Mean corpuscular volume and other concerns in the study of vitamin B-12 deficiency: epidemiology with pathophysiology

Dear Sir:

The controversy surrounding folate effects on vitamin B-12–deficient patients may never be resolved, in part because attempts through population surveys often founder on pathophysiology. The deeper urgency, therefore, may be to repair systemic weaknesses in the ways in which vitamin B-12 deficiency is studied and perceived today. Brouwer and Verhoef (1) and Wyckoff and Ganji (2), in their editorial and article, respectively, in a recent issue of the Journal, show the problem with their call to abandon a basic clinical principle (ie, “by now, every physician should know that measuring MCV does not give any clue to whether the patient has a vitamin B-12 deficiency”). For the sake of their patients, if nothing else, physicians should ignore this advice. We train them to pay close attention to mean corpuscular volume (MCV) regardless of hemoglobin concentration because macrocytosis is an early diagnostic harbinger of serious vitamin B-12 deficiency (3). A rising MCV precedes the anemia by months, and nonmacrocytic anemia never results from vitamin B-12 deficiency (unless microcytic anemia coexists).

Patients with symptomatic vitamin B-12 deficiency occasionally come to medical attention without macrocytosis (4), and macrocytosis often has other causes; thus, as with everything else, MCV must be interpreted wisely. However, what Brouwer and Verhoef are reacting to is the dearth of macrocytosis that characterizes population surveys. The reaction is valid only if evidence supports giving clinical disease and isolated biochemical changes equal weight in the study of vitamin B-12 deficiency. No such evidence exists. Vitamin B-12 deficiencies are not created equal, and they differ in far more serious vitamin B-12 deficiency (unless microcytic anemia coexists).

On the other hand, there is overt, “clinical” vitamin B-12 deficiency, which is marked by hematologic (eg, macrocytosis) or neurologic abnormalities, or both, and which is a medical issue. An often unappreciated key to its serious nature is that malabsorption involving intrinsic factor (IF)–related failures underlies >95% of all clinical cases (6). This severe form of malabsorption typically guarantees that deficiency, even if mild, will progress relentlessly if left untreated. Fortunately, clinical deficiency is uncommon. It represents <10% of all low vitamin B-12 concentrations in most surveys (5, 7, 8).

On the other hand, there is “subclinical” vitamin B-12 deficiency, which must be distinguished from clinical deficiency, and which consists of isolated, mild biochemical changes that are consistent with vitamin B-12 deficiency, although not necessarily specific to it (5, 9). Lacking clinical manifestations (including anemia and MCV elevation), subclinical deficiency is discovered either accidentally or in population surveys, where it accounts for almost 70% of all low vitamin B-12 concentrations, whereas most of the remainder are falsely low vitamin B-12 concentrations (5, 7-9). Subclinical deficiency usually behaves very differently than clinical deficiency in important ways beyond simply being milder. Because nearly all studies agree that subclinical deficiency rarely arises from IF-related malabsorption (5, 9), progression from subclinical to clinical deficiency is not ensured (the cause of most subclinical deficiencies is unknown, and the rest arise from the usually mild food-vitamin B-12 malabsorption or chronic dietary insufficiency, each of which has a very slow and sometimes unsteady course). Observational reports indeed suggest that progression is uncommon (5, 10, 11). It is not known whether subclinical deficiency is even susceptible to the folate-related neurologic progression proposed for clinical deficiency. It can be plausibly argued that documentation of malabsorption predicts the likelihood of progression and the need for intervention better than do biochemical data.

Thus, most clinical (medical) and subclinical (biochemical) deficiencies are pathophysiologically distinct entities with very different origins, characteristics, and expectations, rather than just sequences in one common progression. Yet the current literature makes few pathophysiologic distinctions. Population surveys traffic almost exclusively in subclinical deficiency but affix their conclusions equally to all vitamin B-12 deficiency—the MCV opinion in the editorial by Brouwer and Verhoef is an obvious consequence. Moreover, assumptions travel in both directions, such as the unsupported belief that subclinical deficiency progresses as inevitably and requires treatment as much as does clinical deficiency.

The fact is that neither the natural course of subclinical deficiency nor the benefits of vitamin B-12 treatment have been determined in prospective, controlled studies. Some reports suggest that the biochemical course of subclinical vitamin B-12 deficiency is static or evanescent more often than progressive and that the clinical course may be benign (5, 10, 11). Prospective study of chronic subclinical vitamin B-12 deficiency, including its various hypothesized health risks, is overdue. The studies must be pathophysiologically grounded, so as to avoid unwarranted assumptions and their progeny, unwarranted conclusions and recommendations. The advocacy of Brouwer and Verhoef for dietary vitamin B-12 fortification is an example of pathophysiologically debatable recommendations: it is precisely the persons who have progressive deficiency, including neurologic deterioration, who are unlikely to benefit from fortification, because of malabsorption (5). Absorption will be robust in those who need vitamin B-12 least.

Brouwer and Verhoef also did not think through what could possibly supplant MCV data in clinical settings or in surveys involving health consequences. Their call simply for more biochemical tests misses the main point. Only hematologic data (not only MCV but also neutrophil segmentation) can speak to the presence or masking of megaloblastic anemia, and only neurologic data can speak to neurologic consequences. In their article in the same issue of the Journal, Wyckoff and Ganji (2) considered MCV but not its nuances; they ignored alcohol abuse, the most frequent cause of MCV elevation, and, as a common problem in the aged, probably a major confounder of their data and conclusions.

Surveying broad populations for vitamin B-12–deficient persons truly at risk of folate-mediated hematologic masking or neurologic deterioration is like searching for a needle in a haystack. To ignore MCV encourages mistaking many biochemical straws for that particular clinical needle. Wyckoff and Ganji had already overexpanded their haystack by relying on serum vitamin B-12 alone to define deficiency, even though 22–42% of low vitamin B-12 concentrations are falsely low (7, 8), and by inflating their vitamin B-12 criterion for “deficiency” well into the normal reference interval, which added a few more cases of subclinical deficiency along with many more without any deficiency whatsoever (5, 9). When the Food and Drug Administration mandated folate fortification, it urged close monitoring of adverse consequences for vitamin B-12 status. In providing biochemical surveys largely devoid of pathophysiologically and clinically relevant information, the scientific community has not met the challenge. The deeper fault may lie in misperceptions about vitamin B-12 deficiency.

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LETTERS TO THE EDITOR 1963

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Reply to R Carmel

Dear Sir:

Dr Carmel states that mean corpuscular volume (MCV) is an important marker of serious vitamin B12 deficiency. He also argues that it is important to distinguish clinical vitamin B12 deficiency from subclinical deficiency when discussing possible adverse effects of supplemental folic acid. Furthermore, he makes the case that patients with severe vitamin B12 deficiency are unlikely to benefit from fortification with vitamin B12.

In our editorial, which ended with the suggestion that folic acid may have important health effects for a large group of elderly, we drew a parallel between vitamin B12 deficiency and cognitive decline. In conclusion, although it is not a solution for patients who lack intrinsic factor, fortification with vitamin B12 along with folic acid may correct the otherwise unnoticed low vitamin B12 status in elderly. Moreover, it may have other positive health effects, e.g., on cognitive performance. Recent research shows that low vitamin B12 status is associated with more rapid cognitive decline (5). However, randomized controlled clinical trials will have to show whether vitamin B12 supplementation can indeed delay cognitive decline. In conclusion, although it is not a solution for patients who lack intrinsic factor, fortification with vitamin B12 along with folic acid may have important health effects for a large group of elderly.

Petra Verhoef is an employee of Unilever, which markets food products, some of which are enriched with B vitamins. Neither of the authors had any personal or financial conflict of interest.

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REFERENCES