[\[The use of vitamin B12 in massive doses \(500-1000 micrograms\) in various affections in diabetics\].](#)

(PMID:13166628)

DALLE COSTE P, KLINGER R

Il Policlinico. Sezione pratica [1954 Feb 1;61(5):143-9]

[Treatment of herpes zoster neuralgia with massive doses of vitamin B12.](#)

(PMID:14388327)

HELLE J, OHELA K

Annales medicinae experimentalis et biologiae Fenniae [1955;33(1-2):116-21]

[Massive doses of vitamin B12 in treatment of schizophrenia.](#)

(PMID:14349437)

POKORNY AD

A.M.A. archives of neurology and psychiatry [1955 Mar;73(3):345-6]

[\[Use of intravenous vitamin B12 in massive doses of 500-1000 mcgr. daily in various complications of diabetes\].](#)

(PMID:14383545)

DALLE COSTE P, KLINGER R

Minerva medica [1955 Apr 25;46(33):1187-93]

[\[Treatment of psoriasis by vitamine B12 with 1,000 gammas\].](#)

(PMID:13316370)

RIMBAUD P, RAVOIRE J, RIOUX J

Bulletin de la Societe francaise de dermatologie et de syphiligraphie [1955 Nov-Dec;(5):509-10]

[\[Therapeutic tests of massive doses of vitamin B12 in neurological complications of chronic alcoholism\].](#)

(PMID:13165258)

DELLA BEFFA A, LARICCHIA R

Minerva medica [1954 Mar 31;45(26):892-7]

[The use of vitamin B12 in the management of the neurologic manifestations of diabetes mellitus, with notes on the administration of massive doses.](#)

(PMID:14885885)

SANCETTA SM, AYRES PR, SCOTT RW

Annals of internal medicine [1951 Nov;35(5):1028-48]

[\[Effect of massive doses of vitamin B12 on leucopenias caused by azoiprite\].](#)

(PMID:13331165)

MASETTO I, BUTTO M

Giornale di clinica medica [1956 Feb;37(2):204-16]

[\[Lupus erythematosus treated with massive doses of vitamin B12\].](#)

(PMID:13065170)

GAY PRIETO, ALVAREZ CASCOS

Actas dermo-sifiliograficas [1953 Mar;44(6):446-8]

[\[Per os administration of high doses of vitamin B12 in surgery\].](#)

(PMID:13089760)

MONSUS J

La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris [1953 Jul 2;29(44):2290]

[Refractoriness to intrinsic factor-B12 preparations abolished by massive doses of intrinsic factor; preliminary report.](#)

(PMID:13605608)

BERLIN R, BERLIN H, BRANTE G, SJOBERG SG

Acta medica Scandinavica [1958 Nov 10;162(4):317-9]

[\[Clinical effects of a vitamin B12-factor III preparation in neurological disorders\].](#)

(PMID:13612694)

SCHUTZ E

Medizinische Klinik [1958 Nov 14;53(46):1998-2002]

[\[Treatment of sciatica with massive doses of epidural vitamin B12\].](#)

(PMID:13193349)

HERNANDEZ RUIZ L

Medicina espanola [1954 May;31(182):369-72]

[\[Vitamin B12 in neurology\].](#)

(PMID:12992002)

Medecine et hygiene [1952 Apr 15;10(216):154]

[\[Massive doses of vitamin B12 as an indispensable complement to vertebrotherapy\].](#)

(PMID:13178708)

ALLIES P

La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris [1954 May 26;30(34):2169-70]

[\[Use of vitamin B 12 in neurological diseases\].](#)

(PMID:5884559)

Sobue I

Naika. Internal medicine [1965 Jul;16(1):117-9]

[TRIGEMINAL neuralgia relieved by massive doses of vitamin B12.](#)

(PMID:24542254)

What's new [1952 Nov;60(173):11-2]

[Treatment of psoriasis with large doses of vitamin B12, 1,100 micrograms per cubic centimeter; preliminary clinical report.](#)

(PMID:13157646)

RUEDEMANN R Jr

A.M.A. archives of dermatology and syphilology [1954 Jun;69(6):738-9]

[\[Intrathecal vitamin B 12 use in neurologic diseases\].](#)

(PMID:5953562)

Ulbricht W

Deutsches medizinisches Journal [1966 Aug 20;17(16):481-3]

[Vitamin B-12 in neurometabolism; preliminary clinical report.](#)

(PMID:14361359)

LEVIN MB

The American journal of digestive diseases [1955 Apr;22(4):96-7]

[\[Vitamin B12 in the clinical treatment of diseases of the nervous system. \(Review of the foreign literature\)\].](#)

(PMID:13698159)

FARBER MA

Klinicheskaya meditsina [1960 Sep;38:19-27]

[\[Causal therapy of vascular diseases with high doses of vitamin B12\].](#)

(PMID:13613273)

GRABNER H

Munchener medizinische Wochenschrift (1950) [1958 Oct 31;100(44):1700-4]

[Single massive dose of vitamin B12 in untreated pernicious anaemia.](#)

(PMID:14954174)

WALKER W, HUNTER RB

British medical journal [1952 Sep 13;2(4784):593-5]

[Trigeminal neuralgia: conservative management with massive vitamin B12 therapy.](#)

(PMID:13055099)

ALEXANDER E Jr, DAVIS CH Jr

North Carolina medical journal [1953 May;14(5):206-7]

[Vitamin B12 in massive dosages for herpetic lesions.](#)

(PMID:13055119)

LEITCH GB

Northwest medicine [1953 Apr;52(4):291-2]

[The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B12 deficiency.](#)

(PMID:16704961)

Hvas AM, Buhl H, Laursen NB, Hesse B, Berglund L, Nexø E

Haematologica [2006 Jun;91(6):805-8]

[The master key effect of vitamin B12 in treatment of malignancy--a potential therapy?](#)

(PMID:17640826)

Volkov I

Medical hypotheses [2008;70(2):324-8]

[\[Expediency of the use of large doses of vitamin B12\].](#)

(PMID:13550631)

MILEVSKAIA IuL

Klinicheskaya meditsina [1958 Mar;36(3):93-7]

[\[Expediency of using large doses of vitamin B12\].](#)

(PMID:13540086)

BUKIN VN

Klinicheskaya meditsina [1957 Dec;35(12):118-9]

[\[The efficacy of very large doses of vitamin B12\].](#)

(PMID:13076477)

CHEVALLIER P

La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris [1953 Jun 14;29(39):1953-7]

[\[Justification of the use of massive doses of vitamin B12 in liver diseases manifesting high serum concentrations of this vitamin\].](#)

(PMID:14470762)

MASELLI P

Hospital (Rio de Janeiro, Brazil) [1961 Sep;60:333-42]

[\[Prolonged excretion of vitamin B12 following its intramuscular injection as a depot preparation.\]](#)

(PMID:13583412)

ARNOLD A, BERBERIAN DA, SOBELL SD

American practitioner and digest of treatment [1958 Nov;9(11):1835-9]

[\[Effectiveness of vitamin B12 in diseases of the peripheral nervous system\].](#)

(PMID:13676898)

TOROSIAN SA

Zhurnal nevropatologii i psikiatrii imeni S.S. Korsakova (Moscow, Russia : 1952)

[1959;59(6):742]

[\[Treatment with vitamin B12 of diseases of the peripheral nervous system\].](#)

(PMID:13592476)

FARBER MA

Sovetskaia meditsina [1958 Jun;22(6):64-8]

[\[Vitamin B12 treatment of diseases of the peripheral nervous system\].](#)

(PMID:13443484)

POEMNYI FA, ROIZEN ShS

Zhurnal nevropatologii i psikiatrii imeni S.S. Korsakova (Moscow, Russia : 1952)

[1957;57(2):191-2]

[\[High doses of vitamin B12 used in episodic states in schizophrenia\].](#)

(PMID:13246049)

MOTTA E

Rassegna di studi psichiatrici [1955;44(2):229-38]

[\[The treatment of herpes zoster with high doses of vitamin B12\].](#)

(PMID:14374879)

JOHNE HO

Zeitschrift fur Haut- und Geschlechtskrankheiten [1954 Dec 15;17(12):378-81]

[\[Long term biweekly 1 mg oral vitamin B12 ensures normal hematological parameters, but does not correct all other markers of vitamin B12 deficiency. A study in patients with inherited vitamin B12 deficiency.\]](#)

(PMID:18768530)

Bor MV, Cetin M, Aytaç S, Altay C, Ueland PM, Nexø E

Haematologica [2008 Nov;93(11):1755-8]

[\[Use of cyanocobalamine in neurological therapeutics; preliminary note\].](#)

(PMID:13308175)

GAUTHIER CA, COULOMBE M

Laval medical [1955 Dec;20(10):1359-65]

[\[Vitamin B12 in 1 milligram doses in therapy of neuralgia\].](#)

(PMID:13089791)

CHARREYRON L

La semaine des hopitaux : organe fonde par l'Association d'enseignement medical des hopitaux de Paris [1953 Aug 10-14;29(50-51):2546]

[Pernicious anemia. I. Remission by small oral doses of purified vitamin B12.](#)

(PMID:13322979)

ESTREN S, WASSERMAN LR

Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.) [1956 Mar;91(3):499-503]

[\[Action of vitamin B12 in large doses in the reaction state of Hansen's disease\].](#)

(PMID:13191256)

WILKINSON FF

El Dia medico [1954 Jul 15;26(48):1293-5]

[Treatment of pernicious anemia with massive parenteral doses of vitamin B-12.](#)

(PMID:14935513)

REISNER EH Jr, WEINER L

Bulletin of the New York Academy of Medicine [1952 Aug;28(8):539]

[\[Action of large doses of oral vitamin B12 on dyspepsia from fats in breast-fed infants\].](#)

(PMID:13140535)

PERITI P

Bollettino della Societa italiana di biologia sperimentale [1953 Jul;29(7):1391-2]

[\[Summation of peroral subminimal doses of vitamin B12 and folic acid in pernicious anemia\].](#)

(PMID:14919406)

HAEHNER E, LUDES H, EISENREICH H

Munchener medizinische Wochenschrift (1950) [1952 Jan 4;94(1):14-7]

[A randomized, controlled trial of the effects of adding vitamin B12 and folate to erythropoietin for the treatment of anemia of prematurity.](#)

(PMID:16818564)

Haiden N, Klebermass K, Cardona F, Schwindt J, Berger A, Kohlhauser-Vollmuth C, Jilma B, Pollak A

Pediatrics [2006 Jul;118(1):180-8]

[Patient and family fact sheet. Vitamin B12 deficiency and the nervous system.](#)

(PMID:16688019)
Kernich CA
The neurologist [2006 May;12(3):169-70]

[\[Intensification of neural therapy by vitamin B12 administered in high doses\].](#)

(PMID:13265056)
PEPLAU G
Die Medizinische [1955 Aug 6;(31-32):1089-91]

[Oral vitamin B12 supplementation reduces plasma total homocysteine concentration in women in India.](#)

(PMID:17215186)
Yajnik CS, Lubree HG, Thuse NV, Ramdas LV, Deshpande SS, Deshpande VU, Deshpande JA, Uradey BS, Ganpule AA, Naik SS, Joshi NP, Farrant H, Refsum H
Asia Pacific journal of clinical nutrition [2007;16(1):103-9]

[Oral treatment of pernicious anaemia with vitamin B12 and purified intrinsic factor. I. The value of serial estimation of the vitamin B12 levels of serum.](#)

(PMID:13532514)
KILLANDER A
Acta medica Scandinavica [1958 Mar 29;160(4):339-52]

[Oral treatment of pernicious anemia with small doses of vitamin B12 combined with mucinous materials derived from the hog stomach.](#)

(PMID:13093761)
GLASS GB, BOYD LJ
Blood [1953 Oct;8(10):867-92]

[\[Hematological reaction to small peroral doses of vitamin B12 in pernicious anemia in infants \(Gerbasi\)\].](#)

(PMID:13340751)
BURGIO GR, RUSSO G, LO JACONO F
Archiv fur Kinderheilkunde [1956;152(2):109-21]

[\[Vitamin B12 in therapy of skin diseases, especially those of allergic origin\].](#)

(PMID:13265687)
NEBER H
Munchener medizinische Wochenschrift (1950) [1955 Aug 26;97(34):1102-3]

[Diabetic neuropathy: controlled therapeutic trials.](#)

(PMID:13158345)
SHUMAN CR, GILPIN SF
The American journal of the medical sciences [1954 Jun;227(6):612-7]

[\[Vitamin B12, intrinsic factor and vitamin complex B in oral therapy of anemia\].](#)

(PMID:13177906)
DONINI P, MARCHETTI E

La Rassegna di clinica, terapia e scienze affini [1954 Jan-Mar;53(1):1-8]

[Progressive vacuolar myelopathy and leukoencephalopathy in childhood acute lymphoblastic leukemia and transient improvement with vitamin B12.](#)

(PMID:16395685)

Olçay L, Irkkan C, Senbil N, Uzun H, Basmacı M, Güreş YK

Pediatric blood & cancer [2007 Oct 15;49(5):754-8]

[Long-term evaluation of vitamin B12 in treatment of pernicious anemia. I. Incidental report on use of combined oral therapy with vitamin B12 and folic acid.](#)

(PMID:13211343)

SCHWARTZ SO, FRIEDMAN IA, GANT HL

Journal of the American Medical Association [1955 Jan 15;157(3):229-31]

[\[Effects of vitamin B12 in dentistry\].](#)

(PMID:13025213)

SACCO S, BOGGERO C

Minerva stomatologica [1952 Oct-Dec;1(4):258-64]

[\[Multifocal neurological syndrome, associated with chronic hepatopathy; remission of neurological symptoms after lipotropic therapy\].](#)

(PMID:13324007)

MARIANI B, BOCCITTO G

Rivista di neurologia [1955 Nov-Dec;25(6):888-900]

[\[Result of use of vitamin B12 in certain dermatoses\].](#)

(PMID:13659768)

LEVIN AM, KSANFOPULO PI, PROPVICH LE

Vestnik dermatologii i venerologii [1959 Mar-Apr;33(2):54-7]

[\[Vitamin B12 therapy of certain dermatoses\].](#)

(PMID:13659767)

STUDNITSIN AA, VINOKUROV IN

Vestnik dermatologii i venerologii [1959 Mar-Apr;33(2):51-4]

[\[Effect of vitamin B12 \(rubivitan\) on various dermatoses\].](#)

(PMID:13573971)

KUHNAU WW

Deutsches medizinisches Journal [1958 Aug;9(8):429-31]

[\[Therapeutic value of vitamin B12 in certain dermatoses\].](#)

(PMID:13261792)

PEISER B

Deutsches medizinisches Journal [1955 Aug 15;6(15-16):519-22]

[\[Results obtained with vitamin B12 in rheumatic pain\].](#)

(PMID:13245660)

TARNOPOLSKY S, MORDUCHOWICZ N, AMOSA EI
Prensa medica argentina [1955 Apr 22;42(16):1116-8]

[Rationale for vitamin-B12 treatment of retinoblastoma.](#)

(PMID:16874996)

Horns JW

American journal of ophthalmology [1966 May;61(5 Pt 1):910-1]

[\[Possible value of vitamin B12 in prevention of neurotropic virus infections, such as postvaccinal encephalitis and poliomyelitis\].](#)

(PMID:13054843)

KEUNING FJ

Nederlands tijdschrift voor geneeskunde [1953 Jan 31;97(5):284-5]

[\[Radioactive vitamin B12 and the diagnosis of neurologic disorders\].](#)

(PMID:13543403)

Semaine medicale professionnelle et medico-sociale [1958 Feb 6;35(5):177]

[Response of cobalt-deficient sheep to massive doses of vitamin B12.](#)

(PMID:13002444)

MARSTON HR, LEE HJ

Nature [1952 Nov 8;170(4332):791]

[\[Subcutaneous injection of suspension of homoplastic peritoneum in diseases of the nervous system\].](#)

(PMID:13023914)

DUMBADZE DN

Klinicheskaya meditsina [1952 Nov;30(11):86-7]

1. Okuda K, Yashima K, Kitazaki T, Takara I. Intestinal absorption and concurrent chemical changes of methylcobalamin. J Lab Clin Med 1973;81:557-567.

60

61 2. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find Exp Clin Pharmacol 1995;17:539-544.

62

63 3. Nishizawa Y, Yamamoto T, Terada N, et al. Effects of methylcobalamin on the proliferation of androgen-sensitive or estrogen-sensitive malignant cells in culture and in vivo. Int J Vitam Nutr Res 1997;67:164-170.

64

65 4. Shimizu N, Hamazoe R, Kanayama H, et al. Experimental study of antitumor effect of methyl-B12. Oncology 1987;44:169-173.

66

67 5. Tsao CS, Myashita K. Influence of cobalamin on the survival of mice bearing ascites tumor. Pathology 1993;61:104-108.

68

- 69 6. Miasishcheva NV, Gerasimova GK, Il'ina NS, Sof'ina ZP. Effect of
methylocobalamin on methotrexate transport in normal and tumorous tissues.
Biull Eksp Biol Med 1985;99:736-738. [Article in Russian]
- 70
- 71 7. Yaqub BA, Siddique A, Sulimani R. Effects of methylocobalamin on diabetic
neuropathy. Clin Neurol Neurosurg 1992;94:105-111.
- 72
- 73 8. Kikuchi M, Kashii S, Honda Y, et al. Protective effects of methylocobalamin,
a vitamin B12 analog, against glutamate-induced neurotoxicity in retinal cell
culture. Invest Ophthalmol Vis Sci 1997;38:848-854.
- 74
- 75 9. Iwasaki T, Kurimoto S. Effect of methylocobalamin in accommodative
dysfunction of eye by visual load. Sangyo Ika Daigaku Zasshi
1987;9:127-132.
- 76
- 77 10. Yoshioka K, Tanaka K. Effect of methylocobalamin on diabetic autonomic
neuropathy as assessed by power spectral analysis of heart rate variations.
Horm Metab Res 1995;27:43-44.
- 78
- 79 11. Weinberg JB, Sauls DL, Misukonis MA, Shugars DC. Inhibition of
productive human immunodeficiency virus-1 infection by cobalamins. Blood
1995;86:1281-1287.
- 80
- 81 12. Araki A, Sako Y, Ito H. Plasma homocysteine concentrations in Japanese
patients with non-insulin-dependent diabetes mellitus: effect of parenteral
methylocobalamin treatment. Atherosclerosis 1993;103:149-157.
- 82
- 83 13. Moriyama H, Nakamura K, Sanda N, et al. Studies on the usefulness of a
long-term, high-dose treatment of methylocobalamin in patients with
oligozoospermia. Hinyokika Kiyo 1987;33:151-156.
- 84
- 85 14. Isoyama R, Kawai S, Shimizu Y, et al. Clinical experience with
methylocobalamin (CH3-B12) for male infertility. Hinyokika Kiyo
1984;30:581-586.
- 86
- 87 15. Uchiyama M, Mayer G, Okawa M, Meier-Ewert K. Effects of vitamin B12
on human circadian body temperature rhythm. Neurosci Lett 1995;192:1-4.
- 88
- 89 16. Tomoda A, Miiike T, Matsukura M. Circadian rhythm abnormalities in
adrenoleukodystrophy and methyl B12 treatment. Brain Dev
1995;17:428-431.
- 90
- 91 17. Yamada N. Treatment of recurrent hypersomnia with methylocobalamin
(vitamin B12): a case report. Psychiatry Clin Neurosci 1995;49:305-307.
- 92

- 93 18. Ohta T, Ando K, Iwata T, et al. Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12). *Sleep* 1991;14:414-418.
- 94
- 95 19. Mayer G, Kroger M, Meier-Ewert K. Effects of vitamin B12 on performance and circadian rhythm in normal subjects. *Neuropsychopharmacology* 1996;15:456-464.
- 96
- 97 20. Hashimoto S, Kohsaka M, Morita N, et al. Vitamin B12 enhances the phase-response of circadian melatonin rhythm to a single bright light exposure in humans. *Neurosci Lett* 1996;220:129-132.

Welsh, 1., *Brit. Med. J.*, I, 1 133 (1952)

Lereboullet, J., and Pluvinage, R., *Sem. Hop. (Paris)*, 29, 1849-54 (1953)

urley CP, Brewster MA. Alpha-tocopherol protects against a reduction in adenosylcobalamin in oxidatively stressed human cells. *J Nutr* 1993;123:1305-1312.

3605. Pappu AS, Fatterpaker P, Srenivasan A. Possible interrelationship between vitamins E and B12 in the disturbance in methylmalonate metabolism in vitamin E deficiency. *Biochem J* 1978;172:115-121.

3636. Glusker JP. Vitamin B12 and the B12 coenzymes. *Vitam Horm* 1995;50:1-76.

3667. Okuda K, Yashima K, Kitazaki T, Takara I. Intestinal absorption and concurrent chemical changes of methylcobalamin. *J Lab Clin Med* 1973;81:557-567.

3698. Heinrich HC, Gabbe EE. Metabolism of the vitamin B12-coenzyme in rats and man. *Ann NY Acad Sci* 1964;112:871-903.

3729. Lederle FA. Oral cobalamin for pernicious anemia. Medicines best kept secret? *JAMA* 1991;265:94-95.

37510. Berlin H, Brante G, Pibrant A. Vitamin B12 body stores during oral and parenteral treatment of pernicious anemia. *Acta Med Scand* 1978;204:81-84.

37811. Tsukerman ES, Pomerantseva TIa, Poznanskaia AA, et al. Effect of methyl-cobalamin and adenosylcobalamin on the process of hematopoiesis and vitamin B12 exchange in experimental

phenylhydrazine-induced anemia in rabbits. Vopr Med Khim 1989;35:106-111. [Article in Russian]

38112. Fochi F, Ciampini M, Ceccarelli G. Efficacy of iron therapy: a comparative evaluation of four iron preparations administered to anaemic pregnant women. J Int Med Res 1985;13:1-11.

38413. Granese D, Retto G, Scurria L, Borgese R. Associazione ferritina, coenzima adenosilcobalaminico, coenzima folico: impiego in gravidanza. Min Ginecol 1986;38:93-100. [Article in Italian]

38714. Korkina MV, Korchak GM, Medvedev DI. Clinico-experimental substantiation of the use of carnitine and cobalamin in the treatment of anorexia nervosa. Zh Nevropatol Psikhiatr 1989;89:82-87. [Article in Russian]

39015. Korkina MV, Korchak GM, Kareva MA. Effects of carnitine and cobamamide on the dynamics of mental work capacity in patients with anorexia nervosa. Zh Nevropatol Psikhiatr Im S S Korsakova 1992;92:99-102. [Article in Russian]

39316. Giordano C, Perrotti G. Clinical studies of the effects of treatment with a combination of carnitine and cobamamide in infantile anorexia. Clin Ter 1979;88:51-60. [Article in Italian]

39617. Eto I, Krumdieck CL. Role of vitamin B12 and folate deficiencies in carcinogenesis. Adv Exp Med Biol 1986;206:313-330.

39918. Liteplo RG, Hipwell SE, Rosenblatt DS, et al. Changes in cobalamin metabolism are associated with the altered methionine auxotrophy of highly growth autonomous human melanoma cells. J Cell Physiol 1991;149:332-338.

40219. Wainfan E, Poirier LA. Methyl groups in carcinogenesis: effects on DNA methylation and gene expression. Cancer Res 1992;52:2071S-2077S.

40520. Christman JK, Sheikhnejad G, Dizik M, et al. Reversibility of changes in nucleic acid methylation and gene expression induced in rat liver by severe dietary methyl deficiency. Carcinogenesis 1993;14:551-557.

40821. Nishizawa Y, Yamamoto T, Terada N, et al. Effects of methylcobalamin on the proliferation of androgen-sensitive or estrogen-sensitive malignant cells in culture and in vivo. *Int J Vitam Nutr Res* 1997;67:164-170.
41122. Shimizu N, Hamazoe R, Kanayama H, et al. Experimental study of antitumor effect of methyl-B12. *Oncology* 1987;44:169-173.
41423. Tsao CS, Myashita K. Influence of cobalamin on the survival of mice bearing ascites tumor. *Pathobiology* 1993;61:104-108.
41724. Miasishcheva NV, Gerasimova GK, Il'ina NS, Sof'ina ZP. Effect of methylcobalamin on methotrexate transport in normal and tumorous tissues. *Biull Eksp Biol Med* 1985;99:736-738. [Article in Russian]
42025. Heimburger DC, Alexander CB, Birch R, et al. Improvement in bronchial squamous metaplasia in smokers treated with folate and vitamin B12. Report of a preliminary randomized, double-blind intervention trial. *JAMA* 1988;259:1525-1530.
42326. Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy. *Clin Neurol Neurosurg* 1992;94:105-111.
42627. Yoshioka K, Tanaka K. Effect of methylcobalamin on diabetic autonomic neuropathy as assessed by power spectral analysis of heart rate variations. *Horm Metab Res* 1995;27:43-44.
42928. Kikuchi M, Kashii S, Honda Y, et al. Protective effects of methylcobalamin, a vitamin B12 analog, against glutamate-induced neurotoxicity in retinal cell culture. *Invest Ophthalmol Vis Sci* 1997;38:848-854.
43229. Nishikawa Y, Shibata S, Shimazoe T, Watanabe S. Methylcobalamin induces a long-lasting enhancement of the field potential in rat suprachiasmatic nucleus slices. *Neurosci Lett* 1996;220:199-202.
43530. Iwasaki T, Kurimoto S. Effect of methylcobalamin in accommodative dysfunction of eye by visual load. *Sangyo Ika Daigaku Zasshi* 1987;9:127-132. [Abstract]
43831. Oishi S. Prevention of di(2-ethylhexyl) phthalate-induced testicular atrophy in rats by co-administration of the vitamin B12

derivative adenosylcobalamin. Arch Environ Contam Toxicol 1994;26:497-503.

44132. Moriyama H, Nakamura K, Sanda N, et al. Studies on the usefulness of a long-term, high-dose treatment of methylcobalamin in patients with oligozoospermia. Hinyokika Kiyo 1987;33:151-156. [Abstract]

442

443

44433. Isoyama R, Kawai S, Shimizu Y, et al. Clinical experience with methylcobalamin (CH3-B12) for male infertility. Hinyokika Kiyo 1984;30:581-586. [Abstract]

445

446

44734. May BA. A novel antiviral strategy for HIV infection. Med Hypotheses 1993;40:93-94.

45035. Tang AM, Graham NM, Chandra RK, Saah AJ. Low serum vitamin B-12 concentrations are associated with faster human immunodeficiency virus type 1 (HIV-1) disease progression. J Nutr 1997;127:345-351.

45336. Weinberg JB, Sauls DL, Misukonis MA, Shugars DC. Inhibition of productive human immunodeficiency virus-1 infection by cobalamins. Blood 1995;86:1281-1287.

45637. Araki A, Sako Y, Ito H. Plasma homocysteine concentrations in Japanese patients with non-insulin-dependent diabetes mellitus: effect of parenteral methylcobalamin treatment. Atherosclerosis 1993;103:149-157.

45938. Bhatt RH, Linnell JC, Barltrop D. Treatment of hydroxycobalamin-resistant methylmalonic acidemia with adenosylcobalamin. Lancet 1986;2:465. [Letter]

46239. Glass GBJ, Boyd LJ, Ebin L. Radioactive vitamin B12 in the liver. J Lab Clin Med 1958;52:849-859.

46540. Leevy CM, Thompson A, Baker H. Vitamins and liver injury. Am J Clin Nutr 1970;23:493-499.

46841. Iwarson S, Lindberg J. Coenzyme B-12 therapy in acute viral hepatitis. Scand J Infect Dis 1977;9:157-158.

47142. Korsova TL, Morozova NA, Poznanskaia AA, Kurganov BI. Comparative study of the effect of vitamin B12 coenzymes on monooxygenase system and lipid peroxidation in the liver of rabbits poisoned with phenylhydrazine. *Vopr Med Khim* 1989;35:97-102. [Article in Russian]
47443. Tebenchuk GM, Lukashuk VD, Lipkan GN, Stepanenko VV. Antitoxic action of cobamamide in experimental hepatitis. *Farmakol Toksikol* 1984;47:87-90. [Article in Russian]
47744. Tsukerman ES, Korsova TL, Poznanskaia AA. Vitamin B12 metabolism and the status of sulfhydryl groups in protein-choline deficiency in rats. Effects of methyl- and adenosyl-cobalamins. *Vopr Pitan* 1992;1:40-44. [Article in Russian]
48045. Fossati C. On use of cobamamide in a group of hospitalized patients with pulmonary tuberculosis. *Minerva Med* 1971;62:4638-4646. [Article in Italian]
48346. Medina F, Vitali D. Controlled clinical research with cobamamide in the treatment of viral hepatitis. *Clin Ter* 1968;46:139-144. [Article in Italian]
48647. Resta M, Vitali D, Medina F. Controlled clinical trial of a liver extract combined with high doses of nucleosides, cobamamide and adrenal cortex extract in the treatment of acute liver diseases. *Clin Ter* 1972;62:213-223. [Article in Italian]
48948. Teti V, Acerbi F, Nitti G. Protection of liver by a cortico-vitamin-liver extract combination and cobamamide. *Clin Ter* 1974;68:67-73. [Article in Italian]
49249. Uchiyama M, Mayer G, Okawa M, Meier-Ewert K. Effects of vitamin B12 on human circadian body temperature rhythm. *Neurosci Lett* 1995;192:1-4.
49550. Tomoda A, Miike T, Matsukura M. Circadian rhythm abnormalities in adrenoleukodystrophy and methyl B12 treatment. *Brain Dev* 1995;17:428-431.
49851. Yamada N. Treatment of recurrent hypersomnia with methylcobalamin (vitamin B12): a case report. *Psychiatry Clin Neurosci* 1995;49:305-307.

50152. Ohta T, Ando K, Iwata T, et al. Treatment of persistent sleep-wake schedule disorders in adolescents with methylcobalamin (vitamin B12). *Sleep* 1991;14:414-418.
50453. Mayer G, Kroger M, Meier-Ewert K. Effects of vitamin B12 on performance and circadian rhythm in normal subjects. *Neuropsychopharmacology* 1996;15:456-464.
50754. Hashimoto S, Kohsaka M, Morita N, et al. Vitamin B12 enhances the phase-response of circadian melatonin rhythm to a single bright light exposure in humans. *Neurosci Lett* 1996;220:129-132.
51055. Mazurets AF, Gurevich MA, Kubyshkin VF, et al. Coenzyme metabolic therapy in infectious allergic myocarditis. *Klin Med (Mosk)* 1995;73:41-43. [Article in Russian]
51356. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. *Methods Find Exp Clin Pharmacol* 1995;17:539-544. [Abstract]
51657. Katsuoka H, Watanabe C, Mimori Y, Nakamura S. A case of vitamin B12 deficiency with broad neurologic disorders and canities. *No To Shinkei* 1997;49:283-286. [Abstract]

B12 FOR AUTISM:

MB12 Protocol - College Pharmacy

www.collegepharmacy.com/images/download/Neubrande_MB12_Protocol.pdf

B12 FOR CANCER TREATMENT:
IN CANCER, THE 4 PRINCIPAL ENDOGENOUS COBALAMINS HAVE QUITE DISTINCT EFFECTS/LACK OF EFFECT, DEPENDING ON FORM AND INCREASING DOSE. ADOCBL HAS THE GREATEST CYTOTOXIC EFFECT AT THE HIGHEST DOSE, WITH MECBL A CLOSE SECOND, HOCBL LOWER CYTOTOXIC EFFECTS, EVEN AT COMPARABLE HIGH DOSES TO ADOCBL/MECBL. CNCBL EFFECTS ARE NEGLIGIBLE:

Nishizawa et al (1995) Nishizawa Y, Yamamoto T, Terada N, Sato B, and Matsumoto K Inhibition of the proliferation of androgen- dependent sc-3 cells by methylcobalamin. (1995) *Oncol Rep*, 2 129-132.

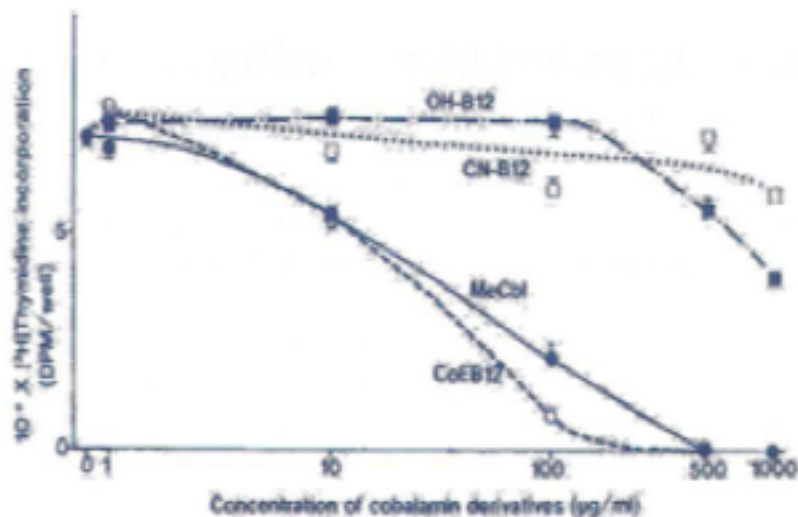


Figure 1. Effect of cobalamin derivatives on the proliferation of SC-3 cells. SC-3 cells were plated onto a 96-well plate (3x10⁴ cells/well) containing 0.15 ml of MEM with 1% DCC-treated FBS. On the following day (day 0), the medium was changed to 0.15 ml of MEM containing 2% DCC-treated FBS and 10⁻⁶ M testosterone in the absence or presence of various concentrations of cobalamin derivatives. On day 3, the cells were pulsed with [³H]thymidine (0.15 µCi/0.15 ml per well) for 2 hours at 37°C, and the radioactivity incorporated into the cells was assayed. MeCbl, methylcobalamin; CoB12, adenosylcobalamin; OH-B12, hydroxycobalamin; CN-B12, cyanocobalamin. Points, means of 4 determinations; bars, SE. The other 3 separate trials also gave similar results.

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ADOCBL SIGNIFICANTLY EXTENDS SURVIVAL IN RATS WITH CANCER:

Brazhenas et al. (1976) Brazhenas GR, Kanopkaite SI, Alenene AI, Narbutene GL, and Bartkiavichene VV [Effect of cobamide coenzyme on the growth of several transplantable tumors in rats and on prolonging the life of rats with grafted Zajdel ascitic tumor]. (1976) Prikl Biokhim Mikrobiol, 12 819-824.

MECBL SIGNIFICANTLY EXTENDS SURVIVAL OF MICE WITH VARIOUS TUMOURS WHEN TREATED DAILY FOR 7 DAYS AT A CONCENTRATION OF 50-100 MCG BY I.P. INJECTION:

Shimizu et al. (1987) Shimizu N, Hamazoe R, Kanayama H, Maeta M, and Koga S Experimental

**study of antitumor effect of methyl-B12. (1987)
Oncology, 44 169-173.**

**Tsao et al. (1990) Tsao CS, Miyashita K, and Young M Cytotoxic activity of cobalamin in cultured malignant and nonmalignant cells. (1990)
Pathobiology, 58 292-296.**

Tsao, Myashita (1993) Tsao CS and Myashita K Influence of cobalamin on the survival of mice bearing ascites tumor. (1993) *Pathobiology*, 61 104-108.

BRIEF CLINICAL TRIAL ON END-STAGE CANCER PATIENTS, USING HIGH DOSE ADENSYLCOBALAMIN -30,000 MCG DAILY- [TO WHICH SOME MECBL IS CONVERTED AFTER INJECTION], FOR TREATMENT OF INTRACTABLE PAIN, DEPRESSION, AND CACHEXIA. PATIENTS WERE SIGNIFICANTLY IMPROVED AFTER 10 DAYS treatment AND WEANED OFF MORPHINE AND PAIN KILLERS:

Caminiti (1972) Caminiti G. Treatment of advanced-stage cancer patients. Antalgic effect of Cobamamide in high doses on advanced- stage tumor carriers. (1972) *Minerva Anestesiol*, 38 305-306.

A CLINICAL TRIAL OF HIGH DOSE INJECTIONS OF CNCBL FOR TERMINAL, FAILED TREATMENT, PAEDIATRIC

NEUROBLASTOMA, AT GREAT ORMOND ST HOSPITAL FOR CHILDREN, LONDON, PRODUCED A SIGNIFICANT NUMBER OF COMPLETE REMISSIONS:

Bodian (1963) Bodian M Neuroblastoma: An Evaluation of Its Natural History and the Effects of Therapy, with Particular Reference to Treatment by Massive Doses of Vitamin B12. (1963) *Arch Dis Child*, 38 606-619.

Bodian (1959) Bodian M. Neuroblastoma. *Pediatr Clin North Am* 1959;6:449–72.

Reilly, et al. (1968) Reilly D, Nesbit ME, and Krivit W Cure of three patients who had skeletal metastases in disseminated neuroblastoma. (1968) *Pediatrics*, 41 47-51.

SYNERGY BETWEEN MECBL AND METHOTREXATE:

Arsenyan et al. (1978) Arsenyan F.G., Myasishcheva N.V., Sof'ina Z.P., Raushenbakh M.O., Rudakova I.P., Chauser E.G., and Yurkevich A.M. Influence of methylcobalamin on the antineoplastic activity of methotrexate. (1978), *Pharmaceutical Chemistry Journal*, 12 1299-1304.

COMBINATION OF HIGH DOSE CNCBL/HOCBL AND HIGH DOSE IV VITAMIN C IS TUMOUR CYTOTOXIC:

Poydock et al. (1979) Poydock ME, Fardon JC, Gallina D, Ferro V, and Heher C Inhibiting effect of vitamins C and B12 on the mitotic activity of ascites tumors. (1979) *Exp Cell Biol*, 47 210-217.

- 1. Poydock et al. (1982) Poydock ME, Reikert D, and Rice J Influence of vitamins C and B12 on the survival rate of mice bearing ascites tumor. (1982) *Exp Cell Biol*, 50 88-91.**
- 2. Poydock et al. (1984)**
- 3. Poydock et al. (1985) Poydock ME, Harguindey S, Hart T, Takita H, and Kelly D Mitogenic inhibition and effect on survival of mice bearing L1210 leukemia using a combination of dehydroascorbic acid and hydroxycobalamin. (1985) *Am J Clin Oncol*, 8 266-269.**
- 4. Poydock (1991) Poydock ME Effect of combined ascorbic acid and B-12 on survival of mice with implanted Ehrlich carcinoma and L1210 leukemia. (1991) *Am J Clin Nutr*, 54 1261S-1265S.**

- 5. Akatov (2000) Akatov VS, Evtodienko Yu V, Medvedev AI, Leshchenko VV, Solov'eva ME, Kudryavtsev AA, Lezhnev EI, and Yakubovskaya RI DNA damage and tumor cell death caused by the combined effect of vitamins B12b and C. (2000) *Dokl Biol Sci*, 373 373-375.**
- 6. Akatov (2000) Akatov VS, Evtodienko YV, Leshchenko VV, Teplova VV, Potselueva MM, Kruglov AG, Lezhnev EI, and Yakubovskaya RI Combined vitamins B12b and C induce the glutathione depletion and the death of epidermoid human larynx carcinoma cells HEp-2. (2000) *Biosci Rep*, 20 411-417.**
- 7. Medvedev et al (2001) Medvedev AI, Akatov VS, Evtodienko Iu V, Leshchenko VV, Solov'eva ME, Lezhnev EI, and Iakubovskaia RI [DNA degradation and repair in human laryngeal carcinoma HEp-2 cells after combined exposure to vitamin B12b and ascorbic acid]. (2001) *Tsitologiya*, 43 274-278.**
- 8. Medvedev et al (2001) Medvedev AI, Akatov VS, Kreshchenko ND, Solov'eva ME, Leshchenko VV, Lezhnev EI, and Yakubovskaya RI Combined**

treatment with vitamin B12b and ascorbic acid causes in vitro DNA degradation in tumor cells. (2001) *Bull Exp Biol Med*, 131 364-366.

9. MECBL OFFERS SMOKERS PROTECTION FROM PRE-LUNG CANCER CHANGES:

10.Heimburger et al. (1988) Heimburger DC, Alexander CB, Birch R, Butterworth CE, Jr., Bailey WC, and Krumdieck CL Improvement in bronchial squamous metaplasia in smokers treated with folate and vitamin B12. Report of a preliminary randomized, double-blind intervention trial. (1988) *JAMA*, 259 1525-1530.

11.ADOCBL PROPHYLAXIS AGAINST CANCER:

12.Golenko et al. (1989) Golenko OD, Ryzhova NI, and Miasishcheva NV [The modifying influence of adenosylcobalamin on the transplacental carcinogenic effect of N-nitroso-N-ethylurea in organ cultures of the kidneys of DBA/2 mice]. (1989) *Eksp Onkol*, 11 11-14

13.Tsao et al. (1990) Tsao CS, Miyashita K, and Young M Cytotoxic activity of cobalamin in cultured malignant and nonmalignant cells. (1990) *Pathobiology*, 58 292-296.

14.Golenko et al. (1991) Golenko OD, Ryzhova NI, and Miasishcheva NV [The carcinogenic activity of N-nitroso-N- ethylurea in kidney organ cultures of mice exposed transplacentally to cobalamin coenzymes and folinic acid]. (1991) *Biull Eksp Biol Med*, 111 292-294.

15.Kondo et al. (1992) Kondo H, Iseki T, Goto S, Ohto M, and Okuda K Effects of cobalamin, cobalamin analogues and cobalamin binding proteins on P388D1 mouse leukemic cells in culture. (1992) *Int J Hematol*, 56 167-177.

16.Tsao, Myashita (1993) Tsao CS and Myashita K Influence of cobalamin on the survival of mice bearing ascites tumor. (1993) *Pathobiology*, 61 104-108.

17.MECBL PROTECTS AGAINST PRE-CANCER CHANGES IN SMOKERS' LUNGS:

18.Kamei et al. (1993) Kamei T, Kohno T, Ohwada H, Takeuchi Y, Hayashi Y, and Fukuma S Experimental study of the therapeutic effects of folate, vitamin A, and vitamin B12 on squamous metaplasia of the bronchial epithelium. (1993) *Cancer*, 71 2477-2483.

19.Saito et al. (1994) Saito M, Kato H, Tsuchida T, and Konaka C Chemoprevention effects on bronchial squamous metaplasia by folate and vitamin B12 in heavy smokers. (1994) *Chest*, 106 496-499.

**REFERENCE SHOWING THE *CONCENTRATION
DEPENDENT TUMOUR CYTOTOXICITY OF MECBL,
ADOCBL, VERSUS CNCBL/HOCBL:***

20.Nishizawa et al (1995) Nishizawa Y, Yamamoto T, Terada N, Sato B, and Matsumoto K Inhibition of the proliferation of androgen- dependent sc-3 cells by methylcobalamin. (1995) *Oncol Rep*, 2 129-132.

21.Nishizawa et al. (1997) Nishizawa Y, Yamamoto T, Terada N, Fushiki S, and Matsumoto K Effects of methylcobalamin on the proliferation of androgen-sensitive or estrogen-sensitive malignant cells in culture and in vivo. (1997) *Int J Vitam Nutr Res*, 67 164-170.

22.Nishizawa et al (1999) Nishizawa Y, Yamamoto T, Tanigaki Y, Kasugai T, Mano M, Ishiguro S, Fushiki S, and Poirier LA Methylcobalamin decreases mRNA levels of androgen-induced growth factor in androgen-dependent Shionogi carcinoma 115 cells. (1999) *Nutr Cancer*, 35 195-201.

**23.EFFECT OF ADOCBL IN CANCER
CACHEXIA:**

24. Jamnik S., Lopes Santoro I., and Gagliardi Nesi D. Study of cyproheptadine and cobamamide in weight loss of patients with

lung cancer. (2001), *Revista Brasileira de Medicina*, 58 75-78.

25.PRO-APOPTOTIC EFFECTS OF MECBL:

26.Nishizawa et al (2001) Nishizawa Y, Goto HG, Tanigaki Y, and

Fushiki S Induction of apoptosis in an androgen-dependent mouse mammary carcinoma cell line by methylcobalamin. (2001) *Anticancer Res*, 21 1107-1110.

27.Goto et al. (2008) Goto GH, Katayama H, Tanigaki Y, Fushiki S, and Nishizawa Y Methylcobalamin inhibits fibroblast growth factor-8 stimulated proliferation and induces apoptosis in Shionogi carcinoma cells. (2008) *Int J Vitam Nutr Res*, 78 21-26.

DOWN-REGULATORY EFFECT OF CBL ON THE MULTI DRUG RECEPTOR IN TUMOUR CELLS:

28.Marguerite et al. (2007) Marguerite V, Beridexheimer M, Ortiou S, Gueant JL, and Merten M Cobalamin potentiates vinblastine cytotoxicity through downregulation of mdr-1 gene expression in HepG2 cells. (2007) *Cell Physiol Biochem*, 20 967-976.

29.SUCCESSFUL VERY HIGH DOSE LONG TERM DAILY TREATMENT OF CANINE TUMOURS WITH NOCBL INJECTIONS OVER 1 YEAR:

30.Bauer (2005) Bauer J.A., Morrison B.H., Tang Z. et al. In vivo anti-tumor effects of nitrosylcobalamin (NO-Cbl) against canine

carcinomas: two case studies. (2005), *AACR Meeting Abstracts*,

110-a.

31.Bauer et al. (2010) Bauer J.A., Frye G., Bahr A., Gieg J., and

Brofman P. Anti-tumor effects of nitrosylcobalamin against spontaneous tumors in dogs. (2010), *Invest New Drugs*, 28, 694-702.

32.SYNERGISTIC EFFECTS IN MURINE TUMOUR MODELS OF MECBL/HOCBL AND INTERFERON OR TAXOL:

33.Pastrak, Cruz (2005).

34.MECHANISM OF ANTI TUMOUR EFFECTS OF NOCBL:

35.Bauer et al. (2002) Bauer JA, Morrison BH, Grane RW et al. Effects of interferon beta on transcobalamin II-receptor expression and antitumor activity of nitrosylcobalamin. (2002) *J*

***Natl Cancer Inst*, 94 1010-1019.**

36.Bauer, Chawla, Serrer (2003) Chawla-Sarkar M., Bauer J.A.,

Lupica J.A. et al. Suppression of NF-kappa B survival signaling by nitrosylcobalamin sensitizes neoplasms to the anti-tumor effects of Apo2L/TRAIL. (2003), *J Biol Chem*, 278 39461-39469.

[illegible]