MEDCH 562-P
AUTUMN 2008
PROBLEM SET #5

1. Match the vitamin or mineral with the corresponding Daily Value.

			Amount	Unit
dz	1. Vitamin D	400 IU	a) 20	x) mg
ey	2. Vitamin B12	6.0 µg	b) 0.3	y) ug
bx	3. Biotin	0.3 mg	c) 5000	z) IU
cz	4. Vitamin A	5000 IU	d) 400	
ix	5. Folate	0.4 mg	e) 6.0	
hz	6. Vitamin E	30 IU	f) 60	
ax	7. Niacin	20 mg	g) 10	
gx	8. Pantothenic Acid	10 mg	h) 30	
fx	9. Vitamin C	60 mg	i) 0.4	

2. Water soluble vitamins in many cases can be taken in high doses without side effects.

a) Explain why.

Water soluble vitamins are readily metabolized and/or excreted due to their hydrophilicity.

b) Give two examples where toxicity has been observed and list the symptoms of toxicity.

B6 toxicity: >200 mg/day leads to increased prolactin.
>1-2 g/day leads to neuropathy.

Niacin toxicity: peripheral vasodilation, GI upset, ulcers, diarrhea, liver damage, increased gout, impaired glucose tolerance in doses over UL.

3. For the following conditions:

a) Name the vitamin that has been shown to be of some benefit .
b) What enzyme/reaction is activated by high doeses of the vitamin?

-Homocystinuera B6, activates cystathionine synthase

-Wernicke-Korsakoff syndrome B_1 (thiamin), activates transketolase

-Methylmalonic acidurea B_{12}, activates isomerase catalyzing transformation of methylmalonyl CoA to succinyl CoA

-Xantheronic acidurea B6, activates kyureninase

4. Using the concept of Km, explain the reasons why very high doses of thiamin can relieve the inborn error of metabolism called hyperpyruvate acidurea.

In the case of hyperpyruvate acidurea, there is an error in pyruvate dehydrogenase, which has a high Km (low affinity) for its cofactor TPP. High concentration of thiamin is therefore needed to restore the enzyme's activity.

5. Provide a metabolic explanation for the following (a scheme may be necessary for a cogent answers-structures are not necessary).

a. A folate deficiency is observed during a B_{12} deficiency.

N5 methyl THFA $\xrightarrow{B_{12}}$ THFA

B12 is required in the conversion of N5 methyl THFA to THFA. B12 deficiency will block the regeneration of THFA in the folate cycle and cause folate deficiency.

b. Methyl malonic acid appears in the urine in a B12 deficiency.

methylmalonyl CoA $\xrightarrow[\text{isomerase or mutase}]{B_{12}}$ succinyl CoA

Without adequate B12, methylmalonyl CoA is excreted in urine as methylmalonic acid.

c. Homocysteine levels may be elevated if B_6 intake is inadequate.

Homocystein $\xrightarrow[\text{Serine}]{\text{PLP}}$ cystathionine

cystathionine synthetase

In low B6 and hence low PLP, homocystein will accumulate.

d. Niacin may be deficient if B_6 intake is inadequate.

Tryptophan $\longrightarrow\longrightarrow \xrightarrow[\text{kynureninase}]{\text{PLP}} \longrightarrow$ niacin

If B6 is inadequate, the convertion from tryptophan to niacin may be blocked, which will result in niacin deficiency.

e. Symptoms of pellagra could result from isoniazid therapy if niacin intake was low.

Pellagra results from niacin deficiency. In isoniazid therapy, isoniazid forms Shiff base with PLP and therefore ties up PLP. As a result, PLP is in deficiency and the transformation of tryptophan to niacin is blocked and niacin deficiency is caused.

6. The following are signs of a vitamin deficiency. For each, list the most appropriate single deficient vitamin.

a. increased urinary xanthurenic acid — B6
b. increased plasma pyruvate — B_1
c. increased plasma homocysteine — B6, folic acid or B12
d. decreased erythrocyte glutathione reductase activity — B2

7. What vitamins are associated with the following functions?

a. decarboxylation — B_1 and B6
b. transamination — B6
c. purine and pyrimidine synthesis — folic acid
d. electron transport — B_2 and B_3
e. niacin synthesis — B6
f. collagen synthesis — C

8. Why is it important that a woman who is pregnant or is planning on becoming pregnant should be receiving a supplemental folate?

Folate deficiency early in pregnancy could lead to teratogenesis with neural tube defects. It is recommended that women who are pregnant or considering becoming pregnant should be receiving the RDA value of 0.4mg/day folate. This in addition to what is provided in the diet.

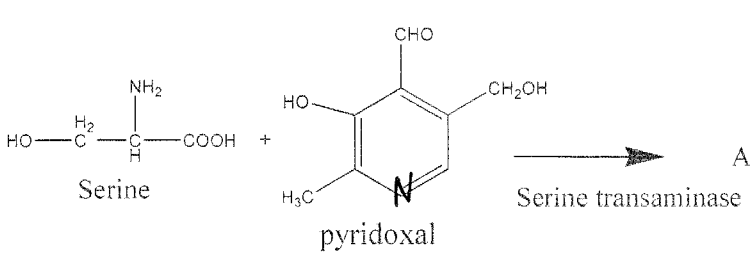
9. Folic acid requires a prescription for high doses, even though it is essentially non-toxic. Why?

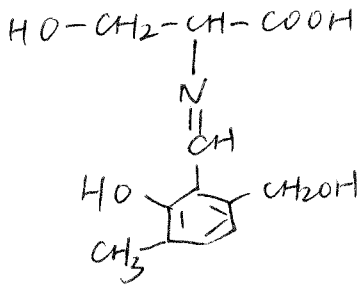
Folic acid deficiency can be caused either by lack of folate intake or lack of B_{12} (involved in the recycle of THFA). B_{12} deficiency can cause megaloblastic anemia and neurological damage, the latter is hard to detect. Therefore high dose folate supplements are risking in cases where there is a possibility of pernicious anemia (B_{12} deficiency) because folate will mask hemotological symptoms while neurological damages go on unchecked

10. Explain why a patient with age-related achlorhydria will benefit from oral B_{12} supplements whereas those with classic pernicious anemia will not.

HCl is needed to break covalent bond between B_{12} and the peptide links in food. If one has low HCl, then oral supplement of B_{12} (unbound form) will be helpful. In pernicious anemia, the problem is lack of intrinsic factor, a glycoprotein transporting B_{12} across ileum wall. So oral B_{12} supplement will not be absorbed.

11. a) Write the structure of A involving Shiff base formation.

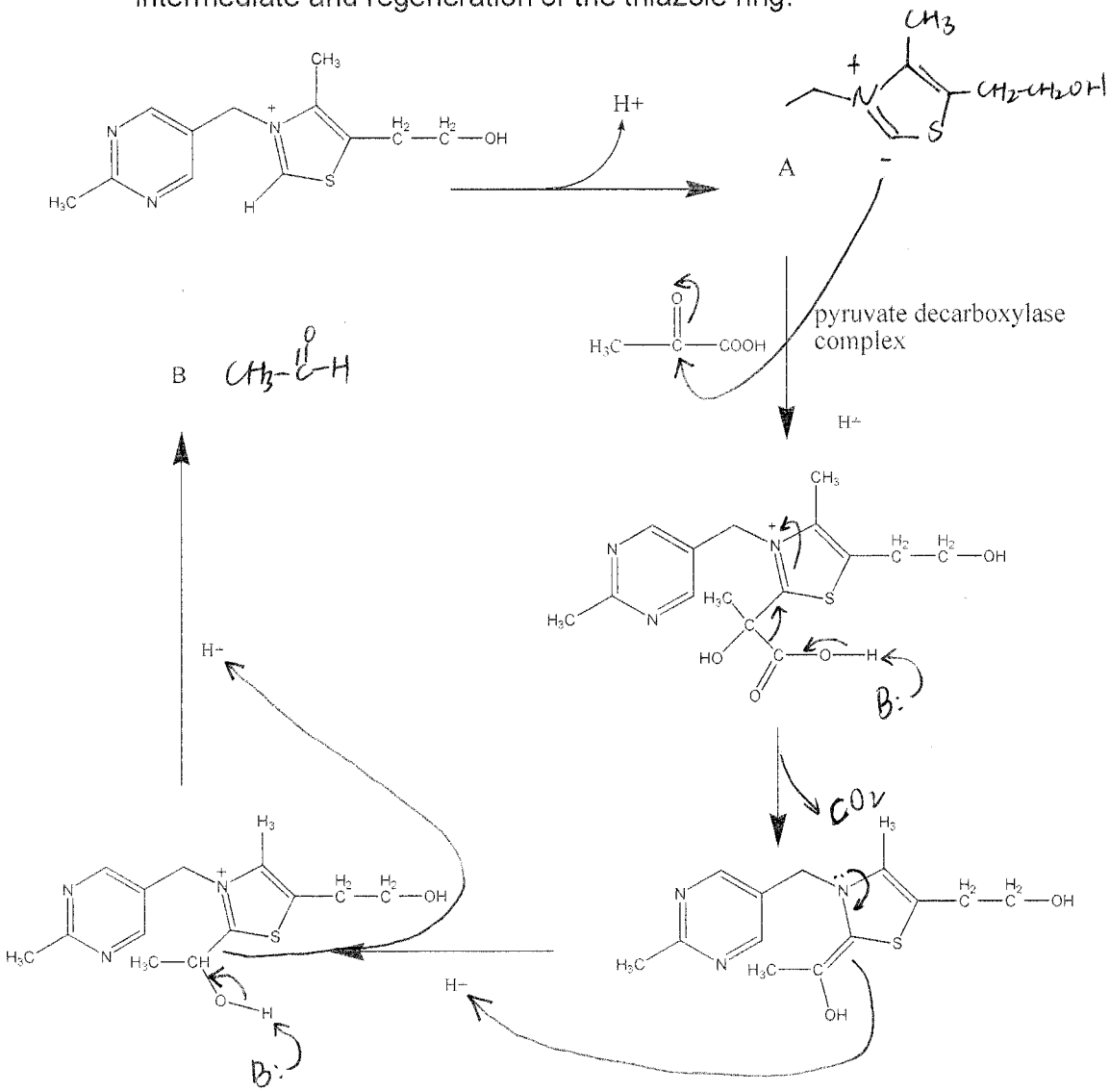




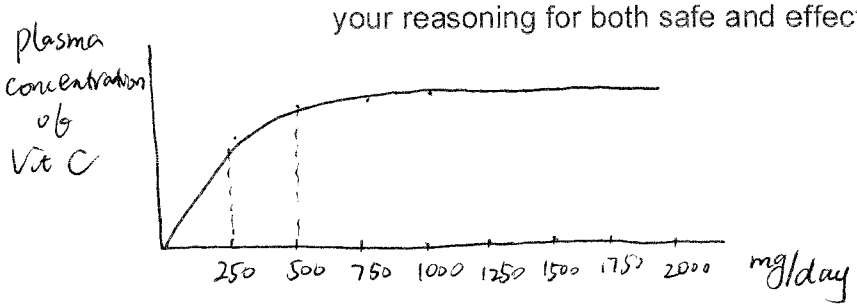
b) Why vitamin B6 is contraindicated in 1-DOPA therapy?

B6 facilitates decarboxylation of 1-DOPA to dopamine, which can not cross Blood Brain Barrier.

12. Below is the scheme showing the formation of adduct with C-2 of thiazole ring in thiamin. Draw structures of A and B (partial structure is OK). Draw arrow-pushing mechanisms of the formation of each intermediate and regeneration of the thiazole ring.



13. Draw the oral dose plasma saturation curve for vitamin C. Label the X and Y axes. Based on this, what would be a safe and effective dose of vitamin C for a one-month treatment to hasten wound healing? Explain your reasoning for both safe and effectiveness.



250-500 mg would be the best dose considering safety and effectiveness as it stays below the UL of 2000 mg and this dose is in the near saturated range on the curve.

14. Long special diets may increase the metabolic demand for certain vitamins. Explain the following cases and indicate what enzyme could be measured to give an indication of deficiency if applicable.

a) High protein and high fat may result in the highest demand for what water soluble vitamin?

B6. High protein load will require B6 as PLP to catalyze the transamination reactions needed to metabolize proteins.
Any erythrocyte transaminase can be measured.

b) A Mediterranean diet (high carbohydrate and low fat) may result in the highest demand for what water soluble vitamin?

B1 (thiamin). Thiamin as TPP is needed to metabolize carbohydrate.
Transketolase activity in RBC (red blood cell) can be measured.

c) A vegan (no animal products) may result in the highest demand for what water soluble vitamin? What would be the most common laboratory sign of the deficiency?

B12. B12 is only found in meats and microorganisms unless fermented soy products are ingested.
A laboratory sign of deficiency is megaloblast or abnormal test result for uptake of B12, such as Schillings test (labeled B12) or methyl malonic acid (in plasma) test.

15. High, chronic alcohol ingestion adversely affects the normal levels of several vitamins. Specifically what is the involvement of alcohol with thiamin? With folic acid?

Thiamin – inhibits conversion of T to TPP
inhibits B1 absorption (↓ active transport)
↑ fluid intake and urine flow causes thiamin washout
Folic acid – inhibits enterohepatic recycling of N5-methyl THFA.