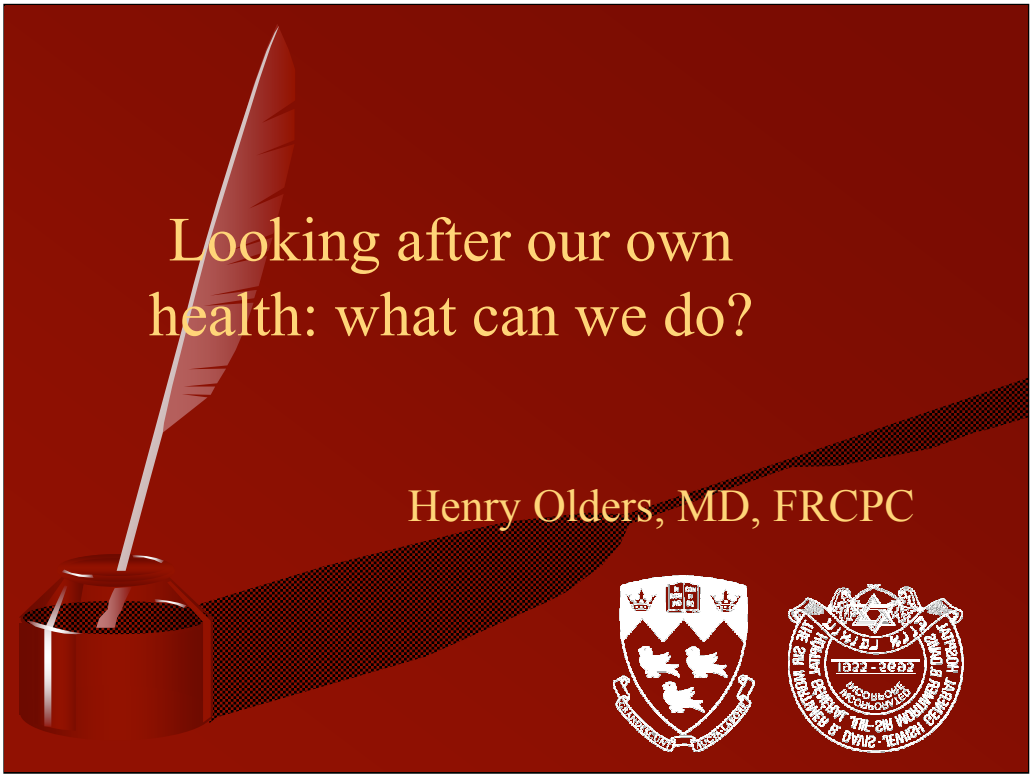



I'm going to talk to you today about Vitamin B12 deficiency. My interest in this topic sprang from something very personal. When I was still a teenager, my mother became very sick with pernicious anemia. Pernicious anemia is a severe form of B12 deficiency, which is deadly if not properly diagnosed and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

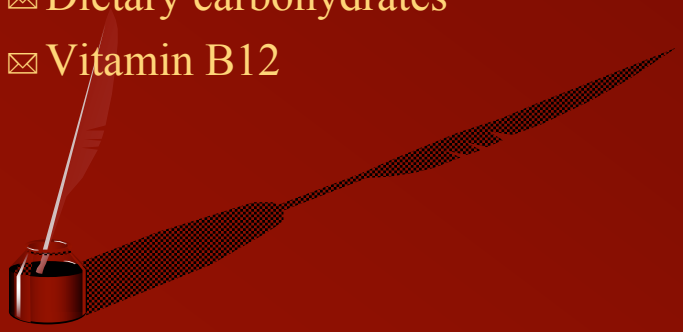
My mother's doctor couldn't understand why she was getting gradually weaker, over a period of several months. Finally, when she could no longer walk without help, we admitted her to hospital where the correct diagnosis was made. She received B12 injections and within weeks was back to her usual self.

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.

# Four self-care topics

- Sleep patterns and depression
- Omega-3 fatty acids
- Dietary carbohydrates
- Vitamin B12




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.

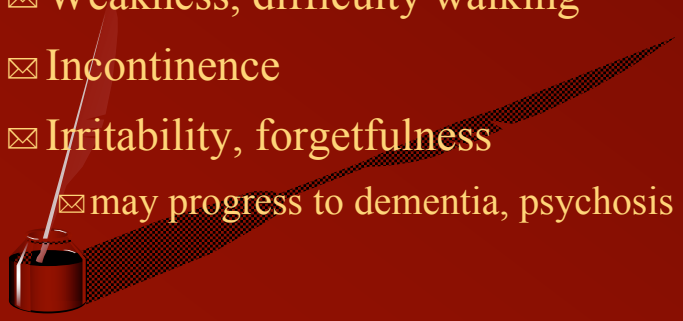
What about neurological side effects? Neurons have very little turnover, if any, so DNA production is clearly not important for them.

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.

# B12 deficiency: neurologic

- Numbness, paresthesias
- Weakness, difficulty walking
- Incontinence
- Irritability, forgetfulness
  - may progress to dementia, psychosis



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.

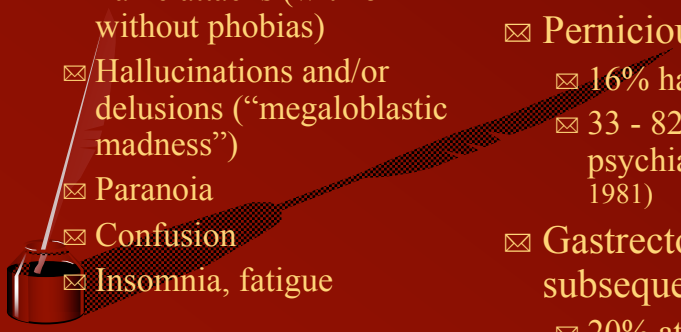
Here are the ♣ signs and symptoms. The ♣ sphincter disturbances can include urinary incontinence, as in Mr. S., the first patient I talked about. Both patients had problems walking, if you recall.

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.

# 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
- Psychiatric disorder
  - can occur many years before first hematologic or neurologic Sx
- Pernicious Anemia pts:
  - 16% have psychosis
  - 33 - 82% have minor psychiatric Sx (Zucker et al 1981)
- Gastrectomy pts with subsequent low B12:
  - 20% attempted suicide (Roos & Willanger 1977)



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.

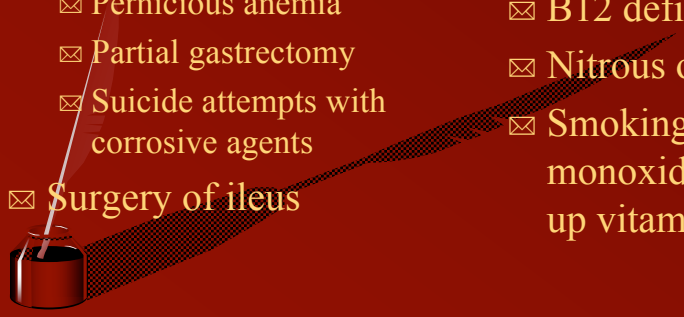
In spite of what I said earlier about depression being more associated with folate deficiency than with B12 deficiency, there may still be an important link with B12. One theory posits a role for B12 in the production of various neurotransmitters, including noradrenaline and serotonin. This may help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

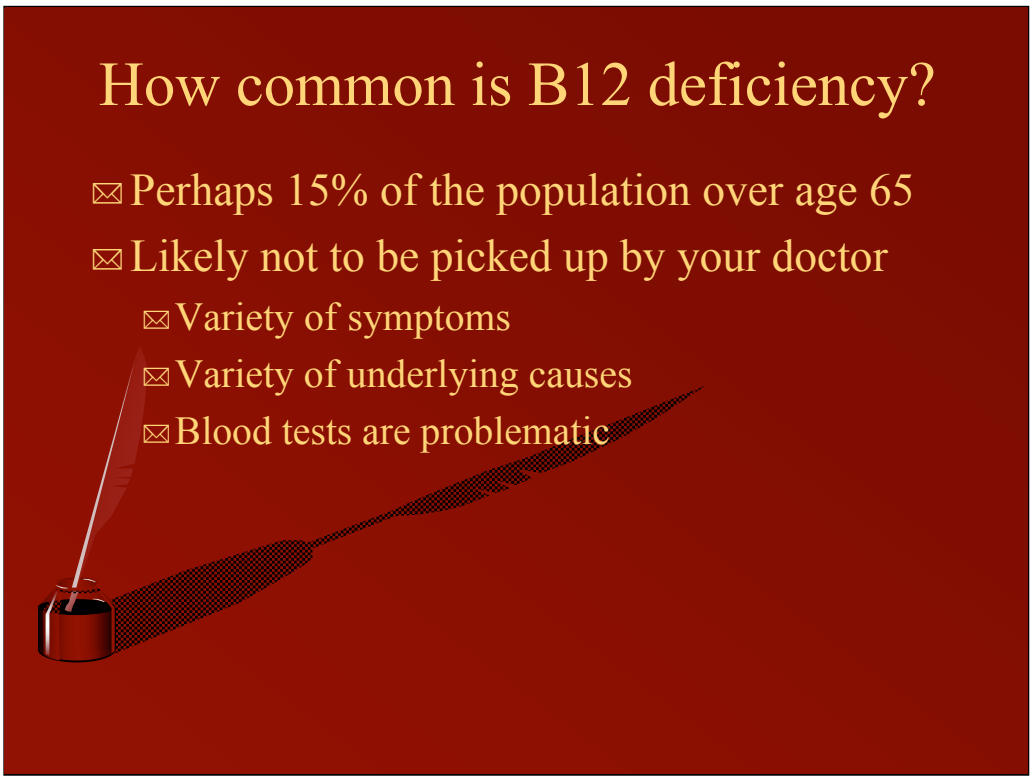
# Causes of B12 Deficiency

- Insufficient B12 in diet
- Atrophic gastritis due to H. Pylori infection (15%)
- Medications for heartburn:
  - Losec
  - Pantoloc
  - Prevacid
- Some antidepressants, eg
  - Elavil
  - Sinequan
- Bacterial overgrowth syndrome:
  - Diabetes
  - Scleroderma
  - Diverticulosis
  - Intestinal obstruction from
    - Strictures
    - Adhesions
    - Cancer
  - opioids

# More causes

- Pancreatitis or surgery involving pancreas
- Lack of intrinsic factor:
  - Pernicious anemia
  - Partial gastrectomy
  - Suicide attempts with corrosive agents
- Surgery of ileus
- Celiac disease (gluten intolerance)
- Crohn's disease
- B12 deficiency
- Nitrous oxide anaesthesia
- Smoking (carbon monoxide in smoke uses up vitamin B12)






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.

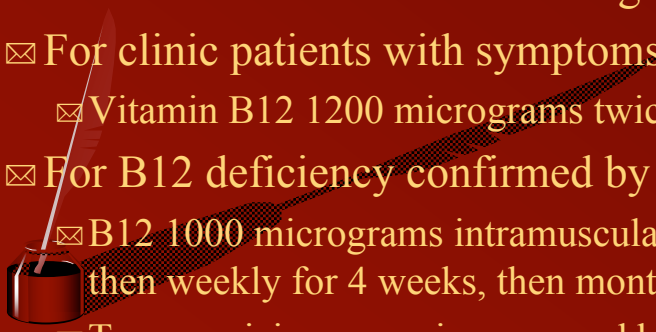
Thus, with all the problems inherent in the serum B12 test, we should look for other ways to pick up B12 deficiencies.

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.

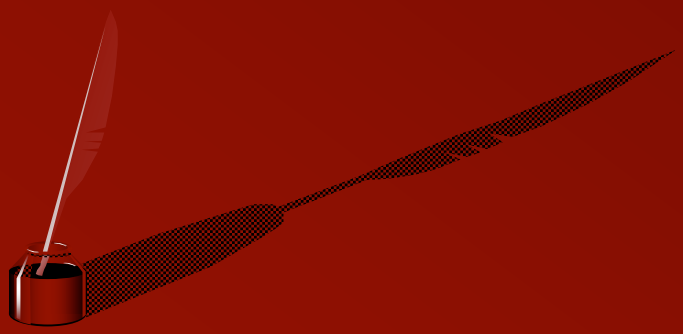
The most specific test appears to be ⇓ methylmalonic acid level, MMA for short. ⇓ It's not done at the Jewish.

# Recommendations for B12 Supplementation

- National Institutes of Health: every adult over age 50 should take synthetic vitamin B12
- No known ill effects from taking excessive B12
- For clinic patients with symptoms:
  - Vitamin B12 1200 micrograms twice daily by mouth
- For B12 deficiency confirmed by blood tests:
  - B12 1000 micrograms intramuscular daily for 7 days, then weekly for 4 weeks, then monthly
  - True pernicious anemia may need higher frequency

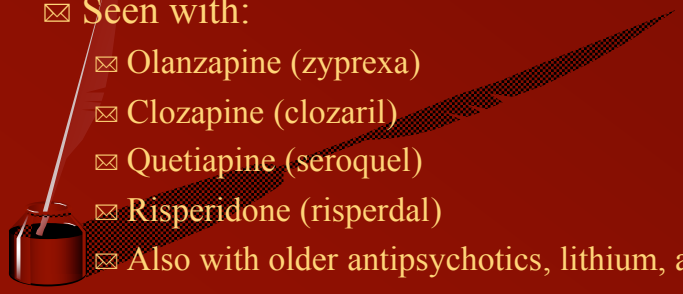


# Dietary Carbohydrates



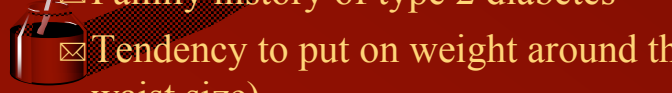
# Metabolic side effects of atypical antipsychotics

- Weight gain
- Obesity
- Type 2 diabetes
- Seen with:
  - Olanzapine (zyprexa)
  - Clozapine (clozaril)
  - Quetiapine (seroquel)
  - Risperidone (risperdal)
  - Also with older antipsychotics, lithium, antidepressants



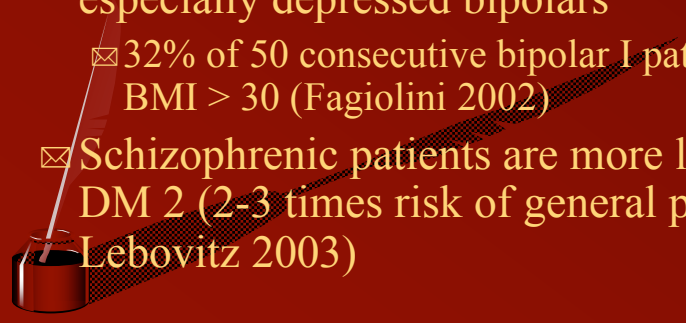
# How does weight gain occur?

- insulin is the signal to fat cells to take up sugar from the blood stream and convert it to fat
- Atypical antipsychotics increase insulin levels
- People most at risk already have high insulin levels
- Identify these individuals on basis of
  - Family history of type 2 diabetes
  - Tendency to put on weight around the middle (large waist size)

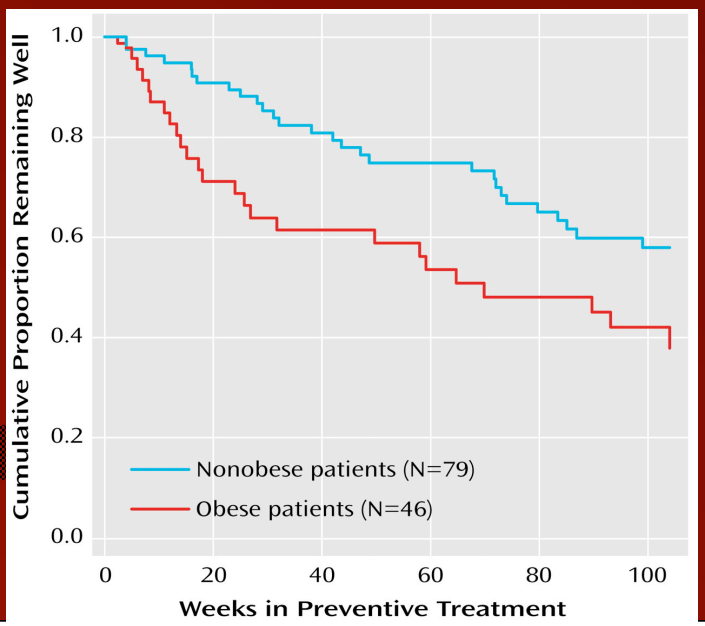


# Which patients are most at risk?

- Genetic predisposition
- Bipolar patients are more likely to be obese, especially depressed bipolars
  - 32% of 50 consecutive bipolar I patients had BMI > 30 (Fagiolini 2002)
- Schizophrenic patients are more likely to have DM 2 (2-3 times risk of general population Lebovitz 2003)

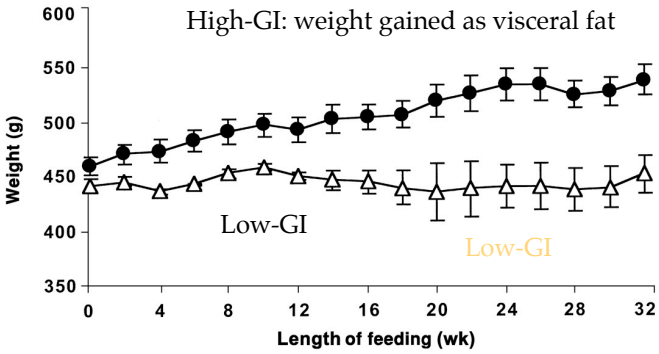


## Bipolar patients who are obese have a worse course of illness (Fagiolini 2003)



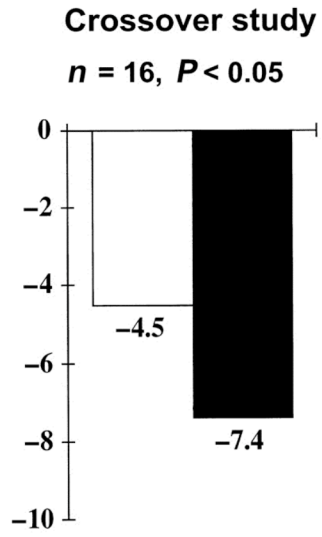
# Prevent weight gain: low GI

- Low glycemic index meals
  - No weight gain in rats fed isoenergetic low-GI, vs high-GI diet (Brand-Miller 2002)



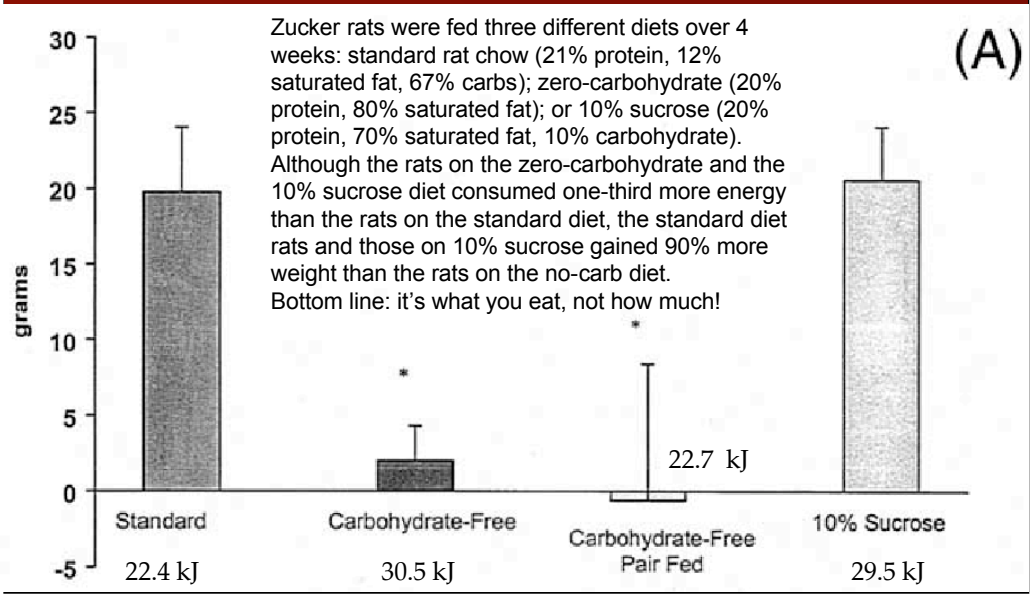
# Weight loss with low GI

- Low glycemic index meals
  - Promote weight loss
    - Weight loss in pounds for overweight women randomly assigned to high-glycemic index (white) or low GI diet (black). Diets equal in calories. (Slabber 1994)
  - The Montignac diet is based on low-GI principles



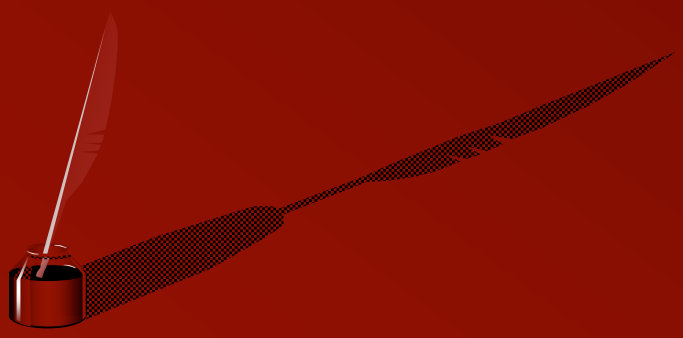
# Reduce carbohydrates

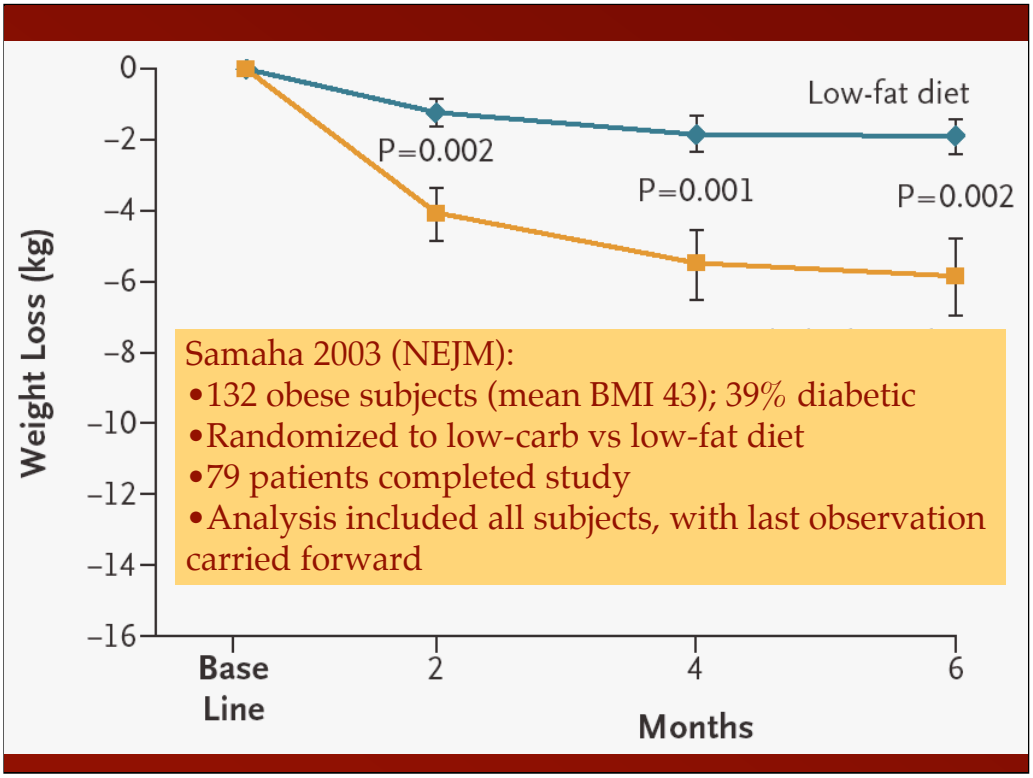
(Morris 2003)




Zucker rats were fed three different diets over 4 weeks: standard rat chow (21% protein, 12% saturated fat, 67% carbs); zero-carbohydrate (20% protein, 80% saturated fat); or 10% sucrose (20% protein, 70% saturated fat, 10% carbohydrate). Although the rats on the zero-carbohydrate and the 10% sucrose diet consumed one-third more energy than the rats on the standard diet, the standard diet rats and those on 10% sucrose gained 90% more weight than the rats on the no-carb diet.
Bottom line: it's what you eat, not how much!

# Low-carb (Dr. Atkins) diet



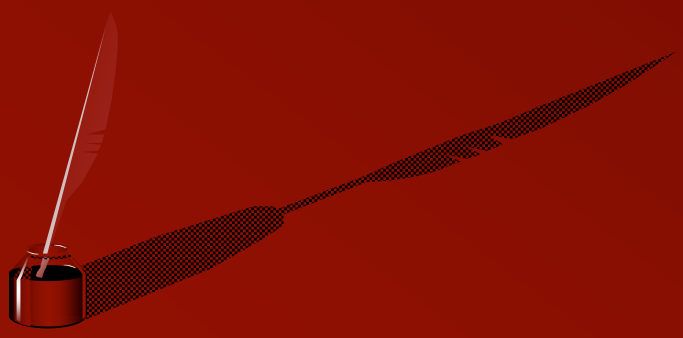



Samaha 2003 (NEJM):

- 132 obese subjects (mean BMI 43); 39% diabetic
- Randomized to low-carb vs low-fat diet
- 79 patients completed study
- Analysis included all subjects, with last observation carried forward

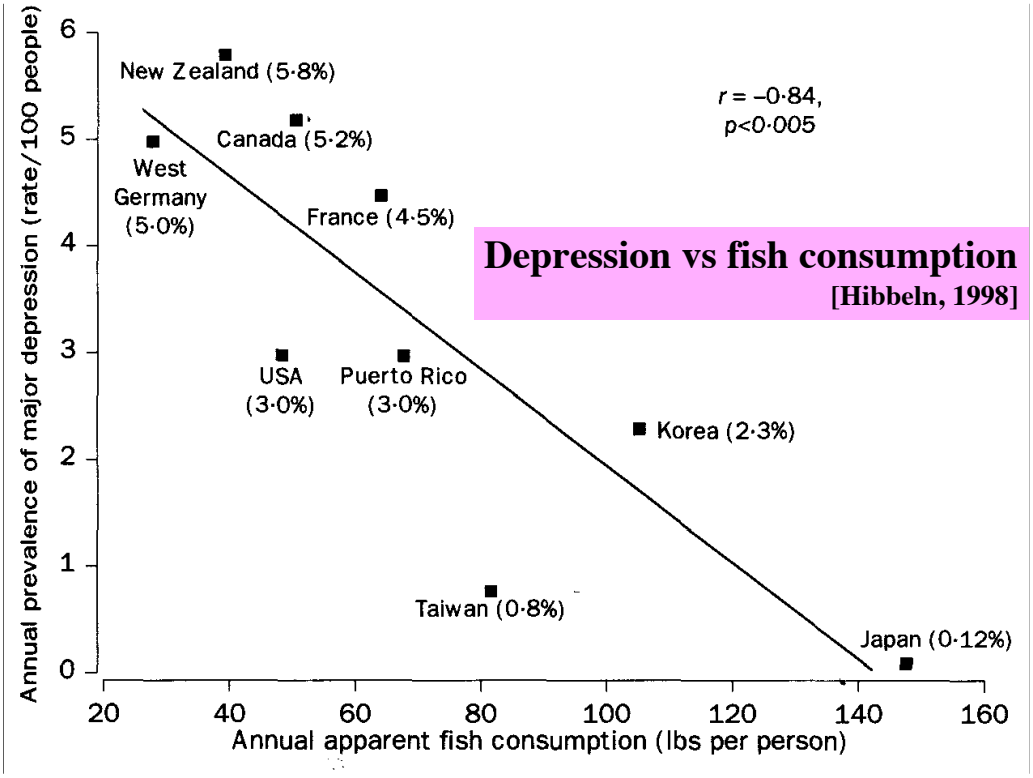
# Diet: conclusions

- Low glycemic index foods (eg, Montignac)
- Low carbohydrate diet (eg, Dr. Atkins)



# Omega-3 Fatty Acids

- We evolved to have 1:1 ratio of omega:3 to omega:6
- Currently in North America: ratio is 1:25
- Omega-6 promotes inflammation
- Omega-3 has anti-inflammatory properties
  - Necessary for heart health
  - Decreases risk of breast and lung cancer
  - May reduce childhood asthma, atopy
  - Treatment for rheumatoid arthritis, hypertension, Crohn's disease, asthma



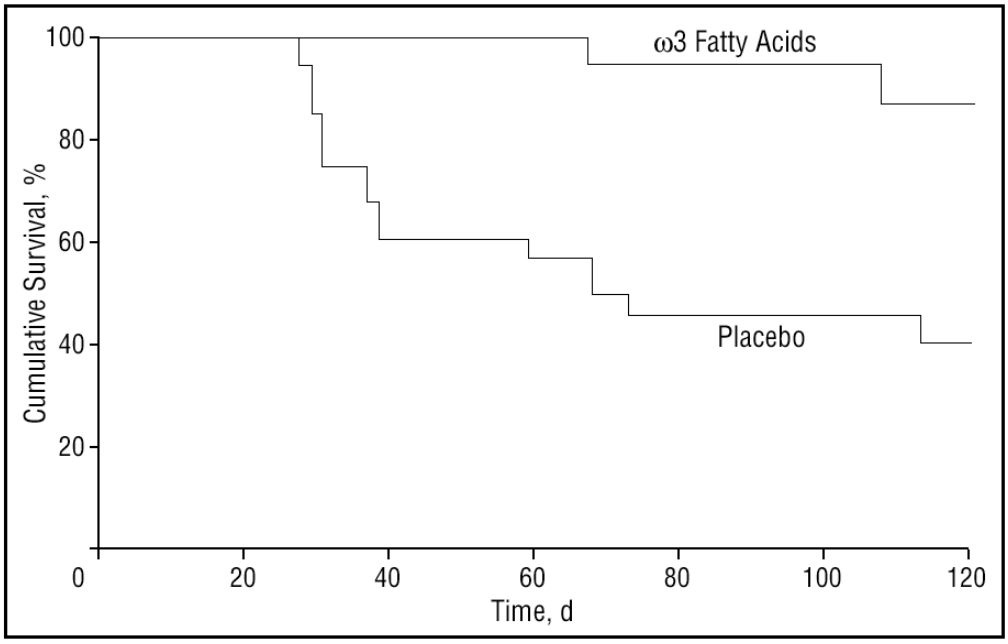

Annual prevalence of depression shows nearly a 60-fold variation across countries. The pattern is similar to that for coronary artery disease mortality, which suggests that there are similar factors at work, such as diet.

This paper used major depression prevalence figures reported by Myrna Weissman and her colleagues. The prevalences were obtained using rigorous methodology, including structured clinical interviews.

Apparent fish consumption was calculated as:

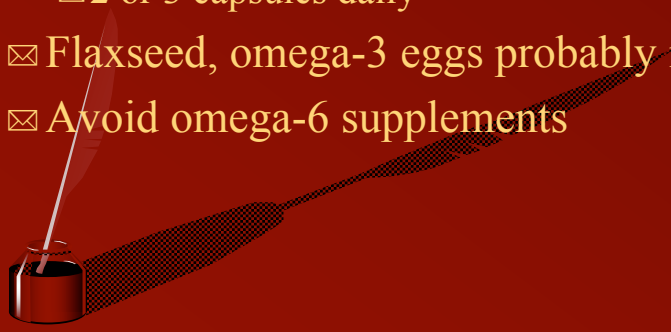
Fish catch + imports - exports

# ω3 survival analysis



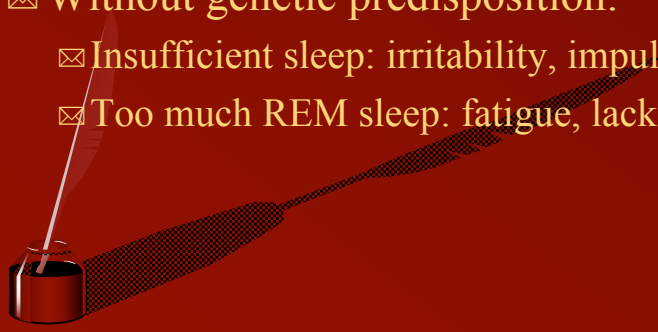
# Recommendations: Omega-3s

- Eat fatty fish several times per week
- Alternate: take salmon oil supplements
  - 2 or 3 capsules daily
- Flaxseed, omega-3 eggs probably ineffective
- Avoid omega-6 supplements



# Sleep patterns

- Sleep deprivation triggers mania
- Too much REM sleep may trigger depression
- Without genetic predisposition:
  - Insufficient sleep: irritability, impulsivity
  - Too much REM sleep: fatigue, lack of energy

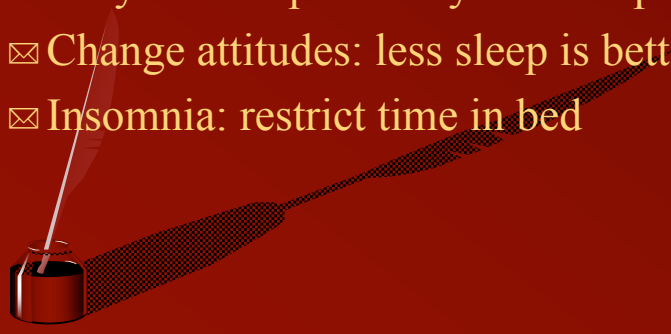


# Controlling your REM sleep

- Sleeping too long or not long enough
- Time of getting up
- Insomnia: is this lack of sleep?
- Attitudes about sleep

# Sleep strategies

- Be consistent about sleep patterns, especially rising times
- Very brief naps for daytime sleepiness
- Change attitudes: less sleep is better
- Insomnia: restrict time in bed



Do these strategies work?

Are they practical?