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The Elusive (and Maybe Non-Existent) Connection Between Vitamin B12 and HIV

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Vitamin B12, or cobalamin, refers to any member of a group of large, cobalt-containing corrinoids and is unique among the vitamins in that it contains not only a complex organic molecule, but also an essential trace element, cobalt. Cobalamin can only be synthesized by microorganisms and is therefore present in vegetables, fruits, grains, and grain products only as a result of bacterial contamination. The main source of this vitamin is animal and, to a lesser extent, dairy products, where it can accumulate as a result of bacterial synthesis. It is also thought that some absorbable B12 is supplied by bacteria in the small intestine (National Research Council, 1993.) The small intestine is also the site for B12 absorption, where its interaction with receptor sites in the ileum is facilitated by interaction with a specific binding glycoprotein, intrinsic factor, secreted in the stomach. Another protein, transcobalamin II, is responsible for the transport of B12 from the intestinal mucosa to cells. Vitamin B12 has a long biological half life due to the fact that it is reabsorbed from the bile, a fact that explains why people who eat no animal products develop Vitamin B12 Deficiency only after 20 to 30 years (National Research Council, 1993).

The problems associated with Vitamin B12 deficiency can be severe, including anemia and demyelination of the spinal cord, brain, and optic and peripheral nerves. Even among vegetarians, however, the incidence of dietary vitamin B12 deficiency are rare; most cases result from decreased absorption, often due to insufficient production of intrinsic factor.

During the late 1980's, clinicians began to notice that low serum levels of B12 were frequently seen in AIDS patients. The first group of researchers to look into the relationship between B12 and AIDS found that this was the case not only in 36% of the AIDS patients they studied, but also among their "presumably healthy" homosexual patient population (Burkes et al, 1987). Even more interesting was the fact that none of these patients had clinical or hematologic evidence of B12 deficiency, and only one evidenced impaired B12 absorption. Subsequent papers echoed these findings, observing low serum B12 levels in up to one third of all HIV patients, but still lacked any explanation as to their significance (Rule et al, 1994).

Further work confirmed that B12 depletion was also found in patients infected with HIV who were asymptomatic, leading to the idea that B12 depletion could serve as an early marker for infection. A study which followed 218 patients seropositive for HIV over 2 1/2 years and found that 64% had declining B12 levels over this time period, with 10% progressing to a deficiency state (Rule et al, 1994). This same study noted that of its 9 subjects that progressed to AIDS over the 2 1/2 year period, 7 showed falling serum B12 levels, suggesting that this might actually be a marker for HIV disease progression. Though CD4 counts also declined over the study period, these drops did not correlate with those in serum B12, further muddying this connection between vitamin B12 and HIV.

Baum et al (1995) also attempted to correlate B12 levels with CD4 counts, but came to very different conclusions. Their study showed significant decreases in CD4 counts in subjects who became B12 deficient over a 6 month study period and showed that a change in B12 levels from deficiency to adequacy was associated with an increase in CD4 cell count and a significant improvement in the AIDS index, a measure of disease progression. Patients lowest in serum B12 experience more rapid drops in CD4 counts and more rapid progression of AIDS. While these results are very suggestive of some link between B12 levels and the progression of AIDS or HIV infection, it is important to note that they do not imply that a drop in B12 facilitates disease progression or that supplementation of B12 is curative.

As puzzling as the link between B12 and HIV is the mechanism by which the vitamin becomes depleted during the course of the disease. As mentioned previously, Burkes' study (1987) concluded that malabsorption was not commonly responsible; tests indicated that only one patient's deficiency could be explained this way. Herzlich (1992) disagrees, however, contending that malabsorption is responsible and is due at least in part to a decreased intrinsic factor secretion as a result of HIV infection. Rule et al (1994) concurred that malabsorption is the most likely mechanism underlying the B12 deficiency associated with AIDS or HIV, but suggest that it is not a lack of intrinsic factor that is responsible. They cite the presence of a specific HIV antigen, p24. Found in the intestinal mucosa of patients at all stages of the disease who present with gastrointestinal complaints, this antigen might lead to the partial villus atrophy and subsequent absorption problems which are commonly seen in AIDS patients. It is also possible that malabsorption of B12 is just one symptom of a panenteropathic process which also inhibits uptake of many other nutrients (Ehrenpreis et al, 1994). Other theories assert that malabsorption is due to autoimmune reaction to gastric

parietal cells, presence of antibodies to intrinsic factor, excessive ileal acid production as a result of HIV infection (Harris and Candeloro, 1991), or to opportunistic infections which reduce secretion of gastric and pancreatic enzymes necessary to split B12 from food (Rule et al, 1994).

Yet another, less simplistic, theory explaining reduced levels of B12 seen in HIV and AIDS patients suggests that the defect is not in absorption of the vitamin, but in its transport and delivery to cells. Herbert (1990) hypothesizes that HIV detaches transcobalamin II receptors from the cell surface, reducing the cell's ability to uptake B12. His work has shown that B12 deficient cells have fewer surface receptors for this cobalamin transport protein and suggest that this protein might be an early and sensitive sign of B12 deficiency, just as an increase in transferrin signals iron deficiency (Herbert et al, 1990).

Perhaps the best explanation of the mechanism behind the B12 deficiency seen in HIV infection and AIDS is that it is multifactorial. Clearly, defects in absorption and metabolism have been implicated, as have direct effects of HIV on the intestinal mucosa and indirect affects via induction of autoimmune responses. There is consensus, however, that given the questions regarding the ability of these patients to absorb B12, the best way to treat its deficiency is by intramuscular injection (Herbert et al, 1990; Baum et al, 1994).

A common illness seen in AIDS patients in the symptomatic phases of the disease is AIDS dementia complex, which involves abnormalities in cognition, behavior, and motor functions (Beach et al, 1992). The presence, timing, and extent of these symptoms varies widely; AIDS dementia complex is the first symptom of AIDS in 10% of patients and a number of groups have shown cognitive changes during the asymptomatic stages (Beach et al, 1992). Since Vitamin B12 has been associated with a variety of neurological and psychiatric disorders, it has been postulated that the low levels of this vitamin in AIDS patients play a role in the cognitive changes seen in this disease. Beach (1992) found B12 levels correlated with decreased information processing speed and visuospatial problem-solving abilities and suggest that the differences in serum levels of this vitamin might account for the differences in the proportion of patients which show cognitive impairment. Herzlich and Schiano (1993) went a step further, drawing parallels between AIDS dementia complex and neuropsychiatric manifestations of vitamin B12 deficiency and suggesting that the vitamin may have a curative effect on the cognitive impairment seen in AIDS patients. They report the case of one patient with advanced AIDS dementia complex who also was deficient in B12. Following a 10 day course of treatment with B12, the patient's symptoms resolved over the following 2 months. Since B12 deficiency occurs in specific organs and systems at different times, Trimble (1993) attempted to resolve its role in AIDS dementia complex by looking at levels within the CSF of AIDS patients and comparing those values to levels seen in known B12 deficient patients and in normal controls. It was found that HIV patients had normal levels of B12 in their central nervous system and lacked, at all stages of the disease, lacked sensitive markers of B12 deficiency. These workers concluded that although B12 deficiency is seen in up to 50% of HIV-positive patients, it is a secondary factor. As such, it could -- as in any other clinical situation -- cause neuropsychiatric problems, but is not a pathogenic factor in HIV-related neurological disease.

It is clear that much work needs to be done in order to clarify the connection between and significance of Vitamin B12 levels and HIV-related disease. Due to the multifactorial nature of this disease, current studies are full of confounding and offer little more than observations of correlation between vitamin B12 levels and other parameters. Though low B12 levels have been found consistently among HIV-positive subjects, there is no consensus as to what these changes result from or what they indicate. There is even some disagreement as to whether the changes are not merely laboratory artifact. Nonetheless, the importance of understanding the possible connection between B12 and HIV infection is underlined by the fact that malnutrition is often the cause of death following HIV infection (Herbert, 1990). Understanding the significance of B12 levels in HIV-positive and AIDS patient might not only enable clinicians to monitor disease progress, but offer insight into other metabolic and nutritional changes which play a role in this disease process.

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