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].
EMAIL: wheatley.carmen@googlemail.com

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.


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:

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

Vitamin B12: the forgotten micronutrient for critical care. - NCBI
by W Manzanares - 2010

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.
******************************************************************************************


*Clinical Toxicology*, 44:17–28, 2006
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].


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

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.

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


[Clinical trials of a non-steroid protein anabolic agent in premature infants].
[Article in French]
Nivelon JL, Badinand P.
PMID: 5948903


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


[Clinical use of 5,6-dimethylbenzimidazolo-5-desoxyadenosylcobamide coenzyme (cobamide) in the premature infant].
5. MECHANISMS OF B12 IMPACT ON THE BRAIN & CNS:

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 ...


by K Okada - 2011


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 ...


by T Watanabe - 1994

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:

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

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]

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)
Myelolytic 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

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 myelolytic 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

Association between tumor necrosis factor-α and disease progression in patients with multiple sclerosis
... 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 ...

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
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
Cited by 13Related articlesAll 6 versionsCiteSave

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
Cited by 6Related articlesAll 6 versionsCiteSave

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 (PrP) 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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[PDF] researchgate.net
Getit@Grifols

**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 myelinotrophic properties) is

**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

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
Cited by 5 Related articles All 7 versions Cite Save

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
Cited by 11 Related articles All 4 versions Cite Save

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
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 Cited by 4 Related articles All 7 versions Cite Save Getit@Grifols

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
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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G Scala|
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

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

G Scalabrino, E Mutti, D Veber... - Muscle & ..., 2011 - Wiley Online Library
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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])
Clarifying the Molecular Basis of Cobalamin (Vitamin B12) Neurotrophism


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.

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)-

Neuroprotective functions of prion protein

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


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

Cited by 161Related articlesAll 4 versionsCiteSaveMore
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

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 [percnt]FVC less than 60[percnt] 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[percnt]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

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

NOTE HOW STEROIDS SIGNIFICANTLY INTERFERE WITH RECOVERY....

Methylcobalamin treatment of Bell's palsy.

Jalaludin MA1.
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:**


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


**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:

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 ...


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:


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


%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

10. **B12 FOR EPILEPSY TREATMENT:**
Intractable Epilepsy as the Presentation of Vitamin B₁₂ Deficiency in the Absence of Macrocytic Anemia

Authors Meng Lee, et al.


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 administrated 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 μM, 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 hydroxocobalamin. 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 B$_{12}$ deficiency could not be excluded, it is reasonable to assume a cause–effect relation between the documented vitamin B$_{12}$ 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 B$_{12}$ 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 B$_{12}$ 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 administrated; therefore the polyneuropathy was most likely caused by a vitamin B$_{12}$ 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 B$_{12}$ is essential for remethylation of homocysteine to methionine (6).
shown in our patient, the homocysteine level increased with the deficiency of vitamin B_{12} 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 B_{12} 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 B_{12} deficiency in the list of etiologies of epilepsy, when adult patients are first seen with unexplained recurrent seizures, even when macrocytic anemia is absent.


CrossRef | PubMed | Web of Science®

2

CrossRef | PubMed | CAS | Web of Science®

3


**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.


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AND:


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B12 FOR AUTISM:

MB12 Protocol - College Pharmacy

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:

ADOCBL SIGNIFICANTLY EXTENDS SURVIVAL IN RATS WITH CANCER:


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:


**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:**


**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:


SYNERGY BETWEEN MECBL AND METHOTREXATE:


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


2. Poydock et al. (1984)


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


11. ADOSCBL PROPHYLAXIS AGAINST CANCER:


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


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


23. EFFECT OF ADOCBL IN CANCER CACHEXIA:

25. PRO-APOPTOTIC EFFECTS OF MECBL:


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


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

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

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


34. **MECHANISM OF ANTI TUMOUR EFFECTS OF NOCBL:**
