Carotenoids
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Chapter 9

Vitamin A and Vitamin A Deficiency

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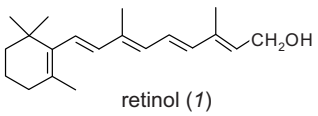
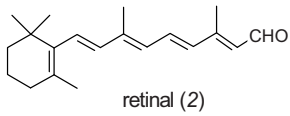
A. Introduction

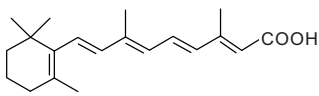
Vitamin A is an essential factor for development, growth, health and survival. Vitamin A (retinol, *1*) and its chemically and metabolically related forms retinal (*2*) and retinoic acid (*3*) play essential roles in such diverse processes as vision and cell regulation.



retinol (*1*)



retinal (*2*)



retinoic acid (*3*)

The role of retinal as the chromophore of the visual pigments such as rhodopsin has been investigated intensively and is summarized in *Volume 4, Chapter 15*. It is well understood, therefore, why prolonged deficiency of vitamin A can lead to reversible night blindness that may be followed by irreversible loss of sight. It is also well understood that vitamin A is a factor in maintaining immunocompetence and that retinoic acid is an essential hormone-like factor in regulation of gene expression in relation to growth and development. Not surprisingly then, vitamin A deficiency (VAD) can have very serious consequences.

Although much of this book deals with those aspects of nutrition and health that are of most concern in richer countries where food is plentiful, we must not forget that ensuring adequate supplies of vitamin A or provitamin A in poor countries to prevent the scourge of vitamin A deficiency remains the most important life-or-death aspect of carotenoids and health. To lose sight of this fact is unforgivable.

Any attempt to cover the subject of vitamin A and vitamin A deficiency comprehensively would take up at least a full volume, not just a short chapter. The subject of vitamin A deficiency has a long history and an extensive literature, including a number of important books [1-4], and reports from International Agencies [5,6]. These should be consulted for details of symptoms and clinical lesions, and for results of surveys and trials in various parts of the world. Sight and Life, in addition to initiating and supporting programmes, provides authoritative and very readable reviews and research reports on all aspects of VAD as well as specific topical reports and developments from all over the world in *Sight and Life Newsletter* (now *Magazine*).

This *Chapter* is not a new analysis of the subject and its primary literature; this has been digested and evaluated by leading authorities who are much more experienced and expert. Rather, it will summarize the main features in a way that seems appropriate for a chapter in a book on carotenoids. It should also be considered together with the detailed treatment of the conversion of the provitamin carotenoids into vitamin A, and evaluation of conversion factors, presented in *Chapter 8*. The topic is of global importance and is a matter of life or death for millions, especially young children. Vitamin A deficiency and the battle to overcome it perhaps has the most important consequences of any involvement of carotenoids in human health.

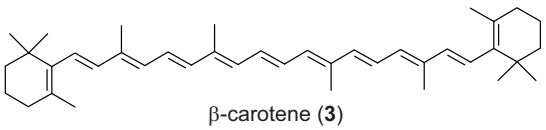
B. Vitamin A

1. Basic biochemistry

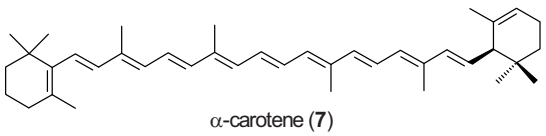
The biochemistry of vitamin A is discussed in detail in reviews (*e.g.* [7,8]). Only a brief summary of the main features is given here.

Vitamin A, retinol (*1*), may be obtained from the diet either as 'pre-formed' vitamin A itself, or as the provitamin, β-carotene (**3**) or other carotenoids containing an unsubstituted β end group, especially α-carotene (**7**) and β-cryptoxanthin (**55**). Nutritional aspects of the conversion of β-carotene into vitamin A are described in *Chapter 8*, including a detailed evaluation of conversion factors and methods for determining them, and of the factors that regulate or influence the efficiency of the conversion. The biochemistry and molecular biology of the central (BCO1) and excentric (BCO2) cleavage enzymes are described in *Volume 4, Chapter 16*. Information in *Chapter 18* complements and extends the outline of the

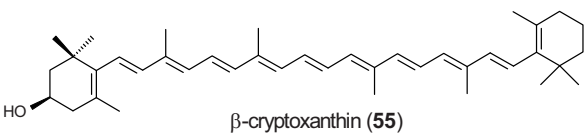
roles of vitamin A, of retinal (*2*) in vision, and of retinoic acid (*3*) as a hormone-like regulator of gene expression in growth and development that was given in *Volume 4, Chapter 15*.



β-carotene (**3**)



α-carotene (**7**)



β-cryptoxanthin (**55**)

The enzymic conversion of the provitamin carotenoids into vitamin A is strictly controlled. A major regulatory factor is blood retinol concentration (*Chapter 8*) so that retinol is only formed from the provitamin when it is needed to maintain an adequate concentration and cannot build up to toxic levels.

In the intestine, retinol, either formed from the provitamin or obtained direct from the diet, is absorbed along with other lipids and transported in chylomicrons to the liver where it is stored as esters, mainly the palmitate [9,10]. Some 10-20% is stored in specialized lipid globules in hepatocytes, but the bulk is stored, also in lipid globules, in stellate cells. Some other tissues have some limited capacity to store retinyl palmitate, also in stellate cells [7-10]. When vitamin A intake is low, the efficiency of recycling is high, so that losses from the body are minimized [11].

When vitamin A is required by tissues, the stored retinyl palmitate is hydrolysed and the free retinol is delivered to the tissues by the specific transporter retinol-binding protein, RBP [12-14]. The 21.2 kDa protein, apo-RBP, is made and stored in the liver. Holo-RBP, with the retinol ligand bound, forms a 1:1 complex with another protein, transthyretin, and this complex delivers the retinol to the cells [15]. The blood concentration of RBP is strictly controlled at a constant plasma concentration around 2 μmol/L in a well-nourished adult, so that the amount of retinol delivered to the tissues is limited, as a safeguard against toxicity. Other, related proteins, cellular retinol-binding proteins (cRBPs) and cellular retinoic acid-binding proteins (cRABPs) are responsible for the controlled transport of these ligands within cells [9]. In extreme protein malnutrition, the body may not have sufficient amounts of these

proteins, so tissues may be deficient in vitamin A even if the dietary supply of vitamin A is adequate.

When large amounts of retinol are ingested, *e.g*. in high-dose supplements, high concentrations of retinyl palmitate are incorporated in chylomicrons and some may bypass the controlled RBP transport system and be delivered to tissues, along with other lipids. The high doses lead to a marked increase in retinyl ester concentration in plasma, though the controlled RBP concentration is maintained.

2. Vitamin A status and requirements

It is customary to use serum retinol concentration, usually given as μg/dL or μmol/L, where 1 μmol = 286 μg, to define vitamin A status [4]. The usual correlation is that a retinol concentration above 20 μg/dL (0.7 μmol/L) is considered as 'normal', 10-20 μg/dL (0.35-0.7 μmol/L) low and <10 μg/dL (<0.35 μmol/L) deficient. Values around 20 μg/dL are often considered as 'marginal'. These are not universal absolute values; deficiency symptoms may be seen in some individuals with >20 μg/dL, but not in some other individuals with low values. In a population with low to marginal average concentration, cases of sub-clinical manifestations (Section **C**.3) are likely to occur and, with 'moderate deficiency', *ca*. 10 μg/dL, cases are almost certain and signs of xerophthalmia (Section **C**.1) are likely to emerge.

To express both preformed vitamin A and provitamin A concentrations in food *etc*., several terms are used. The retinol equivalent (RE) was introduced and is defined as equivalent to 1 μg retinol or 6 μg β-carotene or 12 μg of other provitamin A carotenoids, based on the then accepted conversion factor [16]. This was superseded by the RAE (retinol activity equivalent) to allow for the fact that the conversion factor for β-carotene from food was much poorer than previously thought [17]. 1 RAE (1 μg retinol) is equivalent to 12 μg (all-*E*)-β-carotene or 24 μg other carotenoids. Also used, especially for expressing the size of supplements, is the International Unit (IU) which is defined as equivalent to 0.3 μg retinol or 0.6 μg β-carotene.

Because of variability due to many factors, it is not possible to give a definite universal value, most evaluations indicate that a daily intake of around 300-375 RE of retinol is necessary to maintain adequate liver stores and is considered safe for infants [8].

3. Hypervitaminosis A: toxicity

It is well known that, in excess, vitamin A is extremely toxic. Intake of a large single dose (>0.7 mmol, 200 mg, 660 000 IU, by adults, half this dose by children) may cause some rapid, acute effects including nausea, vomiting, headache, muscular incoordination, and blurred vision [18,19]. Some infants are affected by a dose of only 0.1 mmol. The symptoms are usually transient, lasting only about a day. Extremely large doses (*ca*. 500 mg) rapidly cause drowsiness, skin exfoliation and itching. Repeated intake of large doses or recurrent intake of smaller doses, *i.e*. 0.13 μmol, 3.75 mg, 12 500 IU (>10 x RDA), leads to chronic hyper-

vitaminosis, and severe effects such as defective bone structure and osteoporosis [20], and liver damage. Fatal consequences are likely.

Excess vitamin A also causes serious teratogenic effects [21,22]. It is likely that a single extremely large dose or a week of high daily doses of 30-90 mg in early pregnancy will lead to foetal malformation and birth defects. Healthy women who routinely eat a diet containing adequate amounts of vegetables and fruit do not require supplements of vitamin A during pregnancy. When dietary intake is low and supplements are advisable because of low vitamin A status, the daily intake of preformed retinol from all sources should not exceed 10 μmol (3 mg, 10 000 IU).

C. Consequences of Vitamin A Deficiency

Historically, vitamin A deficiency has been associated with blindness, especially in young, pre-school children. Indeed, night blindness, the inability to see in dim light, was for long used as the first indicator of vitamin A deficiency. It could easily be explained; if vitamin A is deficient, it is not possible to make up for losses during the visual cycle of the retinal-opsin visual pigment rhodopsin in retinal rod cells (*Volume 4, Chapter 15*). This condition could be reversed rapidly by providing vitamin A supplements. If the vitamin A deficiency is more severe and prolonged, it leads to structural changes in the eye, as described in the various stages of xerophthalmia (see Section **C.**1), and to permanent, irreversible blindness.

Serious and debilitating as they are, these effects are not in themselves life threatening. It is now recognized that vitamin A deficiency has other profound consequences, leading to increased morbidity (susceptibility to serious life-threatening diseases) and mortality (death from these diseases).

A history of studies of xerophthalmia and its control [23] provides a stimulating introduction to the topic, and highlights lessons that have been learned and lessons still not learned.

1. Xerophthalmia

The term ‘xerophthalmia’ literally means ‘dry eyes’, due to all causes, not only vitamin A deficiency. During the past 30 years or so, the definition has been standardized [24] so that ‘xerophthalmia’ now includes all ocular signs and symptoms of vitamin A deficiency, from night blindness to keratomalacia (successive softening, ulceration and necrosis of the cornea). A manual provides a guide to recognition of the signs and lesions characteristic of the various stages of xerophthalmia [25]. A series of stages of increasing severity have been classified [6], as listed in Table 1, and related to vitamin A status, defined by serum vitamin A levels [4]. Note that this is a continuum, and there is some overlap between the vitamin A levels associated with the various stages. The Table shows the mean ranges determined in most

surveys, but some values are outside these ranges [4]. A study in Indonesia found a significant incidence of mild xerophthalmia in pre-school children with serum retinol levels above 20 μg/dL [24].

Table 1. Stages of xerophthalmia in order of increasing severity (based on data in [4]).

Stage	**Serum retinol (μg/dL)**
Normal	>20
Night blindness (XN)	10-20
Conjunctival xerosis (X1A)	10-20
Bitot's spots (X1B)	10-20
Corneal xerosis (X2)	5-10
Corneal ulceration/keratomalacia, <33% (X3A)	5-10
Corneal ulceration/keratomalacia, >33% (X3B)	5-10
Corneal scar (XS)	5-10
Xerophthalmic fundus (XF)	5-10

The first four stages (XN, X1A, X1B and X2) are usually reversible by provision of vitamin A. The later effects are much more severe and the damage cannot be reversed.

2. Keratinization

a) Eye tissues

In the more advanced stages of xerophthalmia, the epithelial surfaces of the conjunctiva and cornea undergo keratinizing metaplasia and become dry, hardened and scaly as abnormal keratin synthesis occurs. This leads to irreversible damage to these and other eye tissues and blindness becomes permanent.

b) Other epithelial tissues

One of the functions of vitamin A is to maintain the condition of the skin and various mucus-secreting epithelial tissues. The keratinizing metaplasia associated with vitamin A deficiency extends not only to destruction of the cornea and other eye tissues but to other mucus-secreting soft epithelial tissues, notably the respiratory and genito-urinary tracts, which become keratinized. The terminal differentiation of skin keratinocytes is markedly affected and larger, harder keratins are produced [26].

3. Subclinical, systemic effects

In addition to xerophthalmia, which is a relatively late manifestation of the slow depletion of vitamin A stores [27], vitamin A deficiency leads to anaemia, growth retardation, and increased incidence and severity of morbid infections, thereby resulting in reduced childhood survival, the most severe consequence [1-4]. These effects may appear before any sign of xerophthalmia is detected. Increasing vitamin A status is now considered to be one of the most cost-effective measures for reducing childhood mortality, which is currently about 14 million *per annum*.

There is overwhelming evidence that vitamin A status influences the incidence or severity of a variety of infections, particularly diarrhoea, measles, urinary tract infections and some forms of respiratory diseases. The keratinizing effect of vitamin A deficiency on epithelial tissues and linings may impair the natural barriers against infection. But the rapid response to treatment of existing infections indicates stimulation by vitamin A of defences against established infections, *i.e*. an immune response.

Whereas the appearance of xerophthalmia is readily detected, in its absence vitamin A deficiency is more difficult to diagnose. The association between severe xerophthalmia and increased mortality has been recognized for a long time. Xerophthalmia is not the direct cause of this mortality, however: both are consequences of vitamin A deficiency. The relationship between VAD and infection is complicated by the fact that not only does VAD increase susceptibility to infection but frequently infection leads to reduction in vitamin A status and lowered serum retinol concentration. Also vitamin A deficiency is difficult to dissociate from general malnutrition (protein - energy malnutrition, PEM).

Even when vitamin A deficiency is only marginal, and no visible signs of xerophthalmia are detected, other effects of the deficiency may be serious. Providing sufficient vitamin A to raise the serum retinol concentration from 18-20 μg/dL to 30 μg/dL can reduce mortality rates by as much as 50% [4]. The most serious consequences of the deficiency are described briefly below.

a) Measles

In poor countries, measles is a severe and life-threatening disease [4]. The incidence and severity of measles and its associated pneumonia and diarrhoea in young children are strikingly related to vitamin A status and are increased by VAD. Measles infection has a deleterious effect on serum vitamin A level, leading to severe vitamin A deficiency. Treatment with vitamin A promotes recovery and reduces mortality by 50%. It affects the severity of the disease rather than the incidence of measles.

b) Diarrhoea/dysentry

Because of often appalling living conditions, diarrhoea is a common affliction in poor communities, especially among children, and has a high death rate [4]. The severity of this serious condition is closely related to vitamin A status, and the severe diarrhoea exacerbates the depletion of vitamin A supplies. Vitamin A supplementation reduces diarrhoea-specific mortality. Improvement of the vitamin A status of deficient populations protects pre-school age children from severe, dehydrating, life-threatening diarrhoea, but may have little impact on the frequency of 'trivial' (*i.e*. not life-threatening) diarrhoeal episodes.

c) Respiratory infections

Here the situation is not so clear but results are consistent with a relationship between vitamin A deficiency and risk of respiratory infection. Also, results following supplementation suggest a potential reduction in severity [28]. There are some discrepancies that at first sight are not easy to reconcile, such as between the increased susceptibility of vitamin A deficient children to severe respiratory disease and the failure of vitamin A supplementation to reduce respiratory-related deaths, except in cases of measles.

d) HIV and AIDS

Vitamin A levels are depressed in cases with HIV infection. Mortality among AIDS patients is higher when serum retinol levels are low [29]. Mortality of infants born to HIV-infected mothers is >90% if the maternal serum retinol level is below 20 μg/dL [30].

e) Other infections

Urinary tract infections are commonly reported in cases of vitamin A deficiency and they usually respond to treatment with vitamin A [31,32]. There is also an increased risk of middle-ear infections [33].

f) Immune response

A basic introduction to the human immune response system is included in *Chapter 17*. Many studies have shown that vitamin A improves immune competence in experimental animals. A role for vitamin A in stimulating the immune system has been known for many years. Measles and VAD both impair the immune response. In humans, vitamin A deficiency leads to a reduction in various immune parameters, particularly natural killer (NK) cells. This reduction is reversed by treatment with vitamin A, and especially with retinoic acid. Specific effects are reported on stimulating maintenance of lymphoid organs and cells. In cell-mediated immunity, the effect seems to be on the production of NK cells *etc*., rather than functional impairment.

Effects on the humoural immune system involve dysregulation of signalling processes, not the efficiency of antibody production. The relationship between immunocompetence and vitamin A status has been reviewed [34].

D. Scale of Vitamin A Deficiency

1. Global distribution

Vitamin A deficiency is a global, international public health problem. In 1996 it was known to occur, at different levels of severity, in 73 countries [4,35]. The highest risk is associated with tropical and sub-tropical regions, and VAD is particularly serious in Africa, South and South-East Asia, and parts of Central America. Clinical symptoms are especially prevalent in parts of Saharan/sub-Saharan Africa, the Indian subcontinent and the Philippines. Around 200 million children are estimated to be at risk of sub-clinical vitamin A deficiency, and about 125 million actually deficient, with a death rate of 1-2.5 million each year [4,35]. About 5-10 million develop xerophthalmia and about half a million go blind each year. Within a region, the deficiency typically occurs in clusters, in villages, districts or provinces where environmental conditions and living practices are similar. If at least one child in a village or homestead is known to have xerophthalmia, the risk of others in the same village or homestead developing vitamin A deficiency is higher. There can, however, be distinct differences between villages and districts that are neighbours but have different climatic conditions or different cultural practices. Knowledge of such clustering is a great help in designing and implementing VAD prevention programmes.

2. Contributing factors

a) Age

Although children of all ages and even some adults are at risk, vitamin A deficiency is especially severe and most prevalent among children of pre-school age, <6 years old. The prevalence is usually not so great in the first 6-12 months because of supplies from the mother's milk, but there may be a rapid rise on weaning, especially on to a simple rice-based diet containing little or no vitamin A or provitamin carotenoids [36].

The prevalence of mild xerophthalmia increases with age through the pre-school years [37]. Moderate to severe deficiency also increases, associated with chronic dietary inadequacy.

The prevalence of sub-clinical vitamin A deficiency, estimated by serum levels, can also be expected to increase with age during early childhood.

b) Socioeconomic status

Not surprisingly, it is people from the lowest socioeconomic strata who are most vulnerable to vitamin A deficiency. These are people with few possessions, poor housing and sanitation, a low level of education, and a subsistence-level life, with inadequate food supply. Such people are at 1.5 to 3 times higher risk than more fortunate members of their community [4].

c) Seasonality

The incidence and severity of vitamin A deficiency may vary with season and climatic conditions. Many foods are seasonal, so food availablity and quality obviously depend on climatic factors. At the peak season, there will be better supplies of provitamin A carotenoids. But children often experience a 'growth spurt' associated with increased caloric availability immediately after a rice harvest [38], when there may be no concomitant increase in dietary carotenoids, so the need for extra vitamin A to support growth may not be met.

Water contamination, parasitic infestations, flies *etc*. also lead to seasonal peaks in infectious diseases that are influenced by or can exacerbate VAD.

E. Strategies to Combat VAD

The underlying cause of vitamin A deficiency is a diet that lacks sufficient amounts of preformed vitamin A or sustained levels of provitamin A carotenoids. It is obvious that if the intake of vitamin A, either pre-formed or as the provitamin, is below the minimum requirement, VAD will result, with the likely consequences discussed above. There is thus an urgent need to boost vitamin A status in individuals and populations at risk. A long-term sustainable strategy that would ensure an adequate supply of vitamin A or the provitamin from the normal diet so that VAD does not occur in the first place would be ideal. However, in cases of acute VAD or risk of acute VAD, a different strategy is needed to give a rapid boost to vitamin A levels and status by administration of large-dose supplements. A third strategy, fortification of food with added vitamin A or provitamin A, combines elements of the other two.

For detailed assessment of these approaches and description of some programmes that have been evaluated, see [4,35,39]. Here, just an outline of the main features will be given, especially in relation to the application of intact provitamin A carotenoids.

1. Supplements

a) Vitamin A

Individuals, aged 12 months or more, suffering from the consequences of VAD, such as measles, diarrhoea or other infections, as well as ones showing signs of xerophthalmia, are typically treated by immediate administration of a high dose (200 000 IU, 60 mg) of vitamin A, usually as retinyl palmitate. Smaller doses, usually 100 000 or 25 000 IU, are given to infants aged 6-12 months or less than 6 months, respectively. Vitamin A status, as serum retinol concentration, rises rapidly, liver stores are replenished, and dramatic improvements in health are often seen. In the absence of any other measures to increase the provision of vitamin A or the provitamin, by dietary improvement or fortification, the supplementation is typically repeated every 3-6 months, to maintain the improvements. Repeated supplementation at these intervals is assumed to be safe; in any case the benefits outweigh any risk of toxicity. When a population is identified as having marginal/low vitamin A status and VAD is diagnosed in some individuals, a public health programme of supplementation is recommended.

b) Provitamin carotenoids

Supplementation with the provitamin A, β-carotene, would remove the risk of vitamin A toxicity [40]. The conversion is controlled and there is no risk of vitamin A building up to toxic levels, but the carotene would need to be given in a form with high bioavailability (see *Chapter 8*).

Bioavailability studies with stable isotopic labelling have shown that β-carotene in oil is absorbed efficiently and the conversion efficiency is high (as good as 2.6:1) [41], so that β-carotene in this form can be considered as almost a full equivalent of vitamin A on a weight basis. Some trials have been undertaken. In a comparative study in Orissa State in India, periodic dosing with red palm oil had the same effect on vitamin A status as did the administration of a high dose (200 000 IU) supplement of retinyl palmitate [42]. Although vitamin A supplements may be supplied to young infants either direct or through breast milk after supplementation of the mother, direct supplementation of the infant with red palm oil would not be satisfactory because the high requirement for secretion of lipases and bile salts needed to deal with the large volume of oil would not be met by a digestive capacity suited primarily to human milk with its specialized fat content and composition. The indirect approach has been shown to be satisfactory, however. Studies in Honduras and Tanzania have demonstrated an improvement in the vitamin A status of both mother and infant following supplementation of the mother with β-carotene [43,44].

2. Fortification

There have been various programmes to increase dietary vitamin A intake by fortification, *i.e*. adding vitamin A to commonly consumed food ingredients. The most extensive trials have been undertaken with sugar, in Central America [45], or monosodium glutamate, in Indonesia [46] and the Philippines [47]. Fortification of other food vehicles, such as cereals, condiments and dairy products is under consideration. It is difficult to reach the poorest, highest-risk communities in remote areas, who live a long distance from the markets and cannot afford the fortified products unless the extra cost is subsidized.

The food is usually fortified with vitamin A, but high doses again would lead to risk of vitamin A toxicity. A programme of continued fortification with low doses is difficult to sustain. In principle, fortification with provitamin A carotene should be effective and safe but the strong colour of the carotene may impair consumer acceptance.

3. Dietary improvement

The ideal long-term sustainable strategy would be to ensure that everyone obtained sufficient vitamin A or provitamin A from the normal food components of the diet, especially provitamin carotene from vegetables and fruit.

a) Home gardens

Programmes have been initiated to encourage people to grow more vegetables in home, community or school gardens, to grow varieties with a higher vitamin A nutritional content and to improve cultivation conditions, within the constraints of the local climate and environment. A large-scale horticulture initiative in Bangladesh has led to an improvement in vitamin A status in a number of communities [48]. Dark green leafy vegetables contain sufficient β-carotene to meet the needs of virtually any population, but the bioavailability is not good, and the products are not readily accepted, especially by the most vulnerable group, young children. Fruits, *e.g*. mangoes, are good sources, but may be too expensive for the poorest families who are most at risk. There are some good carotene-rich local sources, *e.g*. 'buriti' and other rich local sources in South America [49,50], 'Karat' bananas in Micronesia [51], the Palmyra palm fruit in Bangladesh [52], and 'gac' fruit (*Momordica cochinchinensis*) in Vietnam and neighbouring countries [53]. The greater use of these should be encouraged and their introduction into other locations perhaps considered. Also, the wider use of the carotene-rich orange-fleshed sweet potato, instead of white varieties would be beneficial [54].

b) 'Biofortification'

Another approach is the use of plant breeding and genetic modification techniques to improve the nutrient quality, including provitamin A content, of foods that are used as dietary staples

by many people. This strategy has been termed 'biofortification' [35]. A good example is the development of a GM strain of carotene-producing 'Golden rice' [55], though, again, the colour is a disadvantage; many populations associate quality with a pure white rice. There are also concerns about bioavailability, which has not been established. Other possible targets include potatoes, cassava, bananas and various cereals [56]. With this approach it is necessary to find the optimum balance between many factors, such as nutritient content, cultivation requirements, bioavailability from the product as it is consumed, consumer acceptance and economic advantages. The wider public concern about the safety and environmental impact of GM crops and practices must also be taken into account.

As mentioned before, some plant oils, especially red palm oil but also oil of 'gac' fruit contain a high concentration of carotene in a form that is absorbed efficiently. Use of these in cooking or as dressings could boost vitamin A status substantially, although the orange-red colour that they impart would not be appreciated in some food.

c) Post-harvest treatment

The importance of good treatment of fruit and vegetables post harvest to conserve provitamin A content should not be overlooked. Losses during transport, storage, cooking and processing can be high (see *Chapter 3*). To minimize destructive effects, prolonged heating should be avoided, as should exposure to strong light and air during drying, storage and transport [57]. The greatest risk of destruction of vital provitamin A carotene comes from the traditional and widespread practice of drying in air and from transport in the open in the heat of the day, in conditions of high ambient temperature and intense sunlight. Storage conditions are often not good; there is no refrigeration and ambient temperatures are high. Cooking facilities may be limited and may be determined by long-established tradition. Harsh but popular cooking conditions such as deep-frying, prolonged boiling and baking can cause particularly severe losses.

The destruction that can be caused by cooking must be balanced against improvement in bioavailabilty due to disrupting, weakening or softening the structural matrix of the food, which is a major determining factor in bioavailability

4. Strategy overall

There is a long standing argument about whether VAD should be treated by vitamin A supplementation or by a food-based programme to increase provitamin A consumption, and different factions tend to promote one at the exclusion of the other. But why should there be this argument? Surely, when several ways are available to tackle the problem, it is realistic and logical to use all of these as appropriate for particular circumstances. All have merits and benefits. All may have limitations and disadvantages.

It seems logical and sensible to make use of all available strategies.

In principle, dietary improvement to increase the availability of vitamin A and of provitamin carotene in a normal diet, from vegetables, fruit and staples, including 'biofortified' strains, augmented if necessary by fortified products, would be an ideal solution. Augmentation could be with vitamin A but fortification with provitamin carotenoids should be given greater consideration. Increased consumption of animal products such as milk, eggs, fat and butter, would provide more preformed vitamin A and carotene, but these products are not readily accessible to many poor families and communities. Increased production of primary sources of carotene – vegetables, fruit, staples – in home, community or school gardens is achievable.

When VAD is acute and rapid action is needed because patients are suffering life-threatening infections, the administration of high-dose supplements of vitamin A gives a rapid boost to vitamin A status and can have a dramatic effect on alleviating symptoms. Single high-dose supplementation is also used to boost vitamin A status in populations at serious risk of VAD, identified by the incidence of mild xerophthalmia, infectious disease and/or low serum retinol concentrations. To be effective in the longer term, this strategy requires the subsequent administration of follow-up doses, to maintain vitamin A sufficiency and liver stores. This raises the obvious concern about the toxicity of large doses of vitamin A. It may also be difficult to reach remote communities and to ensure adherence to the supplementation programme. This strategy is one of intervention therapy, not of sustainable dietary improvement.

F. Underlying Causes

In simple terms we know that vitamin A deficiency results when the intake of vitamin A or the provitamin is insufficient, so vitamin A status needs to be improved. But what is the underlying reason for the low vitamin A intake and status? Why should a particular individual, family, community or population be vitamin A deficient when their neighbours are not? Are they not aware of the problem and its treatment? Why are they not obtaining sufficient vitamin A? Are supplies of vitamin A-sufficient food adequate and affordable? Are they just not making full use of available supplies? Is this because of personal preference or is it determined by custom or tradition? Is lifestyle a factor? If the reasons are known, the scientific basis exists for treatment. A good illustration of this comes from a study of two tribes in Orissa, India. These tribes were living under similar conditions and eating a generally similar diet. A high incidence of xerophthalmia was seen in the children of one tribe, but not in the other. It was found that, in the tribe in which xerophthalmia was common, the infants were weaned early onto a carotenoid-free rice-based diet whereas in the other tribe breast-feeding was continued for much longer [58].

G. Conclusions

1. Place for carotenoid research

Many important challenges remain for carotenoid science. The expertise and experimental tools exist to identify carotene-rich food sources and to enhance crop plants by breeding and GM programmes. Much effort is being directed to optimizing methods to determine bioefficacy for particular sources under natural conditions; stable isotope methods to assess carotenoid uptake and conversion are proving very useful (see *Chapter 8*).

Associated with this is the challenge to identify sources and forms with high bioavailability for use in supplements and for fortification. Red palm oil is an excellent example of a natural material for this, but other carotene-rich oils merit exploration. A wide variety of formulations have been designed for various commercial applications of purified synthetic or natural carotenoids, solubilized or dispersed in various media, as colourants or as an easily assimilated form in animal feed for agriculture and aquaculture. The knowledge and technology exist so, with a similar research effort, carotenoid products and formulations could surely be devised for effective use in supplements and for fortification.

As discussed in *Chapter 3*, the great precision usually reported in food composition tables can be misleading. Analytical results recorded are for a particular sample grown in a particular place under particular, often optimized conditions. The values given may, therefore, bear little resemblance to the real values in actual food that is being eaten in the household in a community at risk. Proper guidance on this is needed and it would be so useful to develop a simple inexpensive method that could be used to determine rapidly the carotene content in such real samples, even in the most remote places.

We know much about carotenoids but there are still serious gaps in knowledge about the human subjects, particularly in regard to the great variability between individuals, not just between different ethnic groups and populations in different parts of the world, but between individuals in the same community. Some differences are due to environmental factors and cultural traditions but many answers may lie in the unseen genetic factors. With the mapping of the human genome, new technologies of molecular biology and molecular genetics hold the key to solving these mysteries. An important example is understanding the basis of ‘responders’ and ‘non-responders’ [59]. Identifying the genetic and other factors that determine how efficiently an individual absorbs and stores carotenoids and converts them into vitamin A would open the door to real progress in defining the needs of individuals and populations. Recent work has revealed that genetic variations (single nucleotide polymorphisms, SNPs) can have a profound influence on the efficiency of the β-carotene-cleaving enzymes [60].

2. Political, educational, cultural

There are areas where more knowledge and understanding are needed, but generally the science base is solid. In many ways, the main battle is not scientific but cultural or economic. At a local level, it can be extremely difficult to overcome or change eating practices that are rooted deep in culture, tradition or religion. Developing education programmes is particularly important to inform about the problem of vitamin A deficiency and its consequences and to encourage acceptance of intervention measures and the adoption of good nutritional practices. Economic reality means that the most vulnerable families may not be able to afford the kinds of food that would ensure them adequate supplies of vitamin A.

It has taken the dedicated efforts of many scientists and others battling against all kinds of difficulties to implement programmes, inform local populations, influence political thought and convince funding agencies of the urgency of action. Without these individuals and the international action of various agencies and bodies such as WHO, UNICEF, Helen Keller International, USAID, Sight and Life and Harvest Plus, and the effectiveness of IVACG and other meetings as a forum for communication, dissemination of knowledge and planning of the implementation of international intervention programmes, the great progress that has been made could not have been made. Emphasis now is likely to be on sustainable measures and action is likely to be shaped by the growing realization that provision of adequate vitamin A is part of the need for a wider integrated programme to ensure adequate availability of all micronutrients. In richer countries there is much interest in 'functional foods' that provide sufficient amounts of substances that are associated with various health benefits, especially reduction in risk of serious diseases. With a food-based approach to providing adequate supplies of provitamin A carotenoids, these poorer people would also be in a position to benefit from health-promoting effects of other carotenoids and other micronutrients that the food, especially fruit and vegetables, provides.

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