Haptocorrin (Transcobalamin I) and Cobalamin Deficiencies

To the Editor:

Based on analyses in cobalamin-deficient patients before and after therapy, Morkbak and colleagues (1) confirm our finding that cobalamin concentrations correlate with haptocorrin (HC; transcobalamin I) (2) but propose that HC concentrations are regulated by cobalamin status rather than being genetically deter-

 mined, which they mistake as my view. In fact, no exclusive theory of HC regulation is likely. Many things affect HC synthesis, release, and clearance, and HC concentrations are altered in many varied disorders (3). Moreover, cobalamin changes often follow, rather than precede, such HC changes because HC’s long half-life disproportionately influences retention of its attached cobalamin (holo-HC). In addition, highly variable release of leukocytic apo-HC (cobalamin-free HC) frequently occurs whenever serum is tested instead of plasma (4); critical effects of this artifact on Morkbak’s vegan serum data cannot be dismissed merely because leukocyte counts did not change after therapy.

Statistical associations between cobalamin and HC concentrations require no complicated theories. The 75% or greater identity between circulating cobalamin and holo-HC, which in turn also constitutes 80% or more of total HC, guarantees significant associations and renders most alternative interpretations speculative. Nor should too much be made of the probably nonindependent statistical associations of methylmalonic acid and homocysteine with HC, given HC’s confounding near-identity with cobalamin.

Morkbak’s claims that HC was “decreased” in cobalamin deficiency and that cobalamin deficiency may explain much HC deficiency are undercut by her data: most patients with low cobalamin (<200 pmol/L) actually had total HC concentrations well within the reference interval (>240 pmol/L). Closer study of those few exceptions with total HC <240 pmol/L [see Fig. 1A in (1)] might have proved enlightening; posttreatment values in Table 1 of (1) imply that some very low HC concentrations persisted after cobalamin therapy, casting doubt on their relation to cobalamin status. Inattention to individually important patients, especially those who do not quite conform to group expectations, is unfortunately commonplace in contemporary studies of cobalamin status, which too often focus exclusively on overall group statistics. Further weakening Morkbak’s thesis is the likelihood that the disparity in posttherapy HC changes between cobalamin-deficient and nondeficient patients had much more to do with the grossly disparate cobalamin regimens the 3 study groups received than with differences in their cobalamin status. Excessive cobalamin doses were given to the cobalamin-deficient vegan group (5 mg orally daily) and the group suspected of deficiency (1 mg intramuscularly every week). As a result, mean cobalamin concentrations rose massively from 97 to 1016 pmol/L in the first group (947% increase) and from 281 to 960 pmol/L in the second (242% increase). Compare these with the nondeficient group, who received only 0.4 mg orally daily and whose mean cobalamin therefore rose just 51%, from 350 to 527 pmol/L. Small wonder that the first group showed significant increases in serum holo-HC and total HC because of apo-HC saturation by massive cobalamin injections converted apo-HC to holo-HC, whereas the third group showed neither plasma HC saturation nor increase because relatively modest amounts of new cobalamin entered the bloodstream. Nor do HC data stratified by MMA response to therapy prove the claimed influence of metabolic cobalamin status on HC concentrations. The 2 groups whose MMA concentrations responded to therapy were those also confounded by massive cobalamin doses and serum testing, unlike the nonresponsive controls. Proof of HC dependence on cobalamin status awaits studies with uniform treatment regimens and uniform testing of plasma.

To dispel potential diagnostic confusion and Morkbak’s concerns about assuming HC deficiency simply from low circulating cobalamin concentrations, the apparently underappreciated diagnostic criteria for primary HC deficiency (as fulfilled in all our published cases save one unusually
inaccessible subgroup) bear reemphas:
low HC and cobalamin along with
absence of clinical, metabolic,
or malabsorptive signs of cobalamin
deficiency are required. These and ad-
tional published features, including
nonresponsiveness of HC to coba-
lanin therapy, established that the low
cobalamin concentrations in such pa-
tients are caused by HC deficiency, not
the other way around (5,6). Many
cases also display familial patterns, but
we have cautioned that some may not be
genetic in origin (6).

Although low cobalamin caused
by cobalamin deficiency may occa-
sionally be accompanied by low total
HC, Morkbak’s Fig. 1A supports my
report that only 5% of patients with
proven cobalamin deficiency had low HC concentrations (6). Subnor-
mal total HC is clearly the exception
rather than the rule in cobalamin
deficiency. Because primary HC de-
ficiency may be far from rare (6),
diagnostic care is needed to avoid
confusing its low cobalamin concen-
trations with those of cobalamin de-
fi ciency. The clinical ramifications
are important.

References
1. Morkbak AL, Hvas AM, Lloyd-Wright ZL, Sanders
TAB, Bleie O, Refsum H, et al. Effect of vitamin
52:1104–11.
2. Carmel R, Brar S, Frouhar Z. Plasma total
transcobalamin I. Ethnic/racial patterns and
comparison with lactoferrin. Am J Clin Pathol
3. Carmel R. Cobalamin-binding proteins in
FM, eds. Contemporary Hematology Oncology.
129.
4. Carmel R. Vitamin B12-binding proteins in serum
and plasma in various disorders: effect of antico-
5. Carmel R. R binder deficiency: a clinically benign
case of cobalamin pseudo-deficiency. JAMA
1983;250:1886–90.
6. Carmel R. Mild transcobalamin I (haptocorrin)
deficiency and low serum cobalamin concentra-

Ralph Carmel
Department of Medicine
New York Methodist Hospital
506 Sixth Street
Brooklyn, NY 11215 and
Weill Medical College of
Cornell University, New York, NY
Fax 718-780-6333
e-mail rac9001@nyp.org

The authors of the article cited above respond:

To the Editor:

Dr. Carmel was the first to report that total haptocorrin (HC) and
cobalamins are related and that this relationship may be associated
with the occurrence of heterozygosity for HC deficiency (1). The rarity of HC
deficiency, however, suggests that this explanation is probably incom-
plete. Furthermore, a continuous rela-
tionship exists between HC and cobalamins, not the stepwise one that
would occur if simple gene dosage were the mechanism. Therefore we—
and Carmel, according to his letter—believe that the genetic factors deter-
mining HC concentrations are more complex. Obviously, further studies
are needed to give a clear picture of the relationship between such factors
and the concentration of HC. So far, Carmel has demonstrated a relation-
ship between HC and cobalamins (correlation not indicated; P = 0.003,
n = 182), a relationship further sub-
stantiated by our study (r = 0.4, P = 0.001, n = 402), which employed
an optimized method using deglyco-
sylation to ensure that HC from dif-
f erent samples are measured on an
equimolar basis (2).

Our data indicating that HC con-
centrations increase in vitamin B12
deficient individuals who are treated with vitamin B12 supplemen-
tation lead us to propose that the HC con-
centration is influenced not only by
genetic factors but also by vitamin
B12 status (3). Carmel challenges this
conclusion, raising some relevant is-

DOI: 10.1373/clinchem.2006.078808

Is the observed increase in HC in the group of deficient individuals treated with vitamin B12 (5 mg per day; n = 63) and placebo (n = 85).

Fig. 1. Increase in total HC in the group of deficient individuals treated with vitamin B12 (5 mg per day; n = 63) and placebo (n = 85).