A Background on Vitamin A:

Have you got what it takes?

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Vitamins. We have all heard of them. Men's, women's, 50+, once daily. Vitamins are ubiquitous in clinical nutrition literature, in grocery stores, and on the news, but what exactly are they? Originally called vital-amines, vitamins are compounds (as opposed to trace elements) found in food that the body requires in small quantities to function properly. Vitamin deficiencies can cause a wide range of maladies that can be cured simply by replenishing the body with the lacking vitamin. The discovery that small amounts of vitamins can be used to cure certain diseases led to the Casimir Funk's proposal of the Vital-amine Theory of Disease. However, even though many diseases are caused by a vitamin deficiency, the opposite can also be true, in which case an overdose of a vitamin can cause disease and deformities.

Vitamins are either fat-soluble or water-soluble, which determines how they are transported through the body. Over-consumption is only a problem concerning fat-soluble vitamins, the category to which Vitamin A belongs. For the vitamin to be properly absorbed into the body from food, it must be absorbed alongside fat. Fat is absorbed through various organs: a properly functioning liver/gallbladder secretes bile acids to emulsify fat globules, the pancreas secretes lipase (a fat digesting enzyme), and the small intestine absorbs the nutrients. The process is complex and has high energy consumption, but is essential. Fat-soluble vitamins can be stored in the body's adipose tissue and liver for time periods up to months or years. Water-soluble vitamins such as vitamins B or C, on the other hand, are easier to absorb, but are easily excreted in urine. Thus, water-soluble vitamins are not stored in the body for any significant amount of time. The potential for long-term storage of fat-soluble vitamins can be useful, but also increases the risk of overdosing.

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We have traced the entry of vitamin A into the body, but where does it come from in the first place? As a fully formed vitamin, it is only found in foods of animal origin, especially liver, milk, and eggs. However, vegetables such as carrots and leafy greens, such as spinach, kale, and collard greens, have compounds called carotenoids, also referred to as pro-vitamin A because they can be converted to vitamin A in the body after ingestion.

Figure 2. Disproportionate limb regeneration in newts with increasing doses of retinoic acid.

Once inside the body, vitamin A, also called retinol, has many functions. First it is converted into one of two products: either retinal or retinoic acid. Retinal is produced in large quantities and is used by the body for vision-related purposes. Retinoic acid has a wider array of functions. It plays an integral part in maintaining growth and development, reproduction, the epithelial system, the immune system, and the nervous system. Vitamin A deficiencies and overdoses both wreak havoc on these essential body functions.

One of the reasons why vitamin A overdose can cause issues is because it is a teratogen, a compound that, when consumed in excess, can cause developmental disorders. A striking example of the teratogenic capabilities of vitamin A is shown in an experiment that examined newt limb regeneration (Dmetrichuk, Spencer, & Carlone, 2005). When a newt with an amputated limb is given one dose of vitamin A, it is able to properly regenerate the

ulna and radius bones of its wrist. When given two doses, it generates two sets of ulna and radii. Given three doses, it regenerates three sets, and so on with correspondingly increasing doses. While adult humans can't regenerate limbs, a human fetus undergoes rapid and drastic development, and vitamin A overexposure can have similar effects during this critical time. Before the harmful teratogenic effects of vitamin A were known in the medical field women who had skin afflictions such as cystic acne or psoriasis vulgaris were often prescribed high oral doses of vitamin A. Of the pregnant women who used these drugs, 84% had a child with structural deformities, such as extra arms and legs (Adams, 2010). Once these adverse affects were realized, doctors began to follow strict measures to ensure that their female patients were not pregnant before prescribing drugs high in vitamin A.

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Another study that was conducted to explore the negative affects of vitamin A overdose was the Hisayama study (Miyazaki et al., 2011). Researchers followed a large Japanese population and found that the incidence of gastric cancer rose progressively with increasing levels of dietary vitamin A. The internal location or histological type of the cancer didn't have any effect of the rate of incidence. The scientists who conducted this study inferred a causal relationship, stating that the increase in vitamin A consumption led to increase in gastric cancer, but it could be a purely correlational effect. People who consume large amounts of dietary vitamin A are likely to be consuming large amounts of meat products, as they are a major source of the nutrient. The boost in rates of cancer could be caused by rising meat consumption.

Currently the recommended levels for vitamin A consumption are 900 International units (IU) for males and 700 IU for females. An international unit of vitamin A amounts to 0.3µg. Too much or too little vitamin A can give rise to an assortment of health problems.

One of the first signs of vitamin A deficiency is night blindness, medically known as nyctalopia. Blindness can occur when the nerve cells in the eye do not function properly. The retina of the eye is made up of two main types of nerve cells: rods and cones. Cones are used to see color and perform best under bright light. Rods, on the other hand, aren't meant to detect color, but can function well in dim light, and are the cells that are critical for night-time vision. For the visual cycle to progress properly, vitamin A interacts with a protein called opsin in the retina to produce the complex rhodopsin. Conformational changes in rhodopsin are needed to send electrical signals to the brain which are then interpreted as vision. When vitamin A levels are deficient, rhodopsin complexes do not form properly. Although rhodopsin is used in both day and night-vision, it is sight in dim lights that is affected first and more severely.

Another vision related problem that arises for vitamin A deficiency is a disease called Xerophthalmia. Rather than affecting the visual cycle, however, this disease causes the epithelial cells of the cornea to degenerate. Death of these cells causes a layer of white, dead tissue to form over the eye, occluding vision.

Epithelial tissue is not just found in the eye, however. It is present in various parts of the body, most commonly in protective layers such as skin or the lining of internal organs. Excessive skin wrinkling has been found to be a problem in diabetic patients with vitamin A deficiencies. Retinoic acid (RA), one of the two compounds that vitamin A turns into in the body, promotes the integrity of skin. RA enhances the tightness of the topmost

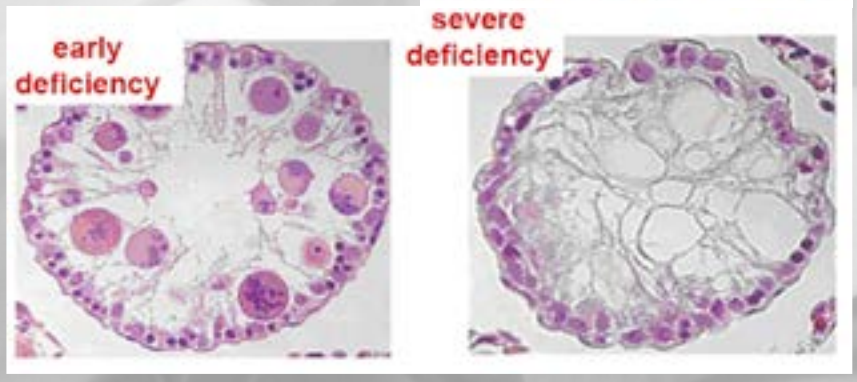

Figure 1. Cross-section of seminiferous tubules under the normal, early vitamin A and severe vitamin A deficiency.

protective barrier of the skin, allows for interdigitation (finger-like locking) of the dermis and epidermis layers, and increases the number of melanocytes (pigment producing cells that help skin tan) in the epidermis layer. RA also induces the production of collagen in the dermis, which gives the skin elasticity, upregulates cell growth, and inhibits the differentiation of epidermal cells skin tissues. A study on mice found that there are two proteins, matrix metalloproteinase and hyaluronidase, which are very important for normal skin maintenance. However, overexpression of these proteins leads to excessive skin wrinkling (Takahashi & Takasu, 2011). How does vitamin A play into this scenario? Rats that were vitamin A deficient in this study naturally had much higher levels of both metalloproteinase and hyaluronidase. Also important is the fact that diabetic rats have much lower blood levels of retinoic acid than non-diabetic rats. When supplemented with exogenous retinoic acid, the diabetic rats' skin condition improved. Although this study has yet to reach the level of human testing, it is reasonable to think that there may be a connection which could possibly lead to a cure. Vitamin A deficiency could, in this case, be exacerbating some of the symptoms of diabetes Supplementation in humans could resolve this side effect of diabetes as supplementation in rats does.

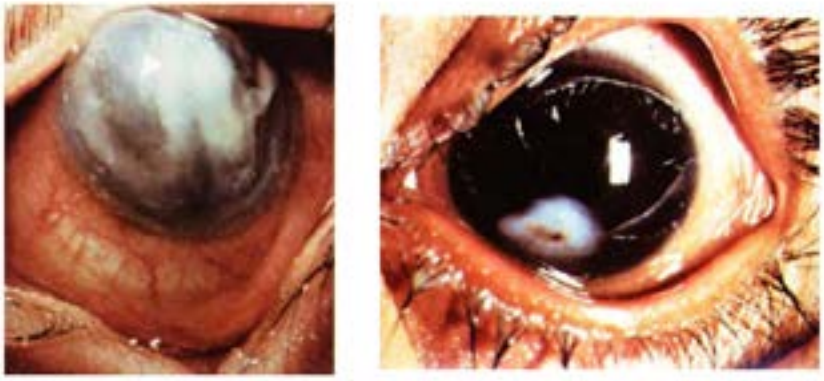

Figure 3. Xerophthalmia: a disease of the epithelial tissue in the eye caused by Vitamin a deficiency

Vitamin A also plays an essential role in the reproductive system of both males and females; deficiency can cause sterility in both sexes. Inadequate vitamin A in males causes deformation of the seminiferous tubules, resulting in the formation of abnormal, infertile, multinucleated sperm. In females, inadequate vitamin A intake leads to inability to conceive, improper formation of the placenta, and developmental defects in the fetus. Observational studies show that when a fetus does manage to develop in the womb of a vitamin A deficient mother, there is a much higher risk of mother to child transmission of HIV infection (Wiysonge et al., 2011). Although there are many factors affecting mother to child HIV transmission, it seems that proper vitamin A consumption could help to reduce this issue.

Given the severity of the negative effects of vitamin A deficiency, the question that naturally follows is: how can the human body protect itself from this shortage? Surprisingly, there are not any common cravings in response to inadequate dietary intake. In response to severe deficiencies of other nutrients, such as iron and zinc, the body usually responds by causing the development of a disease called pica, in which the deficient person starts to crave things that are not usually considered food, including dirt and ice. These abnormal cravings try to bridge the gap of the nutrient deficiency. However, pica does not occur with a vitamin A deficit. One of the reasons for this lack for a coping mechanism may be that it is fairly difficult for a person with a complete and well-rounded diet, living in an economically developed society, to become deficient in vitamin A, since the nutrient can be stored in the body's fat deposits and the liver for long periods of time. One study showed that people in England can go for years at a time without any vitamin A intake and show no adverse affects because they can utilize their already stored amounts of the vitamin (Senoo et al., 2010). Also, when they do start showing negative effects, they can reverse all of the damage by consuming the vitamin again, even in small quantities. This is not always possible, however, especially in countries where starvation and famine are major issues. The inherent lack of food, especially meat products, can lead to wide-spread and severe vitamin A deficiencies. This is often overlooked, though, because of the larger, overarching problem of starvation.

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Despite the body not having molecular coping mechanisms, communities have developed ways to deal

with vitamin deficiencies. While in developed nations doctors can diagnose deficiencies and prescribe pills, cultural home remedies also exist in other countries that follow this same thought process. One example is in Northern Niger. When signs of vitamin A deficiency are noticed in patients (mostly night-blindness), the first recommendation is an increase in consumption of liver, mean, and green leaves, all foods that are high in vitamin A (Blum, Pelto, & Pelto, 2004).

Another way that communities have approached vitamin A deficiency is through a product called Golden Rice. This rice is a genetically modified grain which contains up to 35 micrograms of B-carotene per gram of rice. Natural rice does not have any vitamin A, so populations that have high carbohydrate, low meat diets (such as Southeast Asian populations), have a high chance of vitamin A deficiency. Vitamin A from Golden Rice is equally well absorbed and used in the body as vitamin A from other natural sources (Tang et al., 2009). Using it to deliver the nutrient to certain population is a good method because it does not force communities to change their cultural diet, but ensures proper vitamin a intake.

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Micronutrient deficiencies such as vitamin A deficiencies can be a major issue in the world, but are often ignored, until they start presenting major symptoms. Understanding and moderation are key. Education about vitamin A is crucial, as are efforts to raise awareness and make sure that all populations have equal opportunity when it comes to vitamin A intake.

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