Review Article

Alleviation of vitamin A deficiency with palm fruit and its products*

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The decreased dietary diversity wrought from the adoption of the settled, agrarian system to replace the hunter-gather and pastoralist lifestyles assured a stable supply of protein and calories from grains and tubers while creating a vulnerability for humans to suffer micronutrient deficiencies. The vitamin A from animal tissue is more bioavailable to humans than the provitamin A in the matrix of green plants. Provitamin A carotenes achieve a dietary vitamin A efficacy nearly equivalent to that of the preformed vitamin only in the context of an oily matrix. The homeostatic regulation of carotene bioconversion by the intestine, moreover, prevents any excess toxic accumulation of vitamin A from provitamin A sources. The efficacy and safety of the palm fruit (genus *Elaeis*) as a source of vitamin A, in addition to its cultural recognition as a food, are more consistent with the gentler concept of "alleviation" of the public health problem of hypovitaminosis A, then the more aggressive, medical model of "eradication" with its greater potential for risk and collateral damage. The palm fruit and its derivatives achieve new opportunities for creative contribution and sustained use in formats of supplementation (prophylactic in children and women, for lactation), food-to-food fortification (in bakery goods and snacks, as condiments), and even in food diversification strategies. Experience in India, South Africa, and Guatemala begins to define and delineate the opportunities and limitations for the palm fruit to contribute to the alleviation of endemic vitamin A deficiency.

Key Words: vitamin A, provitamin A, fatty fruits, palm fruit, red palm oil, hypovitaminosis A, hypervitaminosis A, food-to-food fortification, food safety, evolution, North Africa, Guatemala

Evolutionary considerations: of humans, of diets and of fatty fruits

When one speaks of vitamin A deficiency, one is talking about an imbalance in the human diet. If we take *Homo sapiens* as a species, we have developed through an estimated 400,000 year evolution of homonids.[1] One would expect, however, that for humans, like all other evolved species, adaptation in the ecological niche through a combination of behavioural modifications and genetic natural selection would have brought humankind into harmony with its nutrient requirements. In fact, archival and anthropological studies suggest that the tribal hunter-gatherer was, indeed, in a situation that satisfied the nutrient needs[2]; they achieved this by consuming an extremely varied and diverse diet of edible flora and fauna, while the vigorous exercise and varied, unrefined – albeit high in animal protein – protected evolutionary man from today's chronic, degenerative diseases.[3] Short life-expectancy, due to the ravages of infections, accidents and predation, inter-tribal conflicts, and childbirth complications can be credited, in part, for the "protection" from non-communicable disease endemicity in hunter-gatherer populations.

Our focus, however, is on diversity of diet. Humans in evolutions were opportunistic omnivores, consuming all edibles within their reach. The need to assure a *stable* diet led human cultural evolution about 40,000 years ago to begin the domestication of Nature.[4] This started with domestication of hoofed animals to produce dairy herds, and, in that way, the pastoralist lifestyle emerged. Some 10,000 years ago (400 generations), humans began to domesticate seeds and roots.[2] This led settled agriculture as an manner to assure a regular supply of energy, with the nutritional trade-off of greatly reducing the diversity of edible items in the diet.[2] This decision provided the behavioural basis of nutrient imbalance in human dietaries.[5]

Endemic hypovitaminosis A

Hypovitaminosis A occurs in diets with insufficient sources of utilizable dietary vitamin A. Preformed vitamin A (retinol, retinyl palmitate) can only be created in animals. Hence, animal protein sources such as milk and dairy products, eggs, and (especially) the visceral organs of fish, fowl and mammals are also sources of preformed vitamin A. The provitamin A carotenoids in plants also represent dietary vitamin A, but their bioconversion by the human intestine is relatively inefficient,[6,7] at least compared to that of strict herbivores. With respect to the occurrence of human hypovitaminosis A, it has its roots in biological evolution by humans developing as obligate omnivores, and

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in cultural evolution in the aforementioned dependency of post-agrarian cultures on staple grains and tubers in the absence of wide diversification of dietary intake.

Vitamin A deficiency has a series of adverse functional and clinical consequences. The most widely heralded are those of ocular involvement (xerophthalmia), which leads to nutritional blindness.[8] More recently established is the fact that marginal vitamin A deficiency allows for an average 22% reduction in mortality from infectious diseases of childhood according to a widely cited meta-analysis of field intervention trials.[9] Whether hypovitaminosis A adversely influences linear growth has yet to be firmly established. Vitamin A deficiency is considered a major worldwide public health problem by the World Health Organization, and efforts to address it has been galvanized by entities such as the International Vitamin A Consultative Group.

Alleviation -- but not eradication -- of vitamin A deficiency

Four alternative approaches for addressing a micronutrient deficiency have been outlined: 1) supplementation; 2) fortification of foods; 3) diversification of diet; and 4) public health measures to reduce infectious illness.[10] How one defines the concept of "addressing" a public health problem, moreover, is culturally determined. One's cultural traditions influence one's approach to public health interventions. The topic assigned to me by the organizers is "alleviation" of vitamin A deficiency. This is in contrast to that of "eradication" of vitamin A.

Eradication of a public health problem

This latter concept is characteristic of western thought and is reflected in western (allopathic) systems of medicine and the goals of its technological age, which are not averse to radical alteration of the environment and ecology. In fact, except in the context of self-abuse (eating disorders, addictions) or clinical diseases, hypovitaminosis A is currently unknown in the United States, Canada and the European Union. As a public health problem, one might consider that it has been *eradicated.*

The radical (by the roots) fundamental of this approach is inherently "aggressive" and the measures used tend to be severe, and often with the downside consequences of risks of adverse side-effects. It brings to mind the aphorism of having "kill it to save it." When the malady is manifest, such as with a malignant tumor, the rigors of radical therapies of surgery, radiation and therapy can be viewed in terms of a palpable reversal of a lesion. When the issue is prophylaxis against a latent - but not present or palpable - danger, the only perceivable effects are the negative ones of the preventative intervention. Even in Western societies, in which rationality of risk/benefit analysis can be applied, there is often a backlash against the "collateral damage"[11]; this becomes more problematic when the less educated and health-sophisticated are the "beneficiaries" of the action.

In the context of vitamin A policy, the most effective measure to reduce the risk of nutritional blindness has always been considered the distribution of high-dose supplements of the vitamin as retinyl palmitate.[12] The controversy that arose in the Assam Province of India in 2001, documented by Indian observers,[13-15] involved deaths of preschool children attributed to the routine, province-wide campaigns to deliver 200,000 IU to all individuals aged 1 to 6 years. Whether or not the change in measuring receptacle from spoon to medicine cup (allowing for more than the intended dose to reach the recipients' lips) was the cause of the problem - or whether (objectively) there was any increased attributable mortality from the campaign - the perceptions of the population at large was of a problem, and the Indian health authorities and the international vitamin A community was chastened.

In fact, in the affluent countries in which this nutritional deficiency no longer exists to any degree in the free-living public, the consumption of enriched and fortified foods, such as milk, margarine and other spreads, breakfast cereals and beverages is commonplace. This is the reason that consumption of vitamin A is so widely adequate.[16-18] Ironically, the primary concern of the Food and Drug Administration with micronutrients in the US food supply has been with excessive consumption and toxicity.[18]

Alleviation of a public health problem

The theme at hand, however, is that of *alleviation*. It has a milder, less aggressive, connotation, and is more in harmony with the health beliefs of non-Western cultures. Here the notion of health is the *balance* among forces (*Yin Yang*, hot-cold). Disease is seen as imbalance, and remedy consists of restoring the balance.[19] The aspiration is not to make it perfect, but rather to make it better. It is out of low-income and traditional societies, where resources have always been limited, that the concept that "excellent is the enemy of good" would be firmly embraced in folk philosophy.

In theory, the gentler tenor of an alleviation goal will pull the distribution of the population to the right. Some individuals will still be left in a deficient or marginal condition, but many will be shifted out of it. It avoids the upside risk, however, of producing a rebound of excess and toxicity side-effects in wake of the campaign to address the original problem. This is the spirit of culturally-cogent approaches that a Thai research group endorses in an article entitled "Moving a health system from a medical towards a dietary approach in Thailand".[20]

The Palm fruit

An interesting study of history and anthropology is that which involved "globalization" even before the present era. Raymond Grew has edited the book, *The Global History of Food.*[21] This is that cultivars and even cuisines, originating in one area of the world, become disseminated throughout the globe taking roots in a generalized way. The palm fruit (of the genus *Elaeis*) is a fatty fruit that is estimated to have been domesticated somewhere in Western Africa some 5000 years ago.[22] Favouring humid tropical lowland climes, it grows on a large palm which can grow to a height of 9 meters and can support up to a dozen bunches of fruit weighing an average of 70 kg over a period of 12 years.[23]

The fruit itself is red in colour with a soft skin and a large pit. The ratio of seed weight to pulp weight is close to unit.[24] Two oily derivatives are derived from plants of the *Elaeis* genus; the mesocarp (fleshy pulp), which yields an oil (red palm oil, RPO) which is semi-solid at room temperature and can be further refined to *palm olein* and the kernel, from which *palm stearin* is produced.[24,25] The crude palm has a strong taste and a pungent odour, and its content

of free fatty acids makes it subject to rapid rancidity. If prepared and consumed rapidly, the crude product makes for an acceptable and low-cost cooking oil from subsistence production, the form in which it has been used in a wide belt of countries in Western Africa.[23] The same is true in rural Brazil. In both regions, skin ointments are also produced from the crude RPO. It original commercial production in Africa in the mid 1800s was as a fuel oil for Russia[23], but it lost its export value when other fuels became available.

The red colour of the oil from the pulp is constituted of carotenoid pigments, divided between beta- and alpha-carotenes in a ratio of roughly 3:2, depending upon the species; about 15% of the carotenoids content are non-precursors of vitamin A.[25] In the varieties of *Elaeis guinieensis* an average total carotenoid content of 500-700 ppm in crude palm oil is common in the varieties originating in Malaysia, of the *tenera*, a cross between *dura* and *psifera* varieties. *Elaeis oleifera*, a variety growing in South America on the Brazilian coast, has 6 to 8 times as much carotenoid, up to 4000 ppm.[26]

Ong and Goh[25] list a roster of food applications that RPO has taken on in recent years including: trans-free margarine, extruded snacks, reduced-fat spreads, fried nuts, bakery, dairy products with butter-fat replaced, cooking sauces, soup mixes etc. Of special note is its potential for incorporation in ghee, the solid cooking fat (analogous to butter and lard) consumed in Asian societies. The Indian vegetable ghee, vanaspati, is an example of a processed food that can incorporate high melting-temperature vegetable fats. It is estimated that currently 55% of the world's population consumes liquid vegetable cooking oil and the remaining 45% consume solid cooking fats (butter, ghee).

In Central America, a plague on banana plants left the United Fruit Company to turn some of the infested areas to other tropical cultivation. The first palm fruit cultivars reached Guatemala in 1920, from Africa.[27] Both Indonesian and African cultivars were eventually planted along the extent of the company's holdings from Guatemala south to Panama. It was only in recent years, with advances in processing and refining innovations in India and Malaysia, that preparation of a clear (depigmented), appealing (deodourized) and stable edible oil could be commercialized.

Potentials and limitations of palm fruit and derivatives in the alleviation of hypovitaminosis A

The noted biochemist, George Britton, recently posed the question: "Can the carotenoid world and carotenoid research make a practical contribution to the fight against vitamin A deficiency?",[28] almost in a rhetorical sense. Among the formats for public health application against hypovitaminosis A, we can operationally define supplements as high dosages that would provide the equivalents of several months worth of the recommended intake in a single dose. Food fortification would be the addition of a palm fruit derivative into a processed food in processing. Diversification of the diet would be encouraging the increased use of a direct derivative of the palm fruit as a food or condiment. In a 1998 editorial, the present author commented: "it is now time to explore ß-carotene in foods in a matrix-free context, such as the purified pigment and that in RPO as the key to a safe and effective vitamin A supplement, fortificant, and food-based solution all wrapped up in one".[29] Speaking on a similar theme in 2000, Reddy[30] commented: "Although these (red) oils can be used as dietary supplements, they may not be acceptable for a cooking medium because of their red colour." Given their rich content of provitamin A carotenoids it is the basic mission of this inquiry to explore the potential and limitation of the palm fruit and its derivatives to alleviate endemic hypovitaminosis A.

Vitamin A bioefficacy of provitamin A in oil

The manner to express an "average" value to the dietary vitamin A activity in provitamin A-containing foods has been a contentious issue by virtue of both a heritage of mathematical conventions and confusion about the biological issues involved in bioconversion of carotenes to active vitamin A. The culprit for the former was the assortment of units – milligrams of carotenoids; international units (IU) of vitamin A; and retinol equivalents (RE) – which were at play since the convening 1967 FAO/WHO Expert Committee.[31] Since medicinal dosing of vitamin A continues to be expressed in IU, the interconversion of this expression with others for *preformed* vitamin A is essential. This is 3.3 IU equals 1 µg of retinol. Things become more controversial when the carotenoid precursors in foods of the active vitamin are considered. At least from gravimetric units to retinol equivalents, the 1967 convention was consistent: 6 µg of all-trans beta-carotene was considered to have the equivalence of 1 µg of retinol. In the next revision by the United Nations agencies[32], the conversion convention for all other provitamin A carotenes, such as alpha-carotene or beta-cryptoxanthin, was established as 12 µg being equivalent to 1 µg of retinol. All of these supposedly gave the same final vitamin A yield to the host of 1 RE.

For a multitude of reasons, first outlined in 1993 from our group at CeSSIAM[6], and followed up by human study evidence in 1995 from Indonesia,[33] the notion that the efficiency of conversion of provitamin A from actual food sources such as carrots and dark green leafy vegetables was as high as the convention dictated was questioned. Such an overestimation was deceptive both in the degree that a true problem might be overlooked or underestimated and in the risk that a food-based prescription would be overly optimistic and inappropriate.[34] It took a major mobilization of evidence[33-36] and argument,[6,7,34,37] however, to convince policy makers that the projection was too optimistic. Finally, with the convening by the Food and Nutrition Board of the U.S. Institute of Medicine for the *Dietary Reference Intakes* (DRI),[38] the panel evaluated the recent data and felt the evidence justified a major readjustment of the assumptions related to the intrinsic bioconvertibility of provitamin A carotenes from plant foods. This has led to a new unit of conversion for dietary vitamin A activity, the Retinol Activity Equivalent (RAE) (Table 1). It amounted to a 50% devaluation of the contribution of carotenes in plant matrices to the vitamin A tally. From a program and policy standpoint, it means that we are currently overestimating the usual intakes of vitamin A, especially those high reliance on plant protein.[5] For the present discussion, however, the DRI's bold affirmation of the *high* availability of provitamin A in oil media comes into relief (Table 1). Both a review of the original bioconversion evidence[39,40] and modern studies[41,42] indicated that provitamin A in an *oil base* had a bioconversion potential that placed it on a virtual

Table 1. Bioconversion factors for retinol "activity" equivalents according to the 2001 institute of medicine, dietary reference intakes

Consumed	Absorbed	Bioconverted	
Dietary or supplemental vitamin A (1 μg)	→	*Retinol*	→ Retinol (1 μg)
Supplemental β-carotene (2 μg)	→	β-carotene	→ Retinol (1 μg)
Dietary β-carotene (12 μg)	→	β-carotene	→ Retinol (1 μg)
Dietary α-carotene or β-cryptoxanthin (24 μg)	→	α-carotene or β-cryptoxanthin	→ Retinol (1 μg)

After IOM, *Dietary Reference Intakes* [38]

a virtual par with the preformed vitamin. Indeed, a careful reading of the 1967 FAO/WHO expert committee report[31] will reveal that the enhanced bioavailability of beta-carotene in oil had actually been recognized at that time, as pointed out by van Lieshout.[41] Hence, in terms of the 1967 deliberations,[31] the average amount of oral beta-carotene in oil that one would need to consume to provide 1 μg of retinol is 3.3 μg. In terms of the percentage of an oral dose of a provitamin A compound absorbed and convertible into vitamin A (bioefficacy), this represents 28%. The bioefficacy estimation from the IOM report 50%, as 2.0 μg of oil-based beta-carotene is considered to yield the 1 μg.[38] However, another biological contention confounds our understanding of "average" value. Preformed vitamin A is preformed vitamin A; its weight, per se, (retinoid molecule) defines its retinol equivalency. For provitamin A sources, the extent of its bioconversion is regulated and determined by the vitamin A status of the host. It might be useful not to conceptualize retinol activity "*equivalency*" for dietary provitamin A, but rather its "*maximal potential*" or merely "*potential*." That would be the yield of preformed vitamin A from provitamin A in hosts with functional intestinal cells and a major nutritional deficit in vitamin A status. Hence, the estimates for bioconversion in Table 1, in fact, would only be achieved within these two constraints. Presumably, these values apply to vitamin A-depleted persons, and not the entire consuming population. As finally confirmed in free-living individuals,[43] the degree of bioconversion of food provitamin A sources is in proportion to the needs of the hosts to expand their vitamin A reserves.

Referring to the major revision in conventional thinking about bioconversion of provitamin A in an oily milieu, Reddy[30] has commented: "Carotenoids supplied in oil have an advantage over vegetables and fruits because of their higher bioavailability." In fact, some revision of the accepted bioconversion factors, as applied in the past to RPO are in order. Scrimshaw[44] evaluated the carotenoid profile of the commercial product, Carotino, in an earlier article, published prior to the IOM report,[38] and using the FAO/WHO assumptions of retinol equivalents. Scrimshaw's illustration[44] is reproduced in Table 2, and with a column showing the *recalculation* as retinol *activity* equivalents. As one can see, whereas 100g of this refined, reconstituted RPO product (Carotino) would have been credited with offering 6140 RE of dietary vitamin A, using newer considerations, the value rises to 18,420 RAE, the expected three-fold increase.

Table 2. The vitamin A activity of Carotino expressed in traditional retinol equivalents and in the newer retinol *activity* equivalents

Carotenoid	Content (μg/100g)	RE	RAE
cis- α-carotene	17,500	1458.3	4374
β-carotene	28,000	4666.6	13999.8
cis-α-carotene	125	10.4	31.2
γ-carotene	15	1.3	3.9
β-zeacarotene	35	2.9	8.7
Others	275	-	-
Total		6139.5	18418.5

Modified after Scrimshaw[44]

In the same publication, Scrimshaw[44] compared RPO, an oily-matrix source, with other plant sources. As shown in Table 3, in his original presentation, Scrimshaw had erroneously valued the 500ppm, assumed to be in 100g of crude palm oil as 30,000 RE. This concentration of mixed carotenes, in retinol equivalent terms, would have the same value as that of the Carotino in Table 2. So, with the corrections, the first two columns provide the absolute RE values for dietary vitamin A for plant sources with graded levels of provitamin A and their relative activity, in terms of number of times below crude palm oil. With an adoption of a retinol activity equivalent perspective,[38] one sees a relative six-fold change in relative relationships with the three-fold accretion in provitamin A in oil and the 50% devaluation of carotenes in plant matrices. One must now consider that 100g of RPO is six-times superior to other plant sources than would have been rated using the retinol equivalent convention.

The safety factor of provitamin A

The consternation that was caused in India and around the globe by the accusations about induced mortality during a campaign of high-dose retinyl palmitate prophylaxis in the Assam Province was alluded to earlier.[13-15] The retinoid form of vitamin A has its potential for acute and chronic toxicity,[45,46] and accidental overdoses are a latent danger in its use in clinical medicine, public health and self-supplementation. Provitamin A carotenes do not share the same toxic potential. The utilization of the vitamin A potential of provitamin A carotenoids is *homeostatically* regulated, meaning that the body only derives as much active vitamin A from carotenes as the organism needs.[43,46]

Table 3. Relative dietary vitamin Aactivity of red palm oil and other sources of provitamin A carotenes

Source	Retinol Equivalents		Retinol Activity Equivalents	
	RE#/100 g (edible portion)	Relative Activity#	RAE#/100 g (edible portion)	Relative activity
Crude palm oil	6140	1	18420	1
Carrots	2000	3	1000	18
Leafy vegetables	685	9	343	54
Apricots	250	24	125	147
Tomatoes	100	61	50	363
Bananas	30	205	15	1228
Oranges or orange juice	8	768	4	4605

Modified after Scrimshaw[44]. # The data for RE have been recalculated and corrected for what the original author had presented in his 2000 review paper[44]. It is assumed here that crude palm oil has 500 ppm (50 mg/100 g).

The concern factor of saturated fatty acids

Distinct from the situation of oils in plant seeds, which is largely unsaturated, the make up of fats from the mesocarp of fatty fruits has higher contents of saturated fats. Concern has traditionally been expressed for the 16-carbon saturated fatty acid, palmitic acid (deriving its common name from the palm fruit), in palm oil. In terms of atherogenicity, this fatty acid is actually close to neutral in terms of cholesterol-raising capacity.[47] Compared to *trans* fatty acids formed in hydrogenation of liquid vegetable oils to make solid fat, palmitic acid has far more benign atherogenic effects[48] The position of palmitic acid on the 2-carbon of glycerol in the triglycerides of palm oil is a factor in its lesser participation in cholesterol mobilization.[44,47] A balance focus takes into consideration that, although palm olein has 44.2% palmitic acid (16:0), it has 39% oleic (18:1) and 10% linoleic (18:2) acids which have favourable benefits in prevention of atherogenesis.

Moreover, it takes only 10 ml (or 90 kcal of energy contribution from RPO) to provide the recommended vitamin A intake using the traditional conversion factors. This is reduced to 3.3 ml (or 30 kcal of energy contribution from RPO), if we based it on the newer considerations of the RAE (Table 1). [38]

Palm oil versus hypovitaminosis A

The cumulative experience

In recent years, a number of members of the nutritional and public health communities have projected a potential for RPO's efficacy and effectiveness in the combat against endemic vitamin A deficiency.[24,25,33,48-54] Among the public health options, we have evidence to examine in the domains of supplementation and food fortification, and some incipient experience in the domain of dietary diversification.

Red palm oil in periodic supplementation

Table 4 provides the current recommendations for the use of high-dose supplements in preventive and therapeutic situations. Something approaching the periodic prophylactic supplementation has been explored in India, but at one-quarter of the preformed vitamin A pulse dose in landmark studies in Northern India to examine the potential of RPO as a surrogate in supplementation programs.[55] Instead of the 60,000 RE (200,000 IU) dosage of the international recommendations, 15,000 RE (50,000 IU) were given as a single dose to one of the arms (positive control) of a treatment conducted in 12 schoolchildren in the Orissa Province of India. For the experimental treatment groups, they used a deodorized and deacidified crude red palm oil as the intervention vehicle over 15 consecutive days, with daily RPO doses of 4 or 8 g containing a mixture of beta- and alpha-carotenes that would be equivalent in theoretical cumulative potency of 25 mg and 50 mg of beta-carotene over the term of dosing. In the perspective of RAE, the treatment groups would have received 15,000 RAE (vit A-single dose), 12,500 RAE (4 g daily x 15 d) and 25,000 RAE (8 g daily x 15 d). Initially, over 80% of children in each group had a circulating retinol level of <0.70 μmol/L. All deficient levels were corrected at one month into the trial, and remained corrected in the single-dose and the 8 g of oil daily treatment arms at three months. In the 4 g of oil daily treatment, one third of the children had returned to a deficient serum retinol status by three months of observation. In a biological interpretation, this study argues for a functionally lower equivalency than the theory of RAEs. In a practical sense, one could institute periodic 15-day intervention sequences every 3 months (or once weekly over 12 week) with the 8 g doses of this variety of RPO to achieve the protection that an annual 200,000 IU capsule would provide.[29]

The basis for a more consistent and constant supplementation with the dietary vitamin A potential of RPO has been shown by the same research group in an experience in the same setting in which two months of administration of 600 μg of retinol and 2400 μg of mixed carotenes for 60 days.[56] Interestingly, the design of the experiment was based on local, Indian conventions in which the bioefficacy for food carotenoids had been promoted as 25%,[57] rather than the 16% of the U.N. agencies for beta-carotene. So, the two arms were considered by their authors to be equivalent in dietary vitamin A delivery. In the era of the DRI,[38] and assuming a full beta-carotene potency for all of the provitamin A in the oils, the group receiving deodorized - deacidified crude RPO daily would have received twice the net RAEs as the former group, or at least 1.5 times based on the conventional partition of beta- and alpha-carotenes in red palm oil.[25] Serum retinol levels rose by an equivalent amount, more than doubling over the 2 months of intervention, and modified retinol dose response tests improved dramatically and equivalently as a reflection of accumulating hepatic liver reserves of the vitamin.

In an RAE perspective, the children in this second Orissa

study,[56] were on a pro-rated annual daily dosage rate of 3.5 to 5.0-fold greater than the pulse experiment with 8 g of the oil over 15 days in a 3-month period.[55] The programmatic lessons derived in this constant-day intervention trial is one of functional equivalency between the doses and cumulative dosages. Although the RPO would be intrinsically safe, no matter what the cumulative dosage, it is likely that adequate hepatic reserves could be made with RPO cumulative dosing rates lower than either of examples in the Orissa trials. Effectiveness studies would be in order to titrate the dosing into an effective range, still economical of the total utilization of the RPO resource in the population.

Red palm oil as an enhancer of breast milk vitamin A

Among the aims for supplemental vitamin A (Table 4) is that of applying to the nutriture of the lactating mother a supply of the vitamin to enhance the vitamin A content of the breast milk and through this the nutritional status of the nursing infant. Conventionally, high-dose supplements of retinyl esters, applied in the immediate postpartum period, are the modality for this measure in public health application. It is well documented that intakes of retinoids in amounts even as low as 3-6 mg can produce embryonic malformations, with fetal loss or birth defects. The "window-of-opportunity" is generally promoted as 6 wks (42 d) following delivery, based on the biological and cultural assumptions that intensive lactation will preserve amenorrhea and suppress ovulation and that intercourse taboos will obtain in the early postpartum interval. Given the success as a proxy for retinyl palmitate in prophylactic supplementation in children and the inherent safety from hypervitaminosis A teratogenesis of precursor sources of dietary vitamin A, it was logical to examine the potential for contribution of RPO to enhancing vitamin A content of human milk.

Honduras was the site for a series of short-term studies with RPO interventions in lactating women[58,59] with multiple-oral doses (from 2 to 12 doses, but all providing a cumulative dose of 90 mg of beta-carotene) of provitamin A carotene either in the form of red palm oil or a capsule of purified beta-carotene in a capsule. The studies had a convoluted design with different sources given at different sites and follow-up of blood and milk variables at different intervals, as well. There was no, no-treatment group, and the assumption that with no intervention, there would have been a flat response was the "virtual" normative condition of reference.

In the RPO situation, women received their 90 mg of beta-carotene in six doses over 10 days. This treatment provided similar patterns as the other formats, namely a significant increase in maternal milk beta-carotene, 2.8-fold, as well as in serum beta-carotene, 2.5 fold. Comparable increments in milk and blood alpha-carotene occurred. Importantly, in the infants, circulating retinol levels increased at 10 days of follow-up. This all occurred without any changes in maternal serum or milk retinol nor infant serum carotene levels. A similar study, with a more rational and improved design was conducted by Gossage *et al*.,[60] among North American lactating mothers, in which 10 women received a daily supplement of isolated beta-carotene and 10 a placebo capsule beginning on day 4 post-

Table 4. World health organization guidelines for high-dose prophylactic and therapeutic supplementation with vitamin A

	Dose in IU	Dose in RE
Treatment of xerophtalmia		
Immediately on diagnosis (day 1)		
< 6 months	50,000	15,000
6 – 12 months	100,000	30,000
> 12 months to adulthood	200,000	60,000
Women to reproductive age[a]		
Next day (day 2)	Repeat age-specific dosage	
At least 2 weeks later	Repeat age-specific dosage	
Treatment of complicated measles		
Immediately on hospitalization (day 1)		
< 6 months	50,000	15,000
6 – 12 months	100,000	30,000
> 12 months to adulthood	200,000	60,000
Next day (day 2)	Repeat age-specific dosage	
Prevention schedule for high-risk populations		
Infants < 6 months[b] (once)	50,000	15,000
Infants 6 – 12 months (once)	100,000	30,000
Children > 12 months to adulthood (every 4 – months)	200,000	60,000
Postpartum mothers (once)[c]	200,000	60,000

[a]For women of reproductive age, night blindness and Bitot's spots can be treated with a modified dose of 10,000 IU/day (3000 RE) or 25,000 IU/week (7500 RE). With corneal involvement the same regimen as other adults would be used. [b]This is recommended for non-breast fed infants and those whose mothers have not been reinforced with a postpartum supplementation dose; [c]To be administered within 56 days of delivery. Source: Solomons[40]

partum and continuing for 4 weeks. Seven milk samples were collected and analyzed for retinol and beta-carotene. There were no differences in beta-carotene concentrations over time, nor as a result of supplementation. The authors speculate that the milk's carrying capacity may be saturated and not allow for any further accumulation.

In Tanzania, Lietz *et al*.,[61,62] conducted a longer-term intervention trial in lactating African women in which three treatments were applied. In one group, received only dietary advice about leafy vegetables, beginning 1 month into lactation. In a second group, received the advice and a family supply of sunflower oil which should allow the target woman to receive 12 g of oil from the food prepared in her home. The final group received 12 g of RPO in a similar format. A compliant mother in the oil groups should have received a cumulative dose of 720 g of oil from the study. With respect to the response in milk carotenes, over a 2-month interval, at three months, there was a three-fold greater beta-carotene and a five-fold total carotene content of the milk in the RPO group. In terms of milk retinol, normalized for milk fat, there was a significant decline in milk retinol from 1 to 3 months of lactation, an effect not seen in either group consuming the oil supplements. But, sunflower and palm oils were equivalent in terms of milk

retinol per gram of fat. That is to say, the presence of provitamin A in the RPO treatment produced no differential improvement in the preformed vitamin A content of the milk. Since there was abundant tocopherol and tocotrienols in the depigmented oil, the authors speculate that it was the antioxidant content that "promotes" retinol levels in breastmilk. Of course, the infant is capable of using carotenoids for vitamin A, so the impact at the level of the "final consumer" may still have been important, although undetected.

Moreover, it has been difficult to demonstrate any impact on breastmilk vitamin A even in interventions in lactating women involving oral administration of *preformed vitamin A*, itself. In a study in lactating Bangladeshi women[63], it took 10 months of supplementation, either with retinyl palmitate or beta-carotene, before any effects on breastmilk chemistry were seen. By that time, infants were already consuming a mixed diet including complementary foods along with maternal milk. Leitz and colleagues[61] suspect that mobilization of beta-carotene-derived vitamin A to the milk is a slower biological process in the mother.

The safety issues of teratogenesis from poorly-timed high-dose retinoid exposure in the early postpartum period still weigh on public health judgement. Provitamin A would be an intrinsically safer approach. Hence, some further investigations are in order, tinkering with the dosage, frequency and vehicle for the provision of provitamin A from RPO to determine whether any efficacy, comparable to that achieved with the preformed vitamin A in high-dose supplementation, can be realised.

Beta-carotene and reduced maternal mortality

The reduction of maternal mortality of low-income mothers giving birth would be if anything, a functional index of a vitamin's nutritional effect, and is not a well-recognized manifestation of hypovitaminosis A in populations. Nonetheless, a large epidemiological study on intra-pregnancy fortification with vitamin A in Nepal[64,65] – primarily interested in the eventual effect on the health and nutrition of the *infants*, not the mothers – provided serendipitous findings of importance for maternal health. The intervention included arms with both preformed vitamin A and pure beta-carotene (not in an RPO format). Whereas the intra-pregnancy morbidity experience of the mothers was unaffected by the administration of vitamin A, maternal mortality was reduced significantly overall by 44%, and the maternal mortality rate decline 40% overall from 645 deaths/100,000 live births to 385. There was, indeed, a slight – but not statistically significant – tendency of a greater survival with the beta-carotene form of supplementation, with a 49% reduction in that treatment group as compared to 40% in those receiving preformed vitamin A. Curiously, a post hoc analysis of data on illnesses experienced during lactation revealed that both interventions significantly reduced postpartum diarrhoeal symptoms and beta-carotene (but not vitamin A) decreased the incidence of fever in the postpartum period. If confirmed by current follow-up trials in Ghana and elsewhere, one could consider the convenience of RPO as the carotene source being the basis for the vehicle of intervention at the programmatic level in future public health policy initiatives to reduce maternal mortality in low-income societies.

Red palm oil as a food fortificant

In India, a host of settings for food-to-food fortification with RPO have been catalogued by B.S. Narasinga Rao,[52,53] beginning in the colonial period, to explore the use of RPO in diets for the expressed purpose of enriching the diet with vitamin A. The studies in India could be considers as "effectiveness" studies in which the process indicators of acceptability and compliance have been used. Few sensitive and consistently applied markers of vitamin A status are included. The Indian-developed deodorized and deacidified crude palm oil was the subject of studies conducted in the governmental system of community benefit (Integrated Child Development Services), in which different amounts of the oil intended for individual consumption of school children or mothers, ranging from 4 to 10 g of palm oil daily, depending on age and district, have been evaluated.[52] In some pilot trials, blending of palm oil into other standard oils, was tried to increment carotene intakes. Although some recipes were created and children were exposed to the oils, either in home-prepared meals or supplemental meals in schools, it was clear that the taste and odour of the oil, compared to the usual household cooking oil, placed it at an acceptability disadvantage.

The molecular distilling process that creates Carotino, the Malaysian product, eliminated the detractions in flavour and smell for the Indian consumer.[53] In the state of Andhra Pradesh, a private-public partnership to create ready-to-eat food snacks, enriched with the nutrients of Carotino. These products are based on wheat, soy, and sugar, and variously combined with bengal gram, milk powder and maize to form varied snacks.[53] The palm oil was more compatible with the extruded product, as compared to the powdered forms.

An important commentary by Dr. Narasinga Rao is that domestic production of palm oil in India is low.[52] Importation would be needed to meet the distributive demand. One must conclude that, unlike West Africa or tropical Brazil, in which the disagreeable organoleptic properties of the crude palm oil have been accepted into the culture and cuisine as normative, Indian households are loath to embrace the unrefined oil. Efforts are planned to extend the experience in vulnerable groups with food-to-food fortification with the Carotino model.

An interesting experience in food fortification with RPO as the baking shortening in confectionery baked goods has been shown in South Africa at both the food technology and biological level. Benadé[66] reported studies on the 13 baked items ranging from shortbread cookies with 27% fat by weight to banana loaf with 10.8% fat, with other items including fruit cake and carrot cake and plain and oatmeal cookies and crackers among them. For both 7-10 year-old and older children as references, using RPO in the baking allowed the final products, as analyzed, to provide more than 20% of the respective RDAs for vitamin A. This was, of course, using the bioconversion assumptions of retinol equivalents. A three-fold higher value of the contributed vitamin A might now be calculated,[38] with a tripling of the RDA contributions from each of the items.

The same South African research group from the Medical Research Council, has conducted a longitudinal field study in schoolchildren of the ZwaZulu-Natal province in which provitamin A-fortified cookies were fed during the

school-attendance periods over several school cycles.[67,68] In a first-phase study, in which synthetic beta-carotene, providing 2.1 mg per day, in a cookie snack was provided for 12 months, the rate of low serum retinol (< 0.70 μmol/L) were reduced from 40% to 12%, in the intervention group while remaining constant at about 40% in the group with the unfortified cookie.[67]

In a second-phase study, the RPO-shortening, with 400 ppm of total mixed carotenoids, was used to prepare the school-intervention cookies, as a third group for comparison to an unfortified cookie and the original cookie with synthetic provitamin A carotene.[68] Baseline rates of low retinol values were milder in this second study, with prevalences before intervention of 16-18%. These were lowered significantly and comparably from 17.7 to 4.6% after 3-months of intervention with the synthetic beta-carotene cookies and from 15.8 to 6.8% with the RPO biscuits. The control children had no significant reduction in abnormal retinol status.

Studies in Guatemala: listening to the culture

As noted, the United Fruit Company, in the early 20th century, explored the production of the palm fruit throughout the length of the Central American Isthmus.[27] In Guatemala, a local production and commercialization of oil from the palm fruit is just beginning in a serious effort. Cultivation of palm fruit in our country is now occurring in several of the low-land provinces, and a refined (clear) palm olein product is being produced by one of the national edible oil manufacturers.

The concept of food-to-food fortification has been articulated.[52] Looking in Guatemala for an analogy to the application in "vanaspati" in India, that is, could a dietary setting be found to use RPO in Guatemalan cuisine. To begin with, we asked a series of questions about the barriers to effective use of RPO that led to the project which is currently underway at CeSSIAM. The obvious one was its being *red* in colour; the pigments represented by the carotenoids were the substances of interest, but pigmented ("red stained foods") might not be appealing in all formats. A vehicle that was either red itself – or of a deeper colour that would obscure the carotenes' hue – would be ideal. Second, since the bioconversion efficiency depends upon the carotenoids' remaining in their oily matrix, the format would have to be a liquid or gel, not a dry or dried item. Moreover, for constraining the costs, reducing caloric load, and keeping the issue of atherogenicity out of the conversation, the vehicle would have to have a minimum contribution of calories from RPO.

With the collaboration of the Malaysian Palm Oil Promotion Council, we identified some practical formulations for chunk-style sauces. One was based on tomatoes and was to be a sweet, chunky tomato sauce of deep red colour with 0.8% of its weight as Carotino RPO. The other was based on husk tomatoes, and was to be a hot and spicy, green sauce which had 1.2% of its weight as RPO. The food-preparers from low-income households both in Guatemala City as well as in the rural areas outside of the metropolitan zone were enrolled as informants in recipe-creation surveys. The volunteers were given a standard aliquot of 245 mg of one or the other sauce and asked to prepare that evening's main-dish for the family meal using or serving the sauce. Information collected later included acceptability of the product among the family members, the ingredients in the main-dish served and the manner of its preparation, and how many consumers partook in the meal.

The findings among a total of 30 recipes with the red-coloured tomato sauce is that homemakers liked the chunky sauce and used 100% of their supply in the meal. By contrast, with respect to the response in the homes to receiving the spicy green-coloured sauce, the heads of household were reluctant to create recipes for the principal meal as the opportunity for serving the condiment. Rather, it was most often used as a garnish to the components of the meal by the adolescent and adult members of the family, not by the younger children. A typical serving of red sauce delivered 127 RAE of vitamin A activity, whereas that for green sauce, when combined into the dish, delivered 199 RAE of vitamin A activity. For those situations in which consumers used individual servings of the hot sauce with their food, we could make no estimates of individual exposure to the RPO-derived carotenes.

As a way to provide RPO in an acceptable format for Guatemalan cuisine, condiment sauces are promising. To target an intervention to adult members of the family, making the sauce spicy would provide result in some deviation of the nutritional benefits from the younger members of the household. The small amount of oil included into the sauce recipes was a limiting factor in delivering the nutrient benefits of the RPO to the consumers of meals offered with these experimental condiments. A panel of consumers showed that the oil content of the sauces could be increased three-fold without any major reduction in acceptability. Such a tack would triple the per person consumption of dietary vitamin A from palm oil. Using extracted carotene concentrate, rather than standard Carotino, would be an approach with major potential to increment the vitamin A value in sauces. Moving to greater deliveries of carotenoids from the basic sauce recipes seems to be the next step in bringing this intervention from the experimental stage to one of application to the population.

Provitamin A carotenes are a particularly appealing approach to increase the dietary vitamin A in the Guatemalan context, as there is a mandated fortification of table sugar with vitamin A in place. The quality and consistency of sugar fortification varies both in relation to time since harvest and from year to year of operation. When sugar fortification is in optimal operation, adding more preformed vitamin A to other dietary items might risk excessive enhancement of the food supply; hence, the provision of precursor forms of vitamin A from carotenes in oil allows for homeostatic regulation of bioconversion based on need. On the other hand, if the fortification program were ever to weaken or disappear, the population would return to its historically vulnerability for hypo-vitaminosis A. The same foundation of dietary pro-vitamin A in RPO-containing items would become more active in its yield of active vitamin to the population.

Potential future directions

The development of fatty fruits in northwest Africa has brought nobility and prestige to the region. The application of these foods to diversify diets in a world, in which the variety of different items consumed by low-income groups

is reduced[4], can bring a number of benefits. All that is needed fully to realize this potential is creativity of ideas and investment in metabolic, food technology and behavioural research. From our own store of experience, based on the situation of Central America and our research paradigms and approaches, we present a series of futuristic projections.

Altering the palm fruit's genetics

The theme of genetic modification of plants has produced a global confrontation about their safety both as foods for the consumer and as part of the flora in the environment.[69] It has been argued that part of the popular resistance arises from the fact that improvements have been designed to improve the characteristics of the plants as crops (pest resistance, decreased requirement for fertilizer, increased yield), but not as foods (better nutritional quality, more preventive substances; lower disease promotor content). Acceptance of GMOs would be increased, follows this argument, to the degree that the benefits for the human consumers were headlined.[70,71]

The avocado and the olive are both fatty fruits which are edible as such. It is possible, indeed, that modification of the palm fruit could add characteristics of flavor and texture that would make it an "eating fruit" like a peach or tomato. In fact, a fatty fruit, native to Vietnam, the "gac" (*Momordica cochinchinensis*), is an even denser source of available provitamin A, consumed as a fresh fruit snack.[72] Just as adding micronutrients to food staples has value added,[73] intensifying the yield of vitamins from their specialty sources also contributes to the extent these items play any role in an individual's usual diet. In this respect, occasional consumption of such a fruit would serve, as does occasional consumption of beef liver in affluent populations, to be the primary vitamin A source for an individual's hepatic stores.

Provitamin A and iron absorption

A new nutrient-nutrient interaction of potential public health important is that of simultaneous consumption of vitamin A with dietary inorganic iron.[34] Underlying this is the fact that iron deficiency is the most widespread nutrient deficiency of humankind. In the Venezuelan studies, improved bioavailability of food iron has been demonstrated with extra consumption of vitamin A in the iron-containing meal.[74-76] Indeed, not only of retinyl esters (preformed vitamin A) but also dietary vitamin A of carotenoid origin is an effective enhancer.[75] A fortuitous by-product of any co-mixture of RPO with poor quality diets could be a boost in the efficiency of iron absorption and an alleviation of the nutritional anemia problem, as well.

Microencapsulated carotenoids

The deep colours of carotenoid pigments limits the foods and meals with which they can be combined in high amounts.[30] Preformed vitamin A is basically colourless. The acceptability of a food may decline with the consumer if it is off-colour from the anticipated and customary hue. For instance, adding beta-carotene in dairying would produce a salmon-coloured cow milk which would be of dubious acceptability to the public. So, for foods that are too light in colour to obscure and disguise the intense carotenoid pigments, micro-capsulation is an option. This has been demonstrated for iron.[77] It is a variety of nanotechnology that consists of coating the micronutrient of interest with an edible, and easily soluble in acid, coating. The counter-colour of the coating would be that of the vehicle, e.g. white in the case of milk, to disguise the carotenoid pigment. The cost of this micro-encapsulation may be a limiting factor, but the food technology for this innovation should be pursued.

Therapeutic use of high-dose provitamin A in oil

As shown in Table 4, the therapeutic indications for high-dose vitamin A, namely in xerophthalmia and measles. We have so far not covered the topic of applying RPO beyond a prophylactic context in therapy for medical emergencies. Advanced xerophthalmia (keratomalacia) is a blinding process, irreparably damaging a child's eye. The use of plant sources of vitamin A for treatment of keratomalacia has a long history. In the absence of cod liver oil or isolated retinyl esters, Indian clinicians were able to improvise with freshly-prepared green leafy vegetables to control the xerophthalmic lesions in the late 1970s.[78] A similar experience in North East Brazil using a carotene-rich fruit, buruti,[79] was reported in the late 1980s. Antedating this by several decades, however, is experience in the south of India, in which colonial service physicians in Madras in the 1930s found an emulsion of 5g of crude red palm oil, flavoured with glucose and peppermint oils, was equivalent to cod liver oil in resolving problems of keratomalacia.[80] One might speculate, as to whether or not oil-based carotenes would be effective alternatives to retinyl-ester capsules, to recommend for therapy of medical emer-gencies.

In the situation of xerophthalmia, the body's need for vitamin A would clearly be high. However, this ocular complication is often associated with severe protein energy malnutrition or persistent diarrhoea, in which the condition of intactness of intestinal integrity to effect absorption and bioconversion of the carotenes might not be fulfilled.

The situation of measles and therapeutic doses of vitamin A is even more complex. Measles is often associated with an intestinal lesion and diarrhoea that could reduce the response of intestinal bioconversion. Moreover, the underlying vitamin A status is not a consideration. This recommendation (Table 4) obtains for complicated measles occurring in affluent countries such as the United States. Hence, although one might expect a homeostatically down-regulated bioconversion of provitamin A in oil in a measles-afflicted child, getting high-dose vitamin A into the system is still required. Only *preformed* vitamin would be able to guarantee with assurance the achieving of this pharmacological mission.

Only as a last resort, in the absence of pharmaceutical alternatives, improvising with any rich source of provitamin A would be preferable to not doing anything to prevent the progression of ocular damage or complications of measles, but the best medical practice would be the use of preformed vitamin A (retinyl esters) in both of these serious illnesses. One could argue, moreover, that the sight-threatening and life-threatening aspect of such illnesses would make "*eradication*" of the threat a priority over "alleviating" the situation. A more radical framework is called for and the conventional retinyl ester preparation is the medicine of

choice. As long as distribution systems for high-dose vitamin A capsules remain intact, there is no compelling reason to probe the effectiveness of fatty fruit sources for medical therapy.

Summary and Conclusions

Where resources are scare and health needs are multiple, the less aggressive notion of *"alleviating"* the various competing public health menaces – rather than concentrating on one or another to the exclusion of the rest – is the appropriate *triage* for a deprived society. Endemic hypovitaminosis A is a widespread affliction. In an oil base, alpha- and beta-carotene actually can yield three times more vitamin A activity than was previously thought.[38] The risks of hypervitaminosis A (overdose) is negligible, and availability of palm fruits from local cultivation is inherently more sustainable than that of having an imported chemical pharmacological agent, such as pure retinyl ester preparations.

The agriculture is a system that provides better caloric security than its hunter-gatherer predecessor. The transition has sacrificed food diversity and micronutrient adequacy. Accumulated experience shows that RPO can function in situations of prophylactic supplementation and food fortification. With respect to the former, in the domain of a high-dose nutrient supplementation for short-term redress of endemic hypovitaminosis A, RPO sources should be able to replace preformed vitamin A. There are varieties of *Elaeis* in South America with manifold higher concentrations of pro-vitamin A carotenoids, with more potency per gram of oil.[26] Moreover, the Monsanto Co. developed a genetically-modified canola (rapeseed) oil which incorporates pro-vitamin A carotenes in extraordinarily high concentrations.[30]

Meanwhile in the domain for fortification, for those industrialized countries that have eliminated micronutrient malnutrition, it has come on the platform of widespread addition of the nutrients as chemical additives.[16-18] Low-income countries do not have the luxury of this technology nor do they rely on processed foods. The concept of food-to-food fortification, in which a nutrient-dense food is added to nutrient-poor items, seems to be tailored to the reality of developing societies. Substantial progress could be made with concerted efforts to extend and refine this experience. Even in the diversification of diet, palm oil and its derivatives might be able to contribute.[53]

The palm fruit (*Elaeis*) is clearly a food with a high density of available provitamin A and vitamin E vitamers.[24] The creative imagination of public health nutritionists, food technologists, and even plant geneticists is the element needed to carry this potential further.

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