1. Fill out the blanks in the table below.

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Physiological Function</th>
<th>Deficiency symptoms</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-Vision -Cell Differentiation -Inhibition of Cell Proliferation -Antioxidant Activity -Acne Psoriasis</td>
<td>-Night Blindness -Dry skin -Prone to infection -poor tooth development -slower bone growth</td>
<td>-Teratogenic (controversial) -Hypervitaminosis: Vomiting, hypercalcemia, brittle bones, fatigue, etc. -Increased risk of fractures (also a problem with low intake)</td>
</tr>
<tr>
<td>D</td>
<td>-Maintaining Calcium Levels -Modulation of cell differentiation and proliferation</td>
<td>- Rickets - Osteomalacia</td>
<td>- Calcification of soft tissues</td>
</tr>
<tr>
<td>E</td>
<td>-Antioxidant -Free Radical Scavenging</td>
<td>- Neuromuscular abnormalities - Myopathies - Hemolytic anemia in infants</td>
<td>- Adverse bleeding effect (rare) - Exacerbated bleeding when given with warfarin</td>
</tr>
<tr>
<td>K</td>
<td>-Blood Clotting -Inhibiting Artery Calcification -Bone Metabolism -Gla Protein formation -Post translational modification of glutamic acid residues</td>
<td>- Spontaneous hemorrhaging increase</td>
<td>- Allergic reactions</td>
</tr>
</tbody>
</table>
2. What are the key structural requirements for vitamin A activity of the retinol series of compounds?

3. Fill in the boxes for the pathway below:
4. Why might Vitamin A deficiency lead to night blindness?

Vitamin A is used in the rhodopsin visual cycle in rod cells found in the eye which help you see in monochromatic low light conditions. 11-cis-retinal bound to opsin is initially isomerized to all-trans retinal in a light dependent fashion. After releasing from opsin, all-trans retinal is then reduced to all-trans retinol via ADH-NADH. Esterification to all-trans retinyl palmitate leads to isomerization to 11-cis-retinol by retinoid isomerohydrolase. Oxidation by ADH-NAD$^+$ reforms 11-cis retinal which binds to opsin, reforming rhodopsin. A lack of vitamin A would reduce the ability to form new rhodopsin and lead to visual problems.

5. Name two good dietary sources of Vitamin A aside from carotenoid-containing plants:

Cod liver oil, Animal Livers containing retinol esters.

A: A patient is worried about hypervitaminosis A because he/she eats a diet high in carrots. Should he/she be concerned by vitamin A produced by the cleavage of β-carotene (found in carrots)? Why or why not?

No, he/she should not because conversion of the carotenoids to form retinals is inefficient as conversion decreases when body stores of vitamin A are high. The patient might experience yellowing of skin, but no negative symptoms associated with high levels of vitamin A. If the patient has high levels of vitamin A, he/she should avoid eating foods with large amounts of cod liver oil, beef liver, or polar bear liver.

6. The “Vitamin D” normally ingested is not a true vitamin. Please explain how this can be and identify the molecule responsible for the physiological effects of “Vitamin D”. Is it a hormone and what other vitamin can be considered as such?

Vitamin D is a provitamin, it’s converted to the active vitamin form in the body. The active metabolite 1,25 (OH)$_2$D$_3$ (a.k.a. Calcitriol) is the molecule that binds to the Vitamin D receptor and causes changes in gene expression. Hormones are molecules that are produced in one area of the body, enter circulation, and then exert effects on other areas of the body. By this definition, Vitamin D is a hormone because the dihydroxy form is created in the kidneys and circulates to the bones and heart. Vitamin A is also a hormone by this definition because retinoic acid is formed by enzymes in the liver yet functions in the eye and other organs.
7. Fill in the blanks on this diagram:

7-Dehydrocholesterol (Pro-vitamin D3) → Pre-Vitamin D3 → Vitamin D3

SKIN - lower epidermis
UV light
SKIN - Heat

LIVER
25-Hydroxylase
CYP2R1
CYP27A1

KIDNEY
1α-Hydroxylase
CYP27B1

Calcitrol acid
1,25 (OH)2 D3 (Calcitrol) Active Hormone
25-OH D3 (Calcidiol)

CYP3A4
CYP24A1

UGT1A4

1,23,25 (OH)3 D3
1,25 (OH)2 D3 Glucuronide
8. How is 7-dehydrocholesterol converted to Vitamin D3? Show this reaction.

In the skin when exposed to sunlight.

7-Dehydrocholesterol → Pre-vitamin D3 → Vitamin D3
9. Explain the relationship between Vitamin D and PTH.

Vitamin D (1,25 (OH)₂ D) is produced in the kidney by CYP27B1 and will increase absorption of calcium in the gut. Parathyroid hormone (PTH), when circulating in the blood, will increase synthesis of CYP27B1 which will increase levels of active Vitamin D.

When serum calcium concentrations are high, a G-protein coupled receptor (GPCR) will be activated. This releases the G-protein which will activate phospholipase C (PLC) which downregulates secretion of PTH. Eventually, serum calcium levels will lower enough to inactive the GPCR, stop PLC from inhibiting PTH secretion and allow PTH to increase Vitamin D levels again. This negative feedback loop prevents extremely high or low concentrations of serum calcium from occurring.

10. How many micrograms of Vitamin D need to be consumed to achieve the DV?

RDA of Vitamin D is 400 IU (where 40 IU = 1 µg). 400/40 = 10 µg must be consumed daily.

11. Menadione itself has no intrinsic vitamin activity, but can be activated by reaction with what endogenous constituent? What is the product of this reaction?

It is activated with geranylgeranyl diphosphate to make MK4, a K2 Vitamin.

12. Why is Vitamin K’s cofactor activity so crucial?

The reaction that Vitamin K assists in creates γ-Carboxyglutamic acid, which then goes to make many clotting factors. Without these clotting factors, people become hemophilic and are prone to bleeding out.

13. How exactly does warfarin exert its anticoagulant effects?

Warfarin inhibits the Vitamin K recycling process, lowering levels of Vitamin K in the body.
14. How is Vitamin K metabolized and removed from the body?

Vitamin K compounds are ω-hydroxylated by CYP4F2 and CYP4F11. Subsequent oxidative steps forms a carboxylic acid and K Acid 1. Multiple rounds of β-oxidation shorten the phytol chain and final conjugation of sulfate or glucuronide groups to the carboxylic acid allows excretion in the urine or bile.

15. Explain how vitamin E and Vitamin C can function together as antioxidants.

Vitamin E can be used to remove radicals from lipids

It’s regenerated with Ascorbic Acid (Vitamin C)

16. Explain why, from a chemical standpoint α-tocopherol is a more potent antioxidant than γ-tocopherol.

The methyl groups are electron donating, promoting the non-aromatic form, which helps with resonance
17. Why do tocotrienols not contribute to the daily Vitamin E requirement?

Tocotrienols do not possess the 2R configuration required for recognition by the α-tocopherol transport protein and therefore are not transferred into VLDL.

18. Which is the most toxic of the reactive oxygen species? Show how it can be generated from superoxide anion and hydrogen peroxide. What is the name of this reaction?

The most toxic reactive oxygen species is the hydroxyl radical. It is generated in the Harber-Weiss reaction with the aid of iron.

\[
\begin{align*}
\text{Fe}^{3+} + \text{O}_2^- \rightarrow & \text{Fe}^{2+} + \text{O}_2 \\
\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow & \text{Fe}^{3+} + \text{OH}^- + \text{OH}^-
\end{align*}
\]

19. Show how lipid hydroperoxides are detoxified by the glutathione pathway.

20. Which minerals and vitamins are critical to the proper functioning of the glutathione pathway?

Selenium, B2 (riboflavin), and B3 (niacin)