Should we give Vitamin B12 to all our elderly patients?

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learning objectives:

- to review the effects of vitamin B12 deficiency
- to understand the factors contributing to the high prevalence of B12 deficiency in the elderly
- to explore mechanisms for supplementing B12 in our patients

For you guys who want to get credit for showing up today, here are the learning objectives.

- 68-y-o married male, retired teacher, seen in Psycho-oncology Clinic 00-9-11
- P ΨHx: saw psychologist over 7 yrs for depression
- Fam ΨHx: father, brother w/ alcoholism. Depressed mother
- PMHx: mesothelioma Dx Jan 00; CAD, HTN, BPH
- Meds: proscar, norvasc, ritalin, losec, vioxx, imovane
- HPI: insomnia since Ca Dx; weakness, fatigue since midsummer; adm Jul 2000 x 1 mo. for investigation of leg weakness - no cause found. Excessive daytime sleepiness. Denies depression.

I want to start with a case history. Monsieur L. was 68 years old, a retired teacher, when I saw him in the Psycho-Oncology Clinic at the Jewish General Hospital in September 2000. he was referred for complaints of insomnia, weakness, and fatigue. He gave a history of depression in the past, as well as a family history of depression. Medically, he suffered from a mesothelioma, which had been diagnosed 9 months earlier. He also had vascular disease and benign prostatic hypertrophy. He had already been started on ritalin for his fatigue, by his oncologist. He reported that he had been admitted to a medical unit in the hospital for a month in July, to investigate his leg weakness. They never found the cause.

- O/E: comes in wheelchair. Falls asleep 2x in office. Speech a little slurred. No signs of depression.
- Impression: fatigue, leg weakness, daytime somnolence perhaps 2° B12 deficiency
- Plan: blood tests; B12 im; sleep hygiene
- Followup 00-10-23: feels much stronger, more energy; excessive daytime somnolence continues. O/E: walking well; bright, cheerful, alert.
- Plan: wife to monitor for apneas; refer for sleep study if suspect OSA

He came into my office in a wheelchair, maintaining that he was no longer able to walk. I looked in the hospital chart for blood tests, and was very surprised to find that a vitamin B12 level had never been drawn, even during his month long hospitalization. Why was I surprised by this?

In any case, I suspected a B12 deficiency, so I arranged for an immediate blood test and for a first injection of B12 that same afternoon.

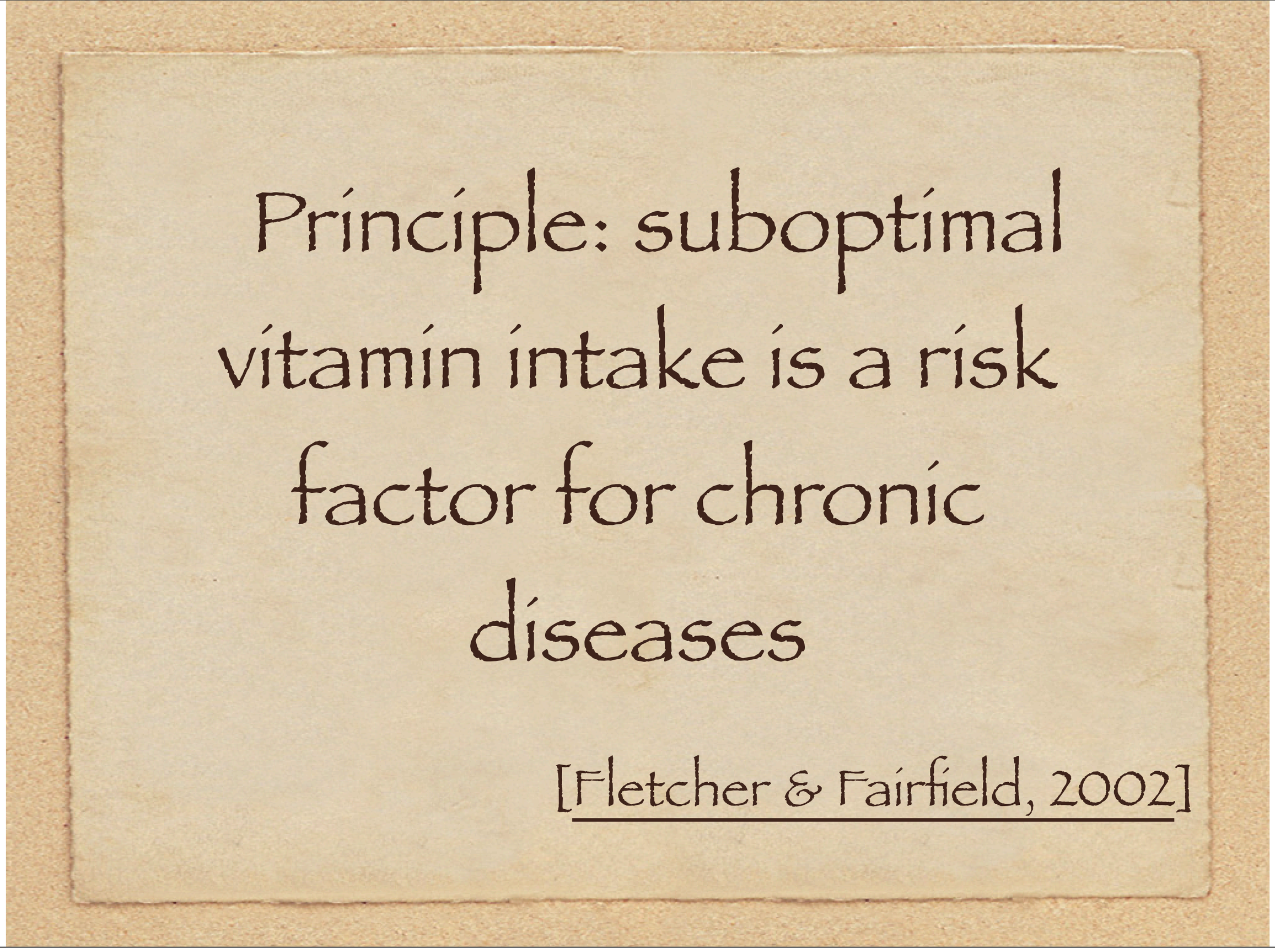
When I saw him in followup a month later, he reported feeling much stronger, and he walked into my office. No wheelchair, no walker, not even a cane.

	27 jul	17 aug	11 sep	Normal	units
Hgb	139	110	114	140-175	g/L
MCV	93.6	96.9	99.6	80-100	fL
MCH	32.3	33.3	34.3	27-33	pg
RDW	15.3	14.9	15.5	11.5-14.5	c/v
B12			325	120-600	pmol/L
folate			21.8	6-40	nmol/L
Hcy			11.2	5.2-14.9	µmol/L

Here are his lab results. Clearly, his hemoglobin has been dropping into the anemia range, and the high and climbing MCV and elevated MCH indicate that it's a macrocytic anemia. B12 and folate levels were in the normal range, however.

So, I gave him injections if vitamin B12 on the basis of clinical findings, not the lab tests, and the fact that he started walking again suggests, but certainly doesn't prove, that his leg weakness was probably caused by a tissue deficiency of B12.

Why did the blood test not show a low level? There are several possible reasons, which we'll get into later.



Should we give vitamin B12 to all our elderly patients? I am going to argue that we should.

I'll start with a general principle: suboptimal intake of some vitamins, although not to the point of causing classic vitamin deficiency, is a risk factor for chronic diseases and may be common particularly in the elderly.

A classic example is vitamin D and calcium. Many postmenopausal women are prescribed this combination. Is that because they have rickets? No, but low vitamin D intake predisposes to osteopenia and fractures.

Fletcher and Fairfield recommend that all adults should take vitamin supplements, and our responsibility as doctors is to ensure that patients do so safely, for example, by avoiding high doses of fat-soluble vitamins.

B12 deficiency is common

- recent review in CMAJ: > 20% of elderly; often unrecognized; >60% of cases are food-cobalamin malabsorption syndrome [Andres et al, 2004]
- 281 community-dwelling elders: 15.6% low B12; but 18.4% had normal B12 but metabolic evidence (high tHcy, MMA, or MCA). Total 33.7% [Garcia et al, 2004]

It is important to emphasize that B12 deficiency is very common in the elderly. A review article published in 2004 in the Canadian Medical Association Journal pegged the number at over 20%. Most of these cases go unrecognized.

The second article involved cognitively intact seniors in Kingston. None of this group had low folate levels. Kidney functioning was not controlled for, so some of the group likely had elevated metabolites on account of reduced clearance by the kidneys.

Various other estimates place the incidence of B12 deficiency somewhere between 20 and 30% of seniors. Is this an epidemic? I sure think so!

Low B12 associated with several conditions

- severe depression [Penninx et al, 2000]
- cognitive impairment and bodily pain in elderly U.S. veterans [Bernard et al, 1998]
- age-related hearing impairment [Houston et al, 1999]
- osteoporosis [Tucker et al, 2005]
- ?urinary incontinence [Rana et al, 1998]

While it is clear that a frank B12 deficiency that results in anemia or neurological symptoms should result in immediate treatment, I would like to focus today on the softer or less readily identifiable manifestations of B12 deficiency, that may affect the 20 to 30% of seniors believed to have deficiency, conditions that affect our residents here at Ste. Anne's Hospital.

First is severe depression. Penninx and coworkers looked at a cohort of 700 disabled nondemented women living in the community. Those with metabolically significant B12 deficiency were 2.05 times as likely to be severely depressed as nondeficient subjects.

The study of elderly U.S. veterans found that those with low B12 levels had more cognitive impairment and higher levels of bodily pain.

The Houston paper describes a study of 55 healthy elderly women. Eleven of these women had impaired hearing; this group had 38% lower B12 levels than the 44 women with normal hearing.

The study by Tucker and colleagues looked at 2576 adults in the Framingham Osteoporosis Study. Men with plasma B12 less than 148 pmoles per litre had significantly lower bone density at the hip, and women at the spine, relative to those with higher B12.

Some studies suggest that B12 deficiency may cause urinary incontinence. An example is the paper by Rana et al. Other studies fail to find differences in B12 levels between incontinent and continent subjects.

Homocysteine (Hcy, tHcy)

- linked to:
  - CAD
  - stroke
  - PVD
  - cognitive impairment
  - dementia
  - depression
  - osteoporotic fractures
  - functional decline

Since 1998, all the buzz has been about homocysteine rather than B12. Homocysteine is one of the metabolites that goes up when B12 is deficient, is itself believed to be a risk factor for a number of chronic illnesses that affect the elderly ❖, as shown here.

After I get the research literature out of the way, I have some slides showing the biochemistry of B12 and homocysteine.

Proposed mechanisms for tHcy

[Kuo et al, 2005]

- angiotoxicity
- neurotoxicity
- inhibition of collagen cross-linking
- simply a marker of B12 or folate or B6 deficiency

The usual short form for referring to homocysteine is the abbreviation tHcy, standing for total homocysteine. This amino acid builds up when any or all of vitamins B6, B12, or folic acid are deficient. It has been suggested that homocysteine itself causes illness through three possible mechanisms. Of course, it may simply be that homocysteine reflects the underlying vitamin deficiency which causes the disease. There is also a point of view that elevated homocysteine may be the result of certain disease states.

tHcy & cardiovascular disease

- review of 80 clinical and epidemiological studies [Refsum et al, 1998]
  - strong risk factor
  - graded
  - no threshold
  - independent of conventional risk factors
  - high tHcy strongly predicts cardiovascular mortality

Refsum and colleagues reviewed 80 studies which together looked at more than 10,000 patients. They concluded that homocysteine is a strong risk factor for atherosclerotic vascular disease. The risk is graded with no threshold and is independent of conventional risk factors. Elevated homocysteine strongly predicts cardiovascular mortality.

tHcy & dementia

- 164 AD patients: OR for AD 4.5 [Clarke et al, 1998]
- Framingham Offspring Study: inverse association tHcy levels to cognition [Elias et al, 2005]
- tHcy and white matter hyperintensity grade on MRI [Scott et al, 2004]

With respect to homocysteine as a risk factor for dementia, I report here on several studies. First, a case-control study of 164 patients ages 55 and up with a clinical diagnosis of Alzheimer's dementia, confirmed by brain biopsy in 76 out of the 164. The odds ratio of having Alzheimer's was 4.5 for those in the upper third of homocysteine levels (ie 14.0 or above) compared to those in the bottom third with homocysteine levels below 11.0, after adjusting for age, sex, social class, cigarette smoking, and apoE status. They found that homocysteine levels were unaltered by duration of symptoms and remained stable for several years, making it unlikely that the dementia was causing the elevation in homocysteine levels.

2096 participants of the Framingham Offspring Study without stroke or dementia were stratified into 3 age groups: 40-49, 50-59, and 60-82. There was a significant inverse association between homocysteine levels and multiple cognitive domains, but only for the oldest group. The association held even after adjustment for age, gender, levels of folate, B6, or B12, and cardiovascular risk factors.

The Scott article looked at geriatric psychiatry inpatients. White matter hyperintensities on MRI were associated with homocysteine levels, as were folate levels. B12 levels were not statistically associated, however.

tHcy & dementia

- patients with dementia: tHcy and Cambridge Cognitive Examination (CAMCOG) scores [McCaddon et al, 2000]
- hospitalized demented patients vs nondemented hospitalized patients and healthy elderly controls [Joosten et al, 1997]
- tHcy predicts cognitive impairment but not rate of decline [Mooijaart et al, 2005]

Elderly demented patients demonstrated a strong inverse association between homocysteine levels and Cambridge Cognitive Examination (CAMCOG) scores. Curiously, the most severely affected patients had both high homocysteine and high B12 levels, suggesting a problem at the level of B12 transport to tissues.

A study which compared hospitalized demented elderly patients with nondemented hospitalized patients and healthy elderly controls living at home found that serum B12 levels were comparable between the three groups. However, MMA levels were significantly higher in the hospitalized groups. Homocysteine levels were significantly higher in the dementia group compared to both other groups.

A population-based study of elderly found that high Hcy values predicted cognitive impairment, but not the rate of cognitive decline.

Interventions to lower tHcy

- vitamin B6 (pyridoxine)
- folic acid
- vitamin B12 (cobalamin, Cbl)

For those of you who are interested, I can show some slides afterwards explaining the biochemistry involved. Basically, there are three vitamins that are involved in homocysteine: B6, folic acid or folate, and vitamin B12.

B6 to lower tHcy

- may be ineffective vs tHcy (but does lower cystathionine) [Bleie et al, 2004]
- neurotoxic at high doses

I won't spend a long time on B6. By itself, it may not do anything to lower homocysteine. And when given at high doses, it can be damaging to peripheral nerves.

Folic acid to lower tHcy

- we are already supplemented since 1998
- folic acid alone may increase neurologic problems from B12 deficiency [Tucker et al, 1996; Klee, 2000]
- high folate intake may speed up cognitive decline [Morris et al, 2005]

In 1998, wheat millers began adding folic acid to wheat flour, mandated by the federal government. This public health measure was taken to ensure that pregnant women would receive enough folic acid to prevent neural tube defects in their children. It has been very successful for this. ❖

However, there are concerns that the folic acid may mask the macrocytic anemia if there is a B12 deficiency. This would lead to failure to recognize the B12 deficiency, and thus irreversible neurological deficits. Some researchers believe that folic acid can also precipitate neurological manifestations of B12 deficiency. ❖

Finally, there is a study of 3718 elderly individuals over a 9 year period, in which high levels of folate intake were associated with faster cognitive decline. For the highest quintile of folate intake, the rate of cognitive decline was more than double that for the lowest quintile.

Cbl to lower tHcy

- 6-month, double-blind, placebo-controlled study, in adults with normal B12 but elevated MMA: Cbl 1000 mcg im monthly reduced tHcy from 11.2 to 9.7 [García et al, 2004]

The third maneuver to lower homocysteine is by giving cobalamin, or B12. In this study of adults with normal B12 levels but elevated methylmalonic acid levels, which is considered a reliable indicator of tissue deficiency of B12, giving monthly injections of B12 lowered methylmalonic acid levels from 454 to 262, and lowered homocysteine levels from 11.2 to 9.7. This was not a big reduction, however; probably because 6 mg of B12 in someone who is deficient is a pretty small amount.

combinations to lower tHcy

- elderly patients with ischemic vascular disease given folate/B12 [Stott et al, 2005]
- cost-effectiveness is highest for across-the-board treatment with 1 mg folic acid and 0.5 mg B12 [Tice et al, 2001]

A study comparing different combinations of vitamins in elderly patients with ischemic vascular disease found significant reductions in Hcy with the folate/B12 combination, but no effects on cognition over one year.

Tice and colleagues looked at the cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of CHD. They examined several different models applied to different age groups, for example, vitamin therapy only for known CHD patients, or only after testing for elevated Hcy, or across the board treatment. They concluded that vitamin therapy with 1 mg folic acid and 0.5 mg B12, in addition to cereal grains fortified with folic acid, provided to all men 45 years or older without known CHD projected to a savings of more than US$2 billion and more than 300,000 QALYs over 10 years. For women, treating all women older than 55 years would same more than 140,000 QALYs over 10 years [Tice, 2001 #4046].

low-dose combinations

- 2 - 37.5 mcg/day of oral B12 prevents B12 deficiency in many seniors [García et al, 2002]
- vitamin supplement users had higher B12 & folate levels & lower tHcy, cf non-users [Paulionis, Kane, Meckling 2005]
- MI risk for regular users of vitamin supplements: 0.79 for men, 0.66 for women [Holmquist et al, 2003]

Dr. Garcia, at Queen's University, has published a number of studies on B12. She concludes that the amount of B12 found in most multivitamin preparations is sufficient to prevent B12 deficiency in many, but not all, seniors.

A study of nursing home residents in Guelph showed that vitamin supplement users had significantly higher B12 and folate levels, and significantly lower homocysteine levels, compared to nonusers.

A large case-control study compared MI survivors with healthy controls. The MI risk for regular users of vitamin supplements was 0.79 for men and 0.66 for women compared to nonusers, after adjustment for cardiovascular risk factors. These risks were modified only slightly when level of fruit and vegetable consumption, intake of dietary fibre, smoking habits, or level of physical activity were taken into account [Holmquist, 2003 #4043]. In this study, 80% of the supplement users took multivitamin supplements.

low-dose combinations

- free-living frail Dutch elderly, randomized to placebo or 17 weeks of enriched foods (0.55 mg B6, 0.125 mg folic acid, 1.25 mcg B12): tHcy decreased 25%, MMA decreased 30% [de Jong et al, 2001]

Even very low-dose vitamin supplements can produce appreciable changes in Hcy levels, although this does not affect neuropsychological test results. This was a 17 week randomized trial involving 217 free-living frail Dutch elderly, where groups receiving enriched foods showed a decrease of Hcy of 25% and of MMA of 30%. The enriched foods recipients received 0.55 mg of B6, 0.125 mg of folic acid, and 1.25 mcg of B12 daily, as well as small amounts of other nutrients.

high-dose combinations

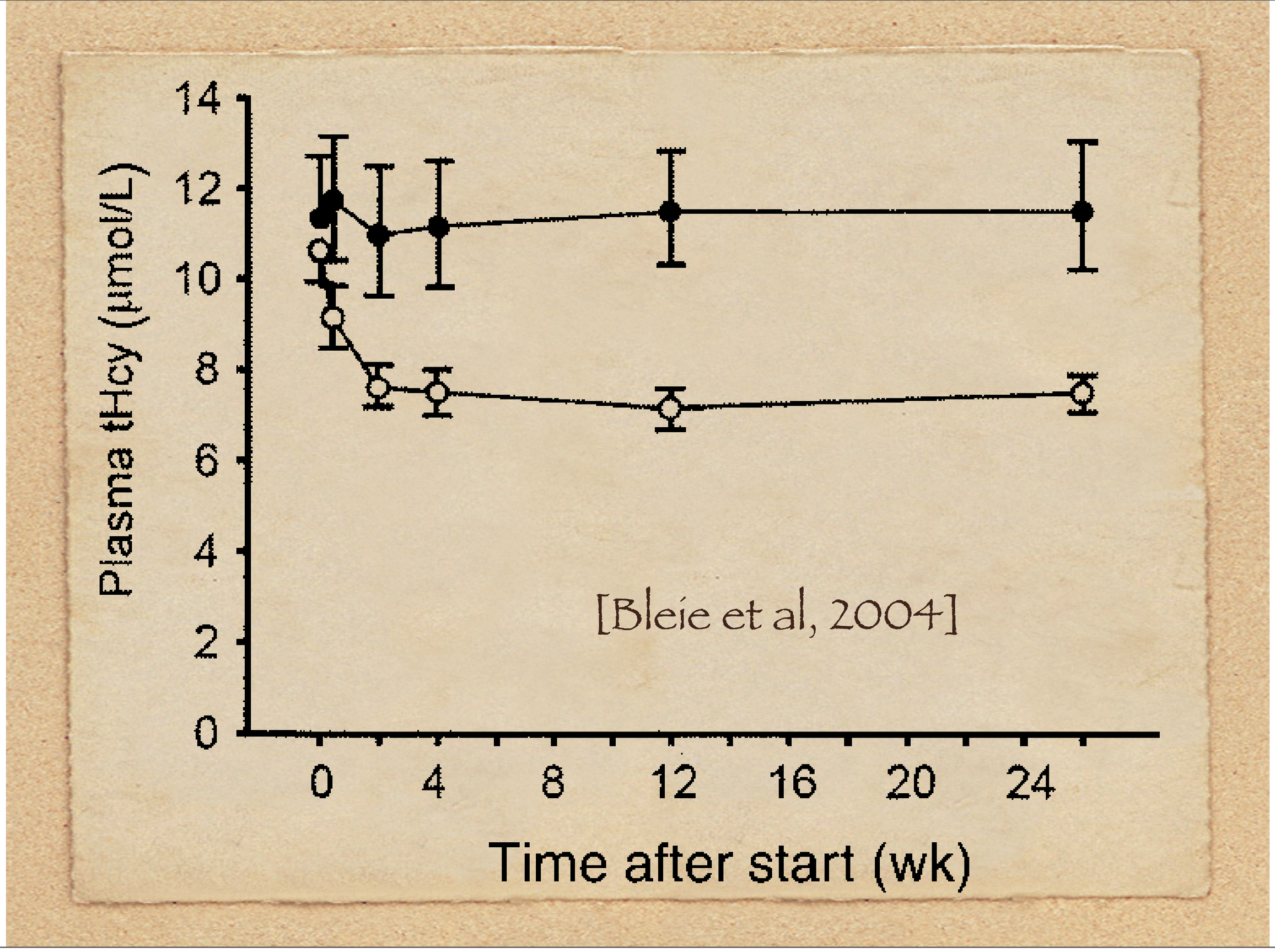
- Vitamin Intervention for Stroke Prevention (VISP) study [Toole et al, 2004]
  - 3680 adults with nondisabling cerebral infarct
  - high-dose: B6 25 mg, Cbl 400 mcg, folic acid 2.5 mg
  - low-dose: B6 0.2 mg, Cbl 6 mcg, and folic acid 20 mcg
  - 2micromole/L lower tHcy in high-dose grp

A double-blind randomized controlled trial involving 3680 adults with nondisabling cerebral infarction at multiple centers. All participants received a daily multivitamin; they were also randomized to either a daily high-dose combination of B6 25 mg, Cbl 400 mcg, folic acid 2.5 mg; or a low-dose combination with B6 0.2 mg, Cbl 6 mcg, and folic acid 20 mcg. After 2 years, the high-dose group had 2 mcmole/L greater reduction in homocysteine levels than the low-dose group. There was no significant difference between the groups in recurrent stroke, CHD events, or death.

VISP subgroup [Spence et al, 2005]

- 2155 patients with baseline B12 levels above the 25th percentile and below the 95th percentile
- 21% reduction in significant events in the high-dose group

An analysis of a subgroup of patients in the VISP study, including only the 2155 patients with baseline B12 levels which were neither very high or very low, showed a significantly better outcome (a 21% reduction in significant events) in the high-dose vitamin group, compared to the low-dose group.
The thinking was that the low B12 patients had absorption problems which would limit the usefulness of the low-dose treatment, and that many of these received im B12 which would affect the study outcome. On the other hand, the high-B12 patients were likely already taking a supplement and thus would not show additional benefit from the study intervention.



Ninety patients with suspected CAD referred for coronary angiography were randomized into 4 groups: folic acid + B12; folic acid + B12 + B6; B6 only; placebo. The groups receiving folic acid + B12 showed a rapid lowering of tHcy of 31% compared to B6 only or placebo where there was no lowering of tHcy. However, B6 reduced basal cystathionine by 31%.
The amounts of daily supplement used were: 0.8 mg folic acid, 0.4 mg B12, 40 mg B6. For the first two weeks, the groups receiving folic acid and B12 got an additional 5 mg daily of folic acid.

does reducing tHcy help?

- methylcobalamin & folate in elderly stroke survivors x 2 yrs reduced risk of subsequent hip fracture by 80%; number needed to treat: 14. tHcy decreased 38%. [Sato et al, 2005]
- patients after successful angioplasty: Rx with combo folic acid, B12, B6 x 1 yr. Rx group fewer major adverse events (death, nonfatal MI, need for revascularization) [Schnyder et al, 2002]

Combined treatment with methylcobalamin and folate in elderly stroke survivors reduces the risk of subsequent hip fracture by 80%; number needed to treat is 14.

Patients who had had a successful angioplasty were randomized to a combination of folic acid, B12, and B6 or placebo. The treatment group had significantly fewer major adverse events (death, nonfatal MI, or need for repeat revascularization) compared to the placebo group, after one year. (RR 0.68).

does reducing tHcy help?

- Rx with folate, B12, & B6 lowered tHcy levels & decreased carotid intima-media thickness (Till et al, 2005]

Treatment with folate, B12, and B6 lowered Hcy levels and decreased carotid intima-media thickness.

does reducing tHcy help?

- frail nursing home or residence inhabitants; Rx enriched nutritional supplement drink x 6 months. Rx group improved in tests of learning & memory [Wouters-Wesseling et al, 2005]
- in the Stott study on elderly patients with ischemic vascular disease, tHcy decreased but no effects on cognition over 1 year [Stott et al, 2005]

In term of cognition, do strategies to lower homocysteine help? There's some evidence out there, but very little.

Nutritional interventions to improve cognition

- Review of literature: 21 studies found which met criteria. Only 12 showed a positive outcome [Manders et al, 2004]

This group looked for randomized controlled trials of nutritional interventions designed to improve cognition in elderly people. They found 21 studies meeting their criteria. Only a very slim majority actually showed a positive outcome. Given the usual publication bias, of negative studies not even being submitted for publication, you can guess that improving cognition by nutritional means is difficult. Well, even medications to improve cognition have a hard time proving they're worthwhile.

- "... as with risk factors for other medical conditions, detection of elevated homocysteine levels in older adults and treatment with B vitamins at an early stage, before cognitive decline is clinically apparent and pathological changes have appeared, may be an effective intervention" [Garcia & Zanibbi, 2004]

A big part of the problem is that, unless there is already cognitive impairment, showing improvement may not be possible.
However, cognitive impairment is not the same as osteoporosis or cardiovascular disease. For one thing, cognitive impairment becomes irreversible once it has gone on for some time. Neurons, once they're dead, don't come back to life. But atherosclerotic plaques in blood vessels can shrink.
Also, we haven't found much correlation between imaging of the brain and its quality of functioning. The number of senile plaques in the brain corresponds poorly with cognition, not at all like doppler ultrasound studies of arteries as a measure of vascular disease.
So it really comes back to: if we can't improve cognition unless the decline is very recent and related to something specific that we can correct in the short term, can we do anything to prevent cognitive decline or slow it down? ❖

Here's a quote from Dr. Garcia at Queen's University.

Focus on B12

- we know a lot about B12
- isolated deficiencies of B12 are common in the elderly
- B12 deficiency may be the most frequent vitamin problem causing high tHcy
- of the 3 interventions to lower tHcy, B12 supplementation is the safest

I propose that we focus on vitamin B12 only. Not only do we know a lot more about B12 than about folate or B6, isolated deficiencies of B12 are very common in the elderly, whether or not homocysteine is elevated.

Manifestations of B12 deficiency

- Hematologic
- Gastrointestinal
- Neurologic
- Psychiatric

I would like to review the manifestations of B12 deficiency. The most important issue is that B12 is involved in the production of DNA, and also in the production of phospholipids.

Every time a cell divides, more DNA must be manufactured.

This means that tissues which have a rapid turnover, such as ♣ blood cells and the lining of the ♣ gastrointestinal tract all the way from the mouth on down, are at high risk when B12 is deficient.

What about neurological side effects? Neurons have very little turnover, if any, so DNA production is clearly not important for them.

It turns out that neurons depend on phospholipids for the formation of cell membranes, and because neural cell membranes are continually being remodeled as axons and dendrites are changed to reflect learning and forgetting, neurons depend on the methyltransferase reactions fuelled by methionine and SAMe. Thus, a vitamin B12 deficiency may have ♣ neurological consequences.

What about ♣ psychiatric symptoms of B12 deficiency? Some authors would say that the psychiatric manifestations are really neurological. This is a debate I don't want to get into.

B12 deficiency: hematologic

- Anemia; rarely thrombocytopenia
- Symptoms
  - weakness
  - Lightheadedness
  - Vertigo
  - Tinnitus
  - Palpitations
  - Angina
  - Sx of congestive heart failure

The hematologic manifestations of B12 deficiency are almost entirely due to the ☐ anemia which results when red blood cells are prevented from dividing because they can ’t make DNA. As a result, individual red cells get bigger. Here are the ☐ symptoms and ☐ signs of anemia that may result.

☐ Macrocytosis is the term used to refer to large cells: this can be seen on a blood smear as large oval red cells, or macro-ovalocytes. Automated blood cell counting machines output a value called the MCH, or mean corpuscular hemoblobin, and another value, the MCV, or mean corpuscular volume. Both of these would be elevated in anemia due to B12 deficiency. However, they will also be elevated in folate deficiency anemia.

B12 deficiency: hematologic

- Signs
  - pale skin
  - slightly icteric skin, eyes
  - rapid pulse
  - enlarged heart
  - systolic flow murmur

B12 deficiency: hematologic

- Lab
  - anemia
  - macrocytosis
  - hypersegmented polys
  - high bilirubin

B12 deficiency: gastrointestinal

- Due to inability of gastrointestinal epithelium to proliferate normally (ie rapidly)
- Signs and symptoms
  - Sore tongue (atrophic glossitis)
  - Weight loss
  - Diarrhea, other GI complaints

Gastrointestinal manifestations of B12 deficiency □ result from the cells lining the walls of the GI tract being unable to reproduce at their usual rapid pace. Thus, we might see □ sore tongue, diarrhea, weight loss, and so on.

When the □ stomach wall is affected, the condition is known as atrophic gastritis. As we'll see soon, atrophic gastritis can impair B12 absorption in at least 4 ways.

The atrophic gastritis may also contribute to bacterial overgrowth in the stomach, the duodenum, and the small intestine. These bacteria may utilise food or oral supplement B12 for their own needs; or they might convert it to inactive analogues.

Either way, this will worsen the B12 deficiency.

It is possible that the inactive B12 analogues will give a falsely normal or even a high serum B12 level.

Folate production by intestinal bacteria may also elevate the serum folate level.

B12 deficiency: gastrointestinal

- Pathology
  - atrophic gastritis decreases gastric acidity; impairs food-cobalamin absorption
  - severe atrophic gastritis also impairs intrinsic factor secretion, causing classic Pernicious Anemia
  - Megaloblastosis of small-intestine epithelium causes malabsorption

B12 deficiency: neurologic

- Pathology
  - Demyelination
  - Axonal degeneration
  - Neuronal death
- Sites
  - Spinal cord
  - Peripheral nerves
  - Cerebrum

In terms of neurological manifestations, there is a progression in ♣ pathology beginning with demyelination, followed by axonal degeneration, and finally, neuronal cell death. At this stage, of course, the process is irreversible. ♣ The spinal cord is usually affected first, then the peripheral nerves, and eventually the brain, but don't count on this order being followed.

B12 deficiency: neurologic

- Signs and symptoms
  - numbness, paresthesias
  - weakness, ataxia
  - sphincter disturbances
  - reflexes: diminished or increased
  - Romberg, Babinski +
  - decreased position, vibration sense
  - mentation: irritability, forgetfulness progress to dementia, psychosis

Here are the signs and symptoms. The sphincter disturbances can include urinary incontinence.

I had to look up what a Romberg sign means: standing is less steady with eyes closed (indicates loss of proprioceptive control).

Finally, it is important to recognize that neurological symptoms can occur even without any anemia.

B12 deficiency: psychiatric

- Saracaceanu et al 1997:
  - Mood disorders (depression or mania)
  - Panic attacks (with or without phobias)
  - Hallucinations and/or delusions ("megaloblastic madness")
  - Paranoia
  - Confusion
  - Insomnia, fatigue

Here are some of the psychiatric manifestations. I think "megaloblastic madness" is a particularly colourful term.

B12 deficiency: psychiatric

- psychiatric disorder
  - can occur many years before first hematologic or neurologic symptoms
- pernicious anemia patients
  - 16% have psychosis [Zucker et al 1981]
  - 33-82% have minor psychiatric Sx
- gastrectomy pts with subsequent low B12
  - 20% attempted suicide [Roos & Willanger 1977]

It appears that psychiatric disorder can appear well before there are any other manifestations of B12 deficiency.

♣ The incidence of psychiatric disturbance is very high in pernicious anemia.

In spite of what I said earlier about depression being more associated with folate deficiency than with B12 deficiency, there may still be an important link with B12. One theory posits a role for B12 in the production of various neurotransmitters, including noradrenaline and serotonin. This may help explain why ♣ gastrectomy patients who subsequently become deficient in B12 have a very high rate of suicide attempts.

possibilities for B12 intervention

- only treat confirmed deficiency states
  - when symptoms appear
  - routinely look for subclinical deficiency states
- treat only people at risk
- treat everybody

I suggest that, given the high incidence of B12 deficiency states in seniors, and the multiplicity of symptoms that can be caused by B12 deficiency, we need to look at what we should do.

There are several ways in which we can intervene.

only treat confirmed deficiency states when symptoms appear

- works not too badly for anemia
- occasionally for gastrointestinal complaints
- rarely for psychiatric illness
- dangerous for neurological dysfunction, either peripheral or central

The first option is to treat only confirmed B12 deficiency states, which we will pick up and investigate when symptoms appear. In other words, do nothing unless there are symptoms that we suspect may be due to a B12 deficiency.

This would work not too badly for anemia, although I am always surprised by how many anemia patients are put on iron supplements when they have macrocytosis, and without doing iron studies.

It may work occasionally for patients who present with GI complaints, like difficulty swallowing or a red, beefy tongue.

My own experience suggests that if a patient presents with psychiatric symptoms, such as paranoia, B12 is rarely considered in the differential diagnosis.

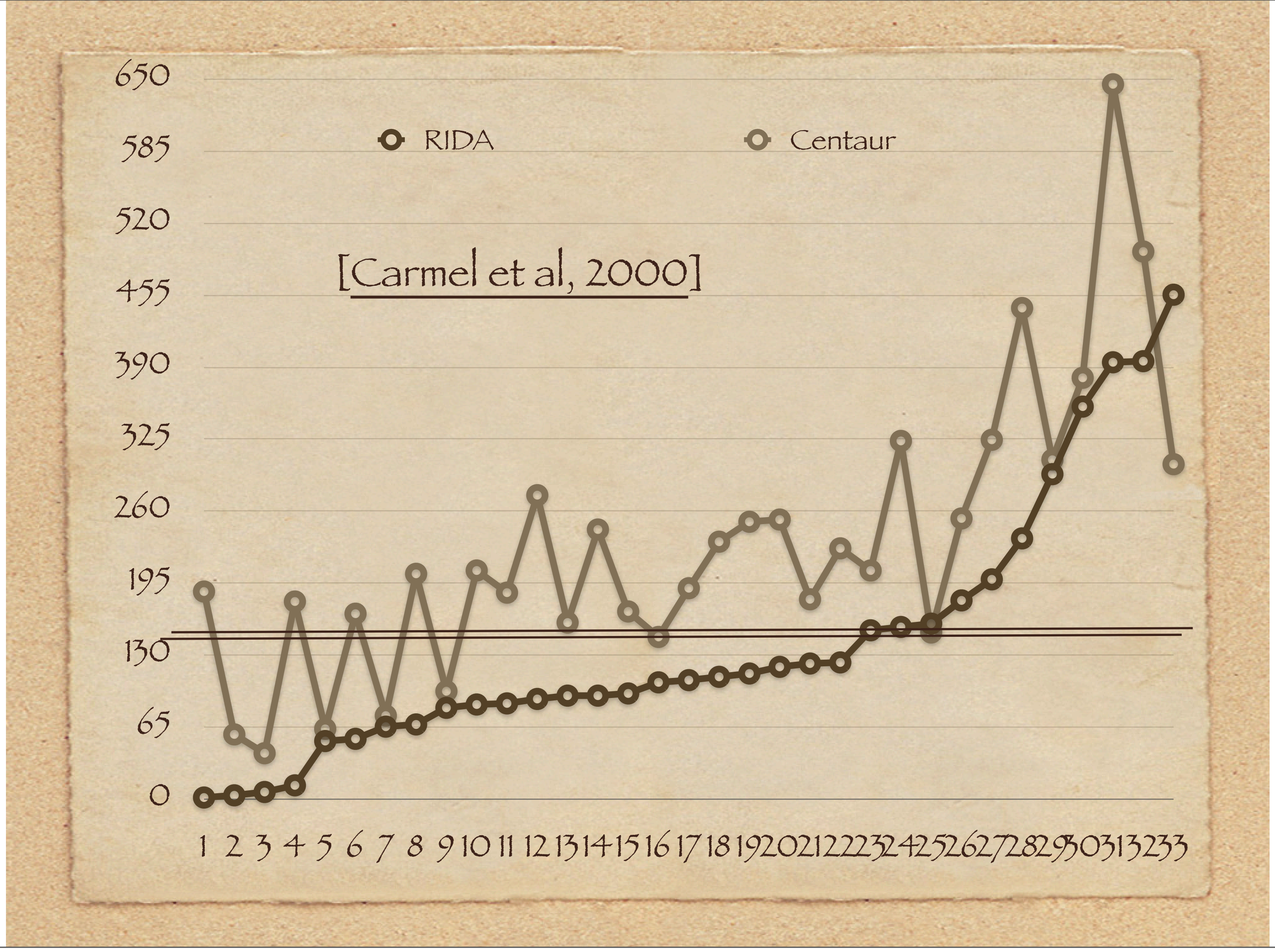
Finally, if the problem is neurological, for example leg weakness, it becomes irreversible once there are contractures. Dementia is also irreversible because dead neurons don't grow back.

routinely test for
subclinical deficiency states

- would work well if we had reliable tests, easily available

The second option would be to routinely test for subclinical deficiency states.

Sounds simple. Just order a B12 level every year. If it's low, give B12 supplements. Piece of cake!
But labs can't even agree on what the lower limit of normal is for a serum B12 level. Our lab uses 135 pmoles/L, but some hospitals in Britain use 300 as the lower limit.



A letter to the editor of the journal “Clinical Chemistry” in 2000 provides evidence of how problematic lab values for B12 are in practice. The graph shows B12 values for 33 sera taken from a research collection that had been assayed with a radioisotope dilution assay using pure intrinsic factor as the binding protein. The lower curve gives the values from that assay; the upper curve gives values for the same blood samples but this time using a chemiluminescence assay called Centaur, from Bayer Diagnostics.

The lower horizontal line is the lower limit of normal, 140 pmol/L, for the RIDA assay; the line just above it is the lower limit of normal for the Centaur assay, specified as 156 pmol/L by the manufacturer.

Using these limits, 16 out of 22 low B12 samples would have been read as normal using the Centaur assay. If we instead used 300 as the lower limit for the Centaur, it would correctly identify all of the low B12 samples, and would have only 3 false positives in this group.

falsely normal or high B12 levels

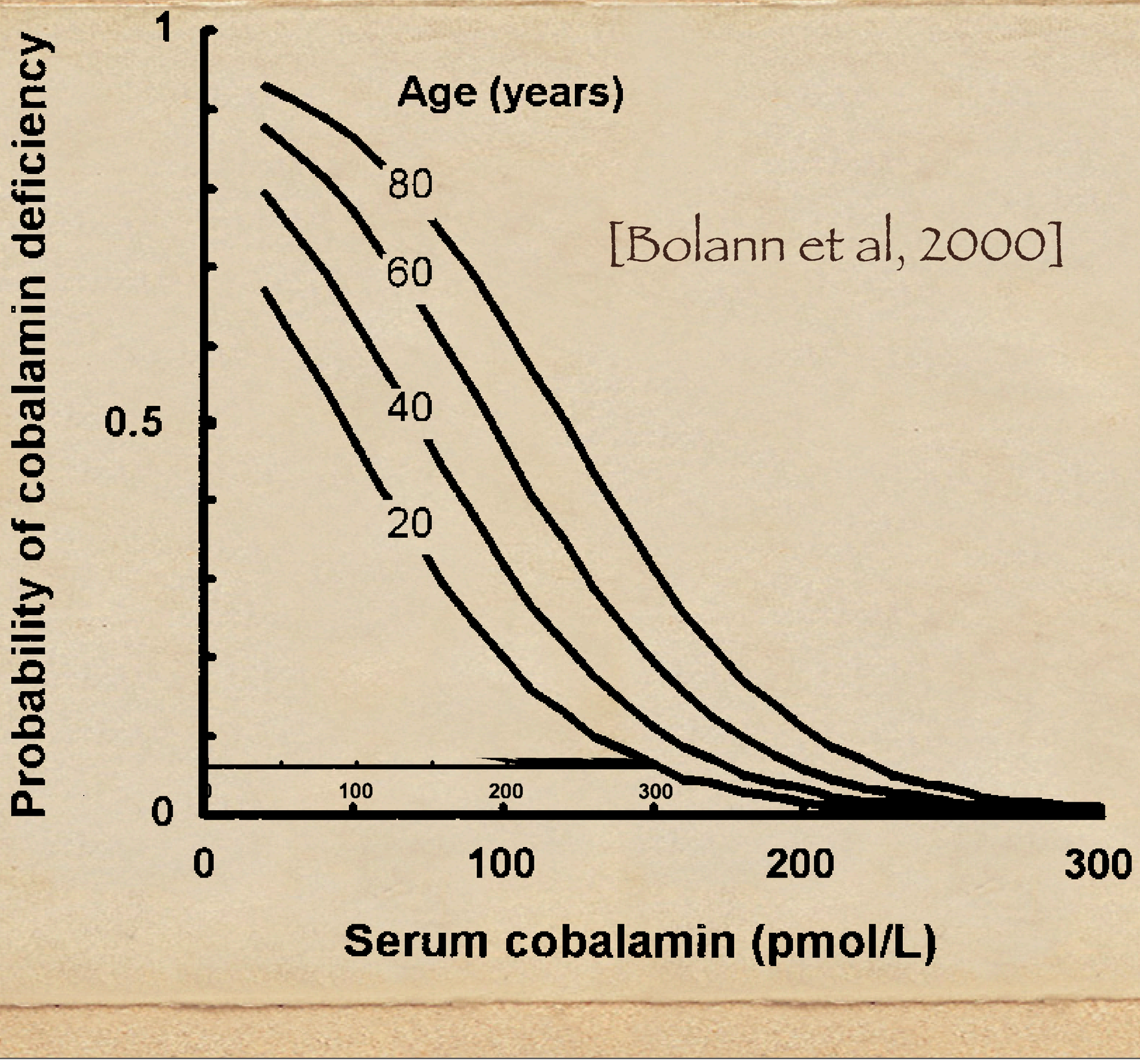
- myeloproliferative disorders
- other cancers, eg liver, breast
- prostate cancer

Even if we could standardise on testing procedures and limits, testing for B12 levels would still remain quite imprecise. Besides a variety of genetic variations which affect the multiple transport proteins involved in B12 absorption, storage, and delivery to target organs, a number of illnesses can cause test results to be normal or even elevated when there is actually a tissue deficiency. These illnesses include myeloproliferative disorders such as leukemia. Less well known is that other neoplastic disorders such as liver cancer or breast cancer can also cause inaccurately high B12 test results.
But of course, the great majority of our patients don't have cancer. Or do they? Autopsy studies show that for caucasian males between 70 and 80 years of age, 63% have high grade prostatic intraepithelial neoplasia.

Metabolic indicators of B12 deficiency

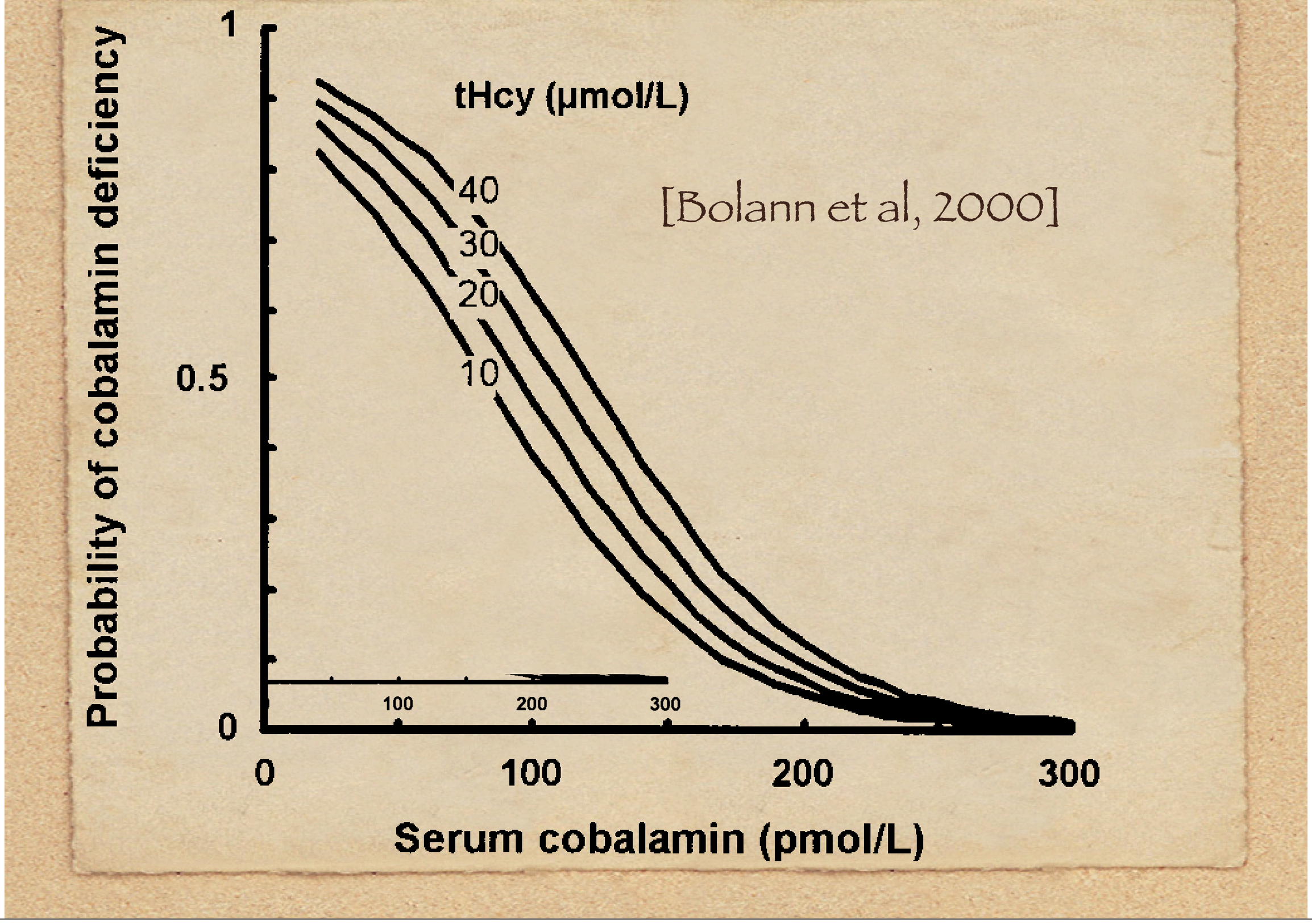
- homocysteine
- methylmalonic acid (MMA)
- methylcitric acid (MCA)

So if blood tests for vitamin B12 are problematic, can we get around this?
This is where homocysteine comes in. Homocysteine can be elevated if there is B12 deficiency. However, if the B12 deficient person is getting enough folate and/or B6, homocysteine will be normal. In addition, there are some genetic conditions leading to high homocysteine levels even when all 3 vitamins are OK.
Methylmalonic acid and methylcitric acid are specific to B12: a B12 deficiency will cause an elevation in both. However, these tests are not readily available and they're expensive; blood for these tests has to be transported on ice, which raises costs and increases the number of inaccurate results.
Unfortunately, reduced kidney functioning can cause high levels of all of these metabolites even in the absence of vitamin deficiencies.
Nevertheless, MMA levels are often used as a gold standard for detecting tissue B12 deficiencies, which are confirmed by looking for a reduction in MMA level of 50% with B12 supplementation.



[Bolann et al, 2000]

This graph is from a study of 196 patients ages 17-87 who were referred for B12 testing: the purpose of the study was to determine the utility of various tests to predict Cbl deficiency, defined here as MMA > 0.26 micromol/L with at least a 50% drop after Cbl supplementation.
The study found that serum Cbl and tHcy were the best predictors. The graph shows a sensitivity analysis of the probability of Cbl deficiency as a function of serum Cbl level, with age as a parameter.
I want you to look at this tiny additional scale which I've added on, where the cutoff for low B12 would be 300 pmol/L instead of 150. You can see that even when the level is 300, for someone 80 years of age, the risk of B12 deficiency is about 30%.



[Bolann et al, 2000]

This graph is from the same article. This time, the parameter that was varied in the sensitivity analysis was the tHcy concentration. Again, I've added the little scale on the x-axis to represent how things would look if our limit of normal of B12 level were 300 instead of around 150, as it might need to be if our lab testing is like in that study I showed you.
You can see that a patient with a B12 of 300 and a Hcy level of 20 would have about a 22% risk of B12 deficiency.

treat individuals at risk

- who is at risk of B12 deficiency?
  - elderly
  - vegans
  - "tea and toast" diet
  - post-gastrectomy
  - atrophic gastritis
    - H. Pylori infection
    - B12 deficiency

So if waiting for symptoms to develop is problematic, and testing for subclinical deficiency states costly and imprecise, what should we do? ❖

The second-last alternative was just to give vitamin B12 supplements to everyone at risk. This is what I recommend.

Who is at risk of vitamin B12 deficiency? ❖

I'm going to go through this very quickly, but for any of you who have time to stay, I have some neat slides which present visually the complicated process of B12 absorption and all the things that can go wrong with it.

Atrophic gastritis is believed to affect about 30% of North American adults over the age of 50. These people are thus unable to absorb food-bound B12, as this requires gastric acidity.

at risk

- reduced gastric acidity
  - medications, eg PPIs, histamine blockers
- lack of pancreatic enzymes
  - after certain surgical procedures
  - pancreatitis

There are other causes of reduced gastric acidity. Very common these days are proton pump inhibitors such as Pantoloc, prescribed for symptoms of gastroesophageal reflux.

at risk

- Stasis syndrome (bacterial overgrowth)
  - diabetes
  - intestinal diverticulosis
  - afferent loop of a gastrojejunostomy
  - intestinal obstruction
  - opioids
  - reduced gastric acidity

at risk

- B12 malabsorption
  - Crohn's disease
  - gluten intolerance
  - ileal resection
  - enteritis, etc.
- lack of intrinsic factor ("pernicious anemia")

preparations

- cyanocobalamin is the only form available in North America
- methylcobalamin, hydroxycobalamin available elsewhere (eg Japan, Britain)

high dose

- overcomes lack of intrinsic factor or absence of terminal ileum
- compensates for excess loss due to enterohepatic circulation
- "loading dose" in patients with symptoms
- may lower tHcy more

high dose

- dose-ranging study [Rajan et al, 2002]
  - 23 elderly veterans
  - B12 deficient (< 221 pmol/L)
  - 6 wks each of 25, 100, 1000 mcg Cbl
  - treatment with 1000 mcg necessary to reduce MMA to normal

In a study of 23 older veterans with B12 deficiency (B12 < 221 pmol/L), Rajan and colleagues gave 6 weeks of 25 mcg po Cbl, followed by 6 weeks of 100 mcg and then another 6 weeks of 1000 mcg. Treatment with 25 or 100 mcg lowered but did not normalize MMA levels, whereas 1000 mcg was most effective.

low doses

- low-dose (eg the typical dose in a multivitamin preparation)
- thought to protect a large proportion of those at risk

Because the problem of atrophic gastritis along with other causes of reduced gastric acidity are so common, the Institute of Medicine of the National Academy of Sciences in the United States, recommends that every adult over the age of 50 get most of their B12 from synthetic sources such as vitamin supplements or fortified food.
I guess that applies to many people in this room.
But what about our residents? Many are here because of illnesses related to homocysteine, such as cardiovascular disease or dementia. I think we should go for maximum homocysteine-lowering effect in these people.

what can we hope for?

- if we can reduce the progression of dementia, cardiovascular disease, strokes, falls, fractures, incontinence
  - better quality of life for our patients and their families
  - reduced burden of care

a useful resource

- http://ods.od.nih.gov/factsheets/vitaminb12.asp

Extra slides

"Psychiatric" symptoms in Pernicious Anemia

12 papers between 1903 and 1924 (before liver Rx)

111 patients with PA, psychiatric Sx Hector & Burton, 1988

Here 's why. Many people believe that B12 deficiency can cause psychiatric symptoms as well. So it may be important for us to know about.

Hector and Burton published an article in 1988, in which they reviewed studies of psychiatric symptoms occurring as part of pernicious anemia. Pernicious Anemia, you will recall, is a particularly severe form of vitamin B12 deficiency, which will kill you if left untreated.

Their review included 12 articles published between 1903 and 1924, during a period when doctors were able to diagnose pernicious anemia, but before there were any effective treatments for it. These articles reported on a total of 111 pernicious anemia patients who manifested psychiatric symptoms as shown on this slide,

- Apathy, somnolence, indolence, languor
- Decreased mental work performed
- Loss of memory
- Restlessness, irritability, peevishness, crankiness
- Stupid indifference to surroundings
- Emotional instability
- Shallow confusion with disorientation
- Abeyance of the mind

- Loss of inhibition
- Gradual mental deterioration
- Dementia or amentia
- Delirium of the low, quiet type
- Neurasthenia
- Confabulations
- Depressed, apprehensive, and without hope

And on this one.

- mania, exaltation, violent maniacal outbursts
- delusions and hallucinations (visual & auditory)
- hysteria
- peculiar paranoid conditions
- epilepsy
- dementia praecox

Reversible "psychiatric" symptoms in Pernicious Anemia

22 papers between 1928 and 1960 (liver Rx, B12 Rx)

371 patients with PA, psychiatric Sx which abated

Hector & Burton, 1988

The same authors also reviewed 22 articles published between 1928 and 1960, during which time effective therapy for pernicious anemia was available, either large quantities of raw liver given by mouth, and later on, injections of vitamin B12. The 22 papers covered a total of 371 patients, who manifested the following psychiatric symptoms which were felt to improve with the therapy for the pernicious anemia.

- Confusion
- Hallucinations, delusions
- Disorientation
- Confabulation
- Anxiety, restlessness
- Fatigue
- Depression
- Irritability
- Sleepiness
- Psychosis

- Introspection
- Stupor
- Slow cerebration
- Decreased memory
- Acute delirium
- Mania
- Apathy, lack of energy

This slide shows more symptoms which improved with pernicious anemia treatment.

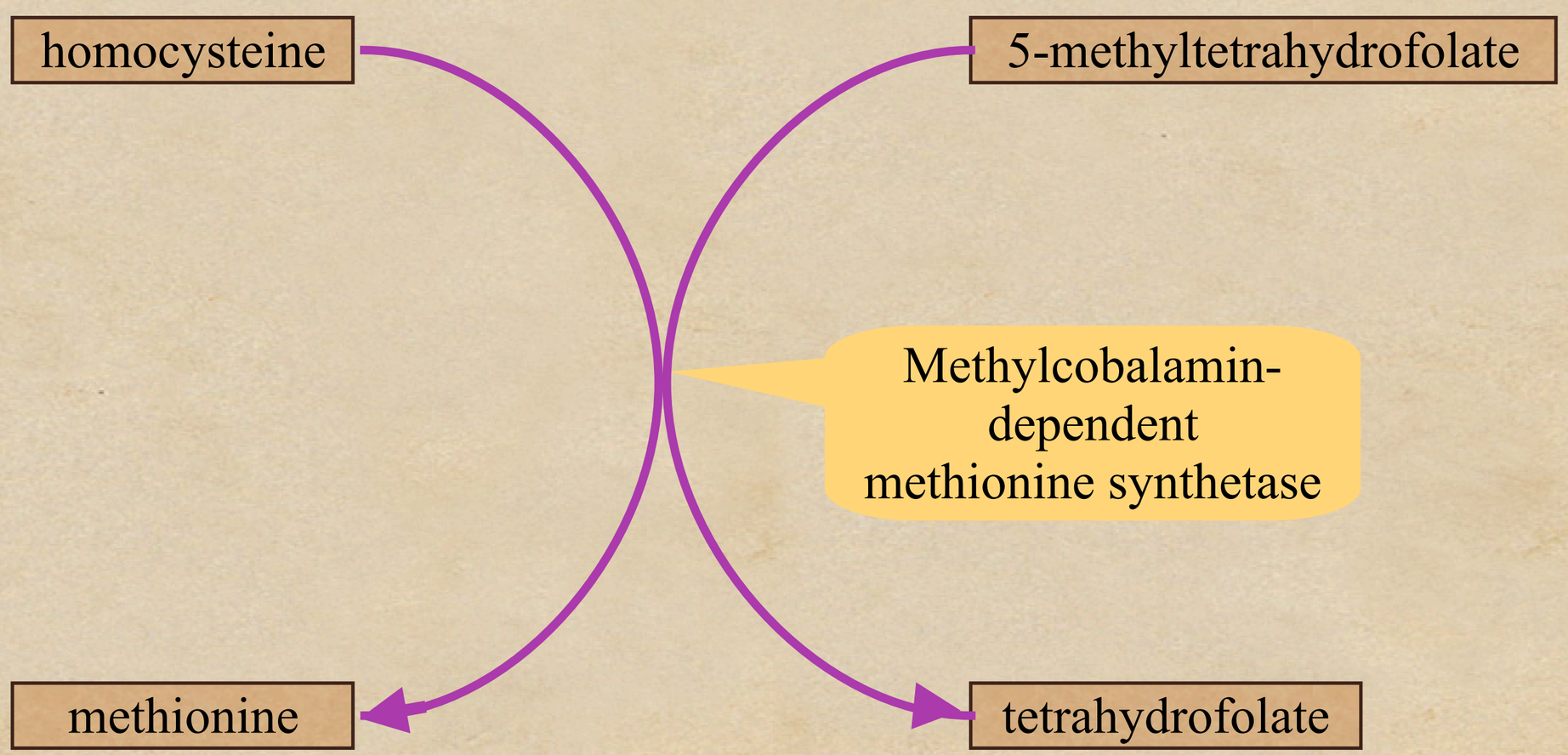
Now, a number of these symptoms we would recognise as being neurologic and not at all psychiatric. Be that as it may, when patients present with any of these symptoms, they may still get referred to a mental health professional.

- weakness
- subacute organic reactions
- violent behaviour
- self pity
- flight of ideas
- negativism
- acute paranoid states

So, let's take the word of these authors that these sorts of symptoms are actually caused by B12 deficiency. How does that happen? What's the mechanism?

To understand this stuff, we have to review some biochemistry.

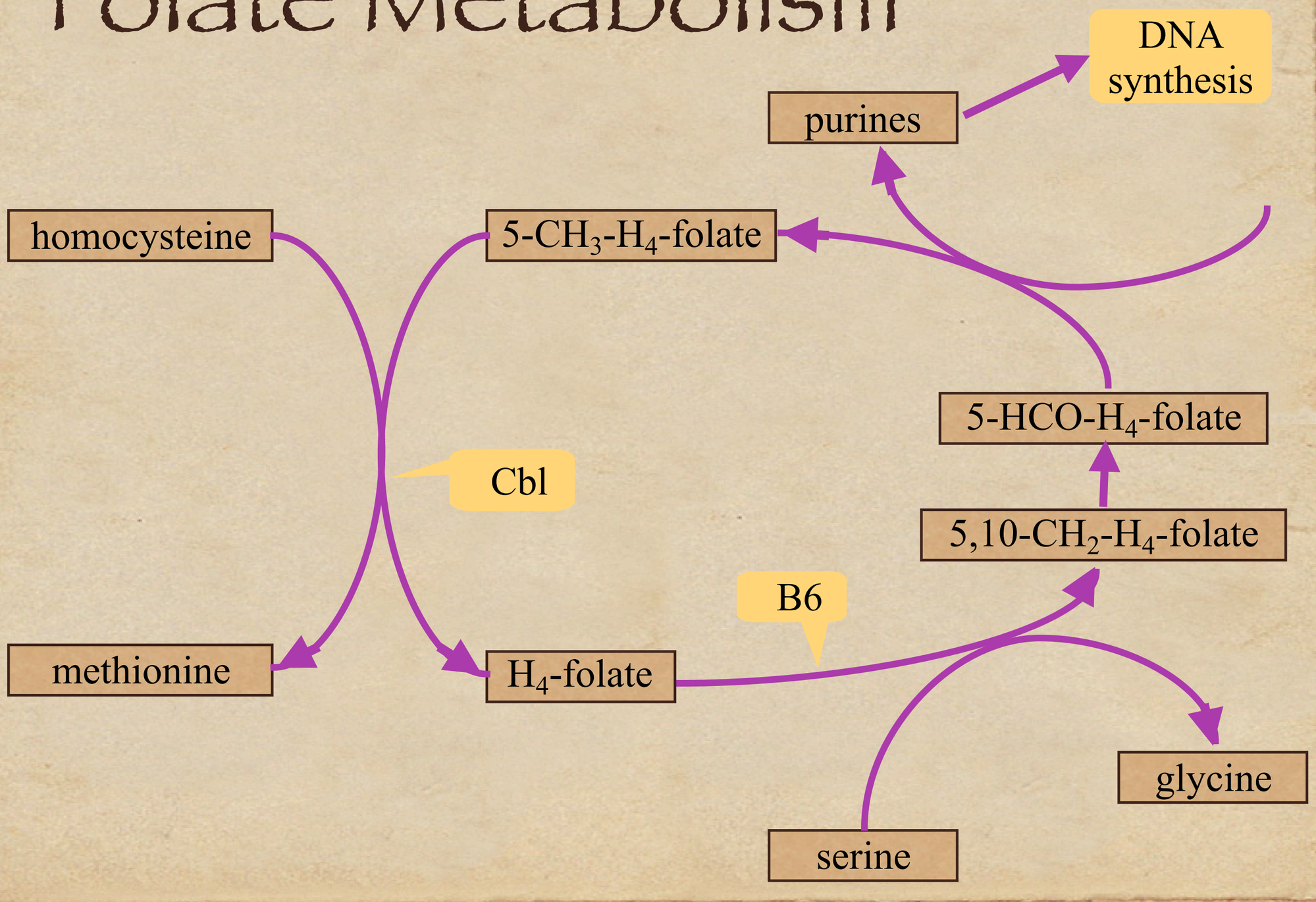
Homocysteine Metabolism



There are two metabolically active forms of cobalamin: methylcobalamin and adenosylcobalamin. However, the form of cobalamin usually found in vitamin preparations is cyanocobalamin, which has no known physiologic role and has to be converted before it can be used by tissues.

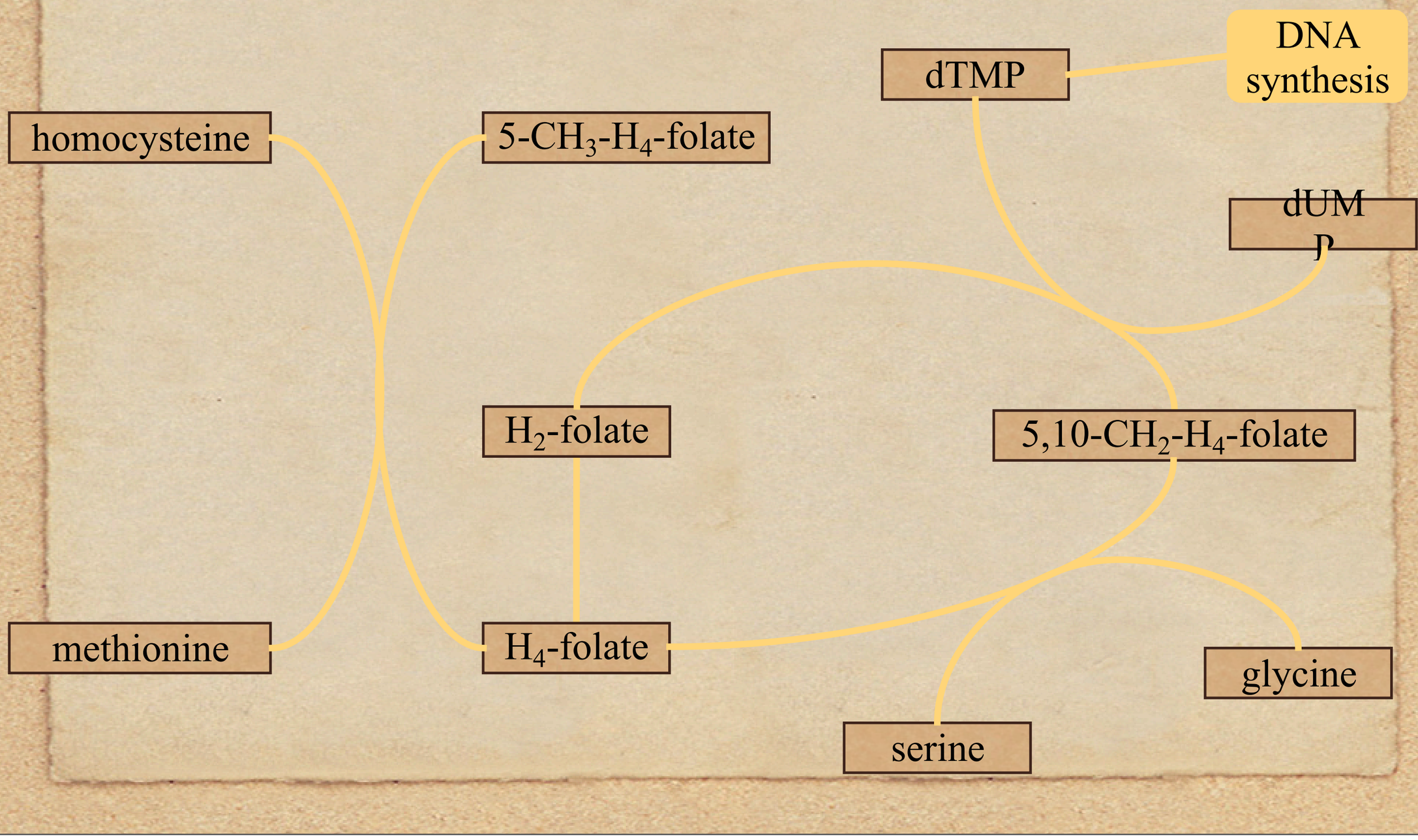
Methylcobalamin is an essential cofactor in the conversion of ♣ homocysteine to methionine. In the absence of cobalamin, not only does homocysteine build up, but ♣ 5-methyltetrahydrofolate which the cell has taken up from the bloodstream cannot be converted to tetrahydrofolate, and so is unavailable for various reactions necessary for DNA synthesis. This is the folate trap hypothesis: the 5-methyltetrahydrofolate is trapped and leaks out of the cell. However, it does contribute to the total folate measured in blood tests. As a result, in B12 deficiency, one can find normal or even high levels of serum folate, even though this folate cannot be used by the cells.

Folate Metabolism



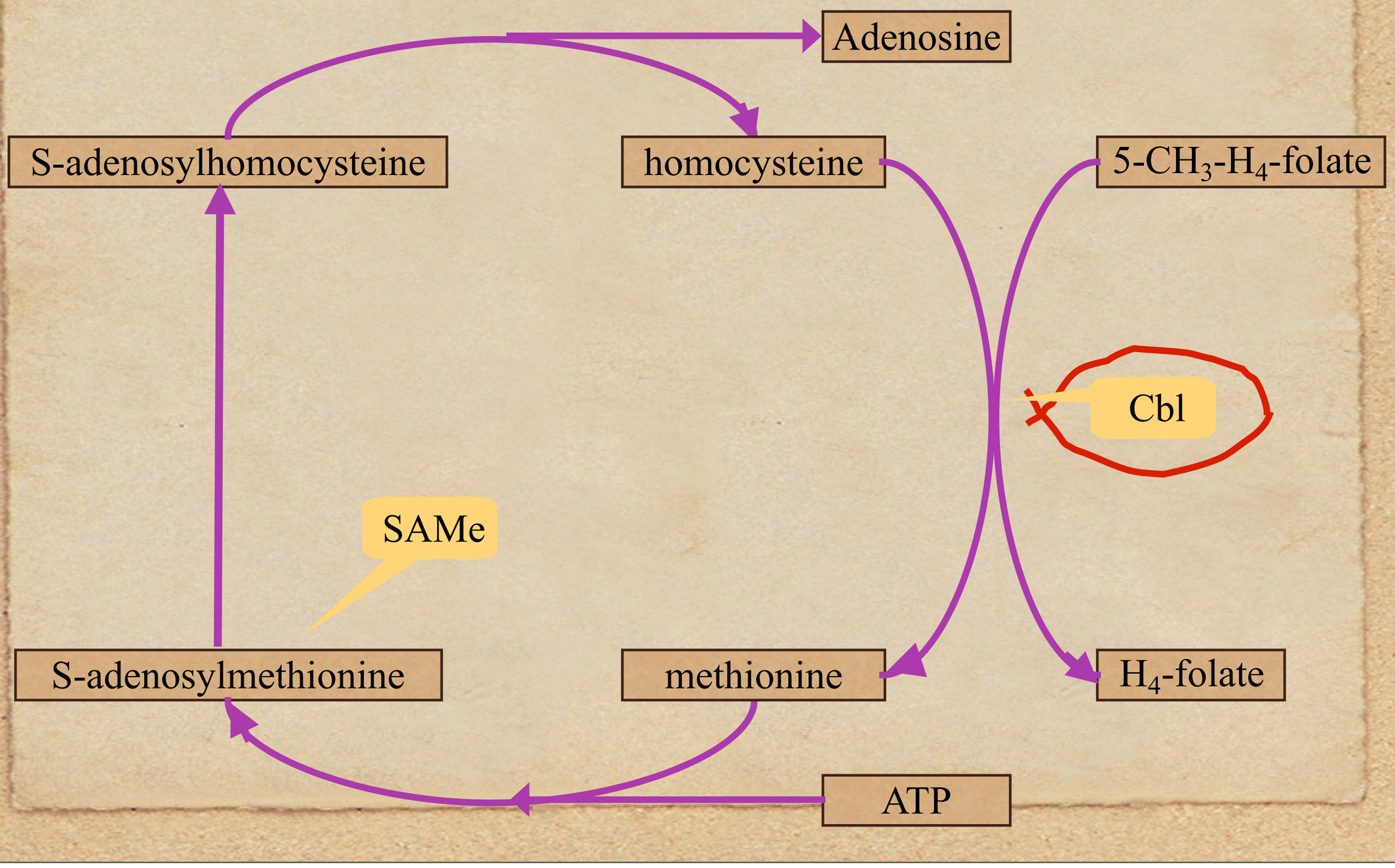
Tetrahydrofolate is the active form of folate; it acquires a one-carbon fragment from ♣ serine, in a reaction which requires ♣ vitamin B6. The resulting fragment is first ♣ oxidized, and then transferred to substrates for the synthesis of ♣ purines (such as the DNA building blocks adenine and guanine. Note that adenine is also a precursor for various compounds widely used in energy metabolism, such as AMP, ATP, NAD, NADP).

Folate Metabolism (2)



An alternate use of tetrahydrofolate is to get converted to ♣ dihydrofolate and then back to tetrahydrofolate. In the process, one-carbon fragments are contributed for the production of ♣ dTMP, or deoxythymidylic acid, another DNA building block.

Homocysteine Metabolism



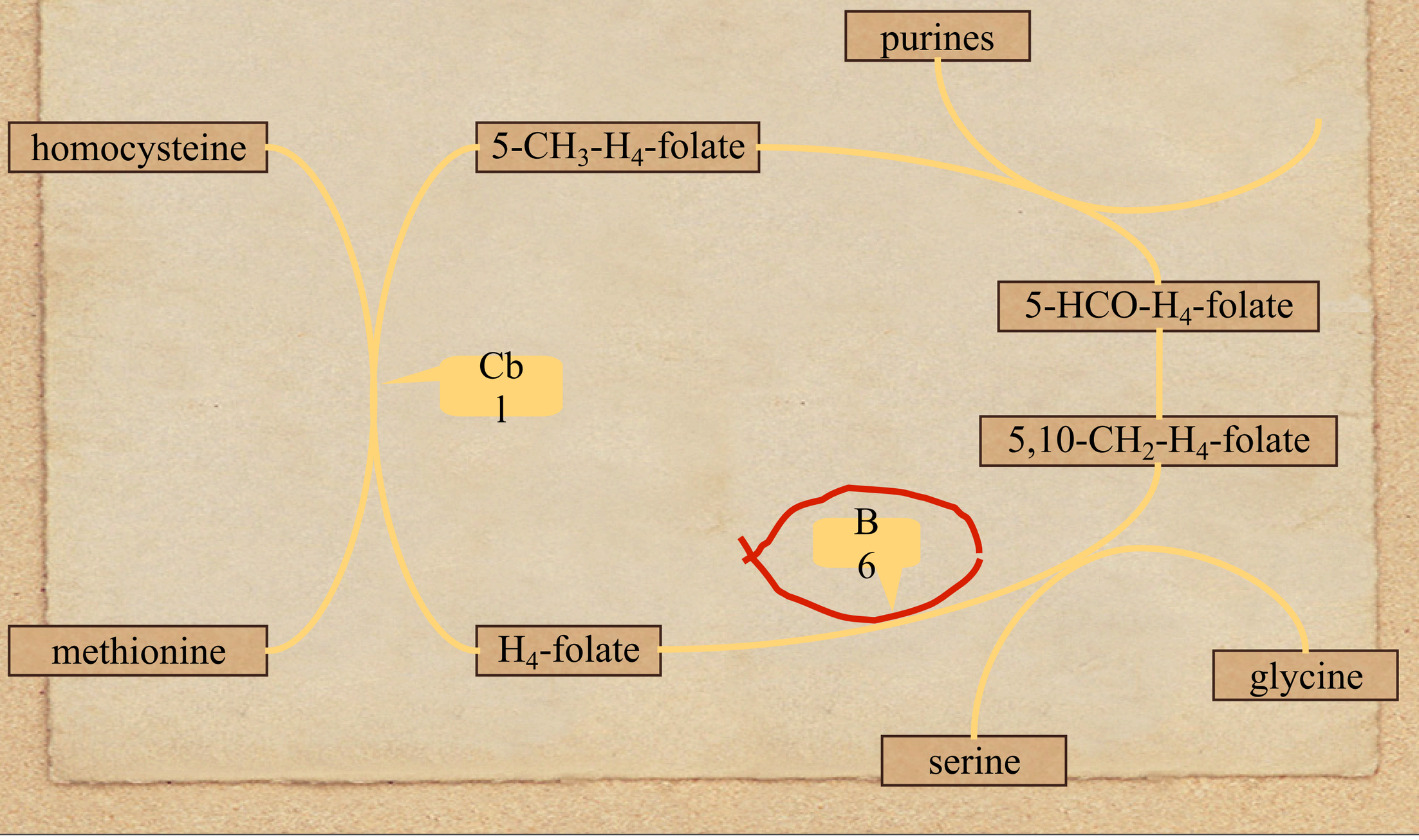
Now let's look at the other side of the cobalamin-aided conversion, that of homocysteine to methionine. Normally, methionine is converted to ♣ S-adenosylmethionine (abbreviated SAMe), which then loses its methyl group to become ♣ S-adenosylhomocysteine. This compound gives up ♣ adenosine to return to homocysteine.

Adenosine, again, is a component of AMP, ATP, cyclic AMP, and so on.

You can see from this cycle that in ♣ cobalamin deficiency, homocysteine will build up. Elevated homocysteine is now recognized as an important risk factor for vascular disease of all sorts, including cardiovascular disease, peripheral vascular disease, stroke, and dementia.

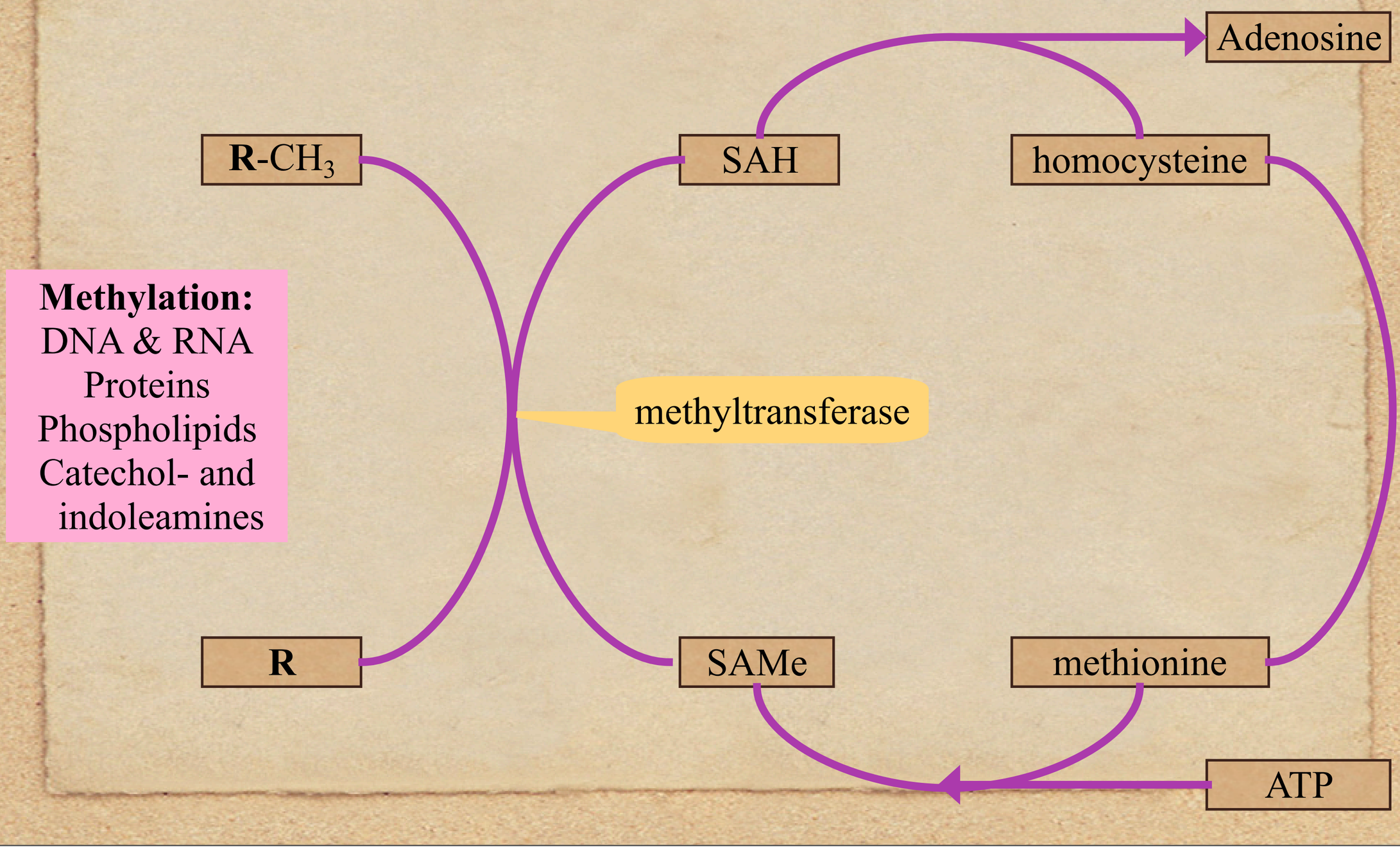
Homocysteine can be measured in the blood, and elevated levels can be a signal of B12 deficiency. However, homocysteine will also be elevated in folate deficiency.

Folate Metabolism



You saw this slide before; I'm bringing it back to make the point that another cause of elevated homocysteine, or hyperhomocystinemia, is a deficiency of ♣ vitamin B6, also known as pyridoxine.

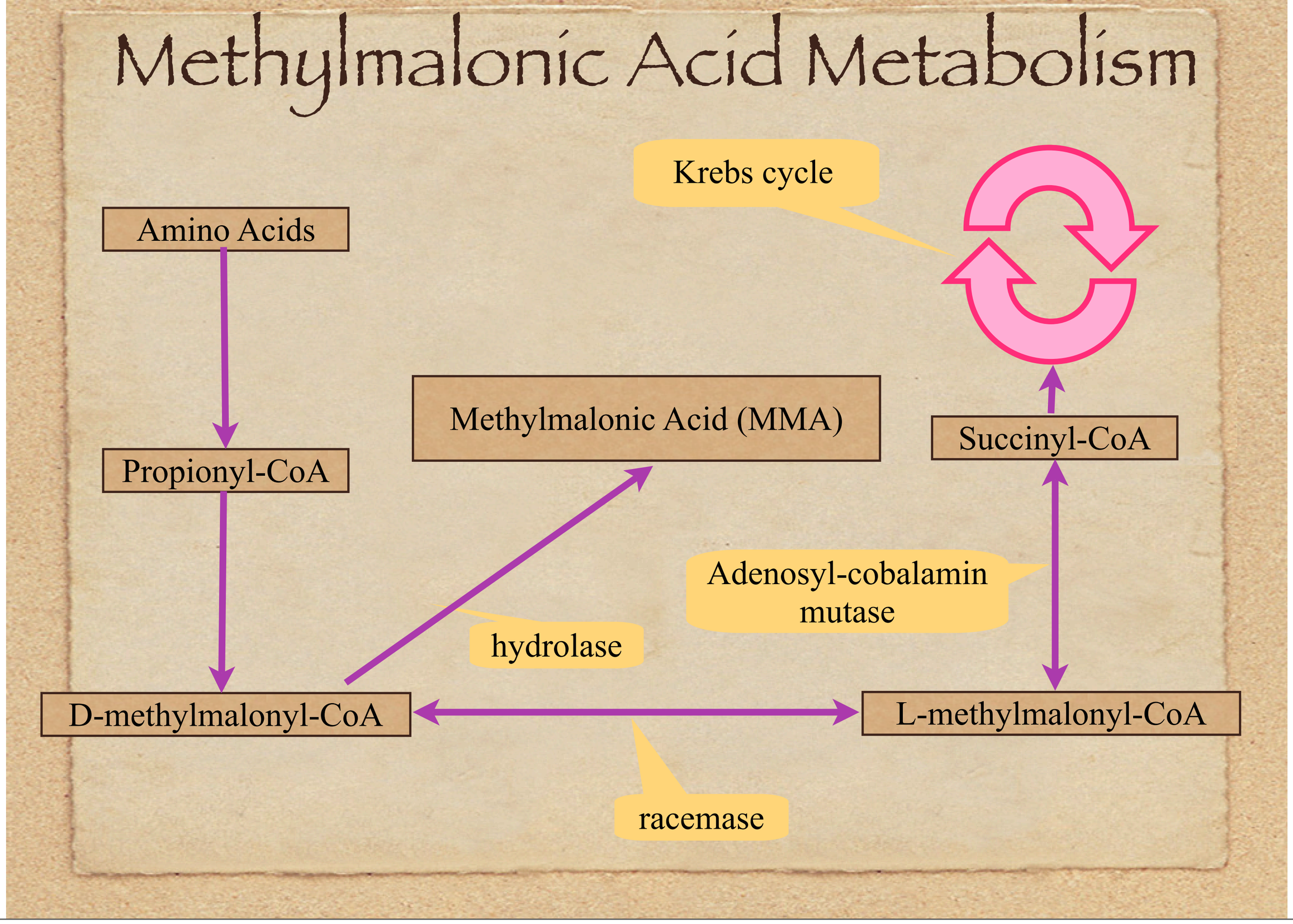
Homocysteine Metabolism (2)



SAMe is available in health food stores; there are a number of studies suggesting that it has antidepressant properties; it may also improve cognitive function in patients with dementia.

What is important here is that SAMe is required as a methyl donor in over 35 different ♣ methyltransferase reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. All of these will be affected with a deficiency of B12.

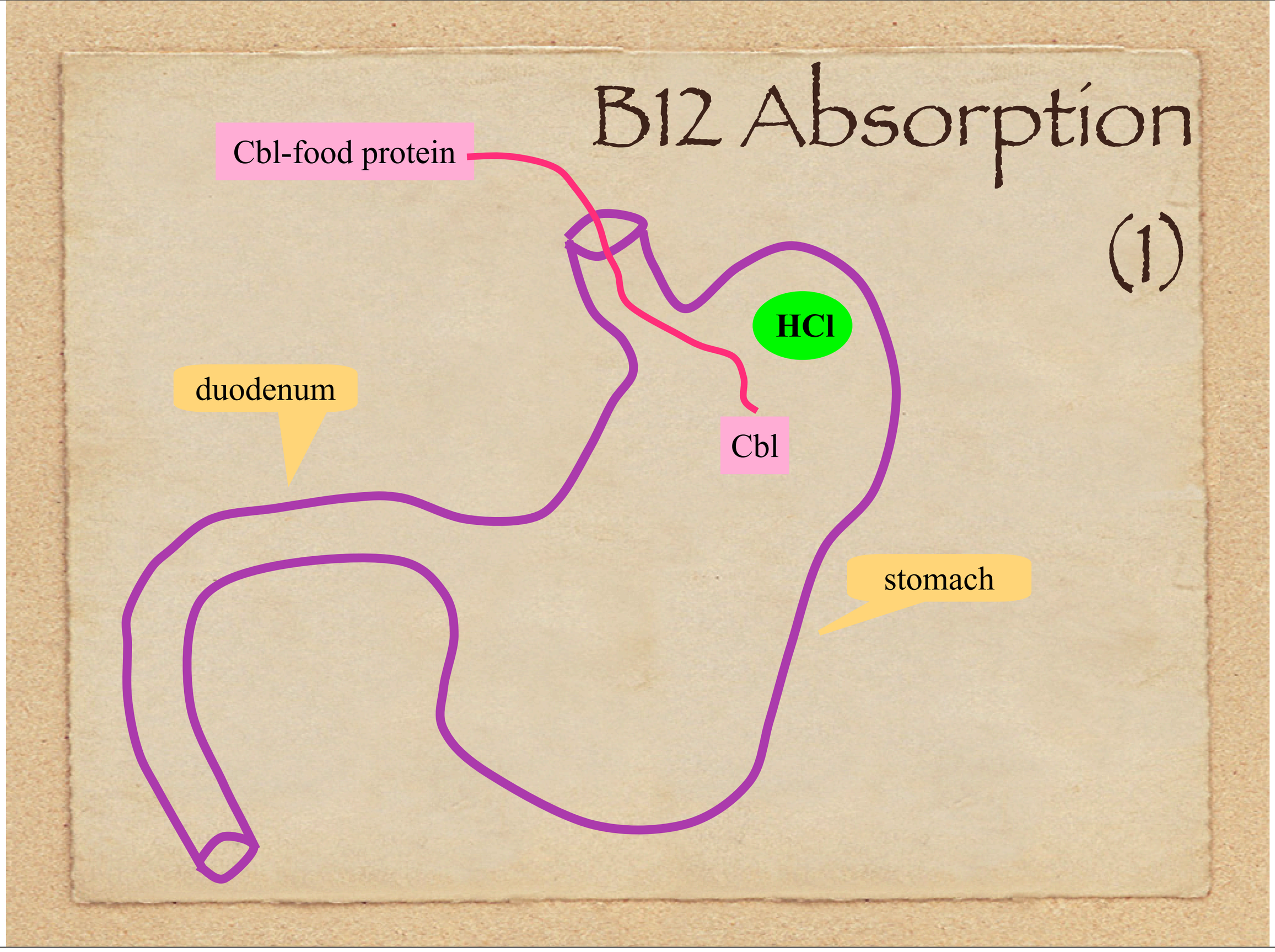
The phospholipids in particular are an important component of nerve cells, and some authors believe that the neurological effects of B12 deficiency are in part mediated through impaired phospholipid synthesis.



This slide shows how a deficiency of cobalamin causes an increase in blood levels of methylmalonic acid, or MMA for short. I won't bore you with the details.

I mentioned earlier that the only two forms of cobalamin which are physiologically active are methylcobalamin and adenosylcobalamin. The methyl form is necessary in the homocysteine and folate reactions we just looked at; Adenosylcobalamin is an essential cofactor in one of the reactions involving methylmalonic acid. Here's how it works: We start with ♣ amino acids, which are building blocks for proteins. So, these amino acids come from proteins in our diet, or from recycling proteins in our body. The amino acids are converted to ♣ propionyl-Coenzyme A, which then becomes ♣ D-methylmalonyl-Coenzyme A. The D form to ♣ L form conversion can go in both directions. This next step requires the B12. The L form is changed to ♣ succinyl-Coenzyme A, which you may remember from your biochemistry plugs into the ♣ Krebs cycle, the major energy-producing cycle of the body.

What happens if there is a B12 deficiency? The L-methylmalonyl-Coenzyme A backs up, and so the D form backs up also. Excess D-methylmalonyl-Coenzyme A is converted into ♣ methylmalonic acid, or MMA, which appears in the blood and also in the urine. Thus, B12 deficiency produces an elevation of MMA.



So why is it that people become deficient in vitamin B12 with such serious consequences? Why this vitamin? What makes it different from all the other vitamins where deficiencies seem to be rare?

For some reason, the absorption of B12 is incredibly complicated. Let ’s go through it. For some reason, I enjoy this more than the biochemistry.

Vitamin B12 consists of a group of cobalt-containing compounds

Overall group name is cobalamin

Made by bacteria

Found in meat, eggs, fish, dairy products; also on fruits and vegetables if you’re not too obsessive about washing all the bacteria off.

Daily requirement: about 2 to 5 micrograms

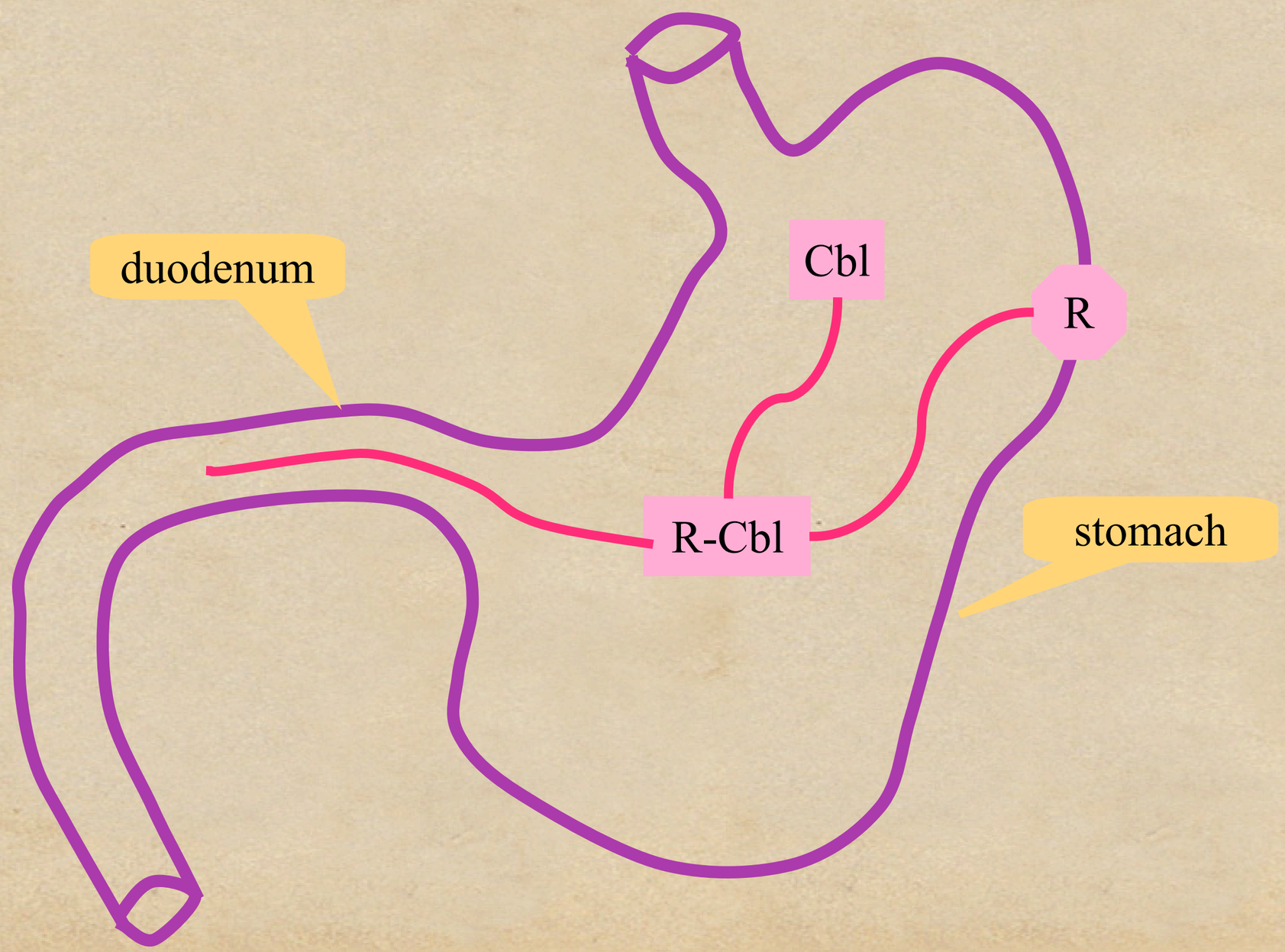
Healthy adults consume 2 - 6 micrograms per day

The body stores 4 to 5 milligrams, about half in the liver.

B12 in food is bound ♣ to food proteins. There may also be some cobalamin analogues, chemically similar to cobalamin, but inactive physiologically. These are sometimes called cobamides.

First step, of course, is to eat the food. ♣ It finds its way into the stomach ♣ , where hydrochloric acid and pepsin ♣ separate the B12 from the food protein.

B12 Absorption (2)

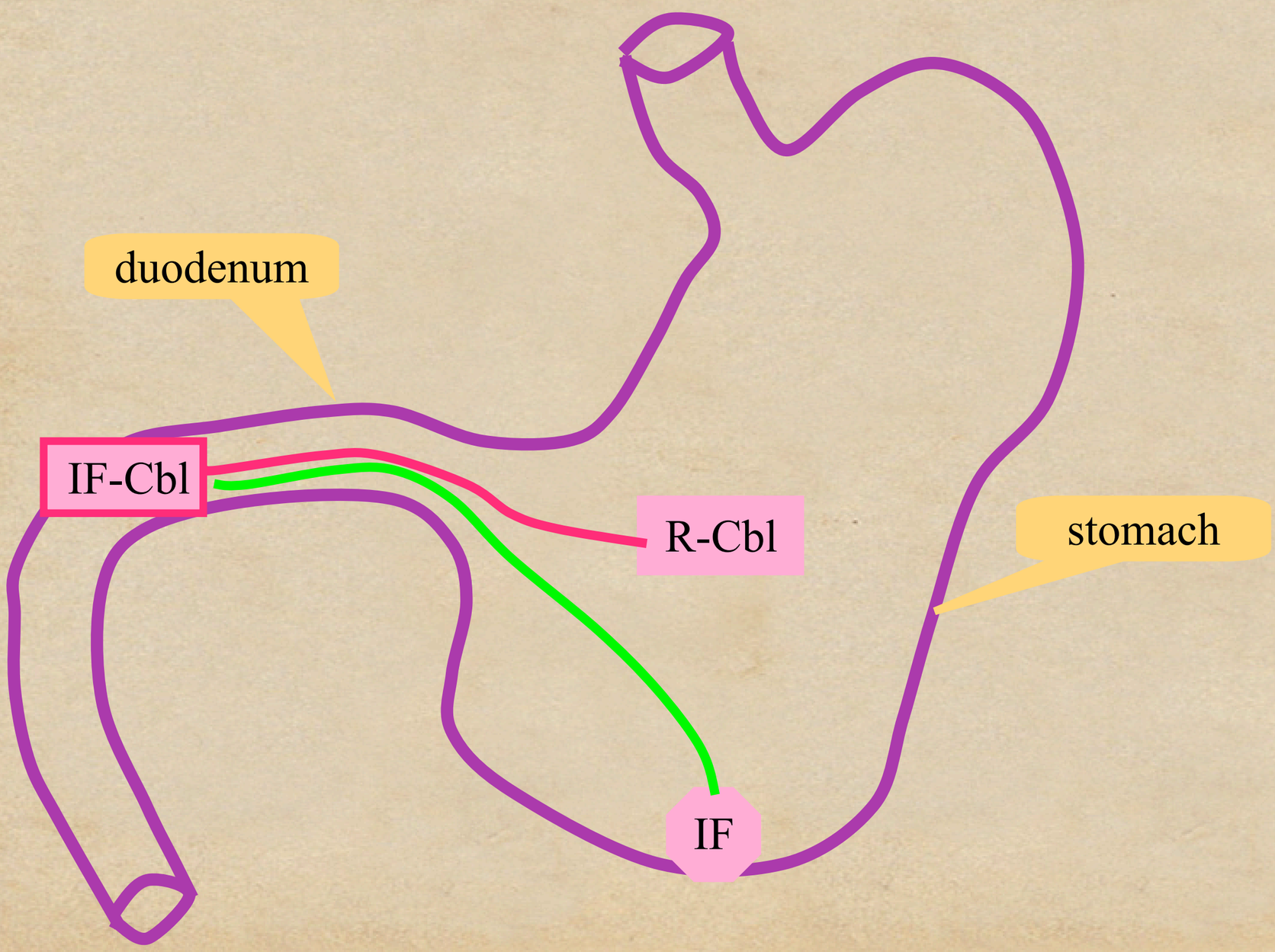


The free cobalamin in the stomach now meets up with a glycoprotein referred to as ♣ R binder protein.

R binder protein is one of a closely related group of glycoproteins found in secretions such as saliva, milk, gastric juice, bile, and also in the blood. We'll see a couple of other examples later.

The free cobalamin immediately binds to the R-binder protein, to form a ♣ complex which is stable at the acid pH of the stomach, and thus remains undigested until it gets to the ♣ duodenum.

B12 Absorption (3)



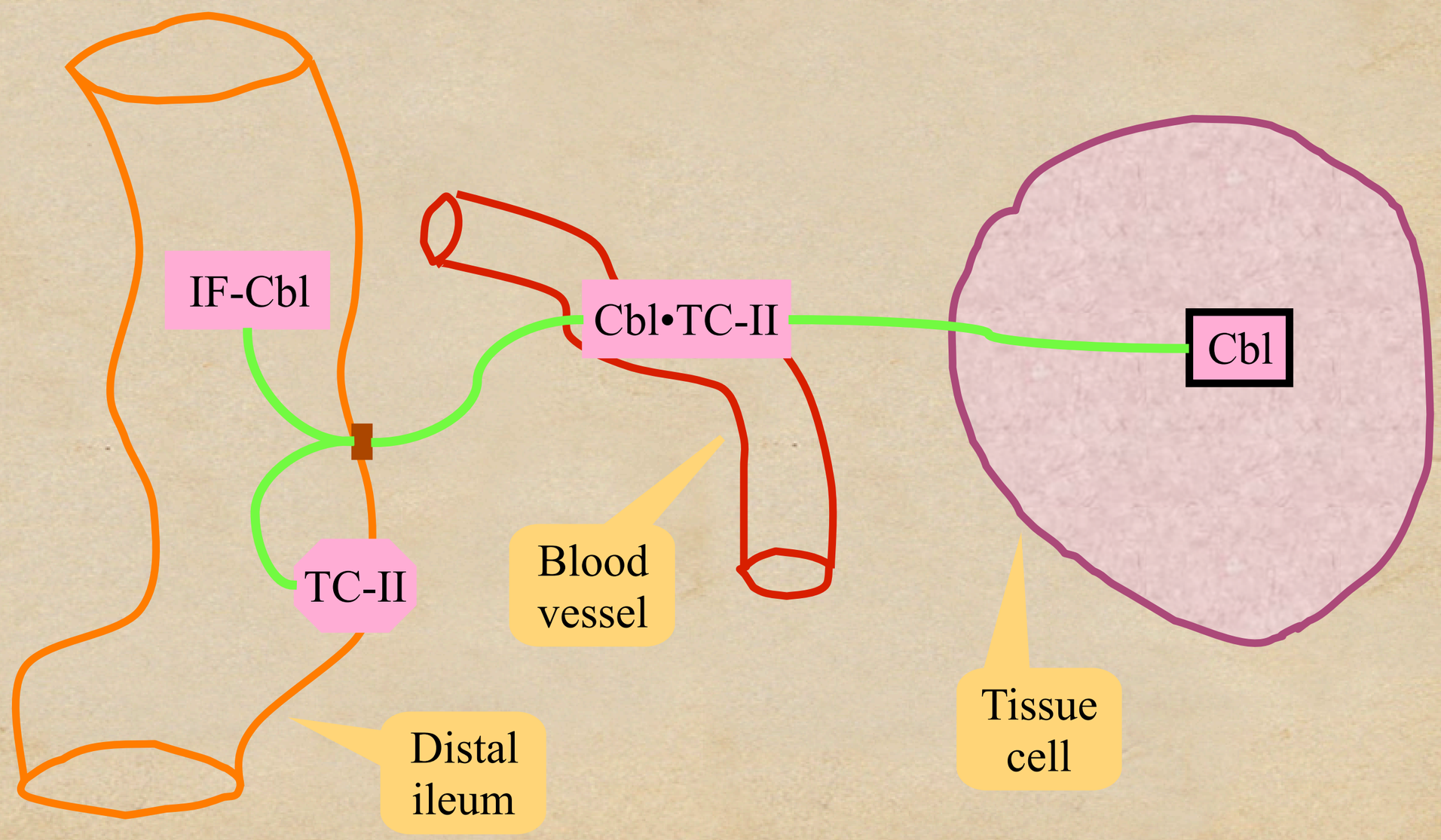
Once in the duodenum, the R-binder-cobalamin complex is digested by pancreatic enzymes, releasing ♣ the cobalamin.

Now, the parietal cells of the stomach manufacture another glycoprotein, ♣ called Intrinsic Factor.

The unbound cobalamin in the duodenum is quickly picked up by the intrinsic factor, which is highly specific for this vitamin. Intrinsic factor doesn't attach to the inactive cobalamin analogues, however, so these will be mostly eliminated via the stool.

The newly formed complex ♣ of intrinsic factor and cobalamin resists digestion, so it can travel down the small intestine.

B12 Absorption (4)



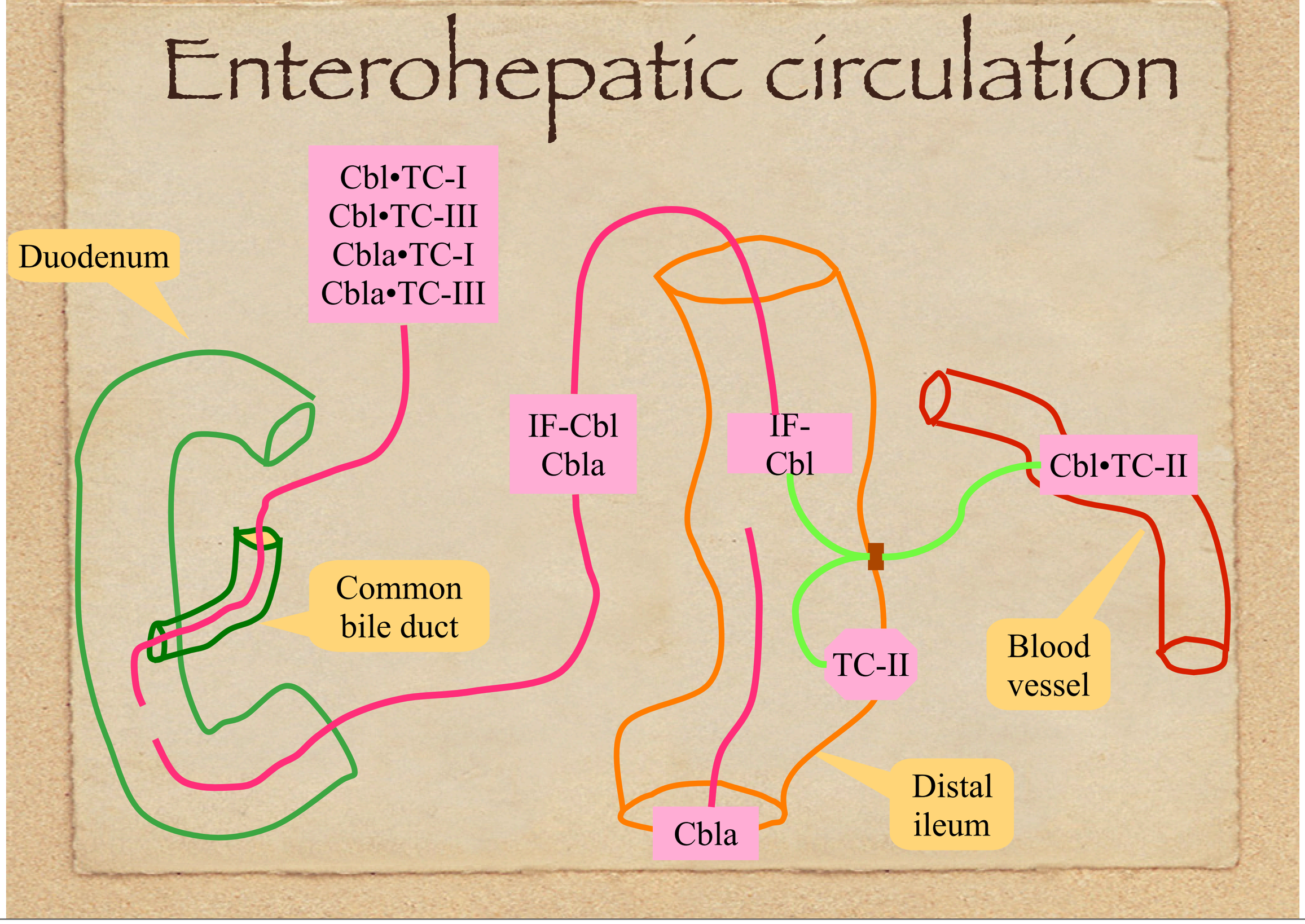
When the intrinsic factor-cobalamin complex arrives at the end of the small bowel, at a place called the distal ileum, it is picked up by specific receptors on the mucosal cells.

Once inside the ileal mucosal cell, the intrinsic factor is destroyed

♣The cobalamin is then transferred to another transport protein, called transcobalamin II, probably manufactured inside the mucosal cells

♣ After several hours, this cobalamin-transcobalamin II complex is then secreted into the bloodstream

♣ It is very rapidly taken up by liver, bone marrow, and other cells in the body which have specific receptors for the Cbl-TCII complex.



The final chapter in the complicated absorption of B12 is the enterohepatic circulation, which involves the duodenum and the common bile duct.

Besides the cobalamin in blood attached to TC-II, both the active cobalamin as well as inactive analogues can also be found in blood, bound to another glycoprotein.

This protein, also known as cobalophilin, exists in two forms, called Transcobalamin I and Transcobalamin III ♣ for historical reasons, even though it apparently does not serve a transport function.

The active cobalamin-cobalophilin complexes are secreted into the bile, along with complexes containing inactive analogues.

These complexes travel down the common bile duct to the duodenum.

As before, the glycoprotein gets digested in the duodenum.

The true cobalamin is picked up by Intrinsic Factor ♣, but the inactive analogues cannot bind to IF.

As before ♣, the IF-cobalamin complex is absorbed by ♣ mucosal cells and thus becomes available for reuse.

The inactive analogues are eliminated ♣ via the colon, although a small percentage may be absorbed by nonspecific diffusion.

Thus, the enterohepatic circulation serves to conserve the vitamin while allowing excretion of the useless analogues.

Whew! What a ride! God, why did you make things so complicated? What possible purpose could all these transport proteins and intrinsic factors and so on serve? The more complicated something is, the more things can go wrong. And that's exactly the situation with vitamin B12.

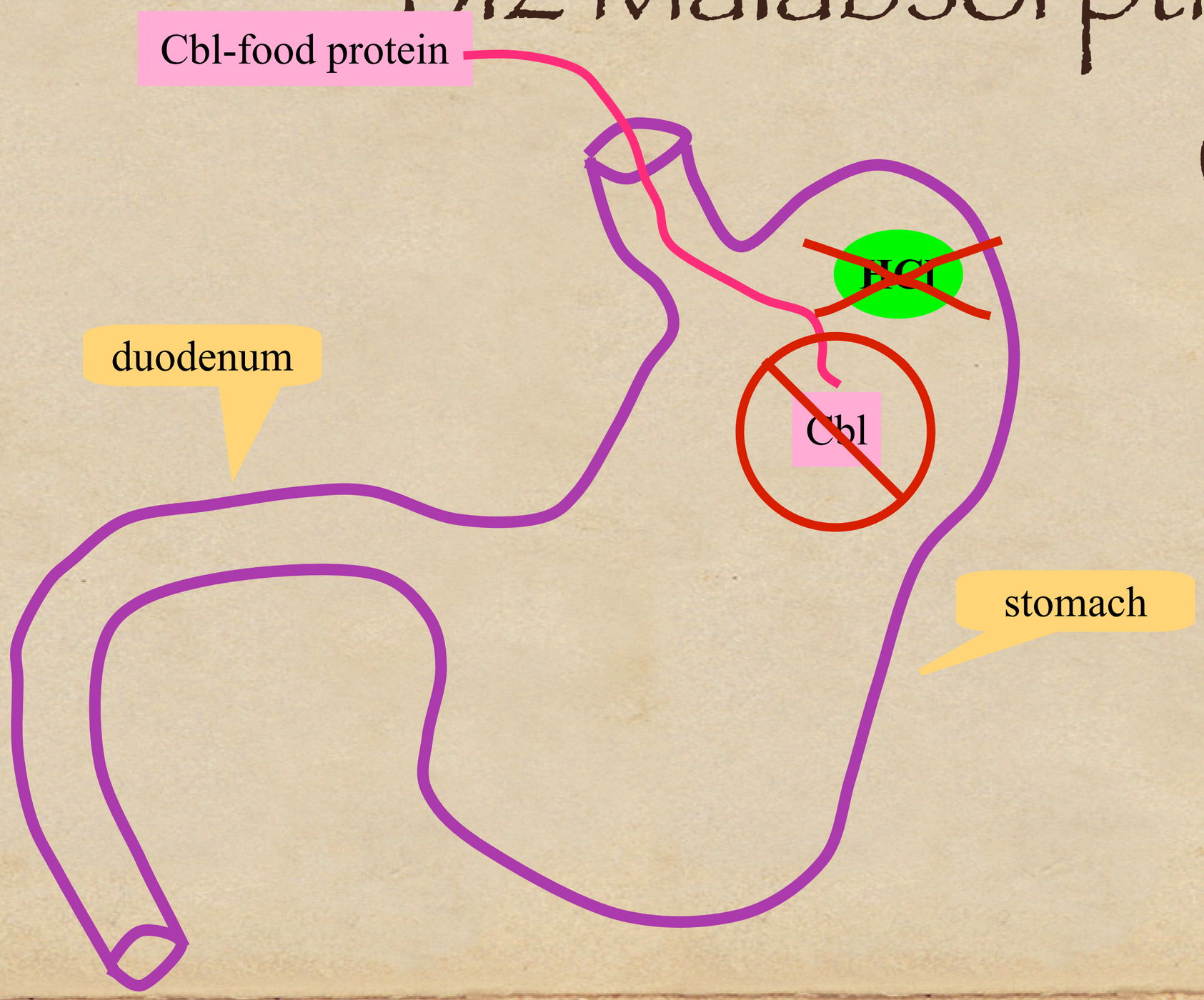
Let's examine some of the things that can go awry.

B12 Malabsorption (1)

- Low or absent dietary B12:
  - Vegetarianism, esp. Veganism
  - "Tea and toast" diet

The first problem, of course, occurs when your food doesn't have enough B12 in it. Vegetarians, particularly vegans, are at high risk. Some elderly are also likely to get insufficient B12 because of a tea and toast diet.

B12 Malabsorption (2)



The next obstacle occurs if the conditions in the stomach are such that the food cobalamin cannot be released from the food proteins to which it is bound. This release step requires hydrochloric acid, so any condition leading to ♣ achlorhydria or hypochlorhydria will impair the formation of free cobalamin.

There are quite a few situations where there is insufficient stomach acid:

Achlorhydria or Hypochlorhydria

- Proton Pump Inhibitors:
  - Omeprazole (Losec)
  - Lansoprazole (Prevacid)
  - Pantoprazole (Pantoloc)
- H2-blockers:
  - Cimetidine (Tagamet)
  - Ranitidine (Zantac)

Many patients are on ♣ proton pump inhibitor medications, such as omeprazole. These drugs reduce the stomach acidity, which can be helpful to patients with heartburn or ulcers. Unfortunately, omeprazole has been shown to reduce the absorption of B12 by more than half. It may be that taking cranberry juice with the B12-containing food will prevent the absorption problem.

Another class of drugs which impair B12 absorption by reducing gastric acidity are the ♣ histamine-2 blockers, such as cimetidine. However, the effect is likely less severe than for omeprazole.

Importantly for psychiatrists, many of the ♣ tricyclic antidepressants are powerful H2 blockers also, in particular amitriptyline and doxepin. This table ♣ compares the H2 blocking activity for several antidepressants with that of cimetidine. You can see that doxepin is 6 times as potent as cimetidine, whereas amitriptyline is an astounding 22 times more potent. Certainly, doxepin has been tested in several trials and found to be as effective as cimetidine for healing ulcers.

Antidepressants

Generic Name	Trade Name	H2 Affinity
Cimetidine	Tagamet	0.1
Desipramine	Norpramin	0.08
Nortriptyline	Aventyl	0.12
Imipramine	Tofranil	0.4
Doxepin	Sinequan	0.6
Amitriptyline	Elavil	2.2

Achlorhydria or Hypochlorhydria (2)

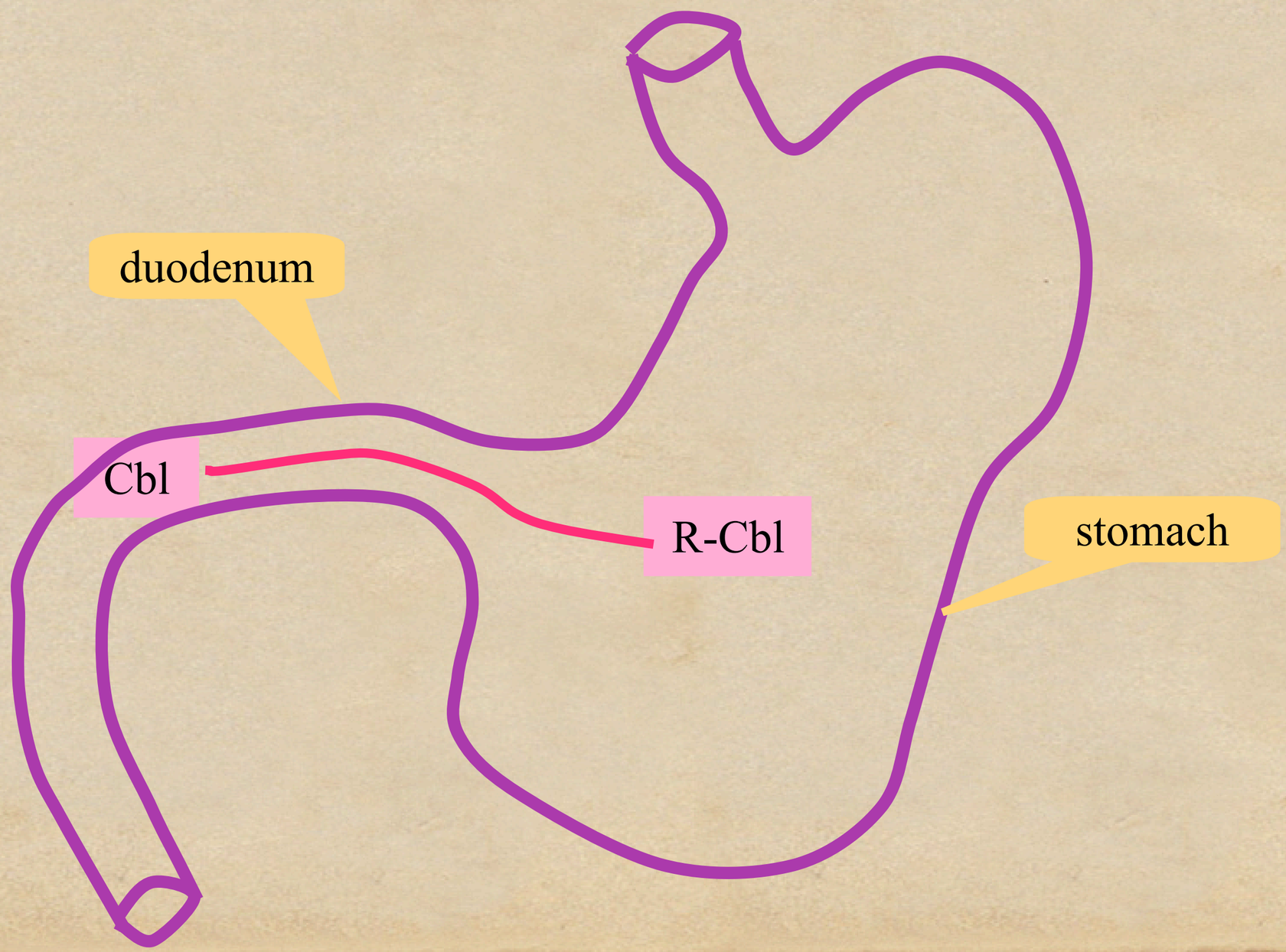
- Atrophic Gastritis due to H. Pylori:
  - H. Pylori infection:
    - >50% of adults
    - 30% of infected people have atrophic gastritis
  - 138 patients with megaloblastic anemia & low B12:
    - 77 (56%) H. Pylori infection
    - 31 (40%) responded to antibiotics
- Atrophic Gastritis due to B12 deficiency

Finally, what may be an extremely common cause of insufficient stomach acidity is the condition called ♣ atrophic gastritis, where the culprit is often H. Pylori. This bacterium infects the stomach of more than ♣ half of all adults in developed countries, and up to 90% of adults in third world areas. Fortunately, most infected people are asymptomatic. However, even asymptomatic people can develop atrophic gastritis, which occurs in up to 30% of infected individuals, according to one study.

Another study looked at ♣ 138 patients who had megaloblastic anemia and low B12 levels. 77 of the 138, or 56%, had H. Pylori infection, which responded to eradication treatment with antibiotics in 40% of the 77. In these 31 patients where the antibiotics were effective, the serum B12 levels normalized and the megaloblastic anemia disappeared without giving them any B12 supplementation.

Atrophic gastritis can also be caused by ♣ B12 deficiency itself, as we ’ll see in a bit.

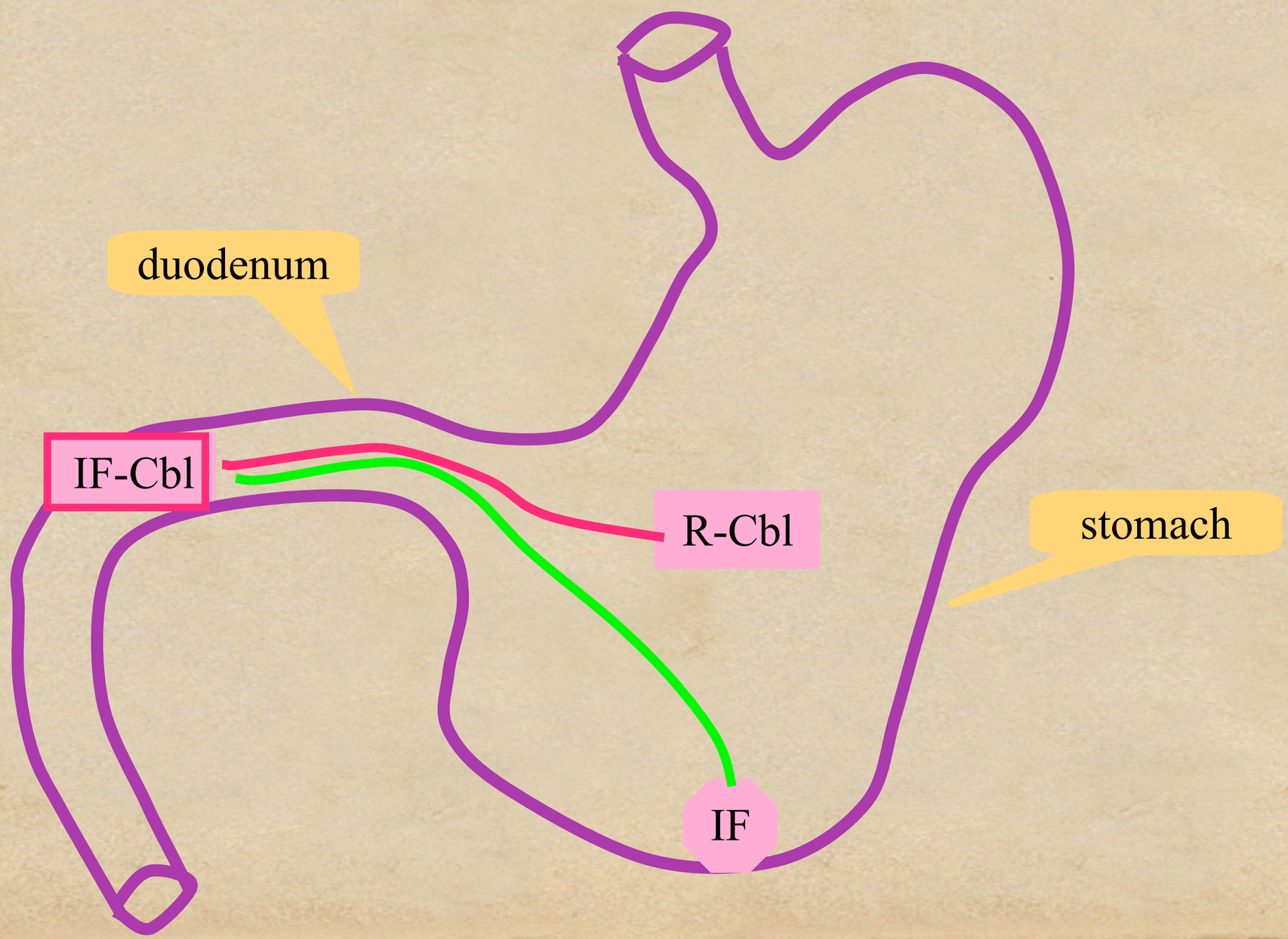
B12 Malabsorption (3)



Recall from this slide that the complex of R binder protein and cobalamin gets digested by pancreatic enzymes in the duodenum to produce ♣ free cobalamin which is then picked up by intrinsic factor.

Conditions such as pancreatitis and some surgical procedures affecting the pancreas or its ducts may impair B12 absorption at this site. Giving pancreatic enzymes by mouth may correct the problem.

B12 Malabsorption (4)



The next type of malabsorption problem has to do with intrinsic factor. Here is the slide showing the formation of the intrinsic factor-cobalamin complex in the duodenum.

An important and extremely serious cause of B12 deficiency is pernicious anemia, as we've just seen, where the parietal cells of the stomach are attacked by what appears to be an autoimmune mechanism. Without intrinsic factor, of course, almost no B12 can be absorbed. On top of this, the body stores of B12, which get recycled via the enterohepatic circulation, cannot be reabsorbed without intrinsic factor, and thus are rapidly lost. This explains why neurologic and hematologic symptoms will occur much more quickly in B12 deficiency due to pernicious anemia than in most other causes of deficiency.

The parietal cell mass can also be destroyed by corrosive agents, which suicidal patients might swallow in an attempt to kill themselves.

Partial gastrectomies, sometimes performed for morbid obesity, can impair intrinsic factor production also.

Stasis Syndrome

- Also known as bacterial overgrowth syndrome
- Whenever there is stasis, intestinal bacteria proliferate locally
- Causes
  - diabetes
  - scleroderma
  - intestinal diverticulosis
  - afferent loop of a gastrojejunostomy
  - intestinal obstruction due to strictures, adhesions, or cancer
  - opioids

The next group of conditions are known as stasis syndrome, also called ♣ bacterial overgrowth.

When the intestinal contents stop moving, ♣ bacteria can grow out of control.

Here is a ♣ list of some conditions that cause stasis syndrome.

Keep in mind that narcotic painkillers also slow down the intestine.

The mechanism by which bacterial overgrowth causes B12 deficiency is thought to be by competition from the bacteria for the B12. Other intestinal parasites, such as the fish tapeworm seen in Scandinavian countries, also divert B12 away from the host.

Perhaps one of the most problematic aspects of bacterial overgrowth syndrome is that some bacteria species can convert cobalamin into inactive analogues, sometimes called cobamides. These may be absorbed to some extent and may artificially raise the values obtained on serum B12 testing.

The bacteria also produce folic acid, which explains the high folate levels often found in patients who have B12 deficiency.

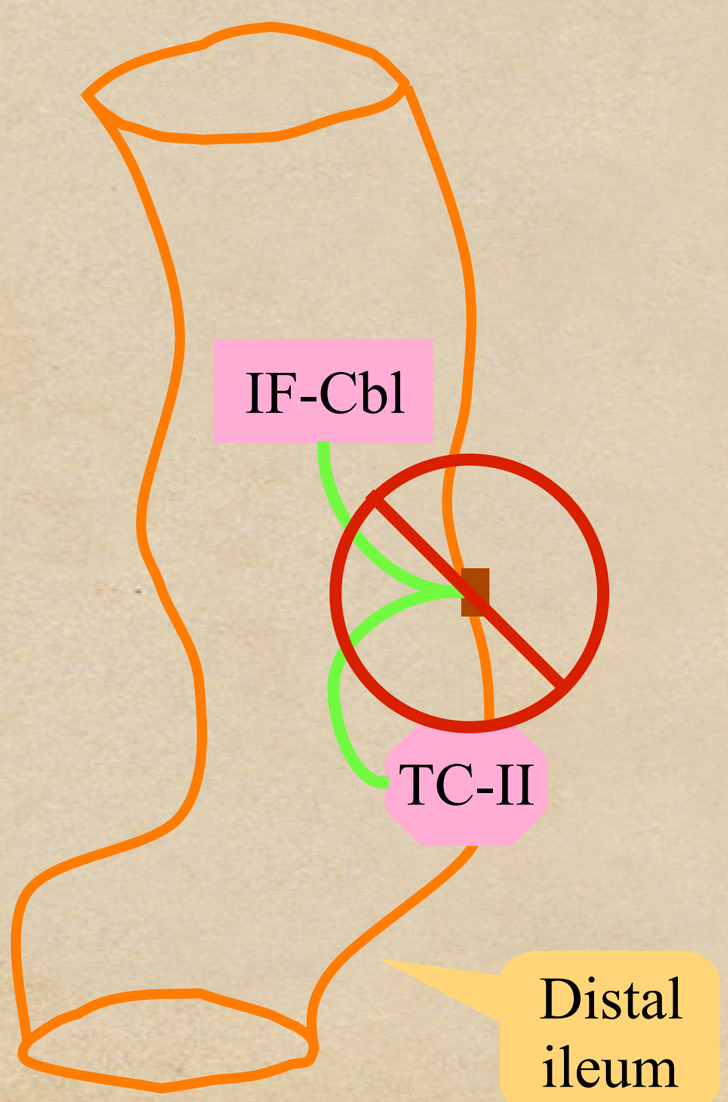
♣ Finally, bacterial overgrowth not only in the intestine, but also in the duodenum and in the stomach itself, can be caused by any condition which reduces gastric acidity. Again, the problems of falsely high serum B12 readings may occur.

Achlorhydria or Hypochlorhydria

- Proton Pump Inhibitors:
  - Omeprazole (Losec)
  - Lansoprazole (Prevacid)
  - Pantoprazole (Pantoloc)
- H2-blockers:
  - Cimetidine (Tagamet)
  - Ranitidine (Zantac)
- Tricyclic antidepressants
- H. Pylori infection
- B12 deficiency

Just to remind you, I'll briefly flash this slide showing the various conditions that can cause low gastric acidity and therefore bacterial overgrowth.

B12 Malabsorption (6)



- tropical sprue
- regional enteritis
- Crohn's disease
- Whipple's disease
- Tuberculosis
- Ileal resection
- Gluten intolerance

Recall that the intrinsic factor-cobalamin complex has to get to the end of the small bowel to be absorbed. Thus, just about any condition that impairs the absorptive capacity of this part of the bowel can lead to B12 deficiency. These conditions include ♣ tropical sprue, regional enteritis, Crohn's disease, Whipple's disease, tuberculosis, and ileal resection. Severe gluten intolerance can also be a factor.

Finally, there are some rare hereditary conditions affecting the transport proteins.

How common is B12 deficiency?

- Serum B12 test limitations
  - Serum B12 level does not reflect amount of B12 available for tissues
  - There is no agreement on the lower limit
    - Today's tests are more specific for active B12 vs inactive analogues
- Homocysteine level
  - Expensive; influenced by folate, B6, renal failure
- Methylmalonic acid level (MMA)
  - Specific to B12; not widely available; expensive

When I started looking at this stuff, I was blown away by how complicated it is. Anything this complicated, has to go wrong a lot!

So, just how frequently does B12 deficiency occur?

This turns out to be quite difficult to answer accurately. The problem is that ☐ serum B12 levels don't accurately reflect what goes on at the tissue level.

The serum B12 test measures the amount of cobalamin attached to transcobalamins I, II, and III in the bloodstream. However, it seems that only the ☐ active cobalamin bound to TCII is available for use by target tissues. Thus, depending on the ratio of TCII to TCI plus TCIII, the serum B12 level may be artificially high.

In our lab, the lower limit for a long time was 80 picomoles per liter. Just this past september, it was raised to 120 pmol/L. ☐ Some authors have recommended that the limit should be raised to 300. On a more positive note, however, ☐ today's tests are more accurate because they use purified intrinsic factor, which is specific for active cobalamin.

Thus, with all the problems inherent in the serum B12 test, we should look for other ways to pick up B12 deficiencies.

One candidate test is the ☐ homocysteine level. Unfortunately, it is ☐ expensive, and high folate levels will reduce homocysteine to normal values even when B12 is low.

The most specific test appears to be ☐ methylmalonic acid level, MMA for short. ☐ It's not done at the Jewish.

How common is B12 deficiency?

- Framingham Heart Study
  - 747 elderly (67-96 yrs) (Tucker et al 1996)
    - 3.8% had B12 < 96 pmol/L
    - 18.5% had B12 < 185 pmol/L
- 548 elderly (Lindenbaum et al 1994)
  - 15% had elevated MMA

This slide shows prevalence data using all three types of test, in community-dwelling seniors.
Look at the numbers: ♣ 18.5% using serum B12 levels;

15% using MMA

♣ 20 % using MMA and/or homocysteine

That's one in five elderly people!

How common is B12 deficiency?

- Family practice setting (Yao et al 1992)
  - 100 consecutive elderly outpatients
    - 20% had elevated MMA and/or homocysteine

How common is B12 deficiency?

- Elderly Chinese vegetarian women (Woo et al 1998)
  - 53.8% of 131 had B12 < 150 pmol/L
- Pernicious anemia in general population: 1%
  - Most cases occur in ages > 60 (Goodman & Salt 1990)
- Elevated homocysteine in general population:
  - 5-10 %; 30-40% of elderly (Booth & Wang 2000)

Here are some more prevalence numbers.

♣ This group eats a diet with little or no foods of animal origin. Over 50% have B12 deficiency.

♣ Pernicious anemia, the autoimmune disease, is quite rare in comparison.

♣ Given the limitations of the homocysteine test, it's not surprising that it produces such high numbers.

Is this an epidemic?

Is it a silent epidemic?

- Percentage of over-65s in Ontario consulting their primary care physician during one year, that received B12 injections:
- 2% (van Walraven & Naylor 2000)

Is this an epidemic? What do you think?

♣ Is it a silent epidemic? By this I mean, are we as health care professionals aware of how high the prevalence of B12 deficiency seems to be?

Here's one ♣ study that bears on the issue: these authors used the computerised billing data from Ontario physicians. They found that of all the over-65 people who visited their GPs over a one-year interval, the percentage who received B12 injections was only 2%.

Interestingly, these authors still considered 2% to be over-, not under-utilisation.

Again, this number may be lower than the number of people who are actually being treated. For example, some might be getting their injections from community clinic nurses or the nurses working in retirement residences; some might get injections from specialist physicians; and some may have been prescribed oral supplements.

Why is B12 deficiency often overlooked?

- Various presentations
- Multiple causes
- Problematic laboratory tests
- Concurrent illnesses
- Low index of suspicion

So if the prevalence is really high, on the order of 15 to 20% in seniors, and only a couple of percent are getting treated, I submit that as health care professionals, we often overlook B12 deficiency. Why?

☐ I've talked about the many and varied symptoms of B12 deficiency, which can occur singly or in any combination, in any order of appearance.

☐ I've talked about the many different ways in which B12 malabsorption can happen, and the many illnesses which can cause malabsorption.

☐ I've discussed the limitations of available laboratory tests for screening or for diagnosis.

☐ I haven't talked about the difficulties we encounter when elderly people present with a long list of pre-existing medical and psychiatric conditions. Is the new symptom due to their heart problem, their recurrent depression, or are they just somatising?

☐ Lastly, I think we often overlook B12 deficiency because we have a low index of suspicion.

Useful clinical indicators

- Unexplained neurological symptoms, esp.
  - Weakness, numbness, paresthesias, esp. of lower extremities
    - Abnormal gait, eg wide-based
- Cognitive impairment
- Fatigue, lack of energy
- Daytime sleepiness
- Urinary incontinence

To raise our index of suspicion, here are some indicators that I've found helpful in pointing to a possible B12 deficiency.

At the top of the list is ☐ unexplained neurological symptoms, particularly weakness in the legs, numbness, or abnormal sensations such as tingling or burning. Difficulty walking or unsteadiness on the feet may reflect loss of position sense.

☐ Cognitive impairment is a biggie. The evidence suggests that B12 deficiency can cause a reversible delirium, and likely is a cause of dementia. Unfortunately, this is not a reversible dementia.

Ever since injectable B12 became available, doctors have been giving it to patients who complain of ☐ fatigue or lack of energy. I'm aware of only one study which addresses this topic, however.

☐ Daytime sleepiness I find particularly interesting. The Japanese have been using vitamin B12 to treat adolescents with delayed sleep phase syndrome. In the case of Mr. S., daytime somnolence was an important presenting symptom. If one has ruled out medications, obstructive sleep apnea, or narcolepsy as possible causes, consider B12 deficiency.

☐ Urinary incontinence was one of Mr. S.'s presenting symptoms, which cleared up with B12.

Useful clinical indicators (2)

- Hx of peptic ulcer disease, "heartburn"
- Treatment for ulcers or heartburn
- Long-term treatment with tricyclics
- Vegetarian diet
- Inadequate diet
- Family history of pernicious anemia
- History of gastric, bowel, or pancreatic disease or surgery
- Nitrous oxide anesthesia

This slide lists some of the more common conditions which can cause a B12 deficiency.

Useful laboratory findings

- Elevated MMA (methylmalonic acid)
- Elevated homocysteine (if folate is adequate)
- Low serum B12
- Macrocytosis (high MCV, MCH)
- If concurrent iron deficiency, any MCV, MCH accompanied by high RDW

As we've already discussed, ☐ MMA is probably the only really useful test for tissue B12 deficiency. However, given its poor availability, we need to look for other tests.

An ☐ elevated homocysteine level, if the folate level is not low and the kidneys are well-functioning, is apparently a good indicator of B12 deficiency.

☐ The limitations of the serum B12 level we've discussed already. However, while a normal or even a high level does not rule out a B12 deficiency, a low level is almost certainly a deficiency.

☐ Macrocytosis is not necessarily present with B12 deficiency, but as for serum B12 level, the cutoff limits may be problematic. Our lab uses an upper limit of 100 femtoliters for the MCV. At least one author that I've read suggests that the limit should be 94 fL, and in fact this is the cutoff used by one of the University of Montreal hospitals.

☐ If there is iron deficiency together with the B12 deficiency (not uncommon, since many malabsorption problems can affect multiple nutrients) the blood smear will have both big cells and tiny cells. This translates into an elevated RDW value on the printout from an automated complete blood count machine.

RDW stands for Red Cell Distribution Width. It measures the distribution of red cell volume, expressed as a coefficient of variation.

Useful laboratory

- Blood smear findings:
  - Macro-ovalocytes
  - Hypersegmented polys
- Other tests:
  - H. Pylori antibodies
  - Schilling tests (stage 1, stage 2, food test)
  - Elevated gastrin

If I suspect B12 deficiency, I request a ☐ manual differential. If there are either macro-ovalocytes or hypersegmented polys on the smear, that usually confirms a megaloblastic anemia. If folate levels are OK, this will almost certainly be due to B12 deficiency.

☐ The remainder of these tests are not helpful in diagnosing the B12 deficiency itself, but may help to determine the cause.

Treatment approaches

- Oral vs parenteral
- How long to treat?
- Dosage and frequency
  - IM: 1000 micrograms im qd x 7 days,
    then qweek x 4 weeks,
    then qmonth
  - PO: 1200 micrograms bid;

Finally, folks! When you suspect a B12 deficiency, even if you don't have laboratory evidence for it, I recommend you treat.

Usually I suggest to the patient to take ♣ injections, even though there are studies which show that the outcome for pernicious anemia is as good after 4 months with oral B12 as with injections.

An injection will provide a more rapid therapeutic response, which is gratifying to the patient and confirmatory to the physician.

♣ How long to treat? Pernicious anemia must absolutely be treated forever. For other conditions, it depends on whether the underlying condition clears up or not.

But in the elderly patients that I see, if there has been any sort of response to treatment by 6 months, I think that the treatment should also be continued indefinitely.

After all, this group seems to have a very high prevalence of B12 deficiency, and even if the original cause is no longer a factor, who's to say that some other condition won't produce a new B12 deficiency?

These are the ♣ treatment regimens I usually use.

Treatment approaches

- Treat the underlying condition:
  - Antibiotics for H. Pylori
  - Correction of dietary deficiencies
  - Re-evaluate need for:
    - Anti-histamines
    - Proton pump inhibitors

Don’t forget the underlying condition may be treatable or modifiable in some way!