The master key effect of vitamin B12 in treatment of malignancy – A potential therapy?

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Summary  Vitamin B12 plays a functional role in a variety of organs and body systems and the list of these organs and body systems is growing. According to our working hypothesis ("Master Key Effect") vitamin B12 has some unique functions, which are still not accepted; vitamin B12 functions to keep body systems in balance, even under the stress of severe pathology. What is the explanation for elevation of cobalamin level in oncological patients?

1. It is well known that there is a high level of vitamin B12 in different kinds of malignancy.
2. There is a positive correlation between level of vitamin B12 and the severity of the disease, the more severe the disease the higher the level of B12.
3. A number of the experimental laboratory studies indicate an inhibition in the growth of malignant cells upon use of vitamin B12.
4. There are no experimental results indicating the opposite, that vitamin B12 stimulates growth of malignant cells.
5. There is no data about toxic effect of vitamin B12 in the treatment of various diseases.

As yet I have not been able to find another explanation for high level of vitamin B12 in oncology patients other than that it is a compensatory mechanism.

Perhaps following this body’s "warning sign", we should start treatment with high doses of vitamin B12 to try to help the stabilization of normal function of the organs and systems. Laboratory researches should be continued to substantiate introduction of cobalamin as preliminary treatment of particular diseases.

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cleverer than we have thought and elevated vitamin B12 is a sign that the body is fighting disease, and that as result of this "battle", there is a mobilization of resources, and an attempt to compensate by activating biologically active substances for "repair" of defects?

Multifunctional systems in the human body need to maintain homeostasis. Man is an ideal example of a system that constantly aspires to attain optimal regulation, even under the stress of severe pathology. There seems to be universal, interchangeable, biologically active substances that regulate the system and keep it in balance. I propose that one of these substances is vitamin B12.

Why vitamin B12? Vitamin B12 plays a functional role in a variety of organs and body systems and the list of these organs and body systems is growing. It affects the peripheral and central nervous systems, bone marrow, skin and mucous membranes, bones, and vessels, as well as normal development during childhood. Vitamin B12 (cobalamin) is unique among all the vitamins in that it contains not only a complex organic molecule, but also an essential trace element, cobalt. Vitamin B12 plays an important role in DNA synthesis and has important immunomodulatory and neurotrophic effects. According to our "working hypothesis" vitamin B12 has some unique, but still unrecognized functions. It is possible that even when the serum cobalamin level is normal, treatment with vitamin B12 can correct defects caused by other biologically active substances. In our studies treatment with vitamin B12 has been successful in the treatment of recurrent aphthous stomatitis of any etiology, irrespective of B12 level in the blood before treatment! We call this phenomenon the "Master Key Effect" [1]. In this article I would like to review known data concerning the connection between vitamin B12 and malignancy and I will attempt to explain this according to the "Master Key Effect" hypothesis.

Elevated levels of serum cobalamin may be a sign of a serious, even life-threatening, disease. Hematologic disorders, like chronic myelogeneous leukemia, promyelocytic leukemia, polycythemia vera and also the hypereosinophilic syndrome, can result in elevated levels of cobalamin. Not surprisingly, a rise of the cobalamin concentration in serum is one of the diagnostic criteria for the latter two diseases. Several liver diseases, like acute hepatitis, cirrhosis, hepatocellular carcinoma and metastatic liver disease, can also be accompanied by an increase in circulating cobalamin. This phenomenon is caused predominantly by cobalamin release during hepatic cytolysis and/or decreased cobalamin clearance by the affected liver. Altogether it can be concluded that an observed elevation of cobalamin in blood merits a full diagnostic examination to assess the presence of disease [2].

Carmel et al. studied 139 patients with non-hematologic malignancy in order to define the incidence of vitamin B12-related abnormalities and correlate them with clinical findings. High serum vitamin B12 level usually implied a poor prognosis in a patient with cancer. However, while most such patients had hepatic and other metastases, hepatic involvement was not universal nor did most of the patients with hepatic disease have high vitamin B12 levels [3].

The relationship between vitamin B12 levels and survival was studied in a group of 161 terminally ill cancer patients. Their average age was 74.7 years. The length of survival decreased with the increase in serum vitamin B12 levels. In multivariate analyses, C-reactive protein was the most important prognostic factor in this population, and vitamin B12 provided information independent of CRP in predicting survival. These data indicate that an elevated serum vitamin B12 level is a predictive factor for mortality in patients with cancer, independent of CRP or other factors [4].

In one prospective study [5] researchers found high vitamin B12 levels in patients suffering from prostate cancer, and their conclusion was that cobalamin stimulates prostate cancer development...

The effect of cobalamin on the proliferation of malignant cells has been examined in vivo and in vitro in numerous studies [6–8]. Methylcobalamin inhibited the proliferation of androgen-sensitive SC-3 cells (a cloned cell line from Shionogi mouse mammary tumor, SC115) in culture at the concentration of 100–300 μg/ml. An inhibitory activity of methylcobalamin on the proliferation was also observed in other cell lines (estrogen-sensitive B-1F cells from mouse Leydig cell tumor and MCF-7 cells from human mammary tumor) at the concentration of 500 μg/ml. Moreover, large doses of methylcobalamin injected intraperitoneally (100 mg/kg body weight/day) were non-toxic and suppressed the tumor growth of SC115 and B-1F cells in mice fed a vitamin B12 deficient diet. These results indicate that methylcobalamin inhibits the proliferation of malignant cells in culture and in vivo and propose the possibility of methylcobalamin as a candidate of potentially useful agents for the treatment for some malignant tumors [6].

Malignancies are common in the digestive tube, although with unequal distribution among segments. The aim of a study conducted by Kurbel et al. was to compare available interpretations of the low cancer incidence in the small bowel and
high incidence in the large bowel. Small bowel mucosa is the main absorptive part of the digestive tube with absorption rates for various nutrients so high that they can even be considered as clearances from the intestinal content. Consequently, these nutrients are not present in the large bowel. An alternative explanation is that an absorbable protective substance from the intraluminal content might protect the mucosa from malignant transformations. It can be speculated that if there are any cytoprotective substances in the digested food their effect would be expressed mostly in the absorptive small intestine, leaving the large bowel mucosa unprotected. Vitamin B12 might be a possible candidate for this role. The results indicated that cobalamin availability showed similar distribution, available in low incidence segments and unavailable in high incidence segments [9].

Cobalamin carrier proteins, the transcobalamins (TC), were found to be elevated during trauma, infections and chronic inflammatory conditions. This remains un-explained. It is proposed that such TC elevations signal a need for cobalamin central to the resolution of inflammation [10]. Animal and human clinical data suggest that high dose cobalamin may prove a promising approach to systemic inflammatory response syndrome (SIRS), sepsis, septic and traumatic shock. Septic shock has an extremely high mortality rate, with approximately 200,000 people dying from sepsis annually in the US. The high mortality results in part from severe hypotension secondary to high serum nitric oxide (NO) concentrations. Initially, vitamin B12 was proposed for use as a scavenger and cytoprotective agent to bind and inactivate NO [11]. The use of vitamin B12 as a carrier to deliver nitric oxide into tumor cells is novel [12,13]. A number of studies have demonstrated that cobalamin is important in maintaining differentiation, proliferation, and metabolic status of cells. NO inactivates vitamin B12 and methionine synthase, thereby impairing DNA formation and, consequently, new cell formation. The vitamins: folic acid, B12 and B6 and B2 are the source of coenzymes which participate in one carbon metabolism [14]. The overall functions of vitamin B12, as a source of coenzymes in intracellular recycling of methionine, in methionine synthase reaction, in the prevention of chromosome breakage, in methylation, and in maintaining a one-carbon metabolic balance, have been reviewed. NO can cause both apoptosis and necrosis, making it a good candidate for antitumor therapy. In one investigational study it was shown that complex NO-cobalamin inhibited tumor growth in vivo and in vitro by activating the extrinsic apoptotic pathway [12]. Inhibition of methionine synthase also creates a “methylfolate trap”, analogous to what occurs in vitamin B12 deficiency [15,16]. Haematological sequel of vitamin B12 deficiency are attributed to disturbed DNA synthesis, but vitamin B12 itself plays no role in DNA biosynthesis. A proposed explanation for this is the methylfolate trap hypothesis. This hypothesis states that B12 deficiency impairs overall folate metabolism, because 5-methyltetrahydrofolate (5MTHF) becomes metabolically trapped. This trap results from the fact that 5MTHF can neither be metabolised via the methionine synthase pathway, nor can it be converted to its precursor, methylenetetrahydrofolate [17]. Methionine metabolism and transmethylation are frequently altered in cancer cells. The alteration is often expressed as an inability of the cancer cells to grow when methionine is replaced by homocysteine in the culture medium, a condition that allows the growth of normal cells. This metabolic defect is termed methionine dependence [18]. Methionine dependence is unique to cancer cells and defined as the inability to grow in a methionine-deprived environment, even if supplemented with the metabolic precursor homocysteine. Cobalamin-dependent methionine synthase catalyses the formation of methionine and tetrahydrofolate from homocysteine and methyltetrahydrofolate, thus linking the methionine and folate pathways [19].

Interactions between adaptive and selective processes are illustrated in the model of recursive causality as defined in Rupert Riedl’s systems theory of evolution [20]. One of the main features of this theory, also termed the theory of evolving complexity, is central to the notion of recursive or feedback causality — the idea that every biological effect in living systems in some way feeds back to its own cause. There is a hypothesis that “recursive” or “feedback” causality provides a model for explaining the consequences of interacting genetic and epigenetic mechanisms, which are known to play a key role in development of cancer [21]. Epigenetics includes any process that alters gene activity without changes of the DNA sequence. The most important epigenetic mechanisms are DNA-methylation and chromatin remodeling. Hypomethylation of so-called oncogenes and hypermethylation of tumor suppressor genes appear to be critical determinants of cancer. Folic acid, vitamin B12 and other nutrients influence the function of enzymes that participate in various methylation processes by affecting the supply of methyl groups into a variety of molecules which may be directly or indirectly associated with cancerogenesis. The enzymes also play a role in development and differentiation of cells and organisms and thus illustrate the close association between evolutionary and developmental
mechanisms. This enabled new ways to understand the interaction between the genome and environment and may improve biomedical concepts, including environmental health aspects where epigenetic and genetic modifications are closely associated. For example, recent observations showed that methylated nucleotides in the gene promoter may serve as a target for solar UV-induced mutations of the p53 tumor suppressor gene [22]. This illustrates the close interaction of genetic and epigenetic mechanisms in cancerogenesis resulting from changes in transcriptional regulation and its contribution to a phenotype at the micro- or macro-evolutionary level. The above-mentioned interactions of genetic and epigenetic mechanisms in oncogenesis defy explanation by simple linear causality, like the continuing adaptability of complex systems. They can be explained by the concept of recursive causality and has introduced molecular biology into the realm of cognition science and systems theory; based on the notion of feedback or recursive causality, a model for epigenetic mechanisms with relevance for oncology and biomedicine is provided.

As was mentioned above, every system in mechanics and nature seeks some sort of balance. The human body, as an example of a multifunctional system, is no exception to this rule. Upon an imbalance or disease, the organism tries to compensate by mobilization of its inner resources. There is an on-going process of accumulation of biologically active substances to fight disease. Parenthetically, one of conventional, as well as non-conventional, ways of treating diseases is using a medicine (substance) or different physical methods which are able to activate these substances. The human organism has been evolved over millions of years and thus, it is reasonable to expect it to react appropriately. Unfortunately, this battle for balance is not always successful. Being stressed the organism "shows" us signs of distress and "calls for help". The only thing that we must do is to know how to read them.

I propose that a high level of vitamin B12 in oncological diseases is such a sign. What is the basis for such hypothesis? The basis for such a proposal can be summarized as follows:

1. The well known fact that a high level of vitamin B12 is present in different kinds of malignancy.
2. There is a positive correlation between level of vitamin B12 and the severity of the disease, the more severe the disease the higher the level of B12.
3. A number of the experimental laboratory studies indicate an inhibition in the growth of malignant cells upon use of vitamin B12.
4. There are no experimental results indicating the opposite, that vitamin B12 stimulates growth of malignant cells.
5. There is no data about toxic effect of vitamin B12 in the treatment of various diseases. Sometimes there is necessary to use very high doses to achieve therapeutic effect [23]. Vitamin B12 is the only known vitamin that does not have any toxic effect even in such cases.

As yet I have not been able to find another explanation for high level of vitamin B12 in oncology patients other than that it is a compensatory mechanism.

Possibly following this body's "warning sign", we should start preliminary treatment with high doses of vitamin B12 to try to stabilize normal body functioning of the various organs and organ systems.

Analyzing the literature of research in cancer which investigated the association with vitamin B12, I do not understand why these studies indicating a positive results did not investigate this association further. Perhaps this can be explained as follows:

1. Preference for treatment with vitamin B12 to modern perspective medicines does not seem appropriate for oncology patients who do not have time for such kind of experiments (an ethical question).
2. The unconvincing or unequivocal results of the research, which could be a consequence of using not high enough doses of vitamin B12, do not encourage oncologists to try vitamin B12 treatment.
3. The paradoxical dilemma, in which the solution is so close, well-known, accessible, and cheap, makes it hard to believe that vitamin B12 may be effective in the treatment of oncology diseases.

Laboratory research should be continued even if it might disprove the above-stated hypothesis. And who knows? It may in fact provide us with more evidence of the effectiveness of vitamin B12 in the treatment of malignant diseases.

References


