

# Vitamin A and Beta-Carotene

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## Introduction, Apology and Definition of Terms

In our reductionistic habit of thought, we scientists tend to isolate substances, name them, split them apart again and then rename the subsequent parts *ad infinitum*. This indeed has proven to be a productive endeavor but, when applied to the question of nutritional medicine, this manner of thought, this “refinement” as it were, carries with it the risk of losing sight of the whole, the natural, organic food and therefore, of forfeiting that which is nutritive. In that light, I therefore commence with an apology to the reader for my focus, in this article, on single substances (vitamin A and beta-carotene) discussed out of their as yet incompletely elucidated biochemical context. Please understand that the account which follows should be considered imperfect to the degree that it ignores these vitamins’ as yet undiscovered vitamers and co-factors. Also, we might agree at the outset, any analysis concerning the effects of a substance such as vitamin A or beta-carotene is suspect to the degree that it gives short shrift to the myriad variables which our patients—complex and ever-changing biochemical individuals one and all—bring to the examination table.

Those disclaimers aside, let’s define some terms: What is a vitamin? We might begin to answer that question in recalling the work of the Polish biochemist, Casmir Funk who, in elucidating the nature of thiamin, generalized his finding of that single “vital amine” and coined the term “vitamine” to encompass all the “accessory factors required for health aside from fats, carbohydrates and proteins.” Sir Fredrick G. Hopkins (Nobel

Laureate, Medicine, 1926 and discoverer of glutathione and tryptophan) noted in 1906 that: “no animal can live on a mixture of pure protein, fat and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal is adjusted to live either on plant tissues or the tissues of other animals and these contain countless substances other than pure protein, carbohydrates and fats.” So, we are concerning ourselves with potent substances which, in proper dosages, support life and promote the enjoyment of optimal health and function but, when absent or deficient render life and productivity itself unsupportable. (Compounding this orientating definition however, is the fact that both vitamins A and D seem also to act as hormones.)

Vitamins, as we know them today, serve four primary biological functions – membrane stabilization, potentiation of hormonal activity, hydrogen/electron donors/acceptors and co-enzyme functions. vitamin A is the generic term for that class of compounds with the biologic activity of retinal and it occurs in nature in three primary forms: retinol, retinal and retinoic acid—the alcohol, aldehyde and acid forms respectively. The retinal activity is a co-enzymatic function involving creating visual purple via a conformational change in rhodopsin (pigment in retinal rods) and opsins (pigment in retinal cones) subsequent to light-induced bleaching. Possessing a large number of double bonds, vitamin A distinguishes itself as being the only known human molecule that can absorb photonic energy (light) and create a new physical bond *de novo* along its backbone of conjugated polyene systems. That, itself, merits our incredulity, being as close as we come to photosynthesis.

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## Forms of Vitamin A

Vitamin A was discovered by E.V. McCollum at the University of Wisconsin (1913-1915)—he also discovered vitamin D and was named Mr. Vitamin by *Time* magazine in 1951—after noting that this new substance prevented xerophthalmia (dry eyes) and night blindness in laboratory rats. Accordingly, the most common physiological association with vitamin A has been visual function which utilizes the retinal form exclusively. However, subsequent research demonstrated that vitamin A deficient animals died prematurely and we now know that the vital effects of systemic vitamin A require primarily the long chain fatty acid retinyl ester (predominately retinyl palmitate) form which is transported in chylomicrons and distributed lymphatically. Both vitamin A and beta-carotene are available for consumption in natural forms (foods and food extracts) as well as in synthetic and analogue forms. Clinical practice seems to indicate that potency and efficacy vary considerably.

## Sources

Vitamin A can occur naturally in animal tissue as the bio-available, pre-formed isoprenoid compounds (retinoids). Animal foods highest in vitamin A include beef liver (10,503 IU/100 g), butter (754 IU/100 g), egg (552 IU/100 g), and fish flesh (mackerel, 130 IU/100 g). Of course, unless these animal products are organic, they can accumulate pesticides, heavy metals and other toxins and therefore are typically unsafe to consume on a regular basis. Another consideration in sourcing vitamin A is quite simply that most anything that goes rancid has some vitamin A. Things that inhibit absorption of vitamin A include high protein diets, antacids (especially those containing aluminum) and most rampantly in the elderly population, laxatives which inhibit absorption of all fat-soluble vitamins (A,D,E).

Another source of vitamin A is the class of isoprenoid plant pigments, the carotenoids, numbering over 500 but of which beta-carotene is of primary importance to humans since it, when cleaved by the soluble enzyme beta carotene 15,15-dioxygenase (situated within cells of human mucosa, liver and corpus luteum) yields two vitamin A molecules thereby earning the designation “pro-vitamin A.” Good food sources are orange or yellow vegetables and fruits. One cantaloupe offers four times as much beta-carotene as one carrot. Broccoli is another good source of vitamin A, but the chlorophyll (green) camouflages the yellow carotene color. If it weren't for chlorophyll, broccoli would be yellow or orange.

Of primary importance, on the other hand, to the old world chameleon, are the other 400-odd carotenoids which it ingests by feasting on exotic bugs which themselves have eaten myriad plant isoprenoid pigments. Once within the chameleon, not only do these carotenoids sequester themselves within reptilian dermal cells (prismatically formed to magnify the color changing effect) but they directly support osteoblastic activity. Now you know why these magnificent lizards rarely survive captivity; without the exotic plants and bugs, their diet offers inadequate carotenoids and their skeletal structure fails them causing fatal electrolyte imbalances.

Returning to human concerns, we accept exogenous “dietary” vitamin A in two distinct forms: “ready-made” retinoids from tissues or milk of animals or “disassembly-required” beta-carotene or pro-vitamin A from vegetables. Both the free retinal and the intact beta carotene diffuse passively across our mucosal membranes in a process facilitated by dietary fat and inhibited by starvation (actual starvation involving inadequate fats and proteins; iatrogenic starvation involving laxatives such as mineral oil, cholesterol lowering statin drugs and antacids which

inhibit digestion and absorption). Biliary, pancreatic or hepatic diseases can also inhibit absorption and compromise utilization of fat soluble vitamins (A, D, E, K) via similar mechanisms. Primary among the rate limiting minerals for the utilization of vitamin A include zinc, selenium and manganese. Nonetheless, the most common source from which most of us get our RDA of 5,000 IU of vitamin A is our own liver which has the capacity to store up to two years worth of vitamin A at a time.

### Consideration of Vitamin A's Risk/Benefit Ratio

The warnings about vitamin A/beta-carotene resolve themselves into two criteria: toxicity from retention of fat soluble vitamins in general, and concerns about disease promoting effect in particular (i.e. cancer promotion and increased fracture risk). We will address each of these in turn.

One cannot read about vitamin A without being warned against taking too much of this substance and yet "too much" remains poorly defined and is currently a source of much debate within nutritional circles. The rationale for caution is easily understood—fat soluble vitamins (A, D, E and K) are not excreted as copiously and frequently as are the water soluble vitamins (the Bs, folate, biotin and C), so they tend to accumulate and can reach toxic levels over time. The logic for limiting vitamin A dosage to 10,000 IU a day therefore is quite clear. However, clinical practice yields a more ambiguous picture. Reports of mega-dosing of vitamin A palmitate for specific orthomolecular indications have informed us of vitamin A's remarkable abilities when given in high doses. Typical of these prescriptions is 200,000 IU given daily over 10 years by Dr. Fred Klenner of Reidsville, N.C. (as reported in the *Medical Tribune*) which at the time of printing, had restored healthy skin to what had been a case of ichthyosis.

Klenner himself took at least 75,000 IU daily for 15 years with no toxicity. These are extreme cases which are worth considering in that they remind us of Roger Williams' tenet of biochemical individuality. Those doses may not be appropriate for everyone and the practice of taking far more than the RDA for vitamin A should not be done without the consultation of a knowledgeable health care practitioner.

Sometimes, however, conservative low dose consistent with the RDA is not enough to achieve a targeted therapeutic effect. Arany et al.<sup>1</sup> observed that all-trans-retinoic acid dose-dependently suppressed the growth of cervical carcinoma cells via a sustained activation of interferon regulatory factor 1 and activation caspase-1 in cervical carcinoma cells. This anti-cancer effect was achieved by high-dose ( $10^{-4}$  M), but not low-dose ( $10^{-6}$  M) treatment constituting yet another justification for dose modification to address specific biochemical goals.

Another recent concern about excess vitamin A involves the statistical correlation of fracture and vitamin A as reported in *JAMA* and the *New England Journal of Medicine*.<sup>2,3</sup> To summarize, one notes that the lowest and the highest quintile of vitamin A consumers had an increased risk of fracture whereas, curiously, those in the middle three quintiles did not. Scientific studies are always challenging in that all confounding variables are difficult to comprehend and account for and as Drs. Cranton and Meiss comment in their excellent apology for retaining the current RDA for of vitamin A: "Statistical correlation, if it exists, is never by itself evidence for cause and effect."<sup>4</sup>

The suggestion that vitamin A might be responsible for an increased fracture rate flies in the face of the understanding of vitamin A's primary effect on bone metabolism: vitamin A deficiency reduces the number of osteoclasts resulting in excessive

deposition of periosteal bone by the unchecked activity of osteoblasts. The subsequent reduction in the degradation of bone-related glycosaminoglycans would also confound anyone claiming that vitamin A toxicity is a risk factor for fracture.

Furthermore, the reader will recall that vitamin A and vitamin D can act antagonistically in general (competition for fat absorption) and in particular (as regards bone metabolism).<sup>5</sup> Any study which discussed vitamin A and fracture risk without addressing the variables of seasonal light and its degree of activation of endogenous vitamin D3 (cholecalciferol) as compared with vitamin D2 (the yeast ergosterol which is often used to fortify dairy products) should be deemed preliminary at best. Furthermore, to attribute the fracture rate to vitamin A in the face of clear scientific evidence that protein rich dairy "liquid meat" has been repeatedly correlated to fracture rate and osteoporosis is naïve at best. (Yes, you read that last line correctly, contrary to the message drummed into us by the American Dairy Council, milk consumption causes osteoporosis and increased hip fractures.<sup>6</sup> In part, this is due to its high protein content which acidifies the blood thereby requiring calcium ions to be released from body stores (bone) in an effort to buffer the sudden increase in blood acidity. Therefore, before proposing vitamin A as the culprit for an increased fracture rate, I would have expected the authors to have considered both the role of seasonal light on vitamin D metabolism as well as the role of high protein dairy consumption as causal agents of fracture.

Now we will consider the question of whether beta-carotene is cardiotoxic (both alone and in combination with other multivitamins including vitamin E) which was debated most recently in the *Lancet*<sup>7</sup> where a careful reading of the discussion reveals a disturbing lack of

scientific rigor. Paolini et al.<sup>9</sup> intelligently critiqued the conclusions of a meta-analysis by Vivekanathan et al.<sup>8</sup> by offering common-sense caveats against extending conclusions from one type of study to another. Vivekanathan et al. had concluded that there was no beneficial effect from vitamin E or beta-carotene supplementation in terms of prevention of cardiac events and went so far as to conclude: "the use of vitamin supplements containing vitamin A and beta-carotene should be actively discouraged."<sup>8</sup> Paolini et al. noted that this conclusion "contrasts with those of preclinical and epidemiological studies" and cautions that opinions regarding the use of multivitamin combinations should be voiced only after meta-analyses have been concluded on these very combinations (as opposed to applying conclusions from single vitamin studies to the effects which those vitamins may demonstrate when delivered in combination with other vitamins and co-factors).<sup>9</sup> Paolini notes that while beta-carotene is an effective trap for singlet oxygen, it is not a potent chain-breaking anti-oxidant. He also reminds the reader of further complexities which might give the careful scientist pause before generalizing conclusions from one study to those involving different variables. For example, Paolini acknowledges that beta-carotene when operating within a context of low partial pressure oxygen can contrast lipid peroxidation whereas it can propagate lipid peroxidation at normal concentrations of oxygen.<sup>9</sup> This word of caution echoes my caveat with which I began this article that discussion of a single vitamin, divorced from its endogenous biochemical context, can be misleading at best and dangerous at worst.

Paolini's appeal for restricting conclusions to those alone which arise through scientific methodology is refreshing. Unfortunately, when invited to

respond to this considered critique, Vivekanathan et al. disappoint by failing to address the query, choosing rather to hide behind precedent and citing a prior paper which itself leaves much to be desired from a scientific perspective.<sup>10</sup>

In summary, these studies which attempted to link vitamin A and beta-carotene to an increased incidence of fracture and cardiac risk were seriously flawed and their uncritical acceptance in the referenced prestigious journals is cause for not a little concern.

### Cancer and Medical Reporting

Because of its well-documented antioxidant and antigenotoxic properties, beta-carotene gained most of the carotenoid attention in the early 1980s and became one of the most extensively studied cancer chemopreventive agents in population-based trials supported by the National Cancer Institute. One of the primary biological anti-cancer benefits of carotenoids is that they confer nuclear protection against intracellular damage.<sup>11</sup> Today, vitamin A and its synthetic retinals are considered among the more promising realms of cancer therapeutics. The chemotherapeutic agent retinoic acid and its derivatives have been used to treat many tumor types. Their anti-tumor effects are due in part to their ability to inhibit proliferation of cancer cells.<sup>12</sup> Therefore, many of us were perplexed by the negative findings of the Carotene and Retinol Efficacy Trial (CARET), (18,314 heavy smokers, former smokers, former asbestos workers given 30 mg synthetic beta-carotene and 25,000 IU of vitamin A or placebo for 4 years) and The Physician's Health Study (22,071 physicians given either 50 mg synthetic beta-carotene or aspirin for 12 years) and The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, aka "The Finnish Study" (29,000 middle aged, 57.2 years, male Finnish

smokers, over a pack a day for 36 years, given 20 mg, or 33,000 IU, of synthetic beta-carotene). These studies reported in general that beta-carotene not only did not confer benefit, it resulted in an increased cancer rate when compared to the group which did not receive a beta-carotene supplement.<sup>13</sup>

In the face of hundreds of studies concluding the opposite (beta-carotene lowers cancer risk), what is a doctor to think when a patient shows him the front page of *The New York Times* from January 18, 1996? That is correct—doctors read it first in the newspaper for, consistent with a rather distressing trend in science today, the results of both the CARET and the Physician's health studies were announced at a Press Conference on January 18, 1996, before either study was published or scheduled for publication. The scientific method—time honored and essential for responsible growth of knowledge—requires diligent effort by investigators and then a frank publication of all resulting data and complete methodology in order that the all-important peer review process may separate the wheat from the chaff. To publish in the lay media prior to peer review is an increasingly common, economically driven abrogation of the scientific process constituting a disservice to the public who read "Vitamin Supplements Are Seen as No Guard Against Disease," on the front page of *The New York Times* (4/14/96). In an unprecedented move, over the objections of the *New England Journal of Medicine*, ABC scooped the prestigious medical journal and used the non-scientific announcement as its lead item for its Evening News that night. The curious observer might note the political economic reality in 1996: a majority of Americans were voting with their wallet and had turned their back on pharmaceutical drugs in favor of nutritional supplements and orthomolecular medicine. This shift in the mar-

ket prompted a response from pharmaceutical companies (delivered via the lay media and through peer-reviewed professional journals) which amounted to a smear campaign. On the political front, a domestic war was ablaze in the U.S. Congress concerning the federal Dietary Supplements Health Education Act (DSHEA) which was enacted over the objections of the Food and Drug Administration (FDA) and allowed the public to retain the right to access nutritional supplements. So, one must appreciate that since the demise of the amateur scientist, scientific methodology always serves a (paying) master and can be used for political economic ends.

Another challenge of responsible research is to consider and report "confounding variables" which might be responsible in part for the declared outcome of a study. In the Finnish study, some significant confounding factors were never considered or reported. These include the incidence of alcohol consumption, the preponderance of a diet high in animal fat and the lack of sunlight—all of which are considered well-known co-factors for cancer. Curiously, the subjects were given 20 mg per day of synthetic beta carotene colored with a known carcinogen, quiniline yellow. More ominously, we recall that this study began soon after the Chernobyl nuclear disaster, and according to Marjorie A. Laughlin, M.D., in a letter to the *Times* (4/28/96). "Finland was one of the first areas to receive heavy fallout." A clearly carcinogenic co-factor was neither considered nor mentioned in either the media blitz or the (later to be published) research paper itself.

A final word on bias relates to the fact that the vitamin A group received a clear reduction in prostate and colorectal cancers as well as a mild reduction in lung cancer, but that positive data was not featured for the American public. Nor were people told the conclusions of the authors of the study themselves whose last words

on this topic are important to consider. "No other studies have shown any harm from taking beta carotene, whereas many studies have shown benefit;" "There are also no known mechanisms for toxic effect" and "no evidence of serious toxic effects of this substance in humans." Their overall study conclusion reads: "In spite of its formal statistical significance, therefore, this finding may well be due to chance."

Barron et al.<sup>14</sup> noted in two large, randomized prevention trials, supplementation with beta-carotene increased the risk of lung cancer in two large, randomized trials whose subjects were predominantly cigarette smokers and consumers of alcohol. The suspicion was that beta-carotene used in conjunction with these life-style habits increase the risk of cancer whereas, when taken alone did not. They concluded that beta-carotene was associated with a marked decrease in the risk of one or more recurrent adenomas among subjects who neither smoked cigarettes nor drank alcohol, but for participants who smoked cigarettes and also drank more than one alcoholic drink per day, beta-carotene doubled the risk of adenoma recurrence. At this point, again, not factoring in other nutritional and life-style parameters, we are left with the statistical correlation that alcohol intake and cigarette smoking appear to modify the effect of beta-carotene supplementation on the risk of colorectal adenoma recurrence.

A voice of common sense, Paolioni et al. concluded in favor of public health consensus that a diet rich in a variety of fruits and vegetables is healthy but warned against a possible detrimental effects of certain isolated dietary supplements and called for further study.<sup>15</sup>

Beta-carotene's anti-cancer properties have been vindicated in many other studies. Pradeep et al., for example, recently noted that beta-carotene inhibited lung

metastasis induced by B16F-10 melanoma cells in the C57BL/6 mice model by 71% compared to controls due in part to a reduction of pro-metastatic agents including hydroxyproline, hexosamine, sialic acid and uronic acid. These researchers demonstrated a potent antimetastatic activity of beta-carotene as have many other investigators.<sup>16</sup>

As far as the Finnish study is concerned, we know from many other studies that smoking decreases serum levels of all carotenoids and that the reduction was statistically significant for beta-cryptoxanthin and beta-carotene. We also know that most foods containing beta-carotene also contain other potent members of the carotenoid family such as alpha-carotene, lycopene, zeaxanthin and lutein and current work suggests that these are more beneficial than beta-carotene though the latter received most of the early praise.<sup>17</sup>

When Wright's group at Yale posed the question about the effect of specific dietary carotenoids and their primary plant food sources on lung cancer risk in a population-based case-control study of women, they determined that consumption of a wide variety of vegetables has a greater bearing on lung cancer risk in a population of smoking and nonsmoking women than intake of any specific pill containing carotenoid or total carotenoids.<sup>18</sup>

The distinction of synthetic vs. natural beta-carotene merits some attention especially for those who think that the difference matters only to romantics. Natural beta-carotene presents with a 50-50 mixture of "all trans" and "9-cis" beta-carotene whereas the synthetic form is exclusively "all trans." Gaziano et al. have demonstrated that the natural form has superior absorption and function compared to the synthetic version.<sup>19</sup> Of note is that none of the three studies reviewed above used natural or mixed carotenoids (alpha-carotene, lycopene, zeaxanthin and lutein) which appear to be the more potent anti-cancer agents.<sup>20</sup>

We see the wisdom of eating naturally

occurring nutrients in the context of whole foods rather than always attempting to extract the active principle and using that to the exclusion of many as yet undiscovered co-factors. In terms of context, I recall a story a friend told me of his research in the Amazon as an understudy to a powerful shaman. Once, early in his relationship with the shaman, when presented with a complicated prescription of rainforest herbs used in the treatment of cancer, my friend the ethnobotanist inquired of the shaman: "Which of these are the most essential herbs for this protocol?" To the western reductionistic mind, that is a reasonable question. To the shaman, however, it amounted to an insult not less offensive than a slap in the face. When the shaman turned and walked away without a word from the interview, my friend inquired of the shaman's assistant (perhaps a "resident" shaman?) whether he had insulted his teacher. The response was "Of course you insulted him. Why would you think that he would use any herbs which are not essential?" Equally so, a bit of humility might be in order as we learn to utilize natural substances; probably things are created with very little waste and powerful as beta-carotene is, one might be better served by eating it within an organic vegetable context rather than taking a synthetic form in a pill.

Logically, therefore, considering the above analysis, we are well advised to note the real role for beta-carotene in tobacco-related cancers. First of all, doctors should get their scientific information from peer-reviewed literature rather than from *The New York Times*. Secondly, doctors should advise those at risk for tobacco-related cancers as follows: "If you have an oral fixation, swap the cigarette for a carrot." For herein lies the real connection between beta-carotene and cancer: chewing the carrot offers non-synthetic, full-spectrum carotenoids which have been proven to reduce cancer risks and furthermore, the carrot is free of quinoline yellow and not

laced with radioactive fallout from Chernobyl. However, even an organic carrot cannot reduce the profound cellular damage done by tobacco so we come round again to the all-important focus on diet and lifestyle. Eat right, exercise, stop smoking and drink only in moderation if you want to stop growing cancer.

### Vitamin A Toxicity

Beta-carotene aside, in considering the risks of overdosing on vitamin A, let's remember the wise words of Hippocrates: "Poison is a matter of dosage" and determine to always practice "medicine by Braille" meaning, give a dose and then stay in "close touch" with the patient in order to gather ample data with which to modify protocols responsibly. We can agree that Mae West's famous quotation, "Too much of a good thing is wonderful," applies delightfully to many things in life but not to vitamin A, which history teaches us can be lethal above a certain dose. In what must rank as one of the worst examples of gauche American tourists ignoring local customs, we recall the story of hungry, arctic explorers who made the mistake of eating polar bear liver (1 million units/gram) and, we assume, never got around to dessert. We now know that animal sources (retinal) are six times more potent than vegetable sources (beta-carotene) a lesson that was not lost on other explorers, most notable S. Stefansson. This more observant "tourist" learned from natives not to eat the liver of arctic animals. In his book *My Life with the Eskimos* (1906), Stefansson records the best way to cook arctic meat: "...according to Eskimo custom, you put the meat into cold water, bring it to a boil, take it off the heat and allow it to cool. You then scrape the fat off the top of the water, drink the remaining juice and eat the meat." In this way, without knowing the name of the fat-soluble vitamin so concentrated in livers, Stefansson kept the vitamin A dosage well within a tolerable range for consumption.

Levels above 100,000 IU of vitamin A are considered toxic (hypervitaminosis) but clinical protocols for skin problems (acne, psoriasis, hyper-keratosis, ichthyosis), visual problems (xerophthalmia, night blindness), and immune deficiencies (viral infections, bronchitis, mucosal resilience), require much higher doses for a discrete period of time in order to bolster vitamin A dependent metabolisms. The signs of excess vitamin A include hair loss, erythema, desquamation, myalgias and headaches as well as mucous membrane reactions including cheilitis, stomatitis and conjunctivitis. The warning signs of vitamin A saturation in the liver include developing a yellow/orange tint to the skin and even the whites of eyes. If this happens, discontinue the vitamin A supplements and the yellow coloring in the whites of your eyes, palms of your hands and soles of your feet will go away in a few months – except for infants. In their case, excessive vitamin A can be lethal. Generally, carotene will turn the skin yellow when the intake is above 20 mg per day (about 34,000 IU) and when consumption is discontinued, no damage results.

Having clarified the risks of vitamin A and beta-carotene, we can now consider the benefits.

### Vitamin A Benefits

In answer to the question, "Who would benefit from supplementation with vitamin A?" we can simply respond from the orthomolecular perspective, "Everyone who is deficient in vitamin A would experience enhanced health and vitality when given a dosage that replenishes their deficiency." Who are these people? You and I, perhaps? The clinical signs of vitamin A deficiency are all around us and they include a generalized loss of appetite and muscular stamina, retarded growth, a drying and keratinization of skin and mucous membranes as well as dry and rough feeling hair. X-rays may show periosteal overgrowth

which can manifest as sciatica since vertebral foraminae can narrow in this condition. The ocular signs, however, are as tragic as they are pathognomic – xerophthalmia (dryness of conjunctiva), crusting and the eventual Bitot's spots (“cheesy” deposits on the conjunctiva near the cornea) all presage easily preventable infant and childhood blindness. If those visual signs are not sufficient, one could have the laboratory quantify liver stores of vitamin. Dr. T. Keith Murray did just this when he examined the livers of deceased Canadians for vitamin A storage and learned that 30% of the specimens had less vitamin A in their livers than would be expected at birth. Additionally, of 500 deceased Canadians, 33% had less than 40 mcg of vitamin A in the liver and 20% had no measurable vitamin A stores at all. This scenario worsens with age as other factors conspire to inhibit absorption of vitamin A—laxatives and cholesterol-binding drugs as well as hypochlorhydria resulting in frank protein deficiency and malabsorption.

### Vitamin A Requirements through Life

One way to appreciate the benefits of vitamin A is to start at the beginning of a life and create a timeline for vitamin A requirements from conception on through life.

**Conception.** Adequate vitamin A is required for fertility and conception. Injections of retinoic acid in testes stimulate spermatogenesis—though there must be better methods available. Vitamin A gradients in uterine mucosal tissue also determine where in the uterus the fertilized egg will implant—a highly significant factor as any obstetrician or midwife will agree.

**Embryogenesis.** Once fertilization is accomplished, embryogenesis and cell differentiation will not proceed normally in the absence of adequate vitamin A and carotenoids. As Lampert et al. point out: “The egg yolk of vertebrates contains carotenoids, which account for its characteristic yellow color in some species. Such

plant-derived compounds, e.g. beta-carotene, serve as the natural precursors (provitamins) of vitamin A, which is indispensable for chordate development. As egg yolk also contains stored vitamin A, carotenoids have so far been solely discussed as pigments for the coloration of the offspring...Our data provide strong evidence that, for several developmental processes, retinoic acid generation depends on local de novo formation of retinal from provitamin A via the carotene oxygenase, revealing an unexpected, essential role for carotenoids in embryonic development.”<sup>21</sup> Subsequent neural growth and development in utero and on through infancy rely to a great degree upon vitamin A and beta-carotenes just as children rely upon these vitamins to support skeletal growth.

**Infancy.** In order to survive infancy and grow into childhood, vitamin A is required in a very dramatic manner. Diarrhea and bronchitis kill more third-world children than any other disease, so what is vitamin A's role in these two diseases? A “chicken and egg” question which perplexed Dr. Al Sommer (and eventually earned him the prestigious Albert Lasker Award) was whether diarrhea caused vitamin A deficiency, or vitamin A deficiency caused diarrhea. Since infant diarrhea is lethal in many parts of our malnourished world, this question merited close consideration. In 1982, then a 40-year-old Johns Hopkins ophthalmologist doing research in infant blindness from vitamin A deficient xerophthalmia (dry eyes), Sommer noted that most of the 4,000 Indonesian children in his study had died of infant diarrhea or bronchitis. Wondering which was causal, he crunched numbers and discovered that a child with night blindness when the study began was three times more likely to die by the end of the study than a child with normal vision. If the child had Bitot's spots, the risk of death was six times higher. With both symptoms, death was nine times more likely. His subsequent publication<sup>22</sup> was met

with indifference, but his clinical trials (Indonesia 1984 and Nepal from 1989 to 1991 demonstrating 34% and 30% less death in vitamin A supplemented groups) got some attention. In the eyes of prominent nutritionists, Sommer went from being an ignorant ophthalmologist mucking about in nutritional matter to a vilified trespasser.

After presenting a new study (N=15,000 infants) demonstrating 34% fewer deaths in the vitamin A supplemented group, Sommer finally got a reaction. "That's when all the knives and spears came out," he says, relishing the memory. Finally in 1985, after deigning to do a patently unethical double-blinded placebo controlled study where 15,000 children received vitamin A and 15,000 unfortunate infants were given a placebo, his finding that the vitamin A group had experienced 30% fewer deaths than the placebo group was considered persuasive. Sommer recounts their ultimate reaction: "It's a famous phenomenon, like the stages of grief," he says. "First they ignored it. Then they got angry. Finally they say, 'We knew it all along.'" What they didn't know, however, until Kozakova et al. published in April, 2003, was the mechanism of action whereby vitamin A deficiency compromises mucosal barriers and leads to diarrhea.<sup>23</sup> These researchers observed that vitamin A deficiency led to a strong reduction of certain enterocyte enzymatic activities, which in turn precipitated a lethal dysbiosis with increased bacterial translocation and consequent diarrhea.

Closer to home, vitamin A deficiency has been implicated in Sudden Infant Death Syndrome (SIDS). Alm et al.<sup>24</sup> found an association between low or no vitamin A supplementation and an increased risk of sudden infant death syndrome during their first year of life. This effect persisted when an adjustment was made for potential confounders, including socioeconomic factors.

**Adolescence.** Once safely into adolescence, people require vitamin A for its anti-viral and anti-acne effect as well as to minimize the unsightly hyper-keratosis

(those bumps on the back of your arms) which you thought was "just something you have to live with". Not so. You can live without it if you avoid saturated fats and sugar and take adequate amounts of vitamin A and flax-seed oil. Vitamin A comes to the rescue with its more generally appreciated benefit—the enhancement of night vision now that the kids are borrowing the car and staying out too late at night. If your visual acuity is diminished in the dark beyond what is expected, try vitamin A as well as selenium and zinc.

**Young Adulthood.** The college students in my practice all have vitamin A palmitate in their first aid kits. We know that stress is an immune suppressant and given the velocity of life at this age with the inevitable "all-nighters" my college students know to take a megadose of vitamin A palmitate at the first sign of sore throat, cough or that ominous feeling of "I am going to be sick tomorrow." They report, however, that after taking the megadose of vitamin A before going to sleep, they invariably awaken the next morning feeling great. Their chief complaint becomes, "I never get any sick days..." The exception to this treatment protocol, of course, is pregnant or potentially pregnant women who understand that megadoses of vitamin A can be dangerous for the fetus. Women enjoy another benefit of vitamin A, however, that the men cannot: rapid, painless resolution of that terrifying Pap smear result: cervical dysplasia. Like most virus-related illnesses, cervical dysplasia is effectively treated with vitamin A along with other complementary nutrients such as selenium, vitamin E and beta-carotene.

**Middle Age.** Years ago, Abram Hoffer, M.D., Ph.D. pioneer orthomolecular scientist and physician, noted that niacin cured his bleeding gums (gingivitis). This simple observation ultimately resulted in collaborative research demonstrating the role of niacin as the gold standard for treatment of hypercholesterolemia. Vitamin A is a

heart-healthy nutrient which can also treat gingivitis. Furthermore, patients with related and compounding diseases such as diabetes and glaucoma also tend to be deficient in vitamin A. Streb et al. noted that retinoids and their synthetic derivatives exert a systemic effect on dermatological and neoplastic processes.<sup>25</sup> Retinoids, the natural and synthetic derivatives of vitamin A, have been used clinically to treat a variety of dermatological and neoplastic diseases through the binding and activation of a family of nuclear receptors that modulate gene transcription. Their work demonstrates that retinoids minimize experimental vessel wall narrowing due to atherosclerosis, post-balloon injury stenosis, and bypass graft failure. Retinoids also promote a differentiated phenotype in smooth muscle cells. Given the similarities in the pathogenesis of neoplasia and vascular disease, we ought not be surprised to learn that many in vitro studies report beneficial effects of retinoids on cell migration, proliferation, apoptosis, matrix remodeling, fibrinolysis, coagulation, and inflammation, all of which should make the cardiologists sit up and take notice.

**Old Age.** Another illness that plagues us as we age is bronchitis. This, too, is humbled before the immune-enhancing and anti-viral power of vitamin A. How does vitamin A protect the mucous membranes and thereby reinforce our barrier immunological defense system? Conceptually speaking, you can understand vitamin A as the protector and nurturer of mucus membranes. That includes the entire gastro-intestinal tract from sniffles to diarrhea. In addition, vitamin A protects the urogenital tract, most specifically the female cervix and vagina, which can be successfully treated with vitamin A if ulcers or dysplasia occur. Through a number of mechanisms including immune stimulation (it increases IgA antibodies), vitamin A allows for proper functioning of T and B cells as well as cellular immune modulators called

cytokines. This means if your vitamin A level is low, you are not immunologically "buffed." Any mucous vulnerability including (from top to bottom) nasal allergies, sore throat, gastritis, ulcers (including Crohn's disease and ulcerative colitis), and cervical dysplasia all signal a deficiency of vitamin A and all benefit from a simple nutrient which third-world doctors have long called "the anti-infection vitamin." These doctors are not concerned with vitamin A toxicity, rather they see patients dying of vitamin A deficiency as it manifests in a great variety of infectious diseases which ravage poor countries, including fatal diarrhea (noted above), many respiratory ailments, tuberculosis, ear and eye infections, and malaria. (Delighting as I do in critters, I can not resist sharing that one common side effect of malaria is vitamin A deficiency. Thanks to Mizuno et al.,<sup>26</sup> we now know why. It seems that the parasite *plasmodium falciparum* covets vitamin A and actually sequesters it away from the human host in order to take advantage of vitamin A's anti-oxidant properties to resist the intra-erythrocyte oxidative stress of the host's immune system.)

### Anti-viral Effects

Antiviral effects are especially important as the flu season approaches, but there is more. Let me assume that you missed the recent American Society for Microbiology meeting where Professor Richard Semba, M.D., of the prestigious Johns Hopkins University Hospital presented his research demonstrating that pregnant women infected with HIV (AIDS virus) who also were vitamin A-deficient were much more likely to transmit the virus to their newborn infants than were HIV-infected mothers who had adequate amounts of this important vitamin. Specifically, with low vitamin A, the transmission rate between mother and infant was 32%, whereas with adequate levels the rate was only 7%. Additionally, 93% of the infants born to the vitamin A-deficient

women died in the first year of life compared to only 14% of those born to women with adequate levels of vitamin A.

If you are pregnant and infected with HIV, you are in a dangerous situation, but more vulnerable still is your unborn child. If you are not careful, the blissful moment of delivery will be dashed by the infection of the newborn with the HIV. Doctors and scientists have long-sought a way to interrupt the viral replication of sexually-transmitted diseases so that a baby can be born while escaping infection from its mother. Vitamin A is our best bet so far according to recent research.

This scenario reminds me of the fairy tale, *Sleeping Beauty*, where all have gathered to bestow blessings upon the infant princess, but the evil aunt, wrathful at not having been invited to the christening, swoops in to cast her lethal spell. Like the fear cast by AIDS, her power appears supreme. None of the assembled can dispel her deed entirely. Grief settles upon the mute throng. Then, quietly, the last good fairy, who had patiently awaited her turn to bless the infant, humbly comes forward to ameliorate the death sentence by decreeing that *Sleeping Beauty* shall not die. Rather, at the appointed time, she will prick her finger and fall into a deathlike sleep to be awakened after 100 years by true love. Thus it is with the humble vitamin A. Semba's research on vitamin A's ability to interrupt the transmission of HIV from mother to child seems to be the stuff of fairy tales. The cost of the vitamin A in Semba's study was a whopping two cents a day. Have you priced AZT recently?

Research of such importance merits follow-up studies and indeed Fawzi et al. published just such work in April of this year. In their study,<sup>27</sup> HIV type 1-infected women from Tanzania (1078 in number) were randomized in a placebo-controlled trial to examine the effects of supplementation with vitamin A (performed vitamin A and beta carotene) and/or multivitamins (vita-

mins B, C, and E). The investigators found that maternal receipt of vitamin A significantly reduced the risk that the child would have cough and pneumonia and concluded that the provision of multivitamin supplements (including those with vitamins B, C, and E) to HIV-infected, lactating women may be a low-cost intervention to improve their children's health. Would someone please recount this to Bill Gates or George Bush since they are so focused on fighting AIDS in Africa with expensive and toxic pharmaceuticals all the while ignoring the fundamentals.

### **Cancer and Vitamin A**

Fundamentals (diet and lifestyle) aside, vitamin A does have proven benefit in the treatment of cancer. The most extensively studied agents in cancer medicine involve vitamin A analogues including all-trans-retinoic acid, 9-cis-retinoic acid, and 13-cis-retinoic acid. Vitamin A has two immune regulatory functions: it has an immune stimulating effect by prodding cellular differentiation of myeloid progenitors toward the beneficial neutrophil lineage.<sup>28</sup> and by lowering IGF-1 (itself associated with increased risk of most cancers).<sup>29</sup> These vitamin A analogues may exert their antineoplastic effects through the regulation of tumor suppressor genes such as RAR-beta2. In addition, the toxicity and efficacy of retinoids administered concurrently with other biological and cytotoxic agents is promising for a broad range of cancers including renal cell carcinoma, breast cancer, myelodysplasia, prostate, cervix, and other malignancies. Newer and more selective retinoids and rexinoids are completing phase I and phase II studies and hold promise.<sup>30</sup> Even more intriguing is the role of vitamin A in preventing metastatic disease process as described by Weinzwieg et al.<sup>31</sup> who found that vitamin A stimulates collagenous encapsulation around several murine breast and lung tumor systems. Tumor encapsulation process such as this can allow

for easier surgical excision at the least and optimally afford life-saving benefit. To quote from their findings:

“Vitamin A could promote the encapsulation of a murine melanoma. Sixty days after tumor inoculation, a 60% survival rate was observed in the control group as opposed to the vitamin A-supplemented animals, which demonstrated a 100% survival rate in both groups (n=5 in each group). Decreased mean tumor size and gross tumor in most vitamin A-supplemented animals were statistically significant when compared with the control animals. The control animals had a mean tumor size of 26.1 mm, whereas the post-vitamin A group had a mean tumor size of 5.7 mm. One hundred percent of the control group exhibited tumor; one animal had distant metastases. The pre-vitamin A group did not exhibit any tumor growth, and the post-vitamin A group exhibited tumor growth in 40% of animals. Neither vitamin A-supplemented group showed any evidence of distant metastases. The animals supplemented with vitamin A demonstrated decreased tumor growth and metastasis.”

The authors concluded that vitamin A offers a potential prophylactic and therapeutic role in the treatment of malignant melanoma.<sup>31</sup> Other researchers demonstrated vitamin A's potent anti-proliferative and anti-inflammatory properties mediated through inhibition of Th1 cytokine production. Kinoshita et al. concluded that treatment retinoic acid significantly alleviates autoimmune renal disorder and prolongs survival in SLE-prone NZB/W F(1) mice; thus suggesting a novel approach to the treatment of patients with lupus nephritis.<sup>32</sup>

### Vitamin A and the Flu

After reviewing the risks and benefits of vitamin A and beta-carotene, I will leave you with a simple message involving the single most beneficial role for vitamin A in my medical practice. However, I must warn you, that my having shared this informa-

tion with patients over the years has done more to keep patients out of my office than any other preventive medicine clinical pearl. In other words, what I am about to tell you is a business loser! This clinical gem concerns the common flu with its fever, sore throat, cough, headachy and nauseous feeling—the common flu that lays us out each year. When I practice, people don't catch the flu. The flu catches you. If you've ever body-surfed and been caught by a monster wave that flung you out beyond the crest, then slammed you down on the not-so-soft beach, then you know what the flu feels like. It wrings you out and hangs you out to dry, aching in every moveable part.

Want to avoid the flu this season? Those post-nasal-drip sore throats and sniffles, sinus congestions that erupt into unbelievable headaches, body aches typical of the flu that reveal a smoldering viral infection? Upset that every time you get a flu shot, you seem to come down with the flu? Wondering how to brace yourself against the damp and howling winter winds? If so, at the next sign of a cold coming on, consider a cheap, easy and highly-effective remedy for you and those you love. My recommendation is to take A (sic) vitamin. That's right: vitamin A. To be specific, the palmitate form and the key is the dosage. I prescribe high doses for a short period of time, 100,000 IU at onset of symptoms and another 100,000 IU at bedtime. Typically, that aborts the flu and my patients awaken feeling great the next morning. For those who need more immune support, that protocol of 100,000 IU twice a day can continue for no more than a week (to be on the safe side). Feeling nervous about recommending that to patients? Well, remember that toxic levels are determined not only by amount but by duration of exposure. Therefore, 100,000 IU for a day or two is not only safe, it's highly effective. Don't let your patients continue on that dosage for more than a week as that can, in some cases, saturate the liver storage capacity. Do not use this

protocol in pregnancy or for women of child-bearing age who might be pregnant since too much vitamin A can be teratogenic to the fetus. Also, to reiterate, this protocol works best if started at the *onset* of the flu and not as well after the symptoms are already wreaking havoc with you. I teach patients to use high dose vitamin A at the onset of an acute immune challenge but they all know to use vitamin C chronically. Once the flu is underway, vitamin C is your best friend, as Dr. Linus Pauling wrote in *Vitamin C and the Common Cold*. So remember: "A for acute and C for chronic" and you will be looking at an empty waiting room in no time.

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