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CORRESPONDENCE

DIAGNOSIS OF COBALAMIN DEFICIENCY

To the Editor:

Stabler et al[1] have made an exceedingly important contribution to the understanding of how cobalamin (Cbl) deficiency affects people. The absence of anemia in the presence of neuropsychiatric manifestations might suggest that the bone marrow has escaped the deficiency, but I doubt that such an interpretation was intended. Earlier studies of the same syndrome reported the examination of the bone marrow,[2-5] and usually typical abnormalities were observed. The megaloblastosis may be expressed to a greater degree in the granulocytic series than in the erythrocytic series.[3,4] Jewesbury[3] described two patients with pernicious anemia (PA) who presented neurologically but whose bone marrow was normal. However, after 1 and 3 years without treatment, respectively, and worsening of their disease, the bone marrow became megaloblastic in both cases. Thus, it appears that the neuropsychiatric presentation does not represent the absence of any marrow deficiency but a different expression of body Cbl deficiency, and if the deficiency is permitted to evolve naturally the expression of the depletion will expand.

Recently I was invited by a group of hematologists to discuss the 1988 study of the same topic by the Denver-New York collaboration.[6] The concept of neurologic expression of Cbl deficiency in the absence of anemia made no sense to many of those present. Although perhaps not well documented, there seems to be a common belief that "neurologic" PA is simply advanced PA, that the anemia per se in some way causes the neurologic manifestations, that transfusion is part of the appropriate treatment, and that Cbl should be given more frequently and in larger amounts. If it can be appreciated that the human brain as well as the bone marrow contains[7] and needs Cbl, then the concept becomes quite understandable.

Bastrup-Madsen[4] pointed out some years ago that the erythrocyte count is a more sensitive indicator of developing Cbl depletion than is the hemoglobin (Hb) or hematocrit (Hct). As the process evolves, erythrocytes tend to become fewer but larger, thus preserving for a time those indicators that relate to cell mass and content. The two unpublished cases of Cbl deficiency in Table 1 illustrate the point. One had moderate and the other mild neuropsychiatric manifestations.

As a generalization, if one is searching for an early expression of Cbl, or folate, deficiency in the bone marrow, observe the red blood cell (RBC) count; if for iron deficiency, observe the Hb.

I doubt that the ways in which Cbl deficiency can affect patients have changed. Included in the series of Stabler et al[1] were seven neurologically affected, and responding, patients without either anemia or an increased mean corpuscular volume (MCV). Based on 86 responders, this is an incidence of 8%. In my own series of 40 with PA only, collected from 1951 through 1964, three had neurologic symptoms without anemia (7.5%). Two of the earlier reports[3,4] do not give the total patient base, but the investigators were able to accumulate six and seven well-studied cases, respectively. What has changed is the way in which Cbl deficiency comes to the attention of the physician. My 40 1965 cases came to the hospital because they were symptomatic.[5] The RBC count was less than $2.0 \times 10^6/\mu L$ in 51% of the cases. Although the MCV was not increased in 19% of the cases, it was greater than 130 fL in 24%. In a more recent series from the same hospital and by the same investigator,[8] the RBC count of four not previously known patients with PA ranged from 3.0 to 4.7, and the MCV was 100 to 102. Their symptoms of Cbl deficiency, some neuropsychiatric, tended to be mild. As a point of interest, the annual rate of accrual had not changed in 30 years. These recent patients were uncovered by an almost random screening by measurement of the serum Cbl, and this has become a common route for the detection of Cbl deficiency today. If long periods of time without treatment are required for full evolution of the clinical spectrum, but cases are now being detected in an early stage, physicians must be alert to an increasing percentage of cases limited to one organ system, whether it be blood or nervous system.

Table 1. CBC in Cbl Deficiency

	RBC ($\times 10^6/\mu L$)	Hb (g/dL)	Hct (%)	MCV (fL)
Pretreatment	3.3	13.4	40.2	124
Posttreatment	4.5	13.1	39.4	86
Pretreatment	3.9	13.4	37.7	96
Posttreatment	4.3	13.5	39.2	92

Conley and Krevans provided a novel facet to this story of the primarily neurologic expression of Cbl deficiency.[2] Their study was conducted during the era when multivitamin preparations contained folic acid. Four of their PA patients were receiving 4.5 to 8 mg/d in this way. Although some of their cases of primarily neurologic PA were of the more conventional type, others may have lost their anemia by the intake of folate.

The attempt to present the many faces of Cbl deficiency to enhance early diagnosis and treatment has been long and frustrating. The dissociation of the anemia and the neurologic expression goes back for almost a century,[9] and according to the analysis of current textbooks by the present investigators, it still is not well accepted. The study by Stabler et al is likely to succeed where others have failed. To accumulate a large number of cases in a short time, the approach had to be retrospective. However, the proper questions were framed in advance of the analysis and rigid criteria were adhered to in obtaining the answers. The study incorporated two essential measures of actual tissue depletion. The objective response to the administration of Cbl is a tool available to all physicians. The measurements of blood methylmalonic acid and homocysteine are not only valuable aids in the detection of tissue depletion, but constitute an objective measure of response. In my own recent study it soon became obvious that patients with Cbl deficiency found in a present-day tertiary care hospital may have fewer symptoms of PA than those of an earlier era, but multiple complicating illnesses, sometimes severe, are more common. A patient may well have two to three causes of his anemia and his blood may simply be unable to respond when a Cbl deficiency is corrected. The blood metabolites will still, nevertheless, respond to appropriate treatment, and this may be the only available objective evidence of the correction of the Cbl deficiency.

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RESPONSE

We would like to thank Dr Hall for his gracious comments and state that we agree with the points that he has raised in his letter. Clearly, there are some patients with cobalamin deficiency in whom the erythrocyte count will be abnormal in the face of a normal hemoglobin or hematocrit. Nevertheless, there will still be others who are cobalamin deficient and respond to cobalamin therapy even though the erythrocyte count is normal. The same is true with regard to the hemoglobin, MCV, LDH, bilirubin, white blood cell count, platelet count, etc. Thus, our study shows that the normality of any laboratory test cannot be used to exclude the diagnosis of cobalamin deficiency, and that this diagnosis needs to be pursued in every patient with unexplained hematologic or neuropsychiatric abnormalities of the kind caused by cobalamin deficiency.

We also agree with Dr Hall's comments concerning the utility of measurements of serum methylmalonic acid and homocysteine both before and after cobalamin therapy. These assays, which are now widely available through a number of national reference laboratories, can establish the diagnosis of cobalamin or folate deficiency before therapy in most patients and are particularly useful, as Dr Hall points out, in patients with subtle manifestations of cobalamin deficiency or in those who have additional complicating illnesses.

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