To the Editor:

The interesting report by Zeitlin and associates of a new case of transcobalamin II (TC-II) deficiency raises several issues worth considering further. The most striking of their observations is the apparent symptom-free maintenance of their patient with oral cobalamin therapy. A note of caution is necessary, however. While various regimens may keep TC-II-deficient patients symptom-free and overtly normal, using the minimal therapy that does so may not be ideal, particularly in the developmental years. Less clinically apparent organ dysfunction may remain incompletely corrected. An obvious example may be persistent cobalamin malabsorption whose mechanism is unknown but could be due to cobalamin depletion of gut cells, as suggested previously. Malabsorption of other substances may conceivably also exist. Another possibility of uncorrected long-term dysfunction could be in the reproductive system. Since TC-II is present in semen in greater concentrations than everywhere else (its presence in the female reproductive system has not been studied but may be similar), reproductive function may be particularly sensitive to TC-II and cobalamin depletion. The answers to such concerns are not yet available. Subtle dysfunction of various organ systems may not become evident until more time has elapsed. While oral therapy has obvious advantages over injections, our limited means of assessing cobalamin status in most tissues dictates caution in deciding on ideal therapy.

The albumin-sized binder of cobalamin that Zeitlin et al observed is also noteworthy. In the two cases of TC-II deficiency that my associates and I recently described in considerable detail, relatively large amounts of this binder, in both "apo" and "holo" form, were found before treatment. We found that this binding seemed to increase greatly with cobalamin therapy. What makes the albumin-sized binder even more intriguing is that slightly increased amounts also seemed to occur in the heterozygous relatives of our TC-II-deficient patients. R-binder deficient patients also have detectable albumin-sized binder as may other patients occasionally, but none to the same extent that homozygous TC-II-deficient patients do, particularly after therapy. It remains unclear whether such elevation is a compensatory mechanism, a part of the binder abnormality syndrome, or merely the unmasking of a relatively common phenomenon.

Finally, I would like to comment on a technical point and on the uncleness of whether the patient described by Zeitlin et al had total absence of TC-II or not. It is unfortunate that fluoride-EDTA anticoagulant was used. Since this anticoagulant causes osmotic dehydration of red cells and significant dilution of plasma, plasma values are regularly falsely lowered. The need to anticoagulate the blood sample arises only when the R-binders are of concern. An ideal anticoagulant for that purpose has not been found, but EDTA alone may be the best available choice. When TC-II is being studied, serum serves as well as plasma. Although Zeitlin et al state that their patient had total absence of TC-II, their Table I indicates that she had some TC-II, 6.5 to 21 ng/L of unsaturated TC-II by chromatographic determination and ~50 ng/L of total TC-II by radioimmunoassay; moreover, these amounts were probably underestimated because of the choice of anticoagulant. If indeed present, even in such greatly reduced amounts, this TC-II might explain the patient's responsiveness to oral cobalamin therapy.

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REFERENCES


To the Editor:

In reply to Dr Carmel's letter, the best evidence we have for a total absence of transcobalamin II (TC-II) in our patient comes from radioimmunoassay. The value obtained was below the first point on the calibration graph and addition of further serum from the patient made no difference. We have no immunologic confirmation that the small amount of protein binding cobalamin in the TC-II position on chromatographic determination is in fact TC-II. We agree that fluoride-EDTA is not the best anticoagulant for TC-II estimations; however, there was no significant difference in the TC-II unsaturated B12 binding capacity when we used serum instead of fluoride-EDTA plasma.

That tissue requirement for cobalamin appears variable is well illustrated by our case and we take the point that the present dose of hydroxocobalamin (1 mg twice daily) may not be sufficient to ensure normal reproduction or indeed growth in adolescence. However, there is no reason that this note of caution should have any bearing
Transcobalamin II deficiency and oral cobalamin therapy [letter]

R Carmel