Cobalamin, the stomach, and aging\textsuperscript{1,2}

**Ralph Carmel**

**ABSTRACT**  
Low cobalamin concentrations are common in the elderly. Although only a minority of such persons display clinically obvious symptoms or signs, metabolic data clearly show cellular deficiency of cobalamin in most cases. The evidence suggests that this is not a normal physiologic expression of the aging process. Rather, the elderly seem at increased risk for mild, preclinical cobalamin deficiency. Classical disorders such as pernicious anemia are the cause of this deficiency in only a small proportion of the elderly. A more frequent problem is food-cobalamin malabsorption, which usually arises from atrophic gastritis and hypochlorhydria but other mechanisms seem to be involved in some patients. The diminished absorption should not be viewed as a natural consequence of aging. The partial nature of this form of malabsorption produces a more slowly progressive depletion of cobalamin than does the more complete malabsorption engendered by disruption of intrinsic factor–mediated absorption. The slower progression of depletion probably explains why mild, preclinical deficiency is associated with food-cobalamin malabsorption more often than with pernicious anemia. Decisions about the optimal management of the very common problem of mild, preclinical cobalamin deficiency in the elderly await further clarification of the processes and the complex issues involved, including the possibility that routine nitrous oxide use during surgery, proposed dietary changes, and other practices may further stress the marginal cobalamin status of many elderly people.  


**KEY WORDS**  
Cobalamin, stomach, aging, vitamin B-12, elderly, *Helicobacter pylori*

**INTRODUCTION**

Low serum cobalamin (vitamin B-12) concentrations are among the most common abnormalities in the elderly. Projections from most surveys imply that 2–5 million Americans aged \( \geq 71 \) y had lower cobalamin concentrations than did 15–40-y-old subjects or 51–70-y-old subjects. Many comparative studies subsequently showed that the elderly have a significantly higher prevalence of subnormal cobalamin concentrations, lower mean cobalamin concentrations, or both, compared with younger adults, and in some cases there is an inverse correlation between age and serum cobalamin concentrations (5–21).

However, there has not been unanimity. Many studies found none of these associations with age (22–31). Even the positive reports sometimes described age-related changes only in subsets of one sex or the other (5, 16, 21). The variability is apparent by simply noting that the published prevalences of subnormal cobalamin concentrations in the elderly range between 0\% and 40.5\%.

The differences become less surprising when the many variations in subject selection, assay methods, and analytic approaches are taken into account (18). Some of the surveys studied hospitalized patients, some studied clinic visitors, some studied healthy volunteers, and some studied combinations of these groups. Furthermore, some surveys studied only “super-healthy” subjects by excluding even those with disorders that sometimes bore little direct relation to cobalamin status. Finally, some surveys excluded persons taking vitamin supplements whereas others did not. Of those surveys that did not, some assigned all supplement users to the cobalamin-deficient group whereas others did not treat them differently from nonusers.

Methodologic variations among the reports have included confining statistical comparisons of age and cobalamin concentrations to within the elderly group rather than over the entire age spectrum, using different definitions of old age, selecting controls of variable appropriateness (eg, comparing

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elderly inpatients with young medical staff rather than young inpatients) or even historical control subjects, and using inadequate assay methods. Several of the reports that found no age differences used R binder instead of pure intrinsic factor (IF) as the binding protein in their cobalamin assay, thus producing many falsely elevated cobalamin values.

Cutoff points between normal and abnormal cobalamin values have also varied. This issue became even more prominent after the suggestion that standard cutoff points may be too low and underestimate the frequency of cobalamin deficiency (20, 32, 33). On the other hand, adjusting the cutoff point upward also greatly increases the number of falsely abnormal cobalamin results.

Ethnic or racial variation may also affect interpretation of cobalamin concentrations in this context but this factor has rarely been considered. Blacks have higher cobalamin concentrations from infancy to old age than do whites both in the United States and in Africa (26, 34–37). This age- and geography-independent consistency suggests, although it does not prove, a genetic difference. Not surprisingly, elderly blacks have had fewer “subnormal” cobalamin concentrations than elderly whites (26; Carmel et al, unpublished data, 1997). The meaning of this phenomenon, its relation to metabolic deficiency, and whether it leads to underrecognition of mild cobalamin deficiency in blacks needs to be determined.

Despite all the aforementioned variations and uncertainties, including the important fact that virtually all the studies of cobalamin and age have been cross-sectional rather than longitudinal in nature, the evidence in sum remains strong that the prevalence of low cobalamin concentrations increases with age. The work of Nilsson-Ehle et al (17) has provided particularly strong support for this concept. In a longitudinal study of elderly inhabitants of a Swedish town, they documented a decline in cobalamin concentrations as the subjects aged from 70 to 81 y. Although the decline was statistically significant only in men, it is noteworthy that it occurred despite an increased intake of supplements as the subjects aged.

Interestingly, the cobalamin concentrations in the Swedish survey declined most noticeably in those subjects whose concentrations tended to be lower at the beginning of the study (17). In contrast, the higher initial cobalamin concentrations tended to remain unchanged as the subjects aged. This observation supports the thesis that the decline in cobalamin status is not a physiologic, age-related change. It appears instead that some elderly individuals are more predisposed than others to declining cobalamin concentrations, a predisposition that suggests dysfunction. This observation is supported by reports of higher frequencies of subnormal cobalamin concentrations in the elderly without an age-related decline in mean cobalamin concentrations in the group as a whole (18, 19).

The evidence, thus, does not favor the thesis that low cobalamin concentrations are “normal” for the elderly, or its corollary that one ought therefore to construct separate reference ranges for the elderly. The elderly seem truly prone to developing subnormal cobalamin concentrations. This is further buttressed by examining the evidence concerning the meaning of the low cobalamin concentrations.

DO THE LOW COBALAMIN CONCENTRATIONS IN THE ELDERLY REPRESENT DEFICIENCY?

It was obvious from the beginning that most of the low cobalamin concentrations in the elderly were not associated with either megaloblastic anemia or neurologic symptoms, the usual clinical sequelae of cobalamin deficiency (5, 17, 18, 20, 38–40). Reports that treatment neither changed the (usually normal) blood count nor provided any obvious clinical or subjective evidence of benefit beyond a placebo effect in elderly patients with isolated low cobalamin concentrations (41) and that withholding treatment brought no obvious deterioration (12) further solidified the impression that the low cobalamin concentrations were inconsequential and perhaps even artifactual.

Despite an early suggestion that low cobalamin concentrations might represent biochemically identifiable, preclinical manifestations of deficiency (7), it was not until more sensitive methods became available that this could actually be shown. This issue was reviewed previously (42, 43).

Evidence that most, but not all, patients with low cobalamin concentrations have metabolic abnormalities strongly suggestive of deficiency at the cellular level is outlined in Table 1. Moreover, subtle, preclinical neurologic changes could be demonstrated in many of the patients. Most importantly, both the metabolic and electrophysiologic defects in these patients usually reversed after cobalamin therapy. Thus, low serum cobalamin concentrations are neither artifacts nor simple physiologic manifestations of aging in most cases.

To strengthen, yet also complicate, this emerging picture of subtle, preclinical cobalamin deficiency as a common phenomenon, even subjects with normal cobalamin concentrations are sometimes not free of metabolic evidence of deficiency. An abnormal deoxyuridine suppression test result, perhaps the most sensitive metabolic marker of cobalamin deficiency (49), was reported in a patient with a normal cobalamin concentration (60). Several surveys have shown abnormal homocysteine and methylmalonic acid concentrations in patients with low-normal and normal cobalamin concentrations (20, 32, 61). These elevated serum metabolite concentrations usually responded to cobalamin therapy. Thus, serum cobalamin concentrations may not be the most sensitive markers of deficiency. However, it may be important to examine how many of the patients with metabolic abnormalities but with normal cobalamin concentrations were black, given the tendency of blacks to have higher cobalamin concentrations than whites.

**Table 1**

Summary of the published evidence for the entity of subtle, preclinical cobalamin deficiency in the elderly

<table>
<thead>
<tr>
<th>Biochemical evidence of deficiency in the absence of symptoms</th>
</tr>
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<tbody>
<tr>
<td>Abnormal deoxyuridine suppression test results (44–49)</td>
</tr>
<tr>
<td>Abnormal metabolite concentrations (methylmalonic acid and homocysteine) (20, 32, 33, 48–53)</td>
</tr>
<tr>
<td>Subclinical defects without corresponding symptoms</td>
</tr>
<tr>
<td>Electrophysiologic-neurologic abnormalities (electroencephalogram, evoked potential responses) (48, 54–58)</td>
</tr>
<tr>
<td>Reversal of biochemical or subclinical defects with cobalamin therapy</td>
</tr>
<tr>
<td>Reversal of deoxyuridine suppression test abnormalities (48, 50)</td>
</tr>
<tr>
<td>Improvement of metabolite concentrations (32, 48–52, 59)</td>
</tr>
<tr>
<td>Improvement of electrophysiologic abnormalities (48, 52)</td>
</tr>
</tbody>
</table>
The evidence cited in Table 1 indicates that 50–75% of all low cobalamin concentrations are accompanied by metabolic evidence of deficiency despite the absence of clinical signs of deficiency. In nearly every case, those metabolic changes correspond to cobalamin therapy. Indeed, even seemingly normal metabolite concentrations often “improve” after cobalamin treatment (49, 50, 59). A lesser proportion of metabolically deficient patients also have electrophysiologic-neurologic abnormalities that improve with cobalamin therapy (48, 52). The possible association of low cobalamin concentrations in the elderly with a blunted immune response to vaccine has also been suggested recently, although its improvement with cobalamin therapy was not tested (62).

Thus, half or more of elderly people who have low serum cobalamin concentrations seem to have subtle, preclinical deficiency. Not only are their bone marrow cells (assessed by the deoxuridine suppression test) and other cells (methylmalonic acid and homocysteine abnormalities) usually deficient in cobalamin, but their central nervous system cells are as well (electrophysiologic abnormalities).

WHY DO COBALAMIN CONCENTRATIONS BECOME LOW IN SO MANY ELDERLY PEOPLE?

As the complex sequence of events in the absorptive and assimilative cycle for cobalamin in Table 2 illustrates, many classes of disorders can create cobalamin deficiency. However, gastric dysfunction predominates by far among them. Gastric dysfunction also encompasses the only disorders in Table 2 that are known to increase with age. Dietary insufficiency of cobalamin is rare in the Western hemisphere, even among the elderly. Postabsorptive defects are also uncommon. Recent data suggest that mild transcobalamin I deficiency is frequently associated with low cobalamin concentrations (63), but it does not seem to affect any age group disproportionately. Therefore, the stomach is the prime candidate to explain the excess prevalence of cobalamin deficiency in the elderly over that seen in all other age groups.

The two major gastric disorders of cobalamin assimilation are pernicious anemia and food-cobalamin malabsorption. Various gastric surgical procedures also predispose to cobalamin deficiency, but most appear to do so by leading to food-cobalamin malabsorption (64, 65).

Pernicious anemia

Despite its hematologic name, pernicious anemia is a gastric disease and is defined as cobalamin malabsorption due to the loss of gastric IF secretion. This disease has been regarded traditionally as the most common cause of cobalamin deficiency. Despite its notable occurrence in some patients aged < 50 y, especially black women (66), patients with juvenile pernicious anemia (67), and others with a familial predisposition (68), the disease clearly predominates in the elderly. Although pernicious anemia accounts for a small minority of all low cobalamin concentrations in the elderly, it is nevertheless relatively common in them and affects blacks as often as whites (69). A recent survey in Los Angeles found that 1.9% of 729 free-living persons aged > 60 y had unsuspected and undiagnosed pernicious anemia, defined by a combination of low cobalamin concentrations and an abnormal result from the Schilling test or positive anti-IF antibody results (69). It is also noteworthy that the resulting cobalamin deficiency was still in its subtle, preclinical stage in most of those individuals.

Gastric histology in pernicious anemia usually shows diffuse atrophy of the corpus with striking sparing of the antrum. This picture, together with achlorhydria or hypochlorhydria and signs of immune phenomena like antiparietal cell antibody, was named type A gastritis by Strickland and Mackay (70). Type A gastritis, a still commonly used term despite the evolving concepts of gastritis, was assumed to be the forerunner of ~ 90% of cases of pernicious anemia. A mathematical modeling study of relatives of patients with pernicious anemia suggested that type A atrophic gastritis, presumably a prepernicious anemia state, accelerated after the age of 50 y (71).

Not only is it uncertain what causes type A gastritis but it is also uncertain exactly where pernicious anemia belongs in its

TABLE 2
Sequence of events in cobalamin assimilation

<table>
<thead>
<tr>
<th>Physiologic event</th>
<th>Disorder affecting this step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Dietary intake</td>
<td>Veganism</td>
</tr>
<tr>
<td>2) Detachment of cobalamin from its binding to food protein</td>
<td>Food-cobalamin malabsorption</td>
</tr>
<tr>
<td>3) Binding of the released, free cobalamin to R binder</td>
<td>Transcobalamin I deficiency?</td>
</tr>
<tr>
<td>4) Secretion of IF by gastric parietal cells</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>5) Secretion of biliary cobalamin (enterohepatic recirculation)</td>
<td>(Unknown)</td>
</tr>
<tr>
<td>6) Detachment of cobalamin from R binder (mediated by pancreatic trypsin and bicarbonate)</td>
<td>Pancreatic insufficiency?</td>
</tr>
<tr>
<td>7) Protection of cobalamin from bacterial utilization</td>
<td>Bacterial overgrowth</td>
</tr>
<tr>
<td>8) Binding by IF of cobalamin freed from R binder</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>9) Uptake of IF-cobalamin complex by IF receptors on ileal epithelial cell membranes</td>
<td>Ileal disease or surgery</td>
</tr>
<tr>
<td>10) Translocation of cobalamin from ileal cell to the circulation</td>
<td>Transcobalamin II deficiency</td>
</tr>
<tr>
<td>11) Uptake of transcobalamin II-cobalamin complex by transcobalamin II receptors on membranes of tissue cells</td>
<td>Transcobalamin II deficiency</td>
</tr>
<tr>
<td>12) Cellular utilization of cobalamin</td>
<td>Cbl mutations, nitrous oxide toxicity</td>
</tr>
</tbody>
</table>

1. IF, intrinsic factor.
2. This disorder does not seem to lead to cobalamin deficiency.
spectrum. Loss of IF may simply be the extreme end of the natural progression of type A gastritis, destined to occur in anyone with type A gastritis who lives long enough. Alternatively, pernicious anemia may occur only in those patients in whom a second event supervenes. Such an event could hypothetically be one that leads to formation of antibody to IF; an antibody that, unlike antiparietal cell antibody, is uncommon in patients who have not developed pernicious anemia (67, 72). However, it is also possible that pernicious anemia is unrelated in pathogenesis to the usual type A gastritis, the only resemblance being its similar expression of gastric damage.

Indeed, pernicious anemia may not be a single entity but a collection of diseases with disparate origins and courses, unified only by the final event of the disappearance of IF. This may explain why the disease is expressed differently in some subgroups, as reviewed elsewhere (73). Pernicious anemia seems strikingly accelerated in some patients, an accelerated form also paradoxically marked by a somewhat lower prevalence of antiparietal cell antibody (66, 74). Further suggestive of diversity is the subset of patients with pernicious anemia who have no demonstrable antibodies to any of the known gastric antigens (67, 72). Moreover, not all patients even have the histologic picture of type A gastritis (75, 76). The gastritis in some patients is more compatible with the so-called type B gastritis, with involvement of antrum as well as corpus and with no signs of immune disturbance (70, 75). Indeed, antral involvement is universal in the form of pernicious anemia found in patients with hypogammaglobulinemia (77, 78).

Type B gastritis, although much less often associated with pernicious anemia, is a much more common form of gastritis overall than is type A (70) and predominates in the elderly (79). It does not usually display autoimmune phenomena and may or may not produce achlorhydria. This gastritis is now thought to be, most often, the end result of chronic infection by Helicobacter pylori (80). The prevalence of H. pylori infection is lower in patients with pernicious anemia than in the general population (81), which is consistent with the usual association of pernicious anemia with type A rather than type B gastritis. However, serologic evidence of remote infection in some cases has led to a proposal that antecedent infection had set in motion the gastritic events that led to pernicious anemia in at least some of the patients (82, 83). The microorganism may have disappeared from the stomach as intestinal metaplasia and achlorhydria created an inhospitable environment.

**Food-cobalamin malabsorption**

Pernicious anemia accounts for only a small fraction of the many low cobalamin concentrations in the elderly. A more prevalent cause of mild cobalamin deficiency seems to be the phenomenon of food-cobalamin malabsorption (Table 2, step 2). This disorder is defined as the inability to absorb food-bound or protein-bound cobalamin by a person who is fully capable of absorbing free cobalamin. The Schilling test and other standard tests cannot detect it because they measure only the ability to absorb free cobalamin.

Low cobalamin concentrations in many patients who had undergone partial gastrectomy but had normal Schilling test results led Deller et al (84) to suggest that the deficiency might be explained by impaired absorption of cobalamin from food. The landmark demonstration that this was indeed the case was provided by Doscherholmen and Swaim (85). The documentation that cobalamin concentrations in patients with gastritis correlated with gastric acid secretion, rather than with Schilling test results or IF concentrations, further universalized the phenomenon (86). Others have confirmed the closer association of low cobalamin concentrations with atrophic gastritis than with pernicious anemia (79, 87).

The reader is referred to previous reviews (64, 65) for details of food cobalamin absorption, the tests used, and the technical considerations. Technical issues are important to the evaluation of the literature in this fledgling field and are summarized in Table 3. The techniques used to test the ability to absorb food cobalamin vary greatly, and it has not yet been established that they all measure exactly the same phenomenon. Although many other variables have undoubtedly influenced results, methodologic problems probably account for many of the discrepancies. One example is the use of fecal collection, which seems to produce falsely normal food-cobalamin absorption results (85, 88–90). The explanation for this apparent artifact is unknown but might reflect prolonged adherence of food cobalamin to the gut wall without it actually being absorbed.

An even more problematic technical issue is the frequent creation of unusually low reference ranges for the elderly, which is usually motivated by one or more untested assumptions. One such assumption is that diminished absorption is a physiologic rather than pathologic event in the elderly. This assumption also leads to the creation of age-specific reference intervals for them (92–94). Another questionable assumption is that all control subjects with normal cobalamin concentrations, by definition, must have normal food-cobalamin absorption; this has led some investigators to adopt very wide reference

<table>
<thead>
<tr>
<th>Problems to consider when evaluating studies of food-cobalamin absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) The &quot;normal&quot; reference range is uncertain</td>
</tr>
<tr>
<td>No independent diagnostic gold standard</td>
</tr>
<tr>
<td>Many methodologic variations</td>
</tr>
<tr>
<td>Selection of control groups has not been uniform</td>
</tr>
<tr>
<td>Assumption by some that subjects with normal cobalamin concentrations, by definition, cannot have food-cobalamin malabsorption</td>
</tr>
<tr>
<td>Assumption by some that declining absorption in the elderly is physiologic rather than pathologic</td>
</tr>
<tr>
<td>2) Methodologic problems</td>
</tr>
<tr>
<td>Use of fecal collection for measuring absorption (and probably absorption and excretion with some methods) often results in low activity counts that are barely above background</td>
</tr>
<tr>
<td>It is not known whether malabsorption from one food source means malabsorption from other food sources as well</td>
</tr>
</tbody>
</table>

| 3) Problems with subjects |
| Studies antedating the report by Suter et al (91) did not take possible antibiotic use by the patient into account |
| Subjects tend to be selected for study according to the focus of the investigation (eg, some studies selected for elevated gastrin concentrations, some for gastritis, and some for low cobalamin concentrations) |

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1. This unsupported assumption has led to the creation of unrealistic reference ranges (see text).
ranges to encompass every single absorption value found in control subjects (95, 96). The usual result of these assumptions has been the improbable setting of the lower limit of normal food-cobalamin absorption in the elderly at or near 0%.

Three important questions raised by food-cobalamin malabsorption concern its connection to the low cobalamin concentrations and subtle deficiency in the elderly, the mechanisms that give rise to food-cobalamin malabsorption, and the nature of the association between the malabsorption and aging.

Is food-cobalamin malabsorption a common cause of mild cobalamin deficiency?

The association has been examined in several studies since the initial documentation of the phenomenon by Doscherholm and Swaim (85). The published data are summarized in Table 4, reanalyzed in some cases to exclude subjects with other explanations for their low cobalamin concentrations, especially those who had an abnormal Schilling test result along with their inability to absorb food cobalamin. The latter subjects, by malabsorbing free cobalamin as well as food cobalamin, do not meet the criteria for food-cobalamin malabsorption.

As shown in Table 4, eight of nine studies found food-cobalamin malabsorption in >30% of patients with otherwise unexplainable low cobalamin concentrations; the sole exception was a study that adopted a reference range whose lower limit approached 0% (99). The two studies that did not report an increased association between food-cobalamin malabsorption and low cobalamin concentrations (94, 99) might be attributed to factors mentioned in the footnotes in Table 4. Reanalysis shows that they, nevertheless, still found more malabsorption in patients with low cobalamin concentrations than in control subjects.

The nine studies summarized in Table 4 show a cumulative 41.5% prevalence of food-cobalamin malabsorption among subjects whose cobalamin concentrations are low, and a median of the prevalences is 43.8%. In contrast, control subjects with normal cobalamin concentrations had a cumulative prevalence of only 15.0% and a median of the reported prevalences of only 13.5%. Although strongly indicative of an association between food-cobalamin malabsorption and cobalamin deficiency, the data do not yet prove that the association is one of cause and effect. They also show that more than half of the low cobalamin concentrations in the elderly cannot be associated with any malabsorption at all and, therefore, must have arisen by some other mechanisms.

The documentation of food-cobalamin malabsorption in ~15% of people with normal cobalamin concentrations also requires explanation. Some of these patients may have been cobalamin deficient despite their normal cobalamin concentrations, but one must address the probability that not all malabsorbers actually have cobalamin depletion.

This seeming paradox, as well as the frequent association of food-cobalamin malabsorption with mild cobalamin deficiency, may be explained by considering the pathophysiology of malabsorption of cobalamin from food in the context of the progression of cobalamin depletion (Figure 1). Estimates of cobalamin stores in relation to daily requirements suggest that depletion of stores takes several years to produce clinically evident deficiency after cessation of cobalamin absorption (67). The usual model chosen to illustrate this is total gastrectomy or partial colectomy. In both conditions, IF secretion is lost and all absorption of ingested cobalamin, whether free or bound, ceases. Reabsorption of biliary cobalamin probably also ceases. The size of the normally reabsorbed biliary pool is not well established, but it is considerably larger than the amount of cobalamin ingested daily in the diet (100–102).

The consequence to cobalamin stores and the time to onset of cobalamin deficiency of this double malabsorption of ingested and biliary cobalamin engendered by the loss of IF-mediated absorption is illustrated by line A in Figure 1.

On the other hand, when the malabsorption is limited to food cobalamin, and IF secretion and function are spared, the reabsorption of biliary cobalamin presumably continues normally. The daily negative cobalamin balance that results is much less, and the resulting slower rate of cobalamin depletion resembles line B in Figure 1 rather than line A.

The difference between the two processes of malabsorption would explain how a person with food-cobalamin malabsorption progresses more slowly through the stage of subtle, preclinical deficiency and takes many years longer to become overtly cobalamin deficient than does a person with pernicious anemia or ileal disease. It might take such a patient as much as several decades to become clinically deficient, depending on the true slope of line B. The longer traverse through subtle deficiency due to the slower rate of progression also means that a patient with food-cobalamin malabsorption spends much more time in a state of subtle cobalamin deficiency than does

| TABLE 4 |
| Association of unexplained low serum cobalamin concentrations with food-cobalamin malabsorption: incidence of food-cobalamin malabsorption in patients with low serum cobalamin concentrations and in control subjects with normal cobalamin concentrations |

<table>
<thead>
<tr>
<th>Patients</th>
<th>Control subjects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/5 (100)¹</td>
<td>—</td>
<td>85</td>
</tr>
<tr>
<td>14/29 (48.3)</td>
<td>—</td>
<td>92</td>
</tr>
<tr>
<td>4/13 (30.8)²</td>
<td>4/26 (15.4)²</td>
<td>93</td>
</tr>
<tr>
<td>23/44 (52.3)</td>
<td>9/49 (18.4)</td>
<td>97</td>
</tr>
<tr>
<td>20/47 (42.6)</td>
<td>3/26 (11.5)</td>
<td>98</td>
</tr>
<tr>
<td>5/6 (83.3)</td>
<td>0/11 (0)³</td>
<td>95</td>
</tr>
<tr>
<td>20/64 (31.3)⁴</td>
<td>0/44 (0)</td>
<td>96</td>
</tr>
<tr>
<td>7/16 (43.8)⁵</td>
<td>15/68 (22.0)⁵</td>
<td>94</td>
</tr>
<tr>
<td>2/17 (11.8)⁶</td>
<td>0/27 (0)⁶</td>
<td>99</td>
</tr>
<tr>
<td>100/241 (41.5)</td>
<td>31/207 (15.0)</td>
<td></td>
</tr>
</tbody>
</table>

¹ Note that malabsorption was not found in any of the five patients when fecal testing was used instead.
² The study used dual-isotope testing of food-cobalamin absorption.
³ The authors selected a reference range to exclude all results found in control subjects.
⁴ The study used whole-body isotope counting to assess food-cobalamin absorption (see text and footnote 1 above).
⁵ The authors used different, age-specific reference ranges and did not clearly specify a cutoff point between normal and abnormal (the implied cutoff value of 0.5% was used in my analysis). Moreover, none of the subjects were tested for absorption of free cobalamin, so that one cannot differentiate between free and food-cobalamin malabsorption with confidence.
⁶ The authors used 0.18%, a value barely above background counts, as the lower end of the reference range. This study is also the only one that analyzed for antibiotic use by the tested patients.
been reviewed elsewhere (64, 65). However, the focus on these gastric acid secretion is presumably the essential event, as cobalamin malabsorption. Gastric surgery, atrophic gastritis, food-cobalamin malabsorption is more commonly represented would a patient with pernicious anemia, thus explaining why cobalamin concentration without signs of deficiency than each hypothetical slope as it traverses the preclinical deficiency stage indicate the time spent in that state in each scenario; the only noticeable abnormalities at this stage might be low cobalamin concentrations and metabolic evidence of deficiency. If each hatchmark on the x axis indicates 5 y, clinical deficiency would appear within 5 y after the absorptive defect began for line A and > 15 y after onset of malabsorption for line B in this hypothetical model.

a patient with pernicious anemia (compare the lengths of the two shaded areas under lines A and B in Figure 1). Such a person would be more likely to be discovered with a low cobalamin concentration without signs of deficiency than would a patient with pernicious anemia, thus explaining why food-cobalamin malabsorption is more commonly represented in the setting of mild, preclinical cobalamin deficiency than is the more rapidly progressing pernicious anemia. In much the same way, the slow rate of depletion could also explain the occasional discovery of malabsorption in surveyed control subjects whose serum cobalamin concentrations had not yet fallen to subnormal levels.

What causes food-cobalamin malabsorption?

The release of cobalamin from its attachment to food proteins is known to require pepsin activity at an acidic pH, and gastric dysfunction is known to be a prime cause of food-cobalamin malabsorption. Gastric surgery, atrophic gastritis, and drugs that suppress acid secretion have been well documented as causes of this form of malabsorption. Inadequate gastric acid secretion is presumably the essential event, as supported by evidence from in vitro studies. This subject has been reviewed elsewhere (64, 65). However, the focus on these gastric disorders may have led to a degree of selection bias and narrowed our vision somewhat. Many clinical studies have selected their subjects for known gastric disease or elevated serum gastrin concentrations.

Other factors must be involved sometimes. For example, some patients with apparently normal gastric acid and pepsin secretion nevertheless absorb food cobalamin poorly (98). In vitro data also suggest that gastric pH is the crucial factor in most, but not all, cases (103). The observation that tetracycline therapy improves food-cobalamin absorption in hypochlorhydric patients (91) is particularly relevant in this regard. Because hypochlorhydric patients who responded to antibiotics had large numbers of anaerobes in their stomachs, it was logical to assume that the bacteria had interfered with food-cobalamin absorption. However, the nature of this interference eluded definition, and attempts to document any effect with in vitro studies were unsuccessful.

H. pylori infection of the stomach may provide a common thread to many of these observations. Antibody evidence of H. pylori infection is significantly associated with severe food-cobalamin malabsorption (104). Additional support for the antibody findings has come from (13C)urea breath test studies (Carmel et al, unpublished data, 1997). Preliminary data from prospective studies of gastric histology and gastric function have provided further support and also suggested new possibilities (105). Of the six patients with severe food-cobalamin malabsorption, three had severe atrophic gastritis and achlorhydria, as predicted by current concepts of food-cobalamin malabsorption. However, the other three patients had nearly normal gastric histology and adequate acid and pepsin secretion. They also had biopsy-proven gastric infection by H. pylori, which the first three patients did not (105). Thus, one can propose at least two mechanisms for producing food-cobalamin malabsorption: 1) classical atrophic gastritis with hypochlorhydria or achlorhydria, often compatible with type A gastritis and sometimes even a precursor stage in the progression to pernicious anemia (47, 92, 93, 98, 106–108); and 2) H. pylori infection without significant atrophic gastritis or achlor-
hydria. Gastric infection by anaerobic bacteria, of course, is a third possibility.

As an alternative explanation to a causative role for anaerobes (91), our preliminary data indicated that food-cobalamin malabsorption responds to even a brief course of tetracycline in the patients with H. pylori infection (105), in whom H. pylori also disappeared quickly from the stomach with such therapy. The rapidity of the response and the lack of association with other definable gastric dysfunction further raise the possibility that H. pylori has a direct malabsorptive effect in addition to one mediated indirectly by its induction of gastritis.

In contrast with the positive antibiotic effect in the patients with H. pylori infection, food-cobalamin malabsorption did not respond to antibiotics in the patients with severe atrophic gastritis and achlorhydria (105). Further studies that evaluate both H. pylori and gastric anaerobes are needed to confirm and extend these observations. Such studies would help to define the heterogeneity of underlying mechanisms of food-cobalamin malabsorption and may open new avenues for treatment.

Is food-cobalamin malabsorption an age-related dysfunction?

Logic suggests that the prevalence of food-cobalamin malabsorption increases with age. The prevalence of atrophic gastritis, an important cause of such malabsorption, increases with age (1), as does that of H. pylori infection (80, 109). However, the evidence has been equivocal. Five studies compared food-cobalamin absorption with age. Two of the reports, which tested absorption in a total of 75 subjects with normal cobalamin concentrations, found no age-related differences (97, 98). Three others described an age-related decline in absorption in a total of 99 subjects with normal cobalamin concentrations (92–94), although the difference was not significant in the smallest of the three studies (92).

Part of the problem may lie in the selection for study of only patients with normal cobalamin status. Such a focus tests a slightly different proposition than whether or not the prevalence of food-cobalamin malabsorption is increased in the elderly. More definitive studies are needed to resolve the question of whether the frequency of food-cobalamin malabsorption increases with age. Ideally, studies should include a large, randomly selected spectrum of subjects of all ages, not a sample selected a priori on the basis of either normal or abnormal cobalamin status.

WHAT SHOULD BE DONE ABOUT THE HIGH FREQUENCY OF LOW COBALAMIN CONCENTRATIONS IN THE ELDERLY?

As it becomes clearer that most low cobalamin concentrations in the elderly are neither artifacts nor normal expressions of aging but represent a mild, preclinical deficiency state (and occasionally a clinically overt one), and as it has become clearer that in one-half of the cases absorption of cobalamin is impaired in one way or another, the usual dismissal of asymptomatic patients with low cobalamin concentrations is being reexamined. A broad spectrum of options can be formulated even as additional data are being sought to provide a more rational basis for a decision (110). None of these options alter the common consensus that symptomatic deficiency must always be treated promptly. The options include the following:

1) Do nothing about low cobalamin concentrations unless they become clinically noticeable. The arguments in support of this approach include the sheer numbers of patients involved, the costs, skepticism about medical intervention for biochemical changes, the fact that only a small minority of affected patients are symptomatic, the likelihood that whatever progression exists is very slow, and the fact that studies have shown no overt ill effects, even after many years of withholding treatment. The counterarguments are that absence of overt symptoms does not necessarily equal a state of well-being, that the underlying gastric disturbance in one-half of the affected people suggests that the cobalamin deficiency will persist and probably progress, that prevention has at least as much merit as cure, and that preclinical cobalamin deficiency may be a sentinel of serious underlying diseases, such as pernicious anemia in a premyelopathic stage or celiac disease.

2) Automatically treat all elderly people with low cobalamin concentrations. The arguments in support of this approach are that it is a cheap, efficient way to ensure that no one who might benefit goes untreated, that a detailed workup may be neither practical nor effective in view of its expense and the limited availability of many of the newer tests, and that cobalamin is not toxic and will not harm those who might receive it unnecessarily. The arguments against this approach are the resulting failure to identify serious underlying diseases that may have caused the deficiency in some of the patients, the failure to identify in some a need for more complex treatment or attention to complications, and the possibility that the amount and presumably oral route of cobalamin therapy such an approach dictates may prove inadequate for some patients.

It is worth noting that cobalamin deficiency, even though less frequent than in nonsupplemented individuals, was still found in elderly people who were taking cobalamin supplements (111; Carmel et al, unpublished data, 1997). Thus, although cobalamin pills are likely to work satisfactorily in people with food-cobalamin malabsorption, this has never been established and may be more complex than assumed. One can ask whether cobalamin pills taken with meals bind to the food proteins and fail to be absorbed adequately by someone with food-cobalamin malabsorption. Moreover, it is not certain that all patients with unsuppected pernicious anemia (estimated to occur in 2% of all elderly and 10–20% of those with low cobalamin concentrations) will absorb enough cobalamin from a pill, especially if doses < 100 μg are taken or if it is taken haphazardly, as routine supplements often are.

3) Give cobalamin supplements to all elderly people, regardless of their cobalamin concentrations. The arguments in favor of this, beyond those already stated in the preceding option, are that a problem of such large proportions may benefit from equally broad solutions, that it saves the cost of widespread cobalamin testing (which in any case may provide falsely normal and falsely abnormal results), and that it may have preventive benefits for patients in very early stages of negative balance. In addition to those mentioned in the previous option, the
counterarguments are that supplements recommended population wide tend to lead to high intakes by those who are more affluent, health conscious, and functionally intact and tend to be ignored by the poor and the impaired.

4) Continue the traditional medical approach of individual evaluation and therapy. The arguments for this approach are based on its laudable goal of making the specific diagnosis; identifying possibly treatable underlying diseases; addressing diagnostic issues; treating those who need it with specific, tailored therapeutic approaches; and avoiding treatment of those who do not need it. The arguments against it are the cost in time and money of evaluating millions of people, and the uncertainty of what constitutes optimal diagnostic evaluation, given that currently standard, clinical tests such as blood counts and Schilling tests give negative results in most cases.

The choice to be made among these options and their variations can reflect only personal philosophies and biases at this time. To the concerns already mentioned can be added uncertainty about the possible adverse effects created by changes in folate status and other changes. Widespread increases in folate intake are being planned to ameliorate the risk of neural tube defects in the elderly with marginal cobalamin status of many elderly people. To these concerns about folate one concern that more work is needed on the disorders of cobalamin status in the elderly to arrive at well-considered, objective answers to the many questions that this very common medical and public health issue has raised.

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