MEDCH 562P
Fall 2011
Problem Set #4 – Answer Key

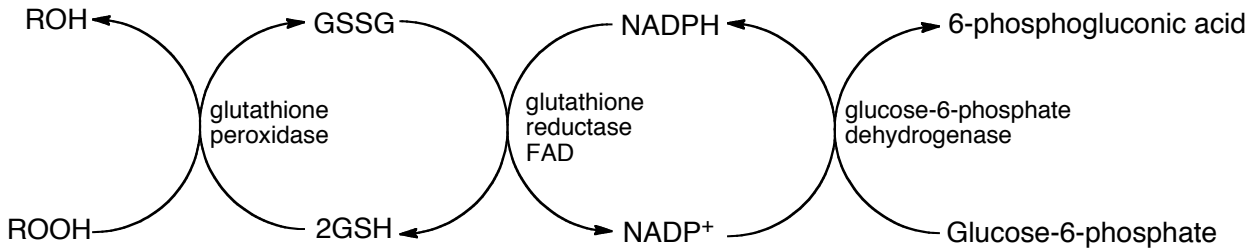
FAT-SOLUBLE VITAMINS

I. Complete the following table:

Vitamin	Deficiency State	Toxicity	Uses	Daily Value
A	Night blindness Xeropthalmia Skin hyperkeratosis	Hydrocephaly Headaches Hypercalcemia (i.e. symptoms of hypervitaminosis A)	Xeropthalmia Psoriasis Acne Promyelocytic leukemia	5000 IU
D	Rickets Osteomalacia	Calcification of soft tissues (i.e. kidney, lung), especially in infants	Rickets Osteomalacia Metabolic bone diseases	400 IU
E	Hemolytic anemia	None	Antioxidant/free radical scavenger (e.g. eye damage in premature infants)	30 IU
K	Hypoprothrombinemia Hemorrhage, especially in neonates	None	Promote coagulation Warfarin overdose	80 μg

II. Why is Vitamin E useful in patients that have hemolytic anemia associated with a glucose-6-phosphate dehydrogenase deficiency (G6PD)?

G6PD is a key enzyme in the glutathione pathway, which reduces lipid peroxides (reactive oxygen species or ROS) to maintain cell membrane structure and function. As shown in scheme below, G6PD provides NADPH to glutathione reductase in order to reduce GSSG to GSH. GSH then converts ROOH (lipid peroxides) to ROH in the presence of glutathione peroxidase. G6P deficiency will thus promote oxidative stress leading to conditions such as hemolytic anemia.



When the above pathway isn't functional due to G6PD deficiency, Vitamin E can act as a radical scavenger at the propagation step of lipid peroxidation by reacting with peroxyl and lipid radicals, preventing formation of further lipid peroxides.

$$RH \longrightarrow R^{\bullet}$$

$$R^{\bullet} + O_2 \longrightarrow RO_2^{\bullet}$$

$$RO_2^{\bullet} + RH \longrightarrow ROOH + R^{\bullet}$$

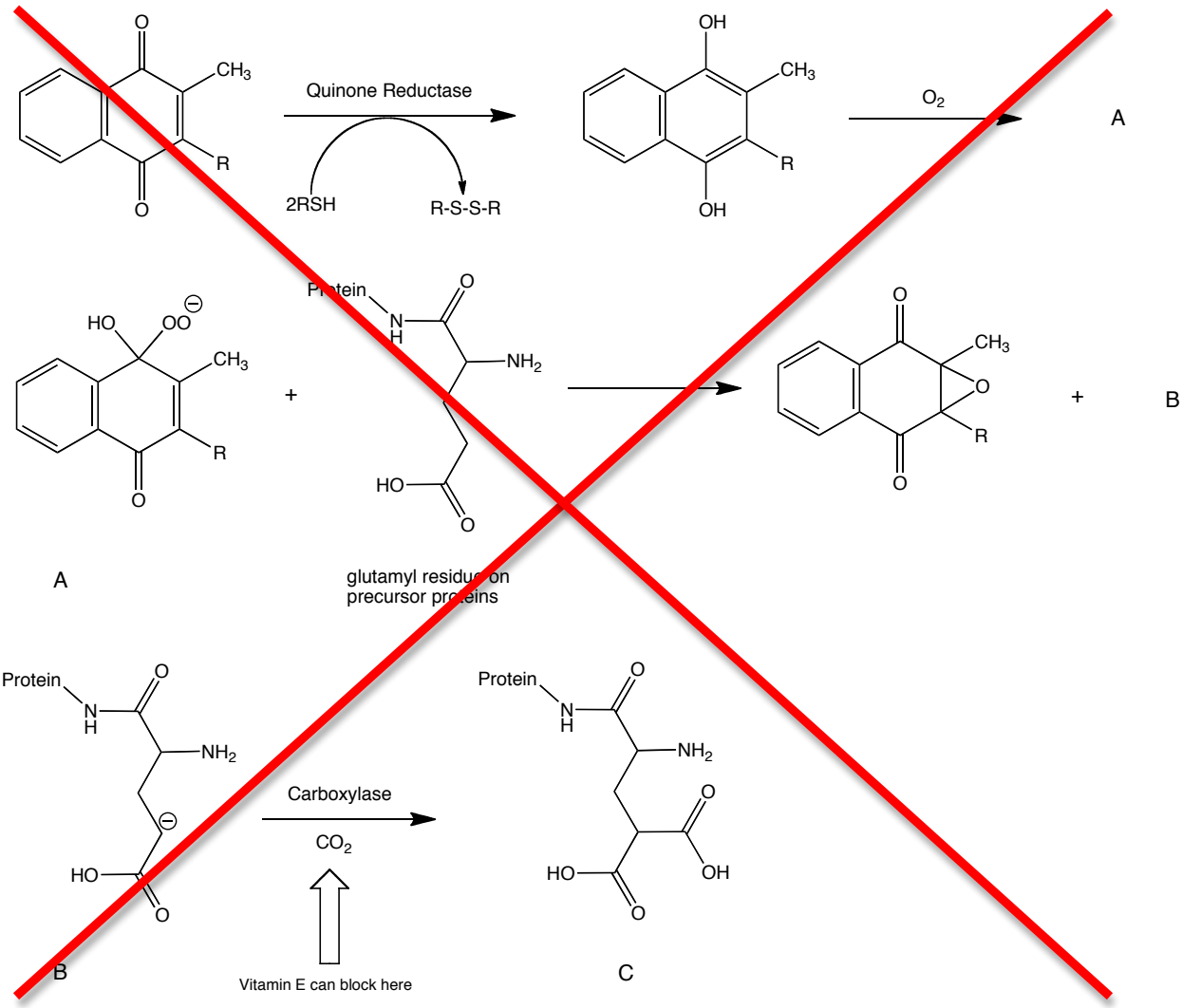
$$R^{\bullet}, RO_2^{\bullet} + \text{Vitamin E} \longrightarrow RH, ROOH + \text{oxidized Vitamin E}$$

III. A patient has been on long-term broad-spectrum antibiotics for a year for Crohn's disease. Recently, there were signs of unexplained hemorrhage. What could be the reason for the bleeding?

Long-term antibiotic therapy can lead to decreased concentrations of intestinal flora. Since some of the body's Vitamin K needs are provided by gut bacteria, the patient might be low in Vitamin K. Vitamin K is important for maintaining blood coagulation. A Vitamin K deficiency could cause an increased bleeding tendency.

IV. **QUESTION DELETED**

Complete the following equations that show Vitamin K involvement in the γ-carboxylation of precursor clotting factors. Give the structures of A, B, and C.



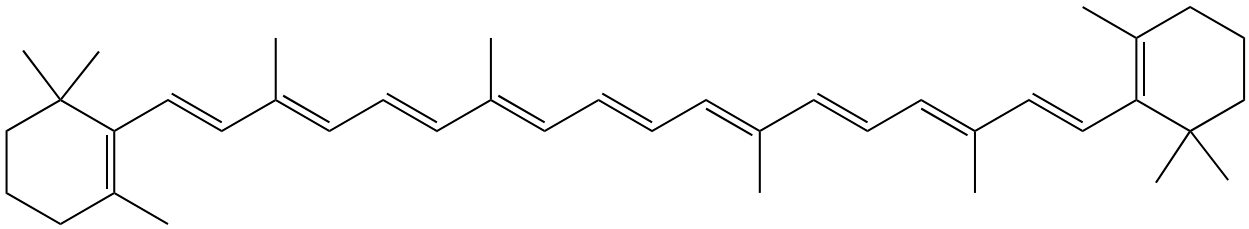
In the scheme above, draw an arrow at the step where a high dose of Vitamin E would block.

V. Night blindness is one important deficiency state of which vitamin? Explain the relations.

Night blindness is caused by a deficiency of Vitamin A, in the form of 11-cis retinal.

Night vision is possible due to the extremely light-sensitive pigment, rhodopsin, a complex of 11-cis retinal and the protein, opsin. Retinyl palmitate is the primary form of Vitamin A obtained from animal products in the diet. Retinoid

isomerohydrolase catalyzes the conversion of all-trans retinyl palmitate to 11-cis retinol. The NAD^+-dependent retinol dehydrogenase then oxidizes 11-cis retinol to 11-cis retinal, which can then bind to a lysine residue of opsin, via a Schiff base, to form rhodopsin. Hence, a deficiency in Vitamin A results in night blindness.



What is this structure? How can it help with night blindness?

The structure above is β-carotene. It is obtained from plants as a dietary source of Vitamin A. An enzyme, 15,15-dioxygenase, will metabolize β-carotene to retinal (theoretically yields 2 moles of retinal, but actually less since the enzymatic conversion is inefficient). Thus, it can be used for treatment of night blindness due to Vitamin A deficiency since it will help replenish 11-cis retinal levels to bind to opsin and form rhodopsin, which is essential for night vision.

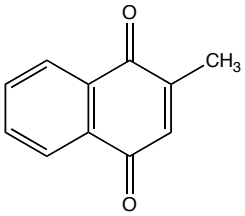
VI. A patient suffering from renal failure (diabetes) is also experiencing osteomalacia. Suggest a possible reason for the complication. Would Vitamin D be a suitable treatment for osteomalacia here? Why or why not?

Osteomalacia is a condition of bone demineralization as a result of calcium depletion. An activated form of Vitamin D, 1,25-dihydroxycholecalciferol (1,25-DHCC) aids in the uptake of calcium from the gut to the circulation. 1,25-DHCC is synthesized in the kidney through a metabolic pathway. In an event of kidney damage, the renal cells may not be able to form this active Vitamin D metabolite, reducing the amount of calcium uptake from the gut, in addition to the fact that there will be decreased calcium readsorption in the kidney tubules. These two factors will cause lower circulating levels of calcium and an increase in parathyroid hormone secretion, leading to increased calcium resorption (depletion) from the bone.

Vitamin D would not be a suitable treatment here because functional renal cells would still be required to do the metabolic conversion to the active 1,25-DHCC form. A better alternative would be to use 1,25-DHCC directly (Calcitriol).

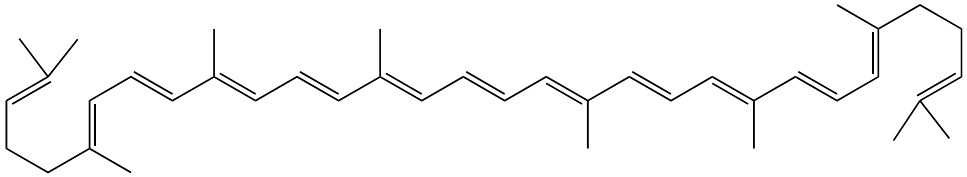
VII. Based on the following structures, suggest possible applications for the drugs.

1.



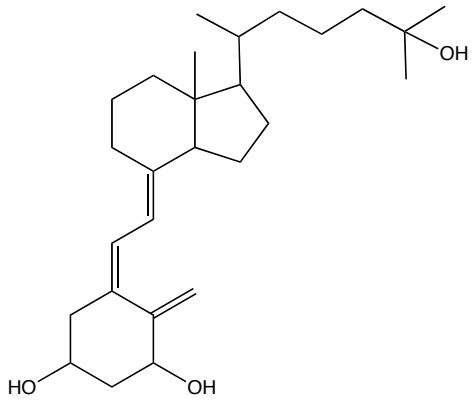
Menadione: Vitamin K analogue, but no intrinsic Vitamin K activity.

2.



Lycopene: Carotenoid found in tomatoes. No Vitamin A activity due to lack of β-ionone ring, but does have antioxidant properties and may help prevent prostate cancer.

3.



Calcitriol: Activated form of Vitamin D. Used to treat metabolic bone disease, resulting fromrenal failure.

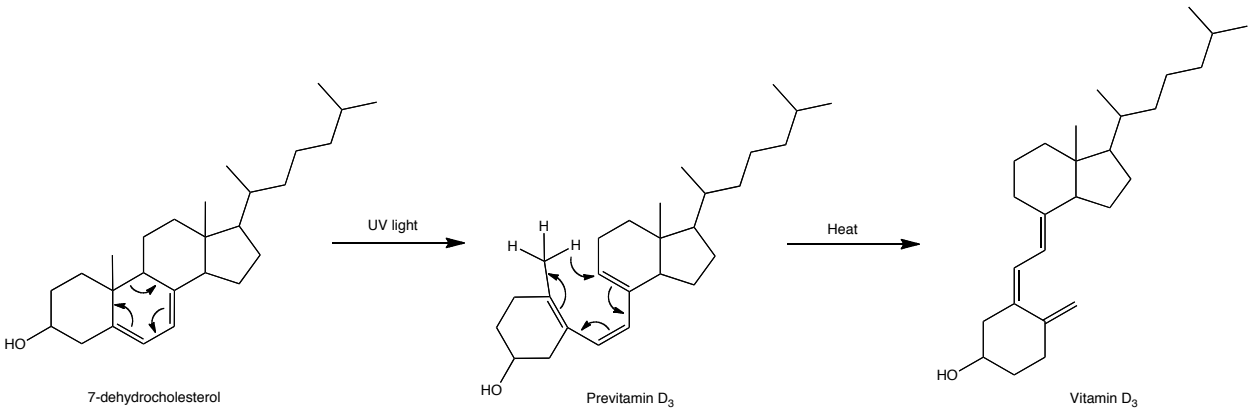
VIII. What would be a major risk of giving a Vitamin K antagonist in high doses (such as an anticoagulant like warfarin)?

Excessive bleeding since Vitamin K is necessary for normal blood coagulation. Vitamin K serves as a cofactor for the γ–carboxylation of certain glutamate residues on precursor clotting proteins.

IX. Briefly describe the role of Vitamin D in the body.

Vitamin D is a prohormone ingested from certain plants or synthesized naturally in the skin upon exposure to sunlight. It undergoes two hydroxylations (at the 25-position by CYP27A1 in the liver and then at the 1-position by CYP27B1 in the kidney) to the active form, 1,25-dihydroxycholecalciferol (1,25-DHCC). 1,25-DHCC acts as a hormone in regulating synthesis of Ca^{2+} binding and transport proteins at the gene expression level.

X. Draw an arrow-pushing mechanism for the conversion of 7-dehydrocholesterol to Vitamin D_3, including the structure for Previtamin D_3.



7-dehydrocholesterol Previtamin D_3 Vitamin D_3

WATER-SOLUBLE VITAMINS

XI. Match the vitamin or mineral with the corresponding recommended daily value amount and unit.

	Answer	Amount	Unit
1. Thiamin	h, x (1.5 mg)	a) 20	x) mg
2. Biotin	b, x (0.3 mg)	b) 0.3	y) µg
3. Folacin	e, x (0.4 mg)	c) 10	z) IU
4. Vitamin B_{12}	f, y (6.0 µg)	d) 1.7	
5. Riboflavin	d, x (1.7 mg)	e) 0.4	
6. Niacin	a, x (20 mg)	f) 6.0	
7. Pantothenic Acid	c, x (10 mg)	g) 60	
8. Vitamin C	g, x (60 mg)	h) 1.5	
9. Vitamin B_6	I, x (2.0 mg)	i) 2.0	

XII. In many cases, water-soluble vitamins 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.
Vitamin B_6 toxicity - 200 mg/day leads to increased prolactin; >1-2 g/day leads to neuropathy.
Niacin (B_3) toxicity - peripheral vasodilation, GI upset, ulcers, diarrhea, liver damage.

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

1. Increased plasma pyruvate – Vitamin B_1
2. Decreased erythrocyte glutathione reductase activity – Vitamin B_2
3. Increased plasma homocysteine – Vitamin B_6 or folic acid or Vitamin B_{12}
4. Increased urinary xanthurenic acid - Vitamin B_6

XIV. 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 doses of the vitamin?

1. Homocystinuria – Vitamin B_6 activates cystathionine synthase

2. Wernicke-Korsakoff syndrome – Vitamin B_1 (thiamin) activates transketolase

3. Methylmalonic aciduria – Vitamin B_{12} activates isomerase (methylmalonyl CoA to succinyl CoA)

XV. Elevated homocysteine is a significant risk factor for coronary vascular disease. What 3 vitamins are involved in homocysteine metabolism (thereby decreasing levels)?

Folic Acid, Vitamin B_6, and Vitamin B_{12}

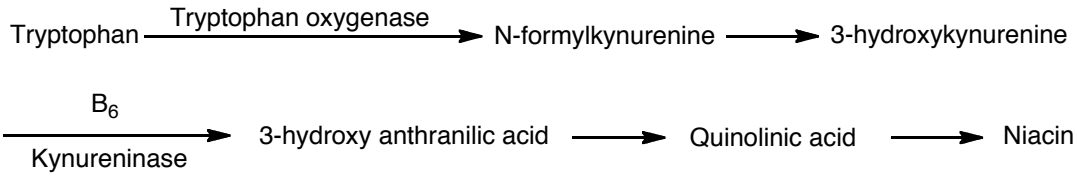
XVI. Which vitamins are associated with the following functions?

1. Decarboxylation – Vitamins B_1 and B_6
2. Transamination – Vitamin B_6
3. Purine and pyrimidine synthesis - Folic Acid
4. Electron transport – Vitamins B_2 and Niacin (B_3)
5. Niacin synthesis - B_6
6. Collagen synthesis – Vitamin C

XVII. Provide a metabolic explanation for the following (a scheme may be necessary for a cogent answer, but structures are not).

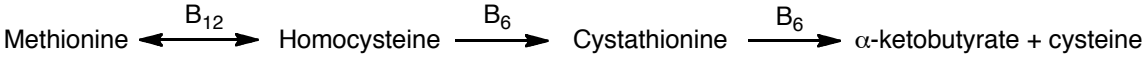
A. Niacin may be deficient if Vitamin B_6 intake is inadequate.

If Vitamin B_6 intake is inadequate, the conversion from tryptophan to Niacin may be blocked, resulting in Niacin deficiency.



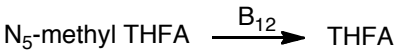
B. Homocysteine levels may be elevated if B_6 intake is inadequate.

B_6 is involved in the conversion of homocysteine to cystathionine to α-ketobutyrate and cysteine. If B_6 intake is inadequate, homocysteine levels will be increased.



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

B_{12} is required to convert N_5-methyl tetrahydrofolic acid (THFA) to THFA. If B_{12} is deficient, this conversion may not occur, and a folate deficiency will result.



XVIII. Why is it important that a woman who is pregnant or planning on becoming pregnant should receive supplemental folate?

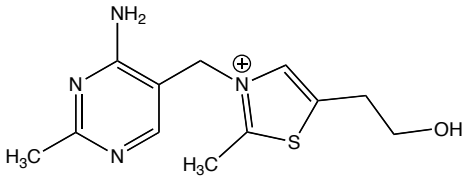
Folic acid deficiency early in a pregnancy could lead to teratogenesis with neural tube defects. It is recommended that women who are pregnant or are thinking about becoming pregnant receive the RDA value of 0.4mg/day folate.

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

Folic acid deficiency (anemia) can be caused by two conditions: lack of folic acid or lack of B_{12} (involved in the recycling of folic acid). By giving a high folate dose, nucleic acids will be synthesized even though folic acid is not regenerated in the process. Therefore pernicious anemia associated with B_{12} deficiency will be masked and nerve damage will progress irreversibly if not treated.

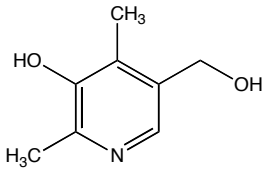
XX. The following are vitamin antagonists. For each:

1. Suggest the vitamin antagonized.
2. Suggest one symptom that you might expect with chronic administration of the antagonist.



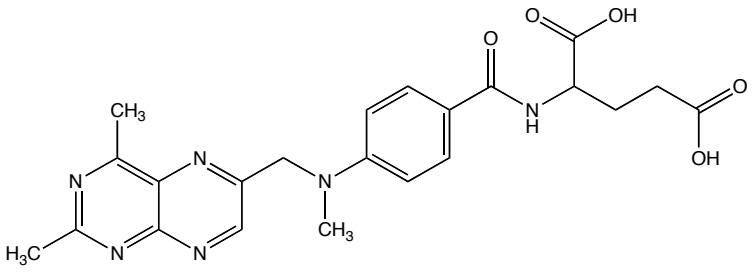
A. Vitamin B_1

B. Wernicke-Korsakoff syndrome (confusion, memory loss, etc)



A. Vitamin B_6

B. Peripherhal Neuritis



A. Folic Acid

B. Megaloblastic Anemia