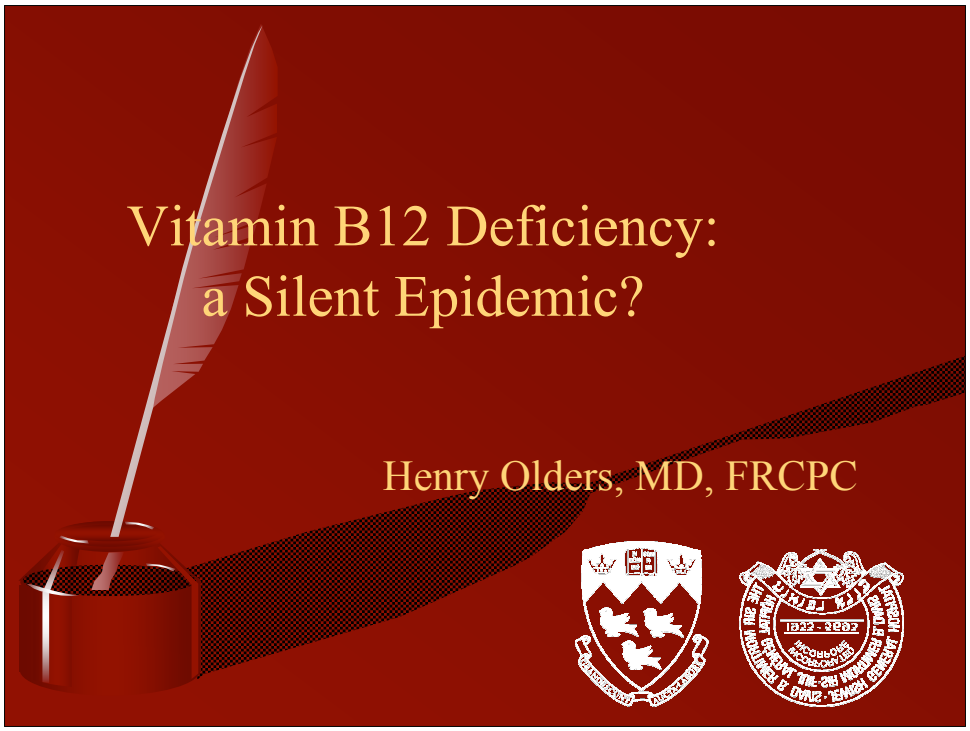



I'm going to talk to you today about Vitamin B12 deficiency. My interest in this topic sprang from something very personal. When I was still a teenager, my mother became very sick with pernicious anemia. Pernicious anemia is a severe form of B12 deficiency, which is deadly if not properly diagnosed and treated.

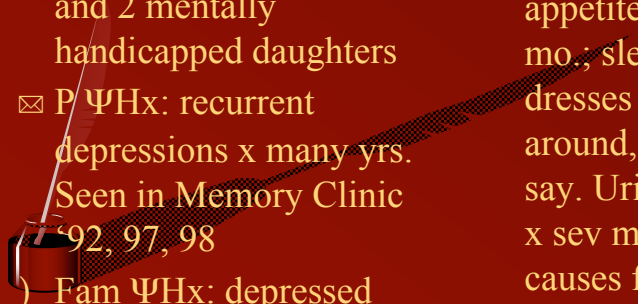
My mother's doctor couldn't understand why she was getting gradually weaker, over a period of several months. Finally, when she could no longer walk without help, we admitted her to hospital where the correct diagnosis was made. She received B12 injections and within weeks was back to her usual self.

Unfortunately, it remains common for B12 deficiency to go undiagnosed and untreated. That's the rationale behind this presentation.

I would like to start by telling you about a couple of patients.

# Mr. S.

- 75-y-o married male, self-employed in garment industry; lives with wife and 2 mentally handicapped daughters
- P ΨHx: recurrent depressions x many yrs. Seen in Memory Clinic '92, 97, 98
- Fam ΨHx: depressed father, brother
- HPI: daytime somnolence; lack of energy, motivation; poor appetite, 15 lb wt loss x 6 mo.; sleeps all day; wife dresses him, drives him around, tells him what to say. Urinary incontinence x sev mo. Poor judgment causes financial problems. Feels hopeless.



First, Mr. S. ⇓ Mr. S. is a 75 year old man, married, father of two mentally handicapped girls. He works for himself. ⇓ His past psychiatric history includes a number of depressions. He has also been seen in the Memory Clinic on three occasions since 1992.

In terms of ⇓ family psychiatric history, the father and a brother were both depressed.

⇓ I first saw him in 1999. His wife complained that he slept all day long, had no energy or motivation; to get him to work, she had to dress him, drive him around to see his customers, and she even had to tell him what to say.

Mr. S. also complained of poor appetite; he reported losing 15 pounds of weight over 6 months. He had also been having occasional urinary incontinence for several months.

His wife related that he had entered into a foolish financial transaction and lost a lot of money.

# Mr. S. (2)

- O/E: Mask-like facies; slow, monotone speech. STM 1/3. Not suicidal.
- Impr: depression; cognitive impairment NYD; daytime sleepiness NYD; urinary incontinence NYD; ?Parkinson's
- Plan: trial of ritalin; decrease ativan; blood tests
- Over next few months:
  - Ativan was stopped
  - Some initial improvement in daytime somnolence with ritalin, but not sustained
  - Trial of aricept seemed to help, but compliance poor
  - Referred to urology; sleep medicine to r/o OSA. Pt failed to go to appts.

On exam, ⇓ Mr. S. presented with a mask-like facies. His speech was slow and monotone. Short term memory was only 1 word out of 3.

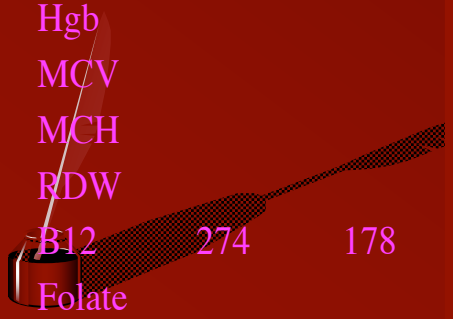
⇓ I felt that he was depressed; however, I had no definitive explanation for the findings of cognitive impairment, daytime sleepiness, urinary incontinence, or parkinsonism.

⇓ At this point, a trial of ritalin was instituted, while tapering the ativan. He went for the usual blood tests.

⇓ Over the next few months, ativan was stopped. Ritalin helped initially, but the improvement was not maintained. Aricept worked somewhat, but he didn't take it consistently. Referrals to other specialists were made but he didn't go.

# Mr. S. (3)

| | 99-6-28 | 00-3-21 | 00-5-5 | Normal | Units |
|---|---|---|---|---|---|
| Hgb | | | | 140-175 | g/L |
| MCV | | | | 80-100 | fL |
| MCH | | | | 27-33 | pg |
| RDW | | | | 11.5-14.5 | c/v |
| B12 | 274 | 178 | | 120-600 | pmol/L |
| Folate | | | | 6-40 | nmol/L |



In May of last year, because of the poor results so far, I went back and reviewed the case, including the lab tests. They were all normal, including the results for B12. Here they are.

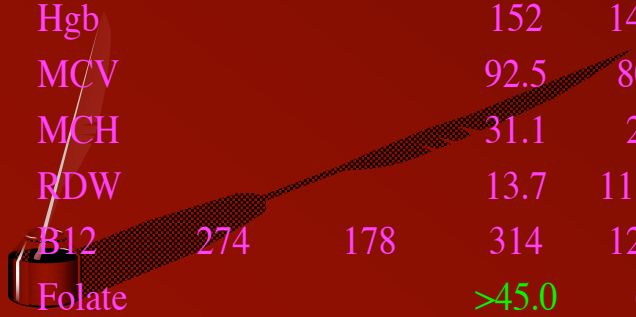
I should note that in 1999, in the Psychogeriatrics Clinic, we were giving B12 supplements to any clinic patient with a serum B12 level less than 200. Mr. S. had obviously been well above that cutoff when I first saw him.

Earlier this year, we raised our cutoff to 300, based on reports from Britain.

Using either cutoff value, Mr. S. should get B12 supplementation, and so I prescribed B12 injections. However, before he actually received the first injection, we sent him to the Test Centre for another blood test. Here are the results:

# Mr. S. (4)

| | 99-6-28 | 00-3-21 | 00-5-5 | Normal | Units |
|---|---|---|---|---|---|
| Hgb | | | 152 | 140-175 | g/L |
| MCV | | | 92.5 | 80-100 | fL |
| MCH | | | 31.1 | 27-33 | pg |
| RDW | | | 13.7 | 11.5-14.5 | c/v |
| B12 | 274 | 178 | 314 | 120-600 | pmol/L |
| Folate | | | >45.0 | 6-40 | nmol/L |

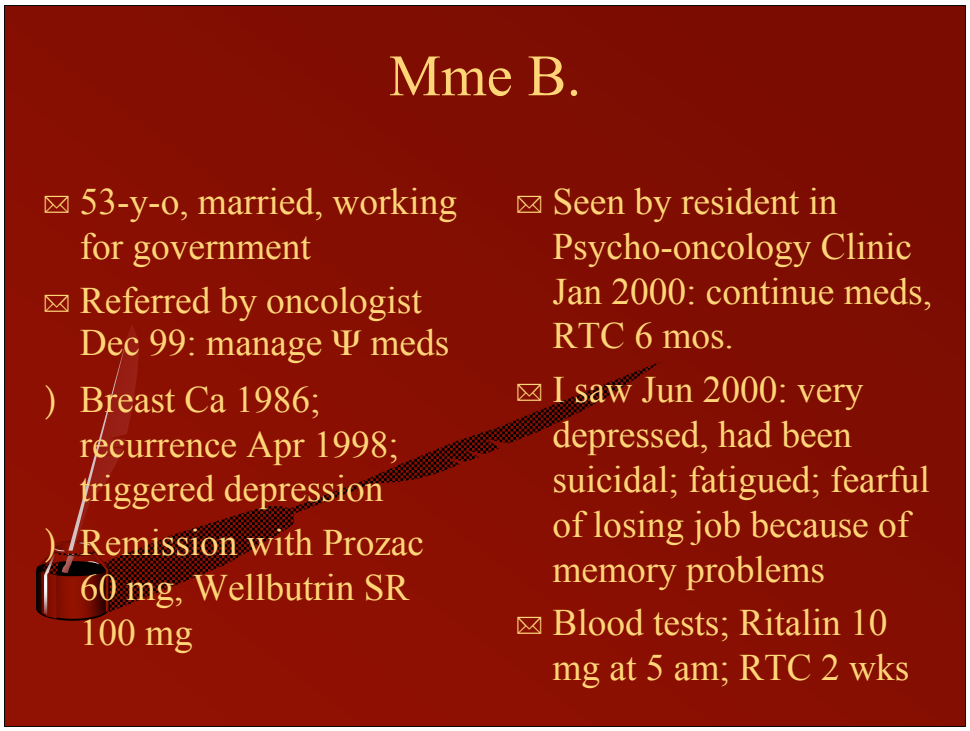


The B12 level now was 314. If I had known that before ordering the B12 injections, I never would have ordered them.

However, here's what happened. Mr. S. and his wife returned 4 weeks later, reporting that the B12 injections had made a real difference. He had more energy, more get-up-and-go, his walking was easier and it no longer hurt him to walk! He was also sleeping less during the day.

He looked a lot better, too. Bright, cheerful, animated, talking a lot

I hadn't even been aware that he had been having a problem with walking, or pain on walking. But we were all happy that he was so much better.




This is another patient, that I saw in the Psycho-oncology Clinic.

⇓ Mme. B. is a53-y-o, married woman, who was working for the government when I saw her.

⇓ She had been referred by her oncologist in Dec 1999, to manage her psychiatric meds.

⇓ In 1986 she had been diagnosied with breast cancer, which recurred in Apr 1998; this triggered a depression.

⇓ The depression had remitted completely on a combination of Prozac 60 mg and Wellbutrin SR 100 mg.

⇓ She was first seen by us in the Psycho-oncology Clinic in Jan 2000. As her depression remained in remission, our recommendation was to continuethe medications, and to come back in 6 months.

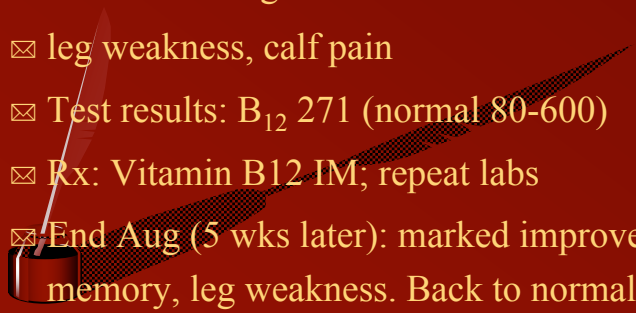
⇓ I saw her 6 months later, in Jun 2000. Now, she was very depressed, and had tried to kill herself a couple of weeks earlier. She complained of fatigue, and was fearful of losing her job because of memory problems

She complained of very poor sleep, and reported being in bed from 9 pm until 6:30 am, 8 am on weekends. Her usual sleep pattern had been from 11 pm until 5 am.

⇓ I encouraged her to start getting up at 5 am once again, and prescribed some ritalin to take at 5 am. She already had an appointment booked with a neurologist for her memory difficulties.

## Mme B. (2)

- Returned 6 wks later, feeling much better, but still memory probs
- Saw a neurologist who sent for CT scan
- leg weakness, calf pain
- Test results: $B_{12}$ 271 (normal 80-600)
- Rx: Vitamin B12 IM; repeat labs
- End Aug (5 wks later): marked improvement in memory, leg weakness. Back to normal.
- Rx: Schilling test



⇓ She missed her appointment 2 weeks later, but came after 6 weeks. She reported that her depression had disappeared with the ritalin and getting up early. However, her memory problems were worse, and she was more worried than ever about losing her job.

⇓ She had gone to see a neurologist, who had ordered a CT scan.

⇓ She had also begun having problems walking.

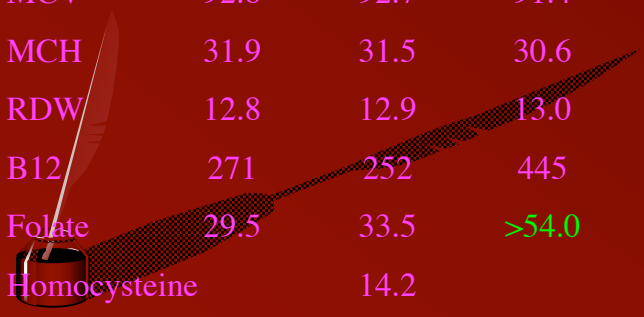
⇓ Her blood test results came back normal, including a B12 level of 271.

⇓ However, because of the memory problems and the leg weakness, I suggested she take vitamin B12 injections.

⇓ Five weeks later, she reported that her memory was much improved, and her leg weakness was gone. She felt she was back to normal. I asked her to go for a ⇓ Schilling test.

## Mme B.

| | 00-6-12 | 00-7-24 | 00-10-23 | Normal | Units |
|---|---|---|---|---|---|
| Hgb | 122 | 128 | 120 | 120-152 | g/L |
| MCV | 92.8 | 92.7 | 91.4 | 80-100 | fL |
| MCH | 31.9 | 31.5 | 30.6 | 27-33 | pg |
| RDW | 12.8 | 12.9 | 13.0 | 11.5-14.5 | c/v |
| B12 | 271 | 252 | 445 | 120-600 | pmol/L |
| Folate | 29.5 | 33.5 | >54.0 | 6-40 | nmol/L |
| Homocysteine | | 14.2 | | 5.2-14.9 | μmol/L |
| Hypersegmented polys | | Present | Present | | |



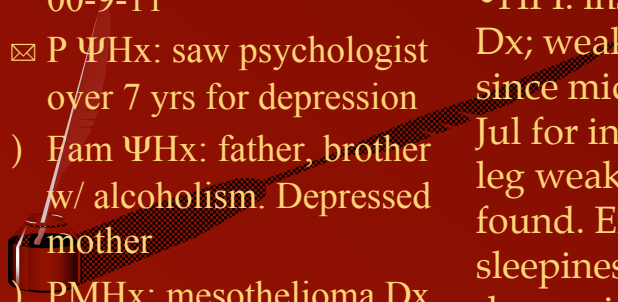
Here are her lab test results. The only abnormalities were an elevated folate level, and hypersegmented polymorphonuclear cells on the manual smear. Hypersegmented polys are pathognomonic for macrocytic anemia caused by either B12 or folate deficiency.

Mr. S. had cognitive impairment; Mme B. had memory problems and difficulty walking. These don't sound like psychiatric conditions to me. So why should we, as mental health professionals, take any interest in vitamin B12, if a deficiency causes neurological problems?

# M L.

- 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

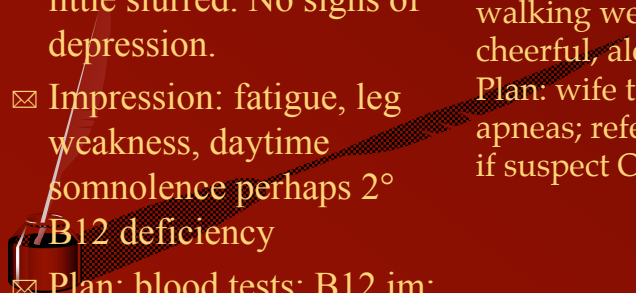
- Meds: proscar, norvasc, ritalin, losec, vioxx, imovane
- HPI: insomnia since Ca Dx; weakness, fatigue since midsummer; adm Jul for investigation of leg weakness - no cause found. Excessive daytime sleepiness. Denies depression.



# M L. (2)

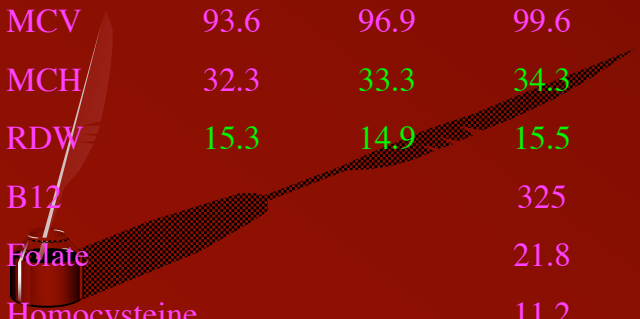
- O/E: comes in wheelchair. Falls asleep 2x in office. Speech a little slurred. No signs of depression.
- Impression: fatigue, leg weakness, daytime somnolence perhaps 2° B12 deficiency
- Plan: blood tests; B12 im; sleep hygiene

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



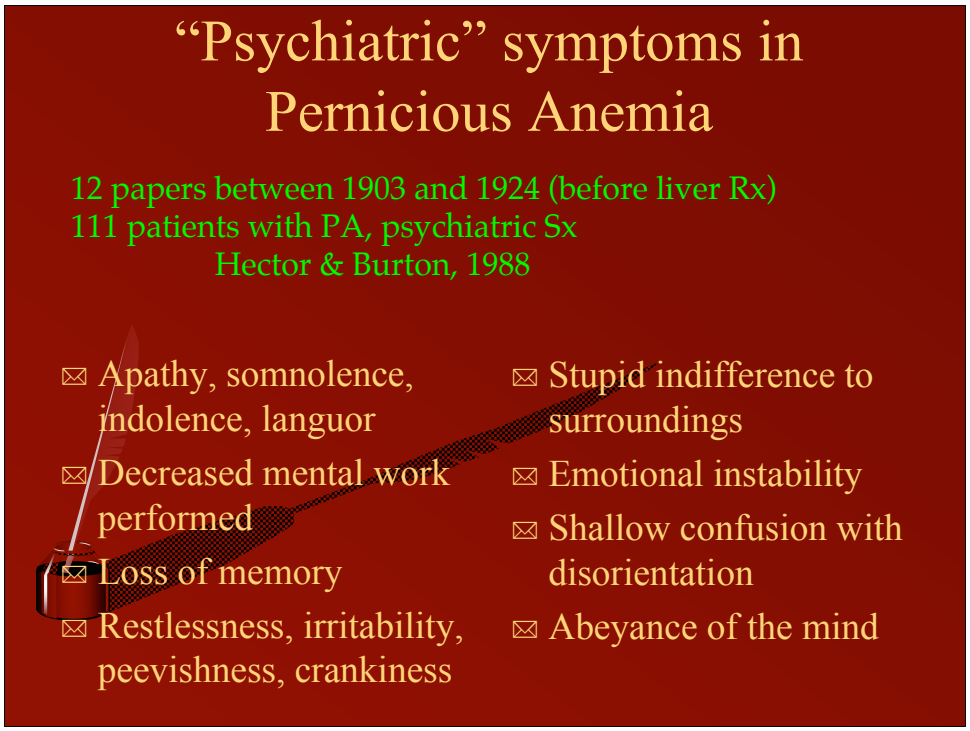
## M L.

| | 00-7-27 | 00-8-17 | 00-9-11 | 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 |
| Homocysteine | | | 11.2 | 5.2-14.9 | $\mu$mol/L |



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

Mr. S. had cognitive impairment; Mme B. had memory problems and difficulty walking; M L. had leg weakness. These don't sound like psychiatric conditions to me. So why should we, as mental health professionals, take any interest in vitamin B12, if a deficiency causes neurological problems?




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.

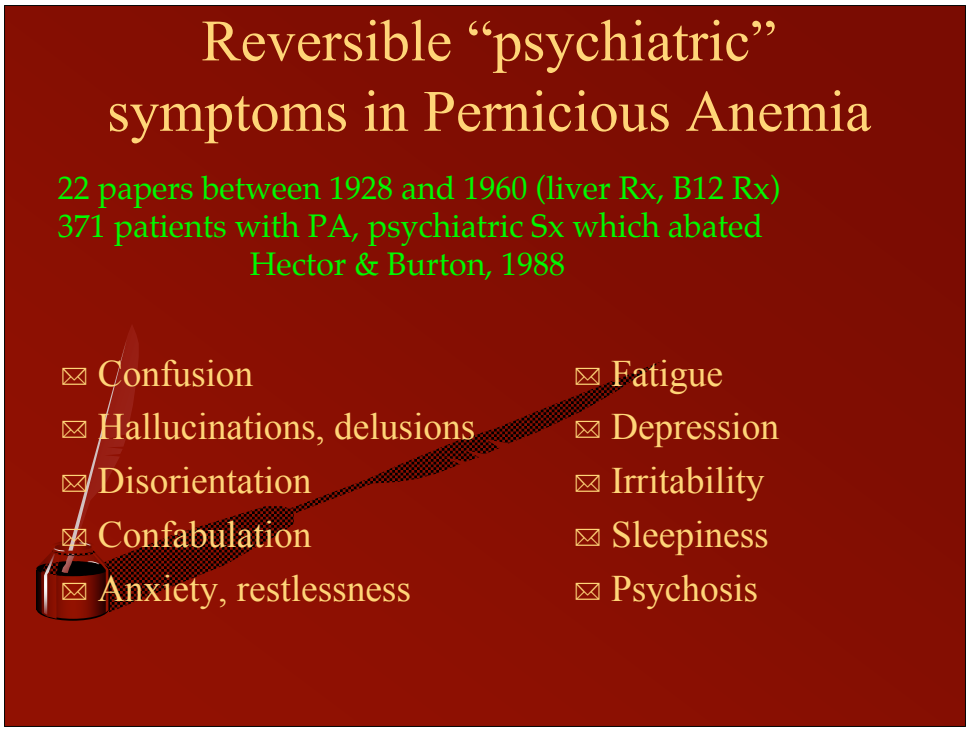
Hector and Burton published an article in 1988, in which they reviewed studies of psychiatric symptoms occurring as part of pernicious anemia. Pernicious Anemia, you will recall, is a particularly severe form of vitamin B12 deficiency, which will kill you if left untreated.

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,

## “Psychiatric” symptoms in Pernicious Anemia (2)

- Loss of inhibition
- Gradual mental deterioration
- Dementia or amentia
- Delirium of the low, quiet type
- Neurasthenia
- Confabulations
- Depressed, apprehensive, and without hope
- Mania, exaltation, violent maniacal outbursts
- Delusions and hallucinations, both visual and auditory
- Hysteria
- Peculiar paranoid conditions
- Epilepsy
- Dementia praecox

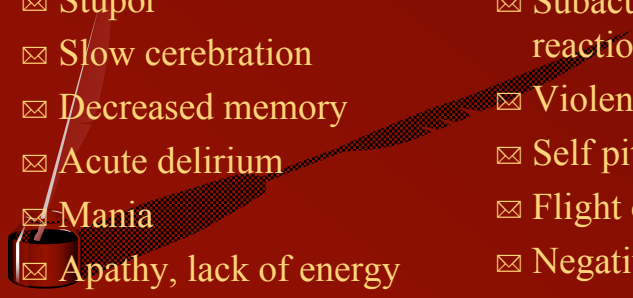
And on this one.




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.

## Reversible "psychiatric" symptoms in Pernicious Anemia (2)

- Introspection
- Stupor
- Slow cerebration
- Decreased memory
- Acute delirium
- Mania
- Apathy, lack of energy
- Weakness
- Subacute organic reactions
- Violent behaviour
- Self pity
- Flight of ideas
- Negativism
- Acute paranoid states

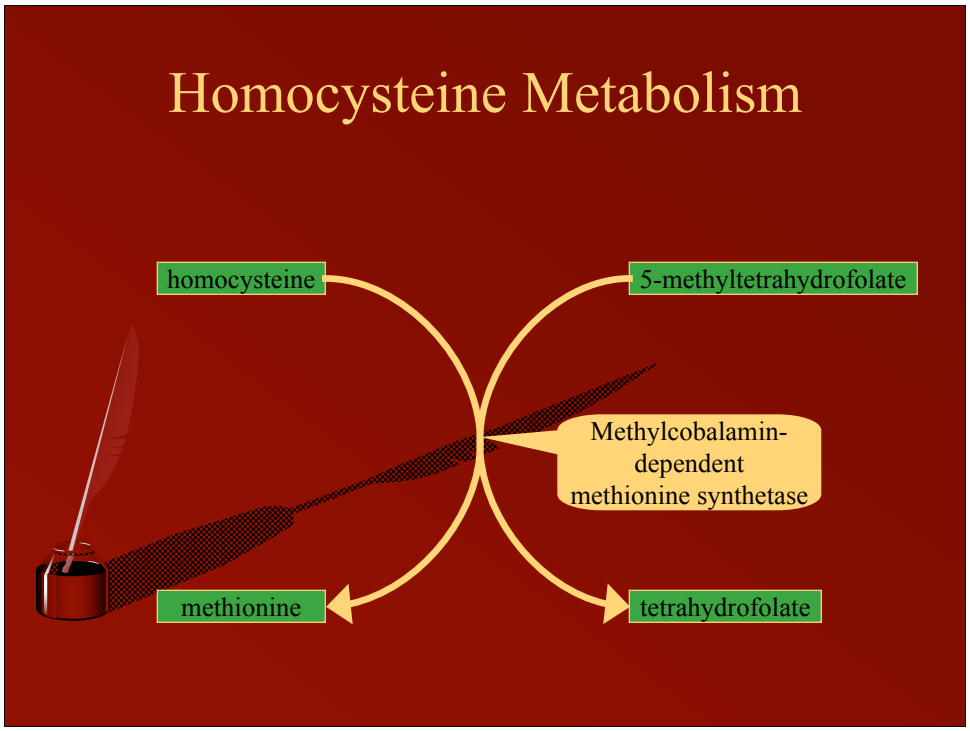


This slide shows more symptoms which improved with pernicious anemia treatment.

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.

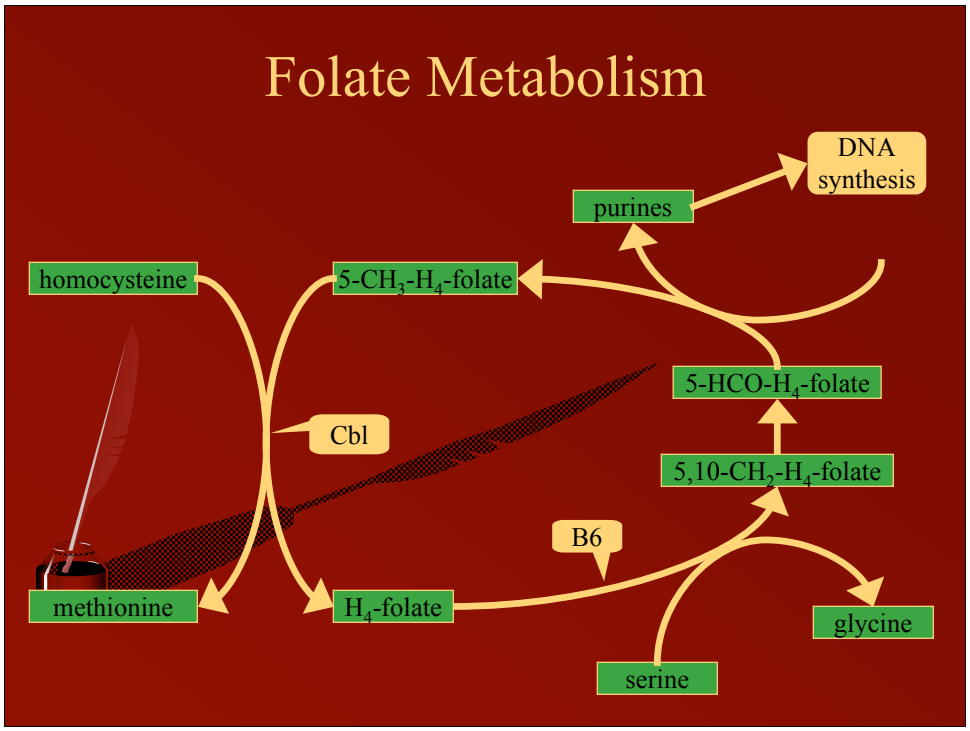
So, let's take the word of these authors that these sorts of symptoms are actually caused by B12 deficiency. How does that happen? What's the mechanism?

To understand this stuff, we have to review some biochemistry. I can't stand this stuff, so I'll try to get through it quickly.

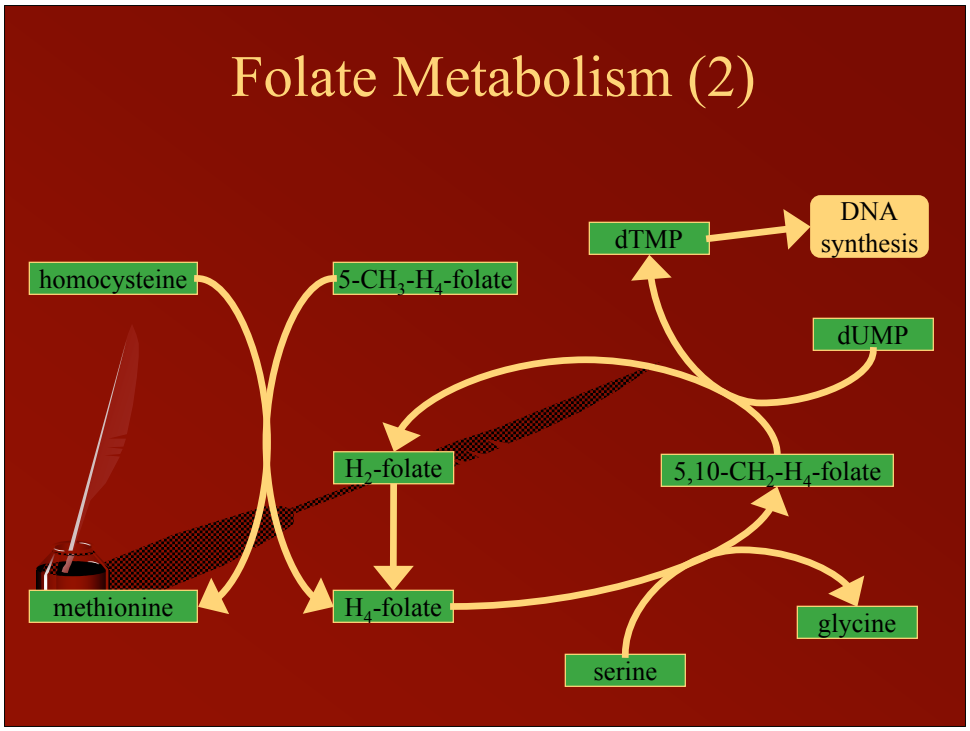



There are two metabolically active forms of cobalamin: methylcobalamin and adenosylcobalamin. However, the form of cobalamin usually found in vitamin preparations is cyanocobalamin, which has no known physiologic role and has to be converted before it can be used by tissues.

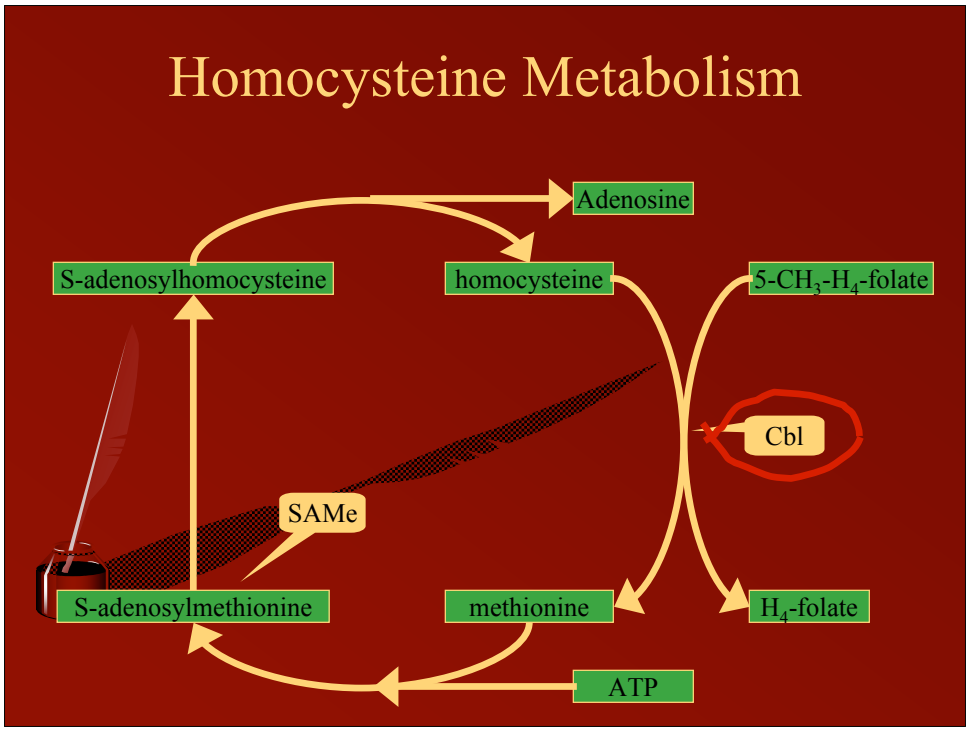
Methylcobalamin is an essential cofactor in the conversion of ♣ homocysteine to methionine. In the absence of cobalamin, not only does homocysteine build up, but ♣ 5-methyltetrahydrofolate which the cell has taken up from the bloodstream cannot be converted to tetrahydrofolate, and so is unavailable 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.




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).




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.

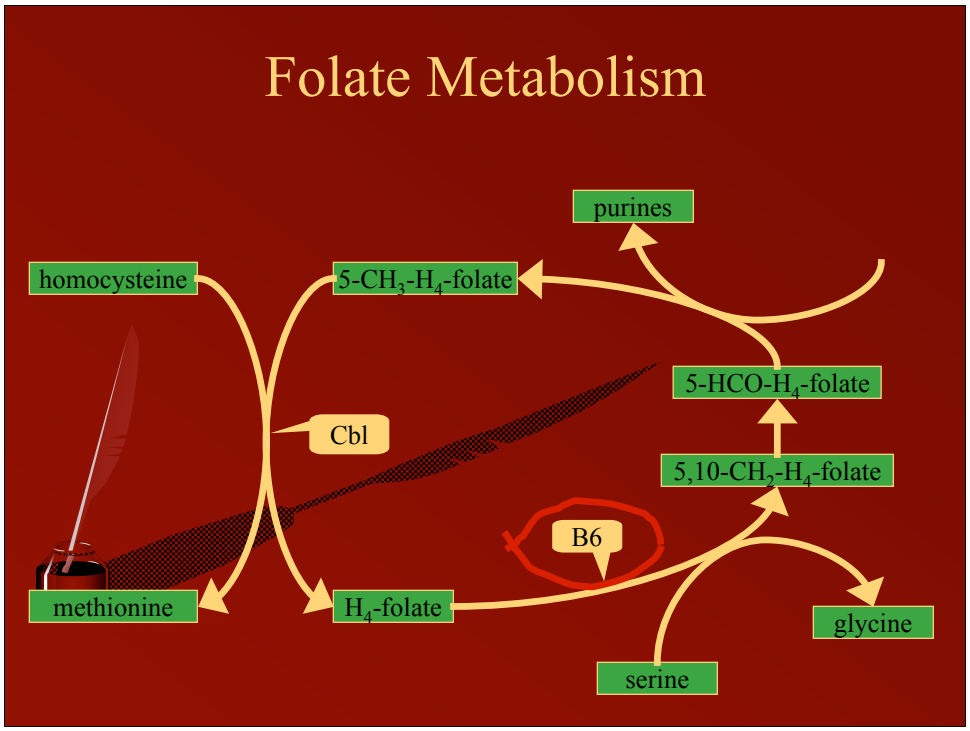



Now let's look at the other side of the cobalamin-aided conversion, that of homocysteine to methionine. Normally, methionine is converted to ♣ S-adenosylmethionine (abbreviated SAMe), which then loses its methyl group to become ♣ S-adenosylhomocysteine. This compound gives up ♣ adenosine to return to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

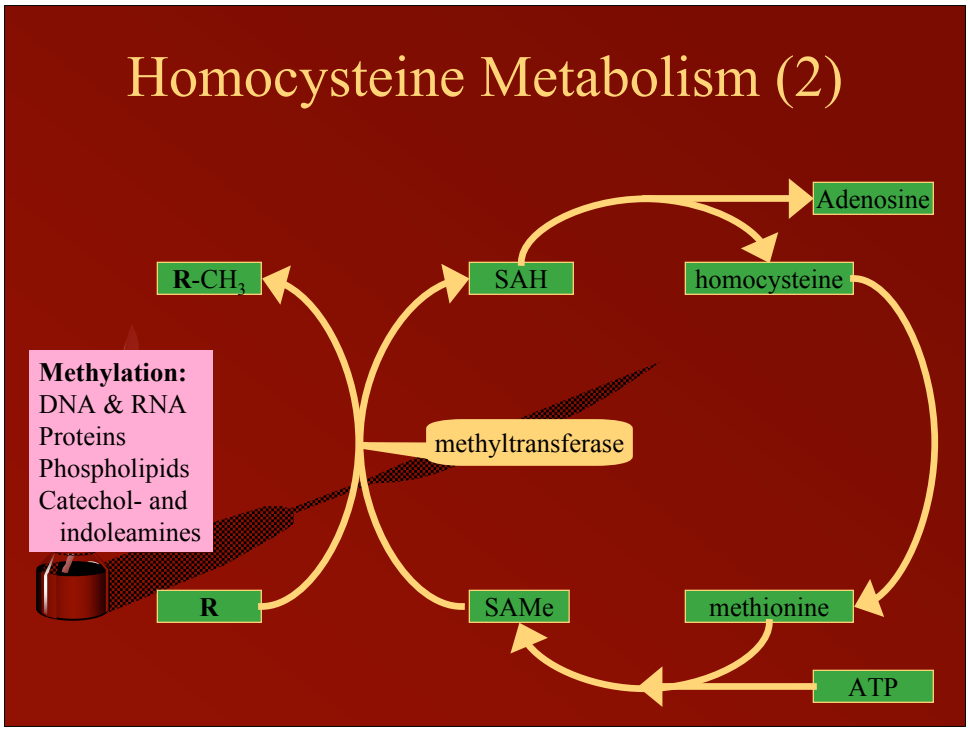
Adenosine, again, is a component of AMP, ATP, cyclic AMP, and so on.

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.



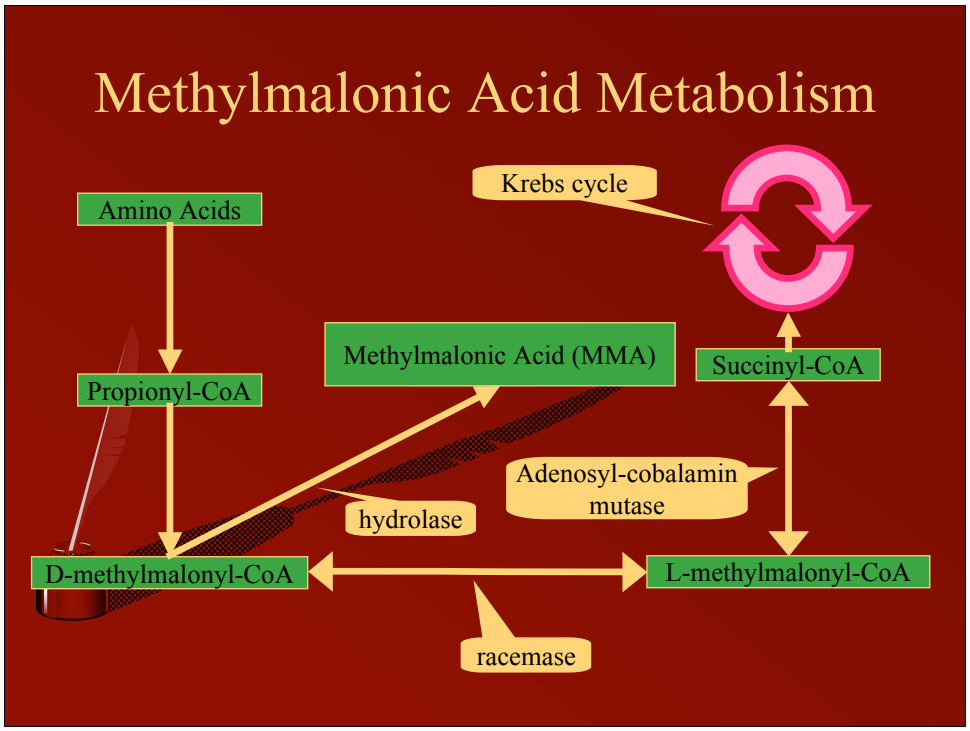

You saw this slide before; I'm bringing it back to make the point that another cause of elevated homocysteine, or hyperhomocystinemia, is a deficiency of ♣ vitamin B6, also known as pyridoxine.




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, what can we conclude? Well, the most important issue is that B12 is somehow involved in the production of DNA, and also in the production of phospholipids.

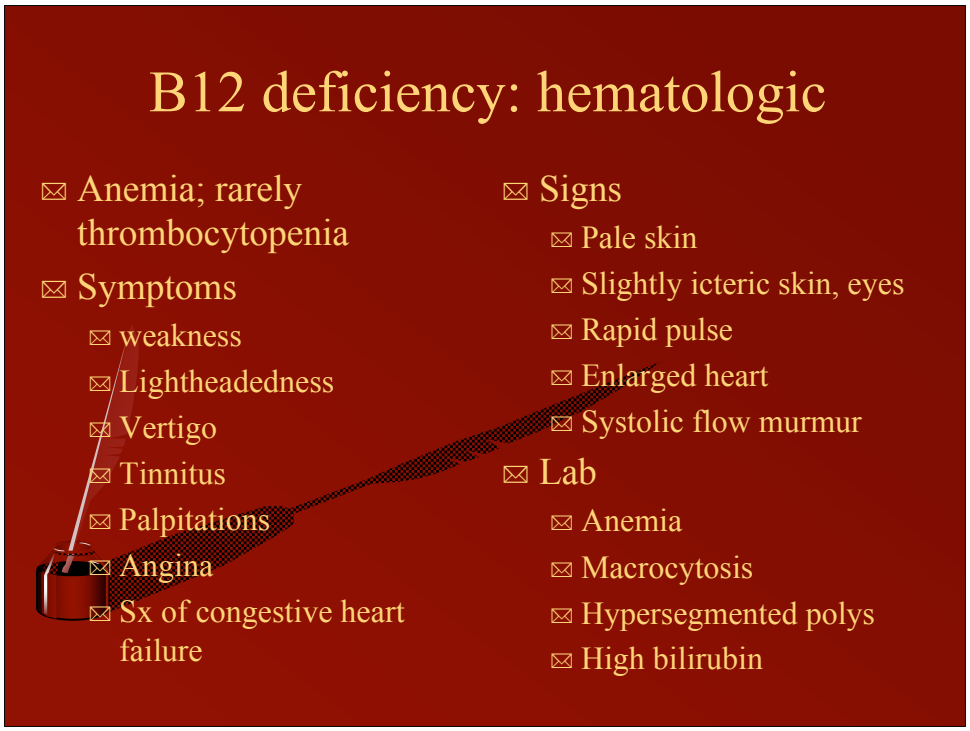
Every time a cell divides, more DNA must be manufactured.

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.

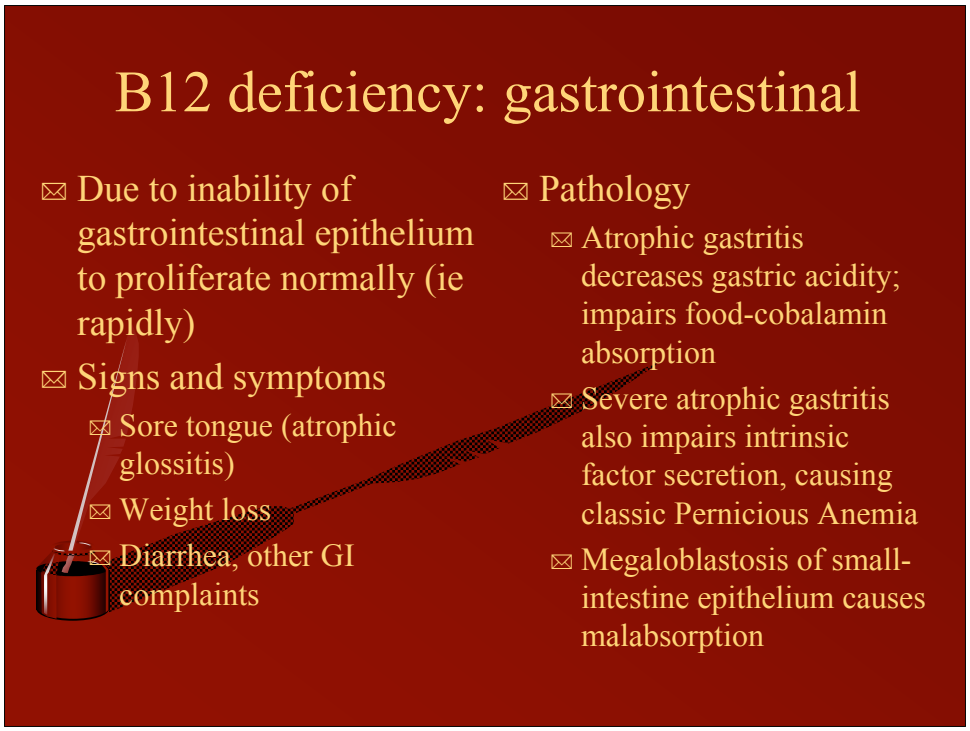
What about ♣ psychiatric symptoms of B12 deficiency? Some authors would say that the psychiatric manifestations are really neurological. This is a debate I don't want to get into.




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.




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.

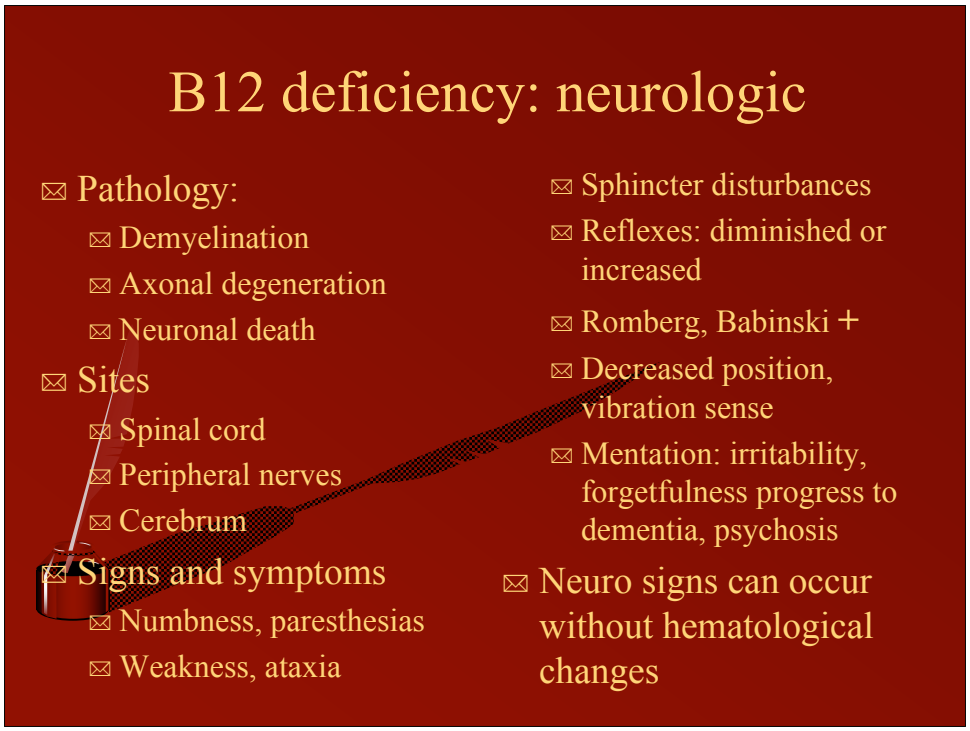
When the ⇓ stomach wall is affected, the condition is known as atrophic gastritis. As we'll see soon, atrophic gastritis can impair B12 absorption in at least 4 ways.

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.



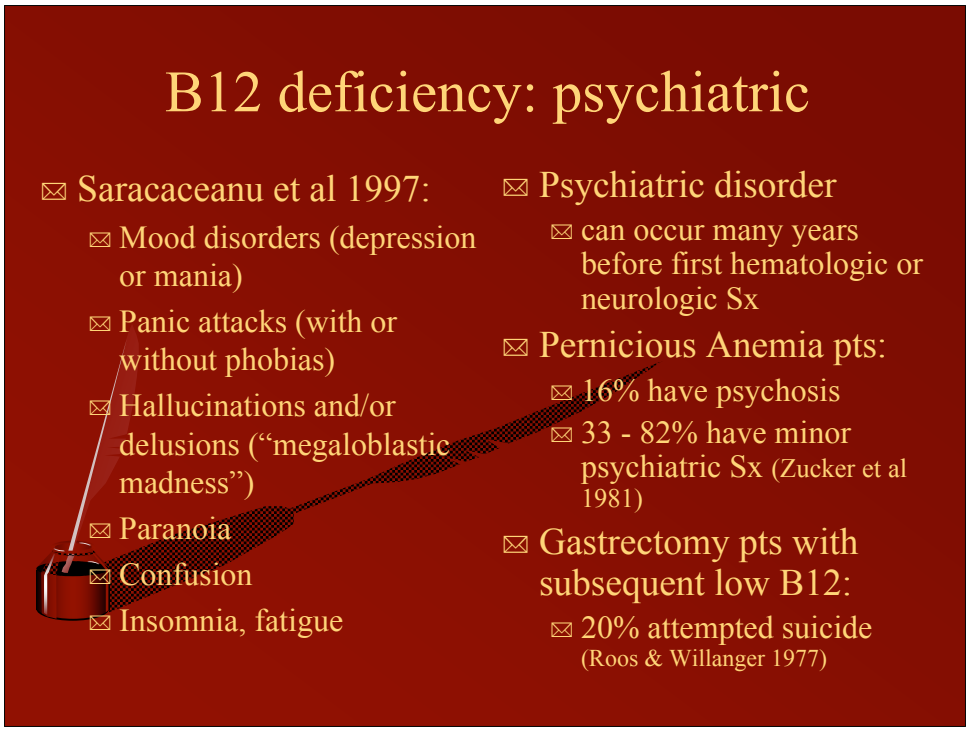

In terms of neurological manifestations, there is a progression in ♣ pathology beginning with demyelination, followed by axonal degeneration, and finally, neuronal cell death. At this stage, of course, the process is irreversible.

♣ The spinal cord is usually affected first, then the peripheral nerves, and eventually the brain, but don't count on this order being followed.

Here are the ♣ signs and symptoms. The ♣ sphincter disturbances can include urinary incontinence, as in Mr. S., the first patient I talked about. Both patients had problems walking, if you recall.

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, as in Mr. S. and Mme B.

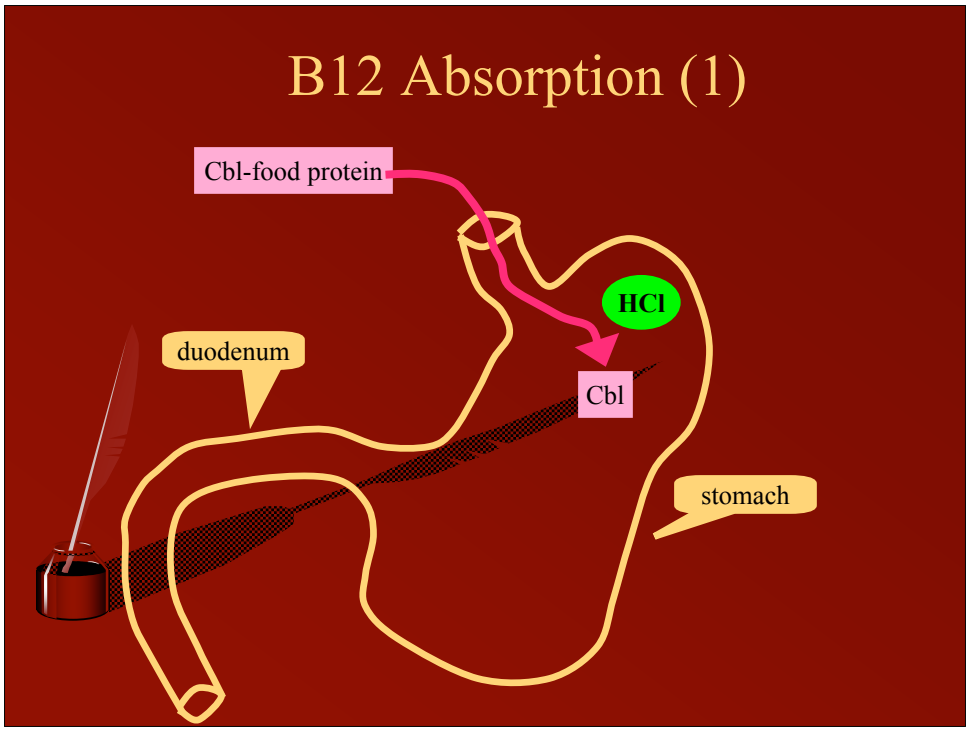



Here are some of the psychiatric manifestations. I think "megaloblastic madness" is a particularly colourful term.

♣ 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.




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.

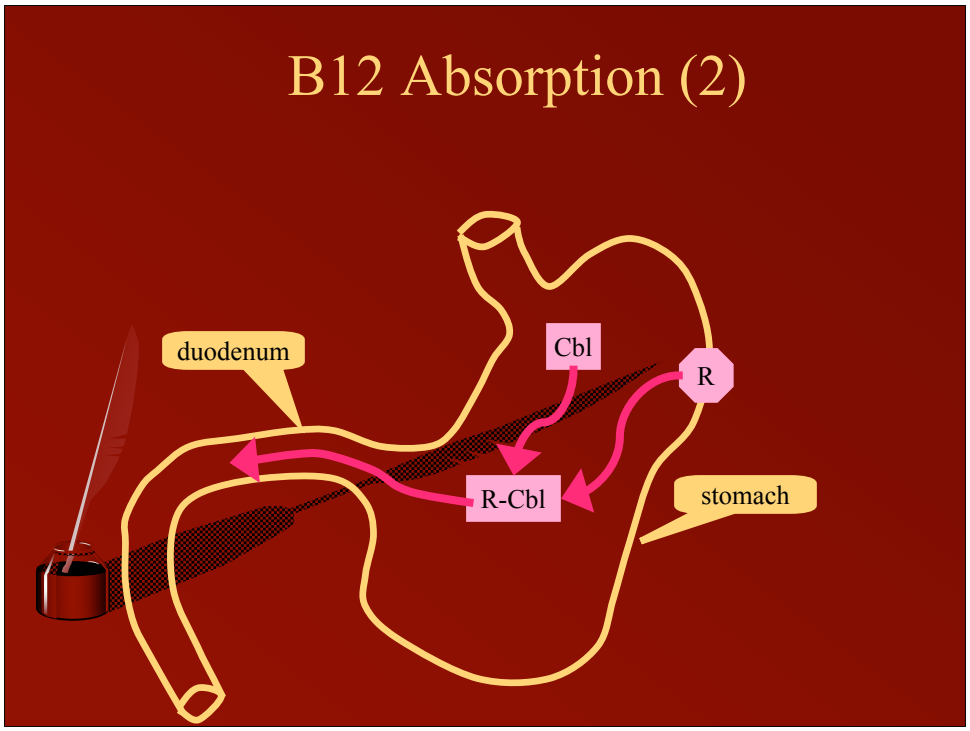
Daily requirement: about 2 to 5 micrograms

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.

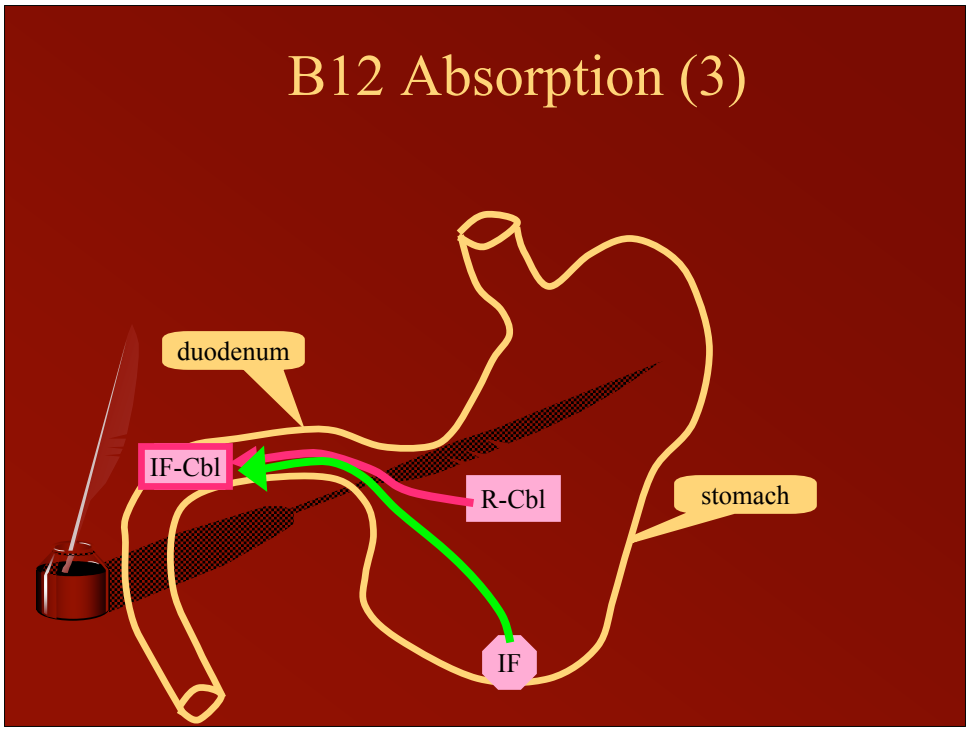
First step, of course, is to eat the food. ♣ It finds its way into the stomach ♣ , where hydrochloric acid and pepsin ♣ separate the B12 from the food protein.




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.

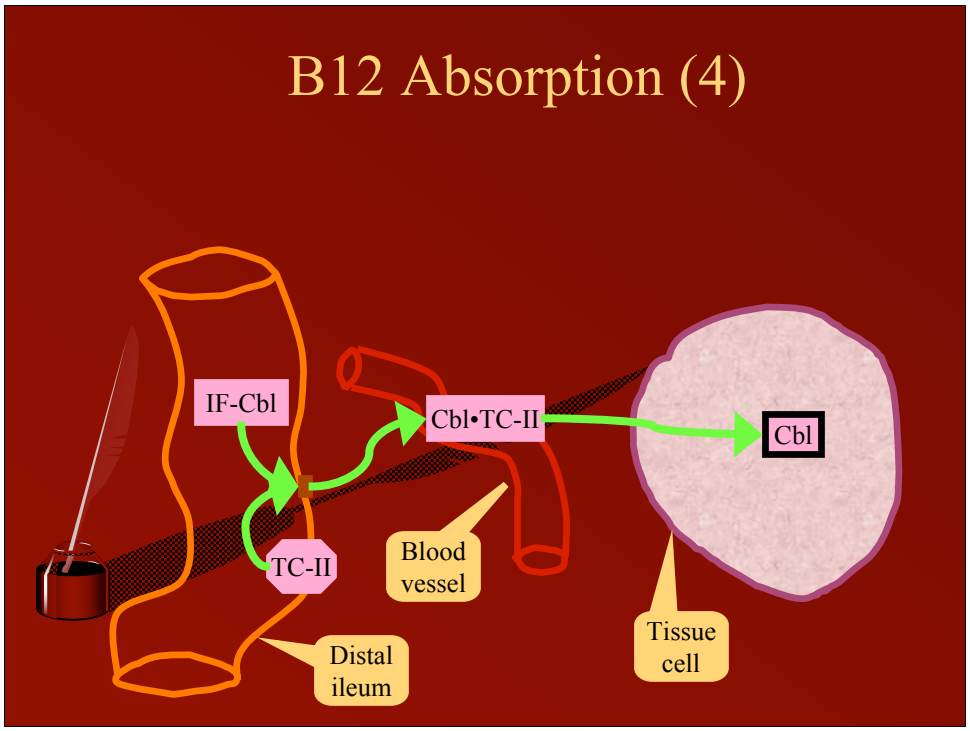



Once in the duodenum, the R-binder-cobalamin complex is digested by pancreatic enzymes, releasing ♣ the cobalamin.

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.



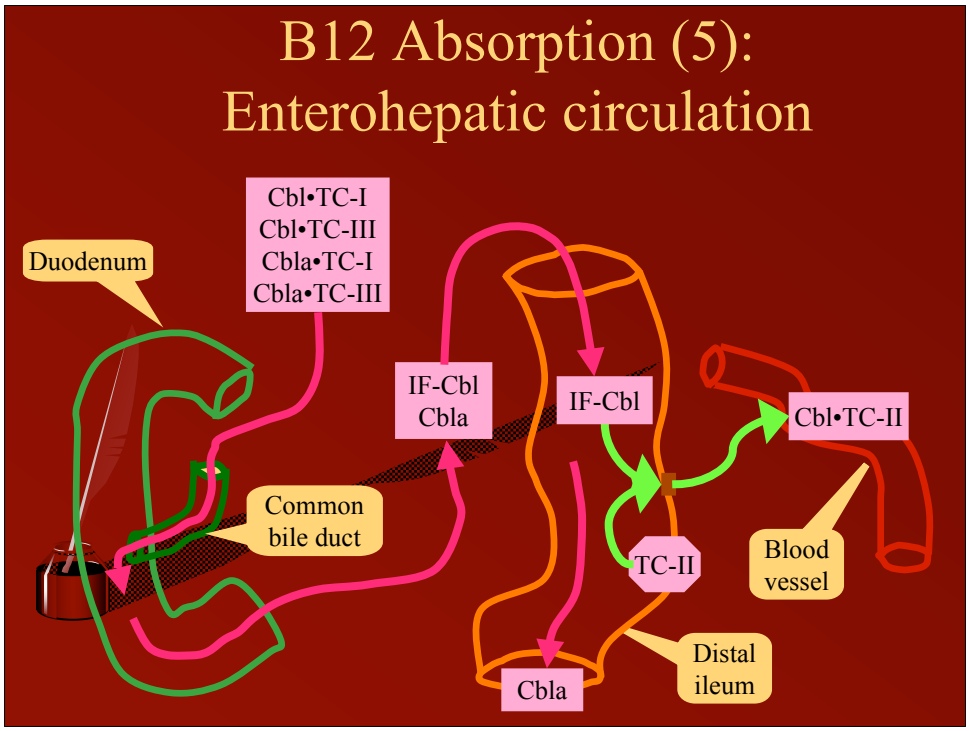

When the intrinsic factor-cobalamin complex arrives at the end of the small bowel, at a place called the distal ileum, it is picked up by specific receptors on the mucosal cells.

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.

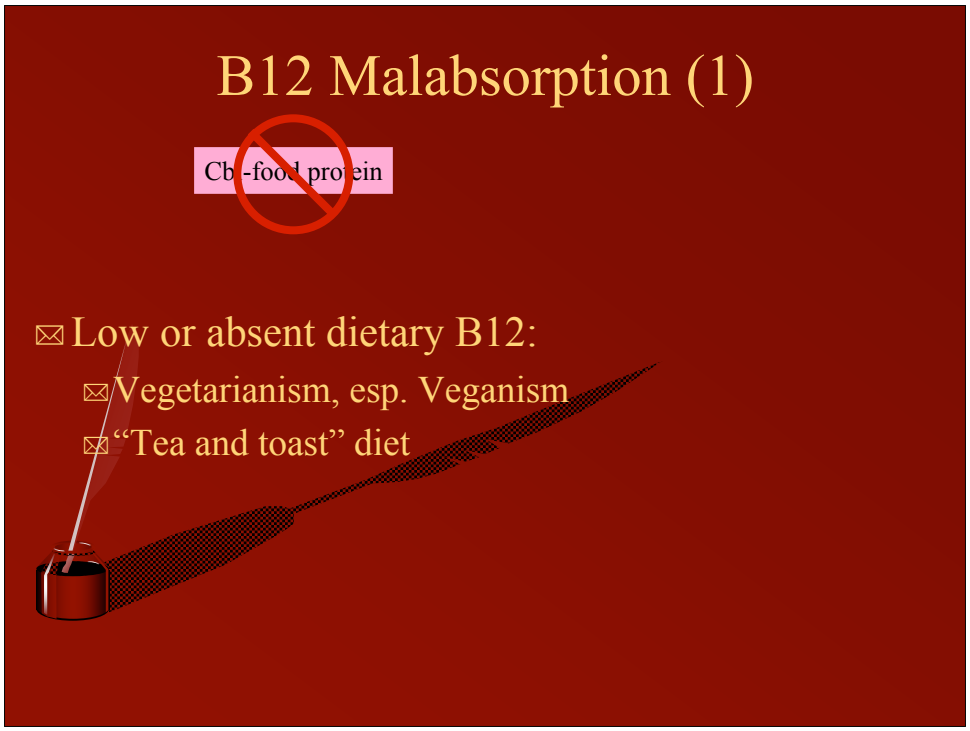
As before ♣, the IF-cobalamin complex is absorbed by ♣ mucosal cells and thus becomes available for reuse.

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

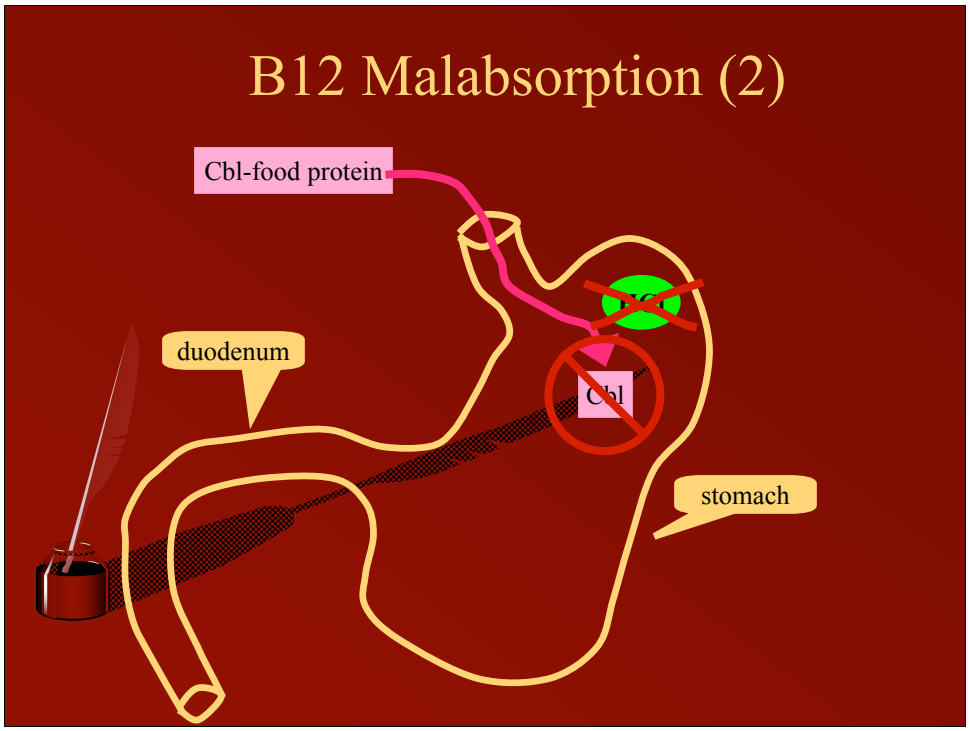
Thus, the enterohepatic circulation serves to conserve the vitamin while allowing excretion of the useless analogues.

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.

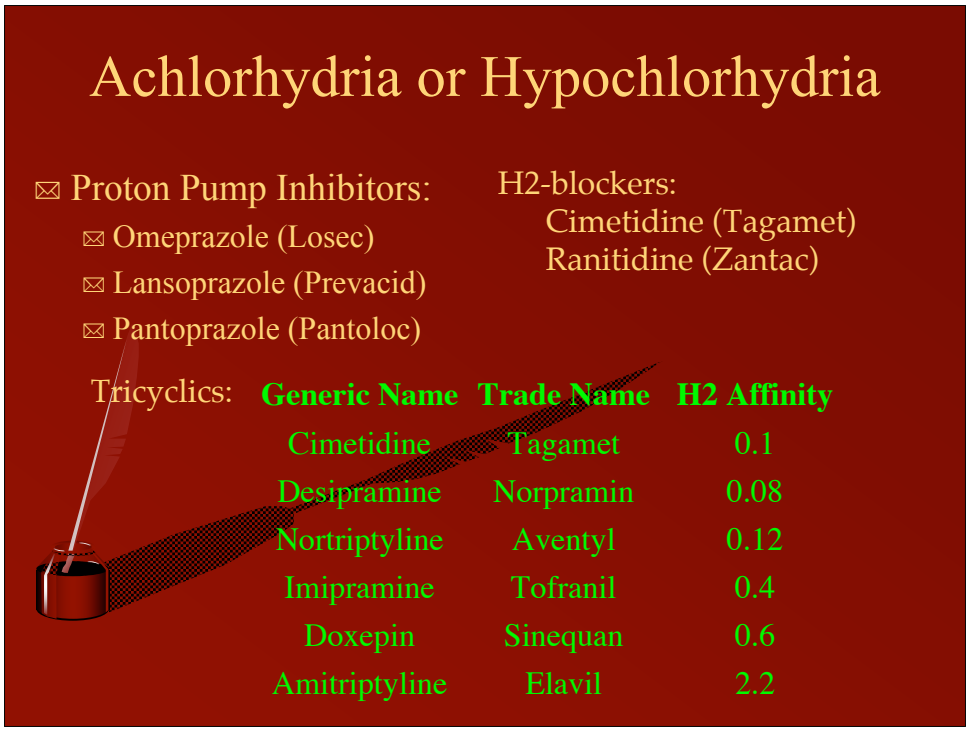



The first problem, of course, occurs when your food doesn't have enough B12 in it. Vegetarians, particularly vegans, are at high risk. Many elderly are also likely to get insufficient B12 because of a tea and toast diet.




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.

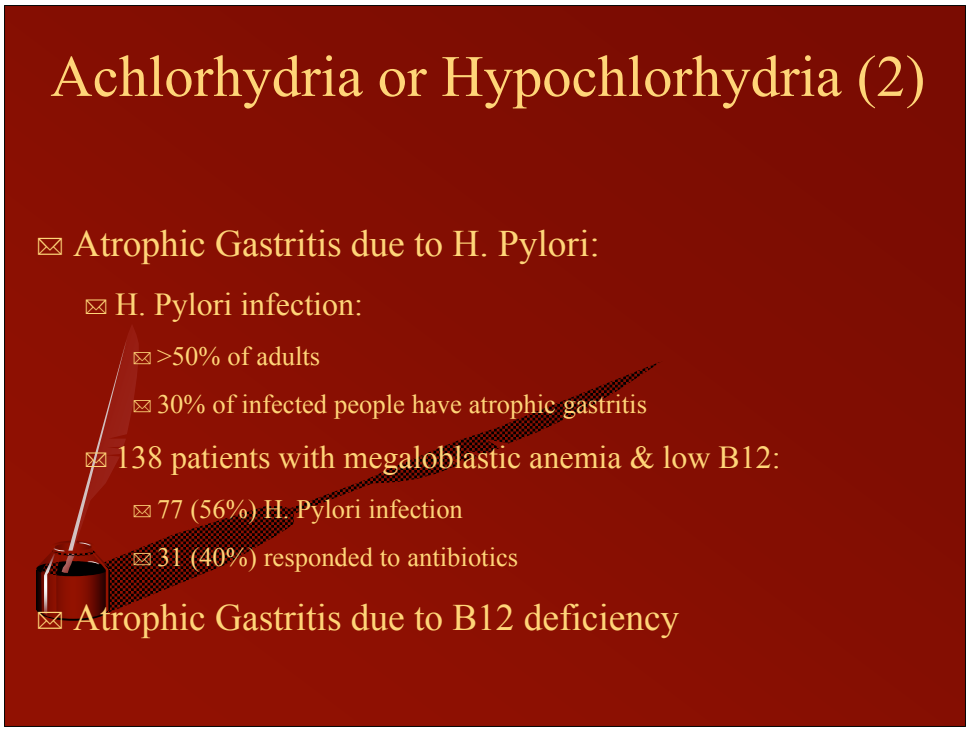
There are quite a few situations where there is insufficient stomach acid:




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.

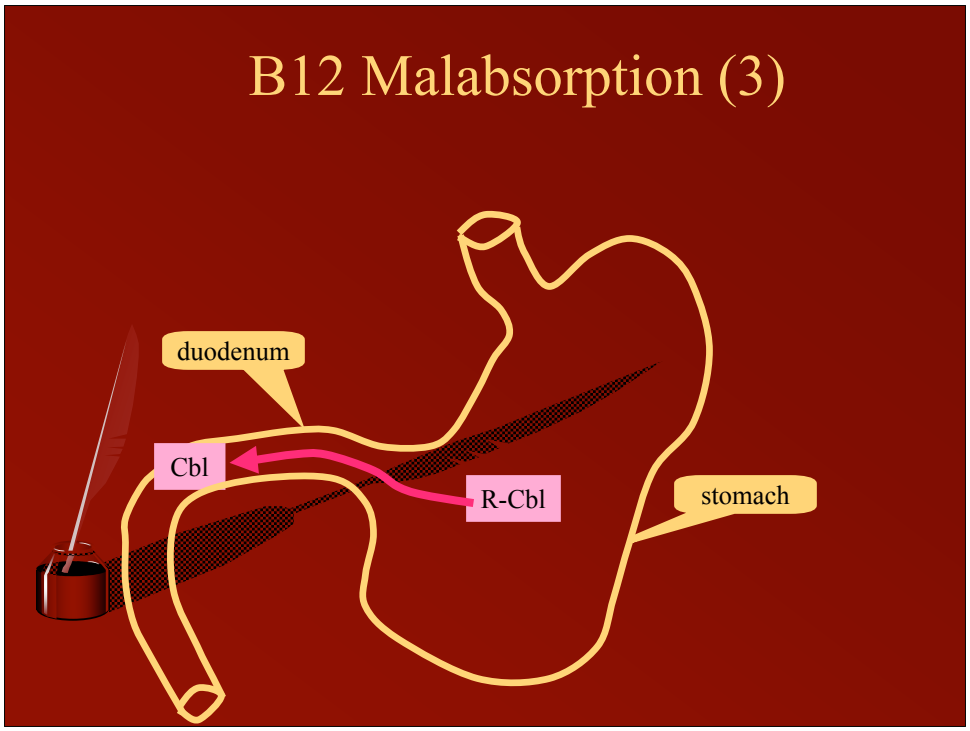
Importantly for psychiatrists, many of the ♣ tricyclic antidepressants are powerful H2 blockers also, in particular amitriptyline and doxepin. This table ♣ compares the H2 blocking activity for several antidepressants with that of cimetidine. You can see that doxepin is 6 times as potent as cimetidine, 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.




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.

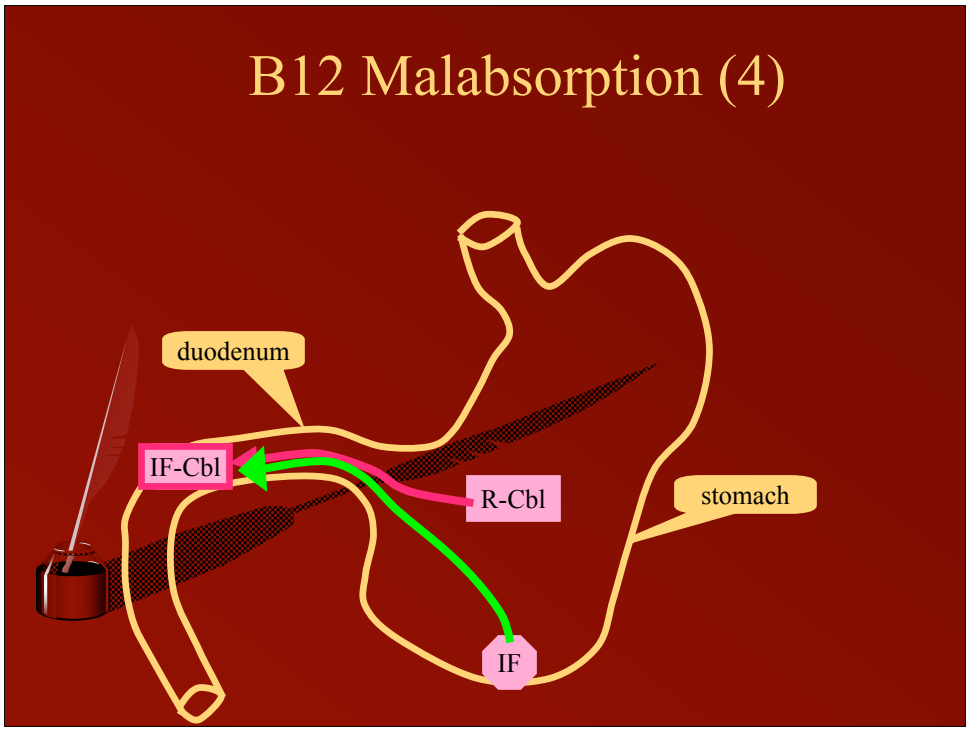
Another study looked at ♣ 138 patients who had megaloblastic anemia and low B12 levels. 77 of the 138, or 56%, had H. Pylori infection, which responded to eradication treatment with antibiotics in 40% of the 77. In these 31 patients where the antibiotics were effective, the serum B12 levels normalized 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.




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.

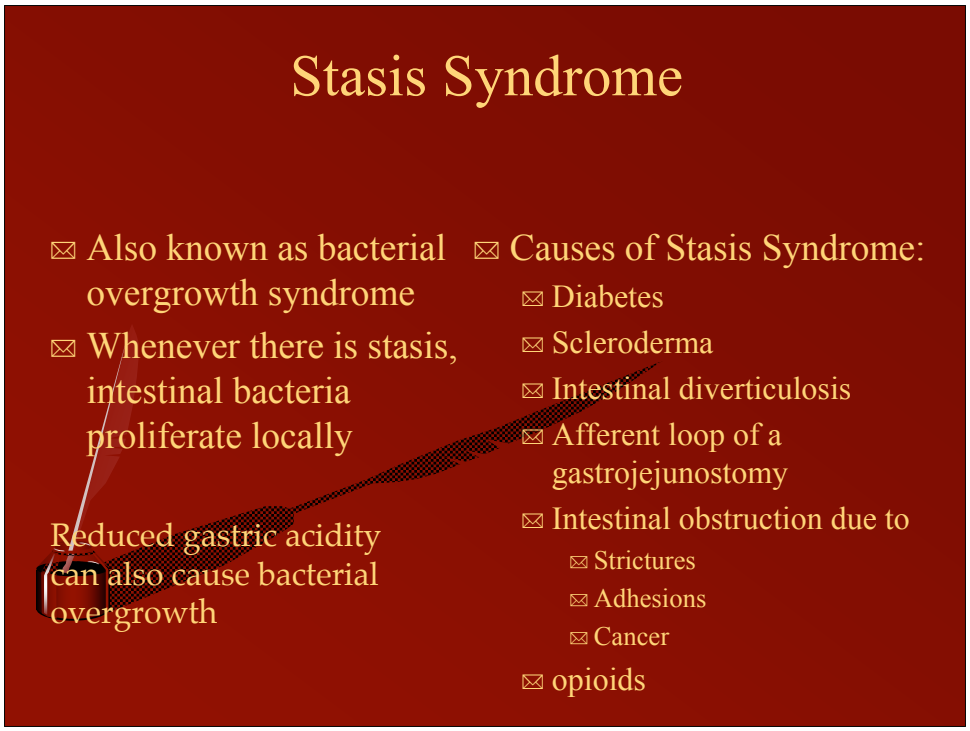



The next type of malabsorption problem has to do with intrinsic factor. Here is the slide showing the formation of the intrinsic factor-cobalamin complex in the duodenum.

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.




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.

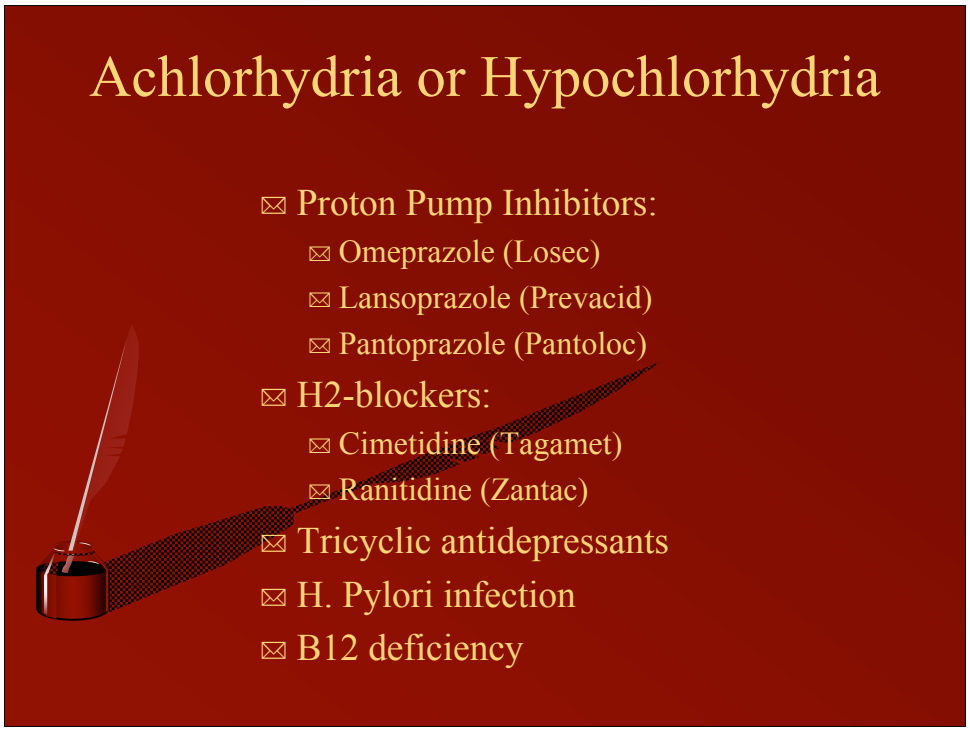
Keep in mind that narcotic painkillers also slow down the intestine.

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.

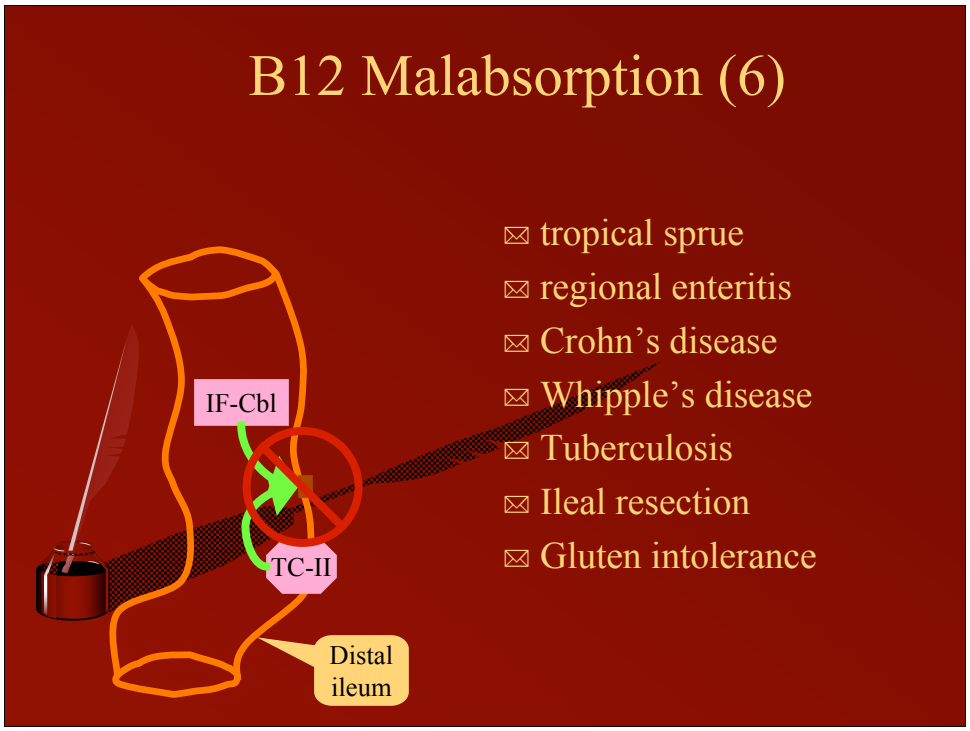
Perhaps one of the most problematic aspects of bacterial overgrowth syndrome is that some bacteria species can convert cobalamin into inactive analogues, sometimes called cobamides. These may be absorbed to some extent and may artificially raise the values obtained on serum B12 testing.

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.

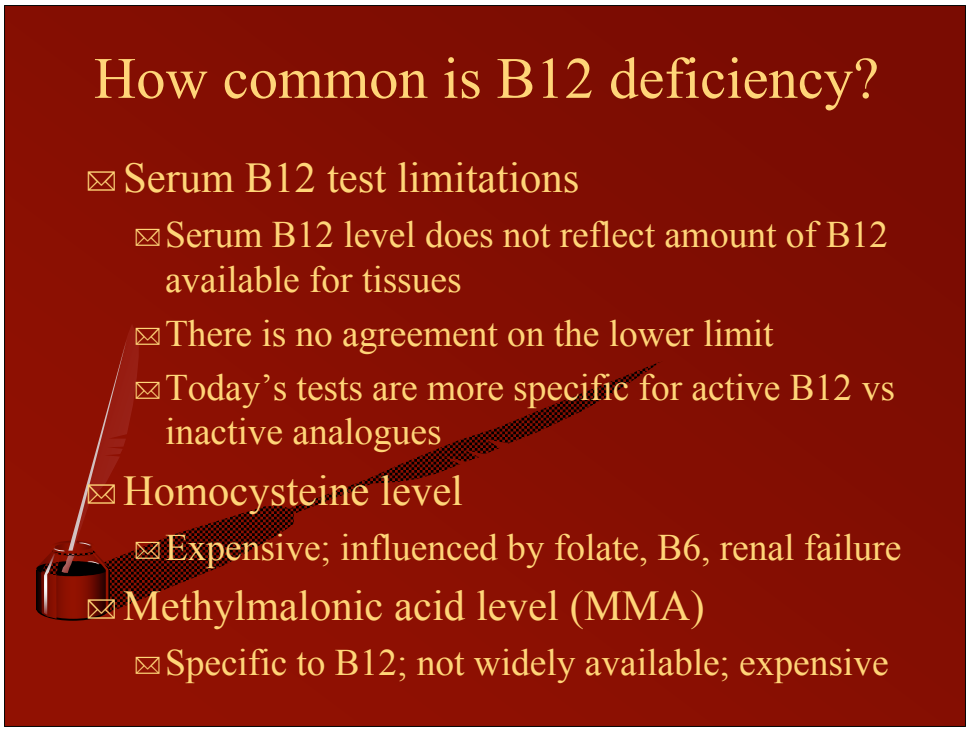



Just to remind you, I'll briefly flash this slide showing the various conditions that can cause low gastric acidity and therefore bacterial overgrowth.




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.




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.

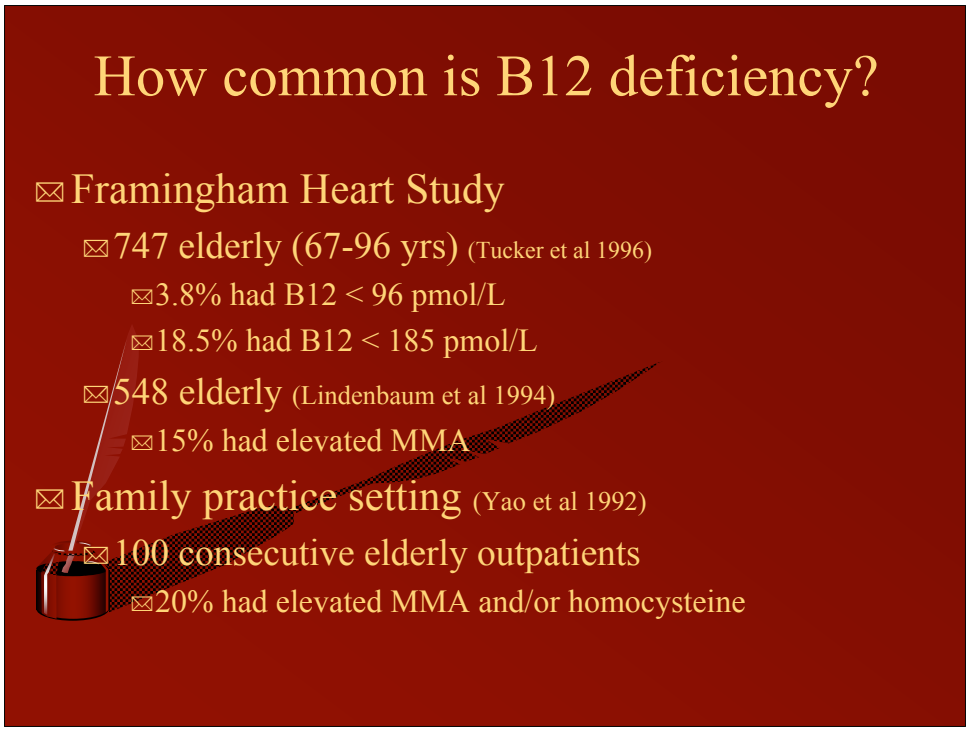
The serum B12 test measures the amount of cobalamin attached to transcobalamins I, II, and III in the bloodstream. However, it seems that only the ⇓ active cobalamin bound to TCII is available for use by target tissues. Thus, depending on the ratio of TCII to TCI plus TCIII, the serum B12 level may be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



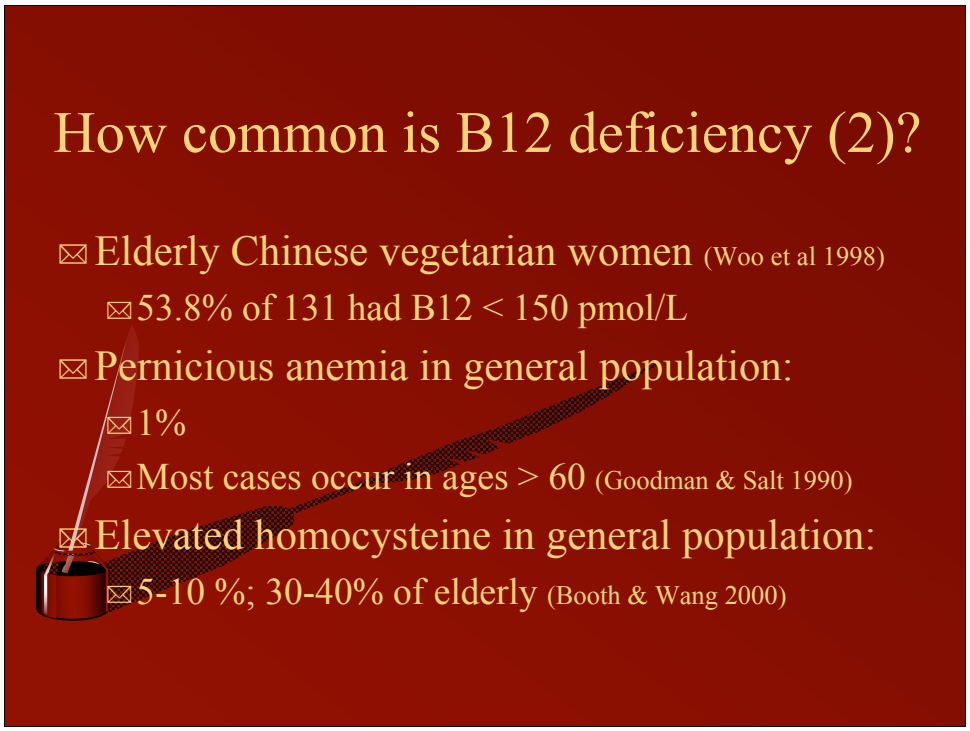

This slide shows prevalence data using all three types of test, in community-dwelling seniors.

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!

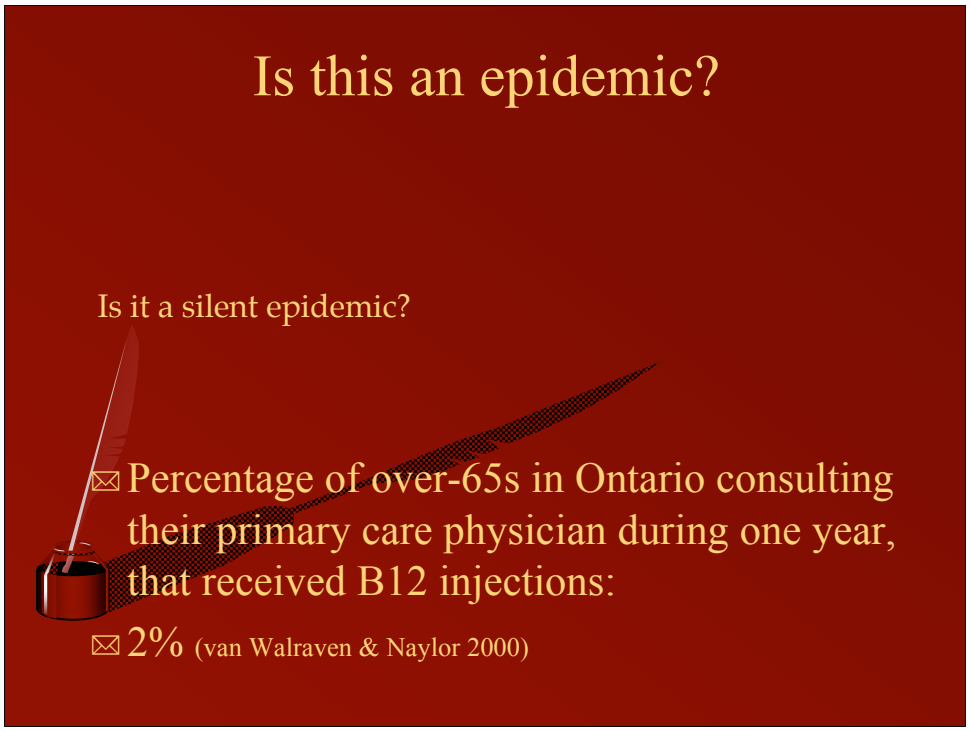



Here are some more prevalence numbers.

♣ 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.



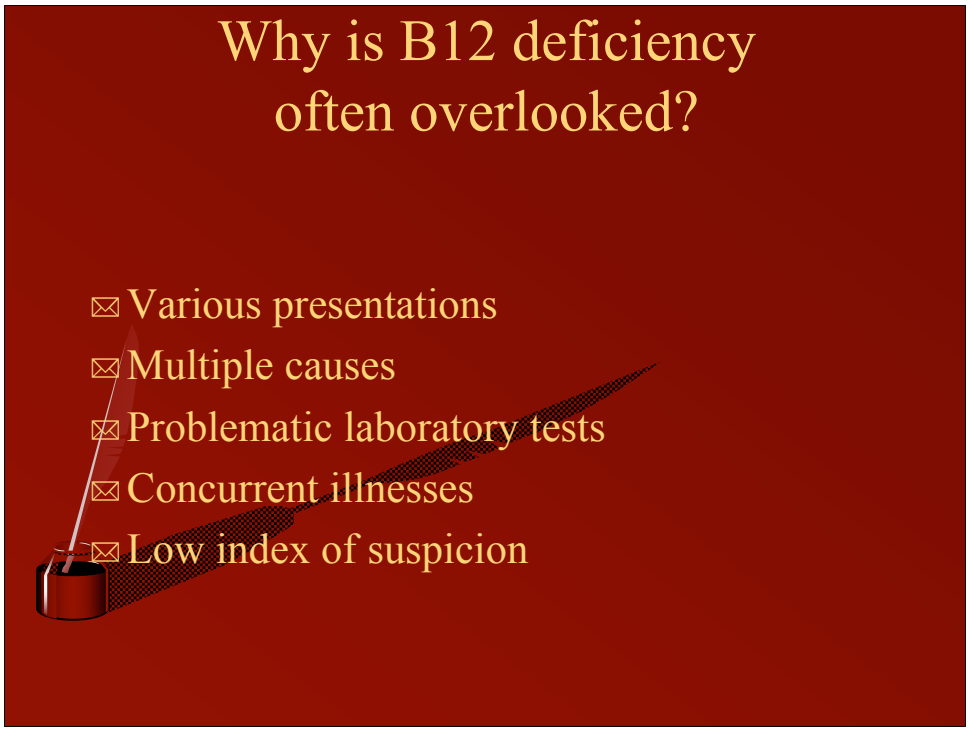

Is this an epidemic? What do you think?

♣ 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.




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?

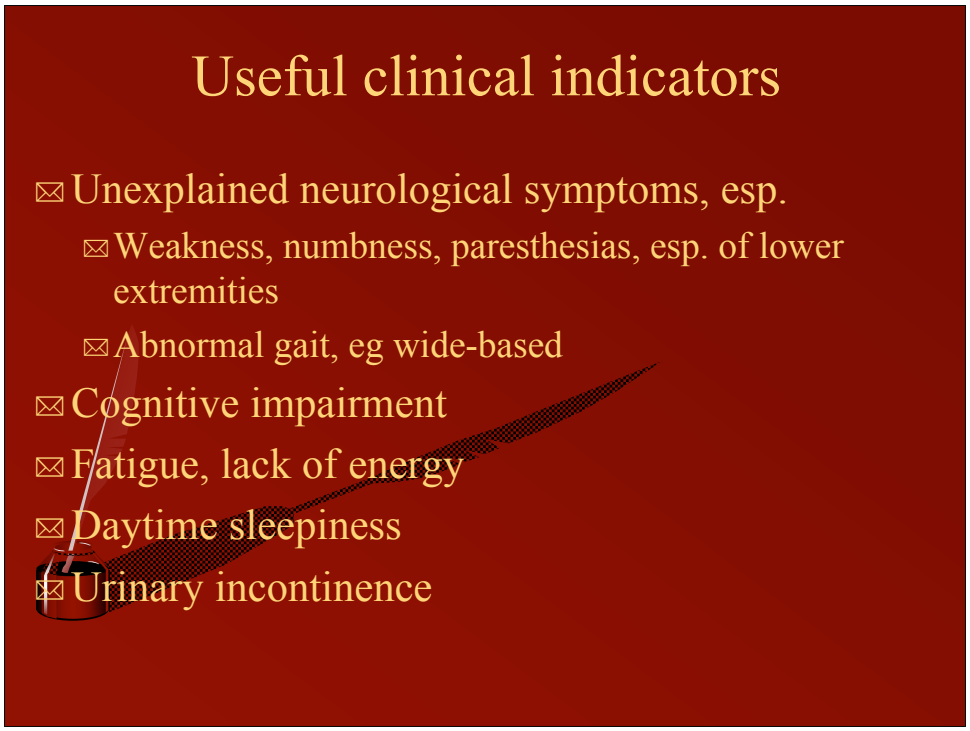
⇓ I've talked about the many and varied symptoms of B12 deficiency, which can occur singly or in any combination, in any order of appearance.

⇓ 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.




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.

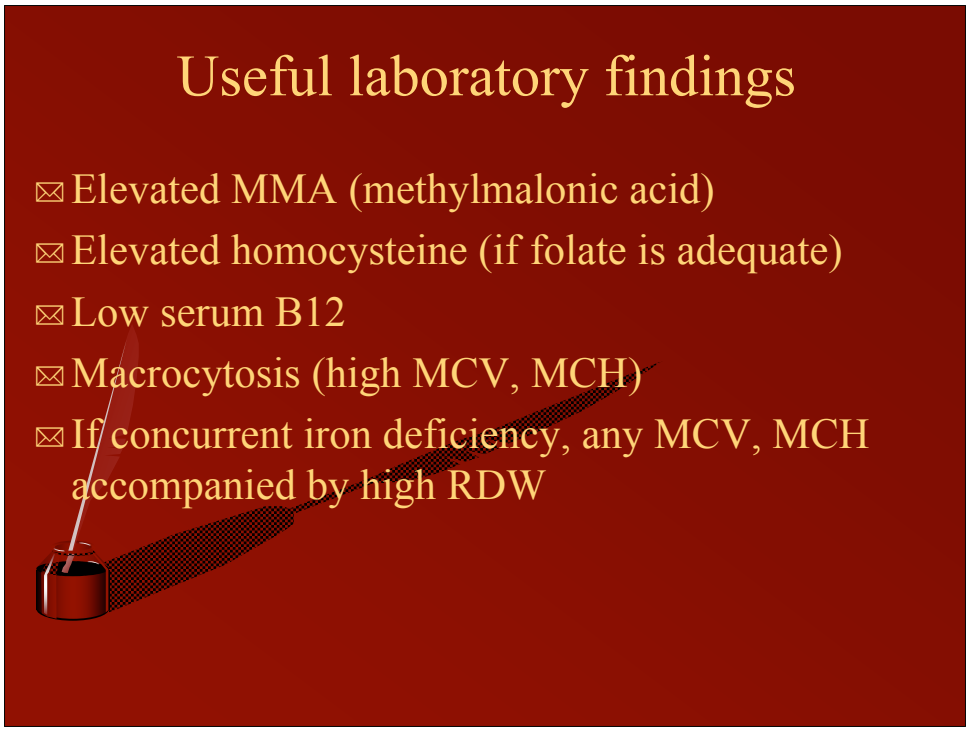
⇓ Daytime sleepiness I find particularly interesting. The Japanese have been using vitamin B12 to treat adolescents with delayed sleep phase syndrome. In the case of Mr. S., daytime somnolence was an important presenting symptom. If one has ruled out medications, obstructive sleep apnea, or narcolepsy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




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.

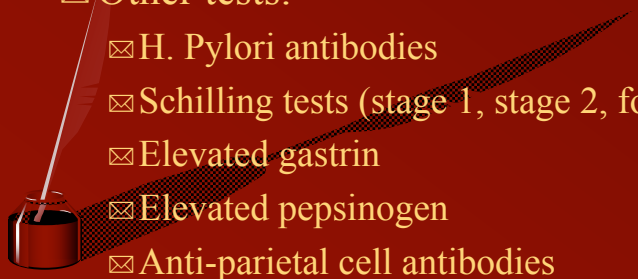
⇓ Macrocytosis is not necessarily present with B12 deficiency, but as for serum B12 level, the cutoff limits may be problematic. Our lab uses an upper limit of 100 femtoliters for the MCV. At least one author that I've read suggests that the limit should be 94 fL, and in fact this is the cutoff used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

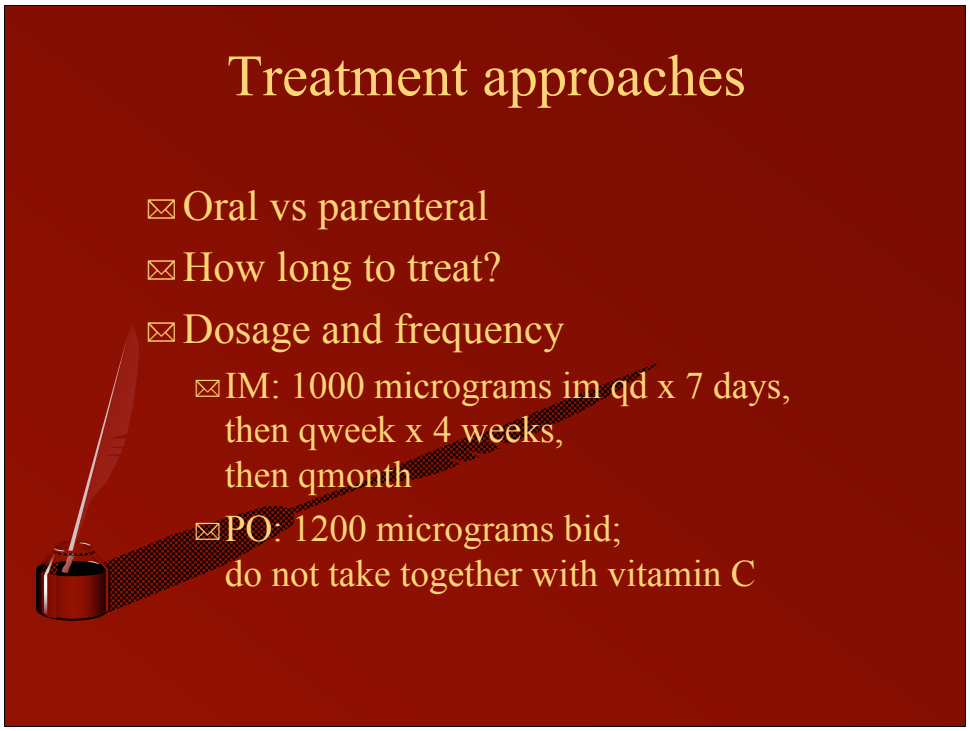
## Useful laboratory findings (2)

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



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.




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.

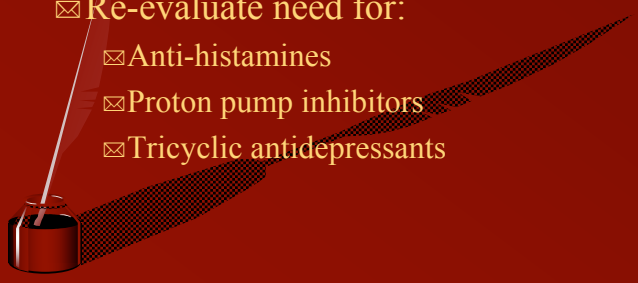
But in the elderly patients that I see, if there has been any sort of response to treatment by 6 months, I think that the treatment should also be continued indefinitely.

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 (2)

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



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