SIGHT AND LIFE Guidebook on Vitamin A in Health and Disease

by

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Second Edition

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Contents

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Introduction

This booklet has been designed for health workers and other professionals for whom an understanding of the basic facts and most recent advances in the field of vitamin A is of great relevance in their work. It is not primarily for those concerned with nutrition, for whom the *SIGHT AND LIFE Manual on Vitamin A Deficiency Disorders (VADD)* may be more appropriate.

In structure this Guidebook follows fairly closely the new second edition of the *SIGHT AND LIFE Manual on Vitamin A Deficiency Disorders (VADD)*. It contains the key messages from the Manual but gives less emphasis to details.

The reader might ask why vitamin A has been singled out from among all the various vitamins and the many other important aspects of nutrition. Comments to this question are given in the following paragraphs.

Vitamin A deficiency is among the most common and serious of all nutritional deficiency diseases and also probably the one for which there is the greatest hope of it being brought under control within the forseeable future.

In recent years startling scientific discoveries have been made that have revealed how vitamin A functions as a hormone at the cellular level in many systems of the body.

Some years ago it was believed that disease resulted only from severe vitamin A deficiency and that it was confined to being a major cause of blindness in young children (xerophthalmia). Although xerophthalmia is much less common than it used to be, due in part to the many prevention programmes that have been set up, many children still go blind every year. However, over and above this we now know that deficiency of vitamin A can lead to a much greater risk of death and also predispose to suffering from many infectious diseases. Of great importance is the fact that these risks occur when the level of vitamin A deficiency is what is called “subclinical” – that is to say there is no clinical disease and the deficiency can be revealed only by carrying out bio-

chemical or other laboratory tests. This subclinical deficiency is very much more common and widespread than clinical deficiency like xerophthalmia. It affects mainly young children and their mothers during pregnancy and lactation. This means that the greatest emphasis now needs to be switched away from blindness and the eye to the area of Maternal and Child Health (MCH). Because many systems are affected by vitamin A deficiency it seems appropriate to use a term that covers all aspects, and vitamin A deficiency disorders (VADD) is now being generally accepted for this purpose.

That having been said, all health workers need to be aware of what is going on in the field of vitamin A. Compared to the common occurrence of deficiency, excess of vitamin A is very rare, however, it can also lead to disease and the danger should be kept in mind. A careful and controlled use of supplements is important.

A link is also being made in Section 8 to carotenoids that are closely related to β-carotene and vitamin A. In recent years they have been shown to have antioxidant and other functions that may prove to be important in the prevention of some common diseases.

It is hoped that some readers will become fascinated with the unfolding story of vitamin A and wish to go on learning about it – for them the *SIGHT AND LIFE Manual on Vitamin A Deficiency Disorders (VADD)* is waiting. It can be obtained from SIGHT AND LIFE.

Section 1

Vitamin A in the world around us

Almost wherever we happen to be we are surrounded by vitamin A in some form or another. Vitamin A itself (retinol), and the closely related acid form (retinoic acid), which carries out most of the functions of vitamin A in the body, are hidden away inside the bodies of animals and humans. However, closely related to vitamin A are hundreds of compounds belonging to the group called carotenoids. They readily attract our attention as yellow, red and brown pigments, which are responsible for the bright colours of many fruits, vegetables and leaves of trees as well as the brilliant colours of many birds, fish and other animals.

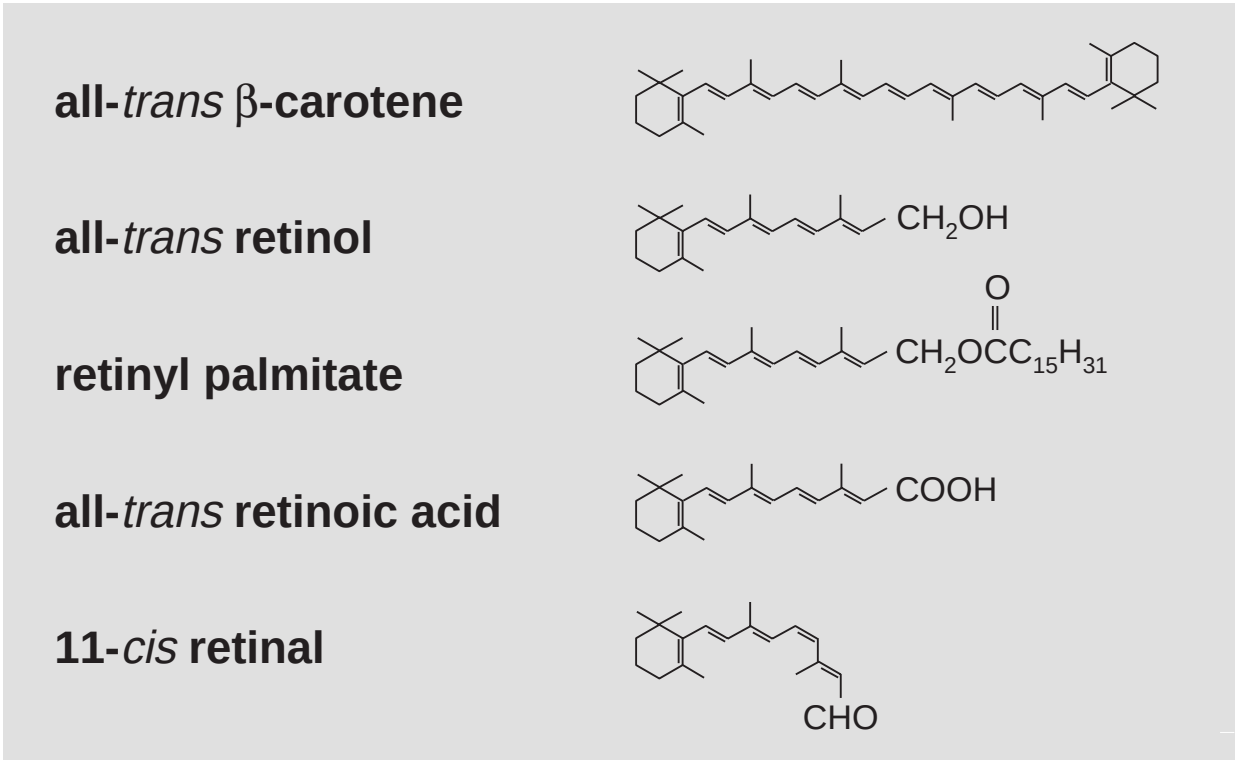


Figure 1. Chemistry of vitamin A (retinol) and some related compounds

Leafy plants and trees have the ability to remove carbon dioxide from the atmosphere and to combine it with water to form carbohydrates, rich sources of energy. This process is known as photosynthesis and requires light from the sun and the presence in the leaf of the green pigment chlorophyll, which acts as a catalyst. Carotenoids also need to be present to help to harvest the light. In this way the sun's energy is captured and stored to make all of life possible on earth. The darker the green colour of leaves the more chlorophyll they contain and also the more carotenoid. This is why dark green leaves are more nutritious than pale ones. Out of the hundreds of carotenoids in nature only a small number are present in our food and these are of two kinds. One kind, of which β-carotene is the most important, can be converted in the body to retinol. This source of vitamin A from carotenoids in vegetables and fruits is the main source for most people in developing countries, it makes up 70–90% of all their dietary vitamin A intake. Figure 1 shows the formulae of β-carotene, retinol, and some of its most important related retinoids. The long chain of β-carotene is usually split in the middle by an enzyme in the intestine to produce two molecules of retinol, although in practice much less than this is available to the body (see page 8). The other kind of carotenoid, including lutein and lycopene and others, cannot form vitamin A but recent research suggests that they may have other important functions (see page 32). Laboratory methods are now available for measuring the amounts of different forms of retinol, known collectively as retinoids, and also individual carotenoids. HPLC (high-performance liquid chromotography) has replaced most other methods but is expensive and requires high-quality facilities.

Section 2

Where we get our vitamin A

Before we consider the kinds of foods that provide us with the vitamin A we require it is necessary to discuss the units of measurement used for the expression of vitamin A activity in foodstuffs and also in body tissues. Weight for weight β-carotene has less vitamin A activity than preformed vitamin A (retinol) itself. It has also been found that other provitamin A carotenoids, like α-carotene, γ-carotene and cryptoxanthin, have only about half the activity of β-carotene. Consequently the term Retinol Equivalent (RE) was coined to make possible comparison between different sources of vitamin A activity. It was decided that retinol is 6 times more effective than β-carotene, which is twice as effective as the other provitamin A carotenoids. Table 1 indicates these relationships.

In recent years research has cast doubt on these values as they apply to the bioavailability of carotenoids to humans. In general it has been found that provitamin A carotenoids in dark green leafy vegetables are much less readily available than from other

Table 1. International Units (IU) and Retinol Equivalents (RE)

Compound	μg/IU	IU/μg	RE/μg	μg/RE
all-*trans* retinol	0.300	3.33	1.000	1.0
all-*trans* retinyl acetate	0.344	2.91	0.873	1.15
all-*trans* retinyl palmitate	0.549	1.82	0.546	1.83
all-*trans* β-carotene	1.800	0.56	0.167	6.0
Mixed carotenoids*	3.600	0.28	0.083	12.0

* Provitamin A carotenoids other than β-carotene

sources and that the relationships in Table 1 overestimate the activity of carotenoids in the body (Figure 2). Among the many factors that decrease the bioavailability of carotenoids the most important probably are:

- the matrix in which the carotenoid is incorporated in the food,
- the presence and amount of substances that affect absorption, such as fat, vitamin E, fibre, chlorophyll, and nonprovitamin A carotenoids,
- the nutritional status of the host and
- parasites such as roundworm and giardia.

It has recently been proposed that the previous RE values for provitamin A carotenoids be halved. This would make β-carotene 1/12 as active as retinol (up to now 1:6), and other provitamin A carotenoids 1/24 (up to now 1:12). Some studies have shown great variability between individuals in their ability to respond to dosing with β-carotene.

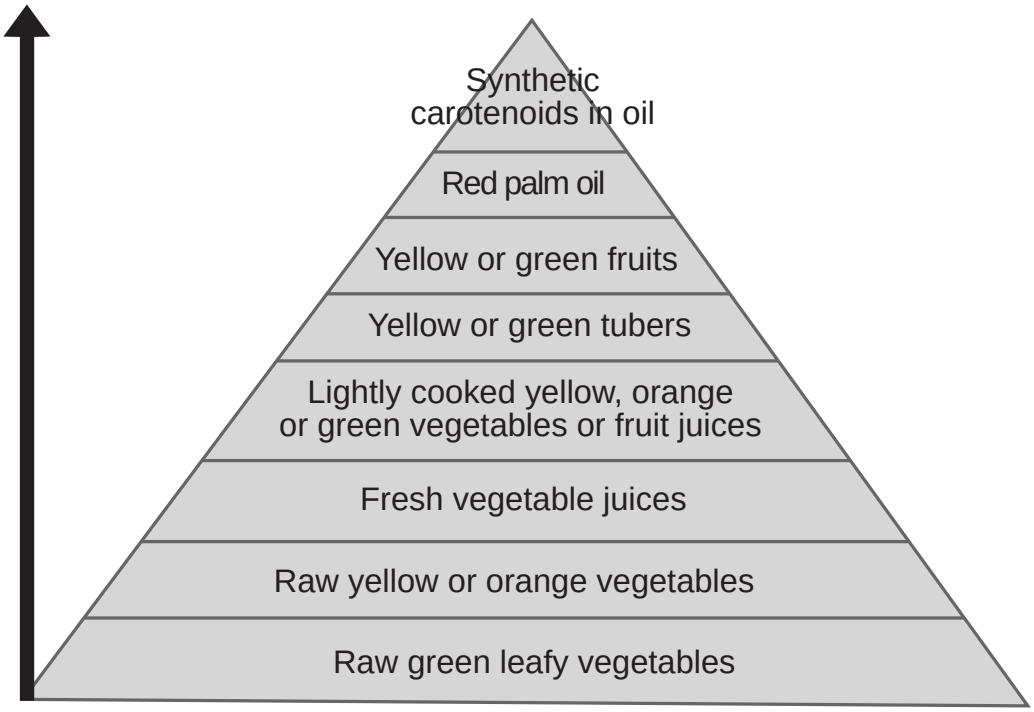


Figure 2. Hierarchy of carotenoid bioavailability.

Table 2. Examples of common vegetable/ fruit carotenoid sources

	RE/100 g edible portion
Mango (golden)	307
Papaya (solo)	124
Cucurbita (mature pulp)	862
Buriti palm (pulp)	3,000
Red palm oil	30,000
Carrot	2,000
Dark green leafy vegetables	685
Tomato	100
Apricot	250
Sweet potato, red and yellow	670

Provitamin A carotenoid sources

Table 2 indicates some common vegetable/fruit carotenoid sources and the approximate amount present.

Leafy vegetables

β-carotene is the major source of vitamin A. Unfortunately, dark green leaves like spinach, which have high concentrations of β-carotene, are often regarded as “poor man’s food” or only fit for consumption by animals. Moreover, young children constantly resist having to eat them.

Fruits

The vitamin A activity of fruits is generally lower than that of leafy vegetables and their carotenoid content is more complex. They are much more readily accepted, especially by young children, but unless they are processed they have a short season.

Tomatoes are high in lycopene, a nonprovitamin A carotenoid that gives them their dark red colour and may have some beneficial effects (see Section 8). Some varieties of tomato are good sources of β-carotene.

Roots and tubers

Carrots are increasingly being grown in parts of the developing world. The provitamin A content in carrots, mainly β-carotene and α-carotene, varies considerably between different species, and raw carrot provides none at all.

The yellow or orange varieties of roots and tubers are quite rich sources, while the more common white varieties contain almost no carotene. Orange sweet potato for instance contains 1140 µg/100 g fresh weight of β-carotene.

Vegetable oils

Most contain little or no carotene, but red palm oil (see Table 2) is the richest vegetable source known. Most is β-carotene. The bioavailability is high. The oil has been refined for domestic use and the strong natural flavour, which is not to everyone’s taste, has been removed. The fat is mostly unsaturated. Introduction of

red palm oil into parts of the world where previously it was unknown is increasing.

Other sources of provitamin A carotenoids

Hen's eggs are rich in carotenoids, but these are mostly nonprovitamin A. Natural extracts containing carotenoids have long been used to colour foodstuffs and make them more attractive. β-carotene is sometimes used for this purpose and then also contributes to the nutrient intake.

Sources of preformed vitamin A

Table 3 shows some common sources. Fish liver oils are the most concentrated sources and are often used medicinally. Dairy products, usually quite expensive, are only moderate sources. Vitamin A has been added to food for a long time and fortification is one of the major long-term approaches to the control of the problem of VAD (see page 33).

Table 3. Examples of common animal vitaminA sources (µg retinol/100 g edible portion)

Fatty fish liver oils	
Halibut	900,000
Cod	18,000
Shark	180,000
Herring and mackerel	50
Dairy produce	
Butter	830
Margarine, vitaminized	900
Eggs	140
Milk	40
Cheese, fatty type	320
Meats	
Liver of sheep and ox	15,000
Beef, mutton, pork	0–4

Section 3

What vitamin A does and how it works

Vitamin A (retinol) in the body comes from two sources, preformed vitamin A in animal foods and from β-carotene and other provitamin A carotenoids in plant sources. Both of these are released from protein in the stomach and like all other lipids are taken up in the wall of the small intestine and become part of chylomicrons that enter the blood circulation. From there they are taken to the liver, where storage takes place as retinyl ester mainly in special cells called stellate cells. For transport to other parts of the body retinol is attached to its own protein, the retinol-binding protein (RBP), and another protein called transthyretin (TTR, see Figure 3).

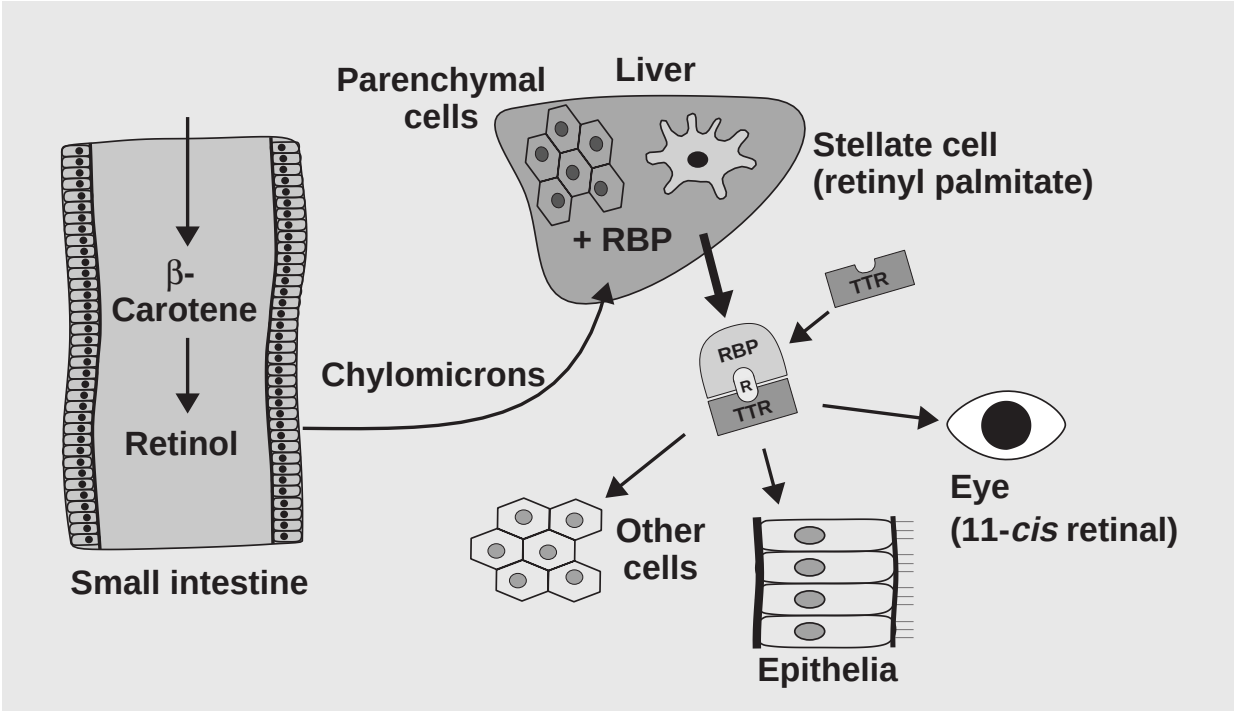


Figure 3. Physiology of vitamin A

At the cell membrane retinol is taken up by receptors (RBP receptors). Within cells there are cellular retinoid-binding proteins (CRBPs) that direct retinoids to specific enzymes and, most importantly, to the nucleus of the cell.

In recent years it has been discovered that within the cell nucleus there are two sets of three nuclear receptors (known as RARs and RXRs). These nuclear receptors are activated by an acidic form of retinol, such as retinoic acid (RA). In cells of organs and tissues all over the body it is RA that is the active form of vitamin A. It has been shown that many genes are activated by RAR or RXR nuclear receptors (Figure 4). These receptors act like hormones, such as steroids and thyroid hormones, with which they are closely linked. It is through this mechanism that the functions of vitamin A are brought about, with one exception, vision. In the rod and cone cells of the retina responsible for vision the functional form of vitamin A is not RA but 11-*cis* retinal (see page 13).

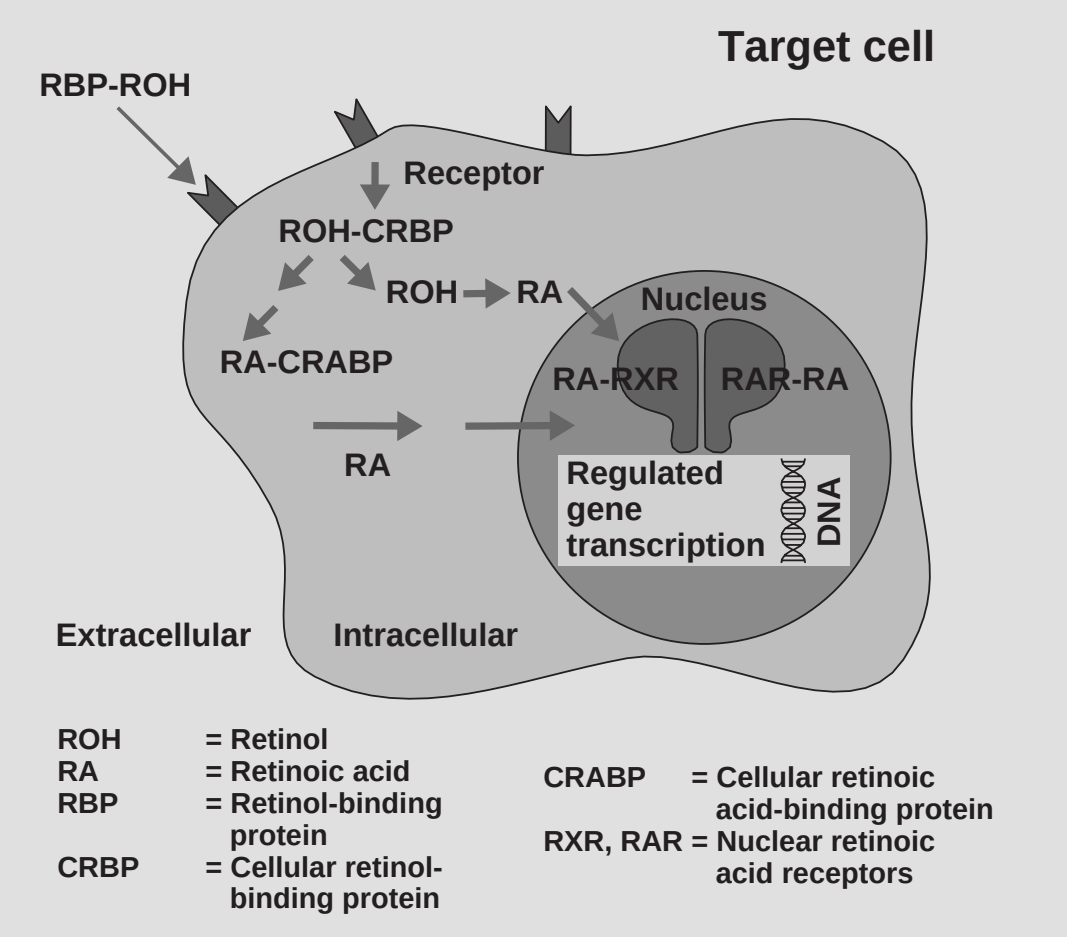


Figure 4. Molecular biology of vitamin A

Table 4. Functions of vitamin A

- **Vision (night, day, colour)**
- **Epithelial cell integrity against infections**
- **Immune response**
- **Haemopoiesis**
- **Skeletal growth**
- **Fertility (male and female)**
- **Embryogenesis**

Functions of vitamin A

Table 4 outlines some of the main functions of vitamin A in the body.

Vision

The rods cells of the retina contain a protein, opsin, attached to a form of vitamin A, 11-*cis* retinal, to form a compound that is sensitive to light, rhodopsin or visual purple. On exposure to light 11-*cis* retinal is converted back to all-*trans* retinal and a nerve impulse is generated. In VAD the supply of retinal is reduced and rod function is impaired.

Cell differentiation

In VAD mucus-secreting cells in many epithelial tissues are replaced by keratin-producing cells. This is responsible for the xerosis and keratinization of the conjunctiva and cornea and other tissues.

Embryogenesis

Reference is made elsewhere (see page 32) to the evidence in animals that both deficiency or excess of vitamin A can cause congenital malformations. Humans appear to be more resistant.

Immune response

Healthy epithelial tissues are barriers to infection, but in VAD these cells are damaged and invasion by pathogens becomes easier. Vitamin A appears to be involved more in cell-mediated rather than humoral aspects of the immune response.

Reproduction

Studies in animals show the involvement of vitamin A in spermatogenesis in the male and the prevention of placental necrosis and fetal absorption in the female.

Haemopoiesis

There is a link between iron and vitamin A in erythropoiesis. Iron deficiency anaemia responds more completely if vitamin A is added to iron therapy than if it is not. The mechanism is not yet understood.

Growth

Vitamin A is known to be involved in normal growth of the musculo-skeletal system. Several field studies have provided evidence that growth is impaired in children if severe VAD is present.

Human requirements for vitamin A

These are usually expressed in terms of recommended dietary intake (RDI) values according to age, sex and physiological state such as pregnancy and lactation. Table 5 gives some representative values which tend to be on the lower side. It will be noted that the requirements are relatively much greater in early life. This is mainly because of the increased needs for growth, over and above those for maintenance.

Table 5. Vitamin A requirements

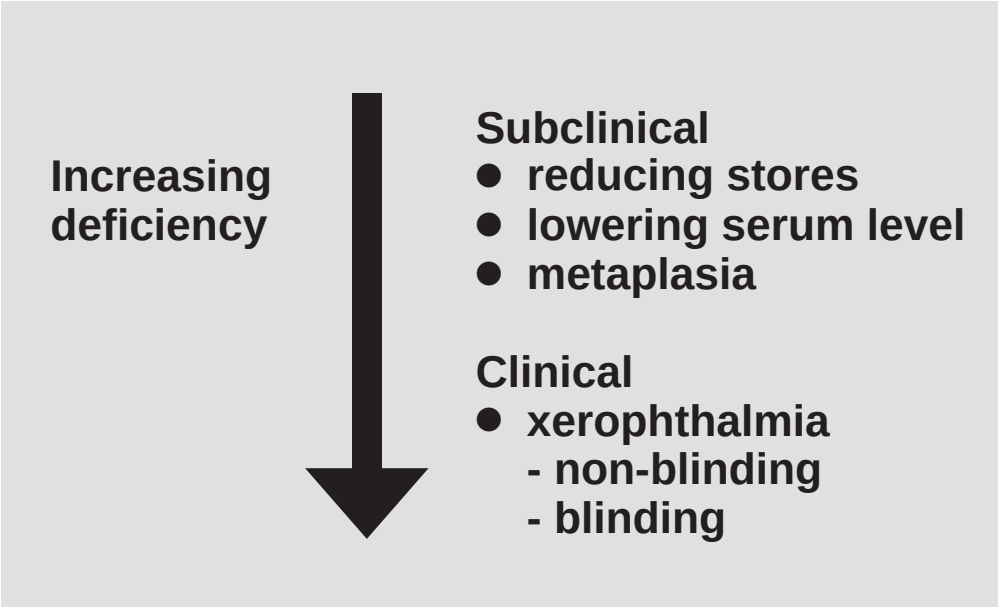
Retinol Equivalents (RE) per day (1 RE = 1 μg retinol)		
Child	1–6 years	400 RE
Adult	Women	500 RE
	Men	600 RE
Pregnancy		600 RE

Section 4

How to test for vitamin A deficiency

There are varying degrees of VAD as shown in outline in Table 6. Different tests are appropriate for detecting different stages of this process. They all measure the state of vitamin A nutriture in the body or what is usually called vitamin A status. The measurement of dietary intake of vitamin A over a given period of time, usually per day, does not measure status but does give a good general indication in a population whether or not there is a serious VAD problem.

Table 6. Stages of vitamin A deficiency



The eye lesions of VAD (xerophthalmia)

In the days when attention was focused on eye disease due to VAD (xerophthalmia) the various stages of damage to the eye were described and some of these were chosen to be used in studies and surveys of the problem. Using some of these eye signs criteria were established by WHO for the diagnosis of a xerophthalmia problem of public health magnitude (i.e. one that required prompt action) and these are shown in Table 7. Characteristics of the eye lesions of xerophthalmia and their use in assessment of vitamin A status are discussed further in Section 5.

Table 7. Criteria for assessing the public health significance of xerophthalmia and vitaminA deficiency, based on the prevalence among children less than six years old in the community

Criteria	Minimum prevalence
Clinical (primary)	
Night blindness (XN)*	1.0%
Bitot's spot (X1B)	0.5%
Corneal xerosis and/or ulceration/keratomalacia (X2 + X3A + X3B)	0.01%
Xerophthalmia-related corneal scars (XS)	0.05%
Biochemical (supportive)	
Serum retinol (vitaminA) < 0.35 μmol/L (10 μg/dL)	5.0%

* Night blindness (XN) > 5% in pregnant women is a new criterion recently proposed.

Assessment of subclinical VAD

With one exception these tests are biochemical and require varying degrees of sophisticated and expensive laboratory equipment. The exception is a histological technique known as conjunctival impression cytology (CIC). It is based on the fact that the conjunctiva becomes xerotic (dry) and keratinized to some extent before it reaches the stage of X1A, conjunctival xerosis (see page 19). A simple light microscope, laboratory stains and cellulose acetate strips to obtain the specimen are all the materials that are required. Although the test showed great promise at first it has not been found possible to standardise the results obtained and even in experienced hands and with modifications the test has not been widely adopted.

The biochemical test measuring serum retinol is the test that has been most widely used. With techniques like HPLC accurate estimates can be obtained. However, the level of retinol in serum does not truly reflect changes in vitamin A status because it is in equilibrium with the stores in the liver and some other organs.

Serum retinol does not fall appreciably until body stores have been virtually exhausted. Even so, serum retinol values for large population groups have been found to be a reliable indication of their overall vitamin A status and are especially useful for comparing one population with another (Table 8). It is now generally recognized that in the presence of inflammation, infection or trauma the acute phase response causes serum retinol to fall, sometimes dramatically. During this phase serum retinol does not reflect vitamin A status.

Serum RBP is easier to measure than serum retinol and is coming into greater use. However, it is also lowered in the acute phase response. Breast milk retinol has been found useful to assess the vitamin A status of lactating women and might be of value for comparing different groups. It has the advantage over other biochemical tests of not requiring blood sampling. The relative dose response (RDR) and modified relative dose response (MRDR) tests assess indirectly the level of liver vitamin A stores, which under most conditions are a truer reflection of vitamin A status than serum retinol. They are mainly used as research tests, as is the more recent stable isotope dilution test.

Table 8. Ranges of prevalence of serum retinol to define a public health problem of subclinical vitamin A deficiency of varying importance in young children

Indicator (cut-off)	Prevalence below cut-offs to define a public health problem and its level of importance		
	Mild	Moderate	Severe
Serum retinol (≤0.70 μmol/l)	≥2–<10%	≥10–<20%	≥20%

Section 5

Eye diseases due to vitamin A deficiency

The term xerophthalmia is used to include all signs and symptoms affecting the eye that can be attributed to vitamin A deficiency. Table 9 lists these changes and gives their shorthand symbols. In a general way they are listed in order of appearance with increasing severity of deficiency.

Table 9. Xerophthalmia classification by ocular signs

Night blindness (XN)
Conjunctival xerosis (X1A)
Bitot's spot (X1B)
Corneal xerosis (X2)
Corneal ulceration/keratomalacia < $^1/_3$ of corneal surface (X3A)
Corneal ulceration/keratomalacia ≥ $^1/_3$ of corneal surface (X3B)
Corneal scar (XS)
Xerophthalmic fundus (XF)

Night blindness (XN)

As we saw earlier (see page 12) the rod cells of the retina require vitamin A to fulfil their function of vision at night. There are instruments to test rod function but they require the cooperation of the subject and are unsuitable for use in young children, in whom VAD is most common. A simple method is in use in the field to gain an idea of the vitamin A status of a community. In areas where VAD is common there is usually one or more phrase in the local language for the inability to see well at night. This information and some other questions about a child's night vision form a short questionnaire (Table 10).

Conjunctival xerosis (X1A)

In extreme cases the dryness, thickening and wrinkling of the conjunctiva are very obvious. Lesser degrees are much more common and in these cases it is very difficult to be sure that the conjunctiva is abnormal.

Figure 5. Bitot's spot (X1B) on temporal aspect of bulbar conjunctiva in interpalpebral fissure. Bubbles of foam are clearly visible.

Consequently it was decided to exclude this sign from use in field surveys. Unfortunately it is still sometimes being used in some surveys and the results are not reliable.

Bitot's spot (X1B)

Figure 5 shows a typical example. The lesion consists of a local heaping up of keratinized material on the surface of the conjunctiva. It is usually present on the temporal (outer) side of the conjunctiva and on the area not normally covered by the lids. It is really an extreme example of X1A in one area. Bitot's spot is rare in infants, and the kind that responds to treatment with vitamin A is most commonly seen

Table 10. Scheme for the classification of night blindness by interview (WHO, 1996)

1) Does your child have any problem seeing in the daytime?
2) Does your child have any problem seeing at nighttime?
3) If (2) = yes, is this problem different from other children in your community? (Note: this question is particularly appropriate where VAD is not very prevalent.)
4) Does your child have night blindness (use local term that describes the symptom)?

in older preschool age children. After that age, in older children and adults Bitot's spots are usually not due to VAD and these spots should not be used as an indicator of VAD.

Corneal xerosis (X2)

This is dryness of the cornea just like that of the conjunctiva. This stage of haziness on its own is short-lived and uncommon. Prompt treatment with vitamin A (see page 34) at this stage will result in complete cure of the eye lesion.

Keratomalacia (X3A, X3B)

This is the final stage of xerophthalmia and results in partial (X3A) or greater or total (X3B) melting and destruction of the cornea. Both eyes are usually affected but not necessarily equally (Figure 6). Blindness is inevitable and mortality is high. In any community keratomalacia is very uncommon and young children are almost always those affected.

Figure 6. Colliquative necrosis (keratomalacia) affecting the greater part of the cornea (X3B).The relative sparing of the superior aspect is typical. Plasma vitaminA was 4 μg/dL in this case.

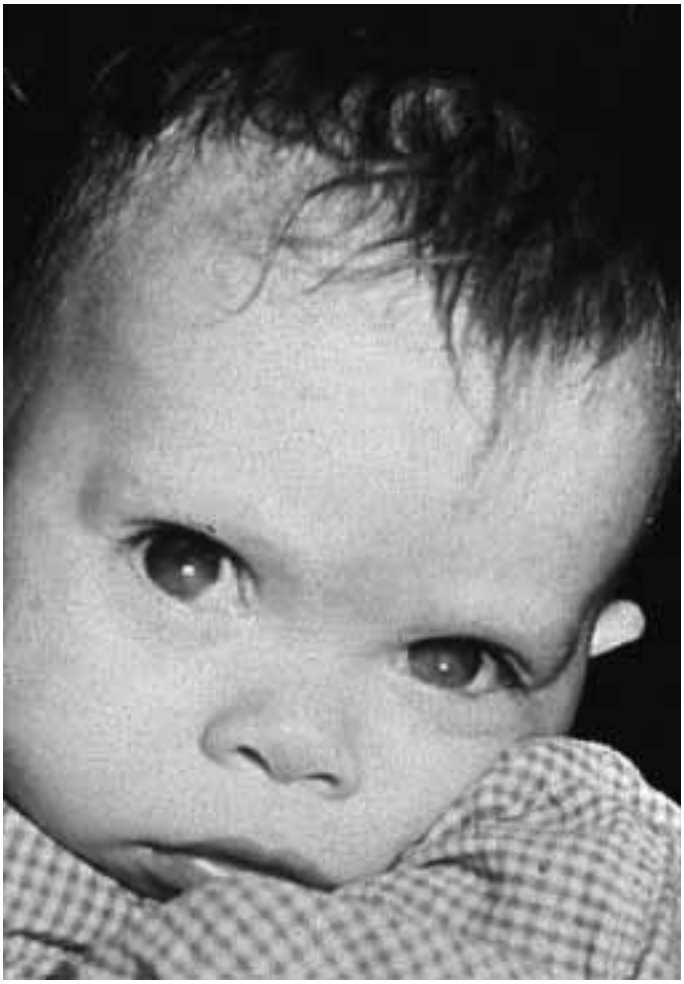


Figure 7. Bilateral corneal scars (leucomata XS) in an anaemic and generally malnourished infant. The inferior situation of the scars is typical.

Corneal scars (XS)

The cornea may be damaged by injury and many infections as well as by xerophthalmia. In survivors of keratomalacia scars of varying sizes may be left on one or both corneas. They are usually situated in the lower part of the cornea and centrally placed; in a “six o’clock” position (Figure 7). A diagnosis of XS should not be made unless the scars relate to a period of malnutrition in the past. These inactive lesions are more common than active keratomalacia and can be used in surveys with care. All the eye signs do not necessarily appear in the order given above and keratomalacia in very young children may develop rapidly with no evidence of xerosis.

Xerophthalmic fundus is very rare and not useful for surveys.

Section 6

Vitamin A deficiency as a cause of death and disease

Soon after vitamin A was discovered in 1913 it became known as the “anti-infective vitamin”. This was because in animals and humans vitamin A, especially in the form of cod liver oil, was found to have a beneficial effect in a number of infectious diseases, especially respiratory infections, measles, and puerperal fever (after childbirth). Some years later effective drugs against many infections were introduced and the benefit from vitamin A was largely forgotten.

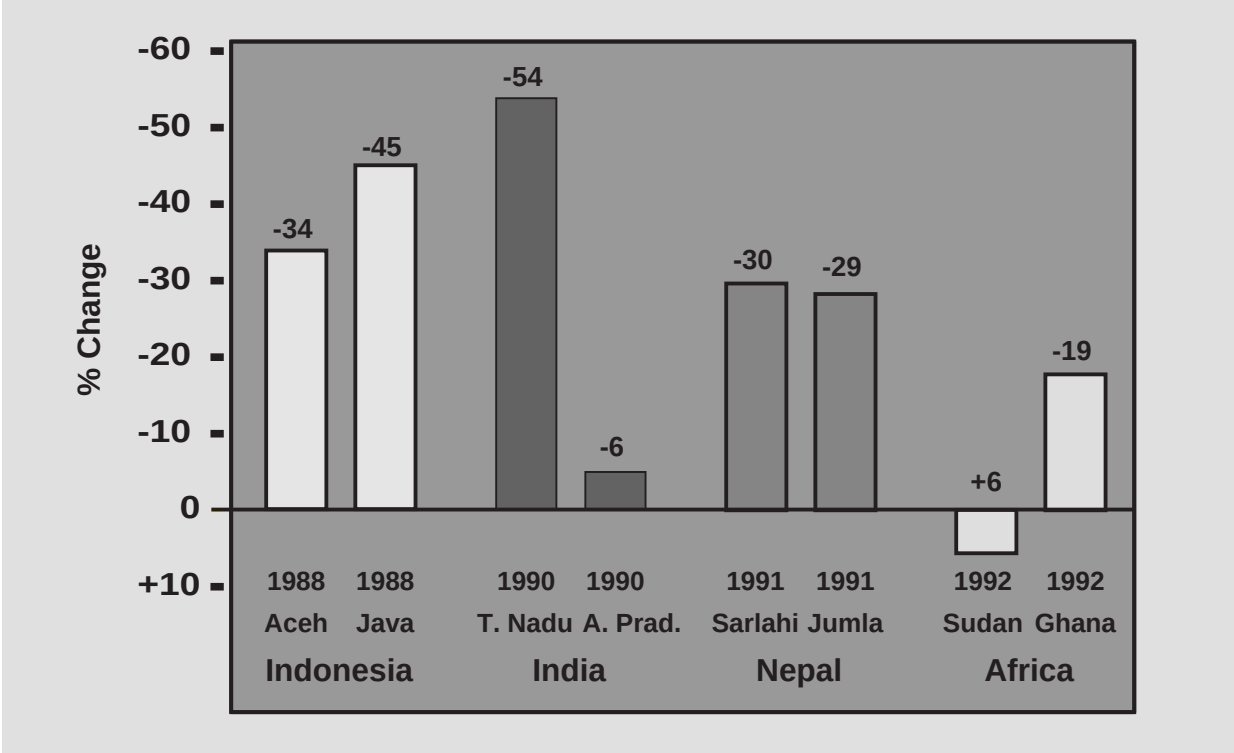


Figure 8. Impact of vitamin A on child mortality

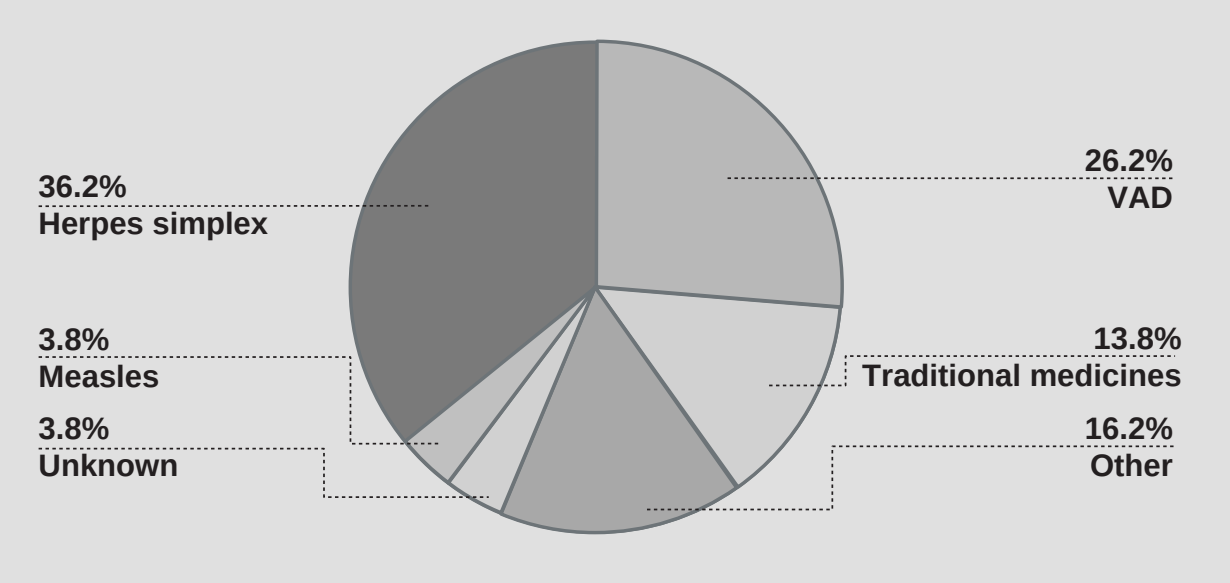


Figure 9. Causes of corneal ulcers in children

The problem of xerophthalmia took centre stage until in the 1980s large field trials with vitamin A supplementation in young children showed significant reduction in mortality (see Figure 8).

More recently one large study has reported significant reduction in maternal mortality with either vitamin A or β-carotene supplementation and also reduction in postpartum infection. If these results are confirmed they might have important implications for the use of vitamin A in various aspects of MCH programmes.

The exact mechanism involved is still not understood but it would seem to be related to a reduction in the impact of infectious diseases. Many studies have investigated the effect of vitamin A supplementation on various common infections in children.

The most dramatic benefit has been obtained in measles with a marked reduction in mortality of this disease which is often severe where malnutrition is common. In Africa eye lesions often occur in measles, and this is frequently due to a combination of xerophthalmia, measles itself, which directly affects the eye, herpes simplex infection, and damage caused by traditional eye medicines. Figure 9 illustrates experience of the problem in one hospital in Africa. The outcome has been reported to be improved with vitamin A supplementation in diseases

like the common causes of infectious diarrhoea, malaria and meningococcal disease.

Research results all tend to agree that the various forms of acute lower respiratory tract infection (ALRI), unlike most infections, do not appear to respond to vitamin A supplementation. The reasons for this are not understood, especially as experimental animals with VAD usually die with respiratory infections, but all agree that patients should be given vitamin A to improve their vitamin A status.

Infants born to women with HIV infection have a higher mortality and poorer growth, and morbidity and mortality among these are reduced by vitamin A supplementation. It was originally suggested that vitamin A may reduce the transfer of HIV infection from mothers to their offspring but more recently several trials failed to confirm this.

It has been calculated that improvement of vitamin A status would reduce the all-cause mortality rate in young children by about 23% and would be expected to prevent 1.3–2.5 million deaths per year in children aged under 5 years. Vitamin A supplementation is one of the most effective and inexpensive of all public health interventions (see page 33).

Section 7

Who is vitamin A-deficient and why

Recent calculations show that nearly 250 million preschool children are subclinically vitamin A deficient – this is almost 50% of those in developing countries. Three million have xerophthalmia at any one time; about 90% of these suffer from night blindness and other non-blinding xerophthalmia. 10% or 300,000 are blind with keratomalacia and this accounts for about 10% of all blind children in the world. While it is encouraging to note that the rate of blindness due to xerophthalmia is steadily decreasing, only in recent years has it become evident how widespread subclinical deficiency is and what an important cause of mortality and morbidity it is. The map (Figure 10) indicates in outline the vitamin A deficiency situation throughout the world. The majority of cases occur in south and east Asia, partly because of the vast populations and also because most of the poor in these countries depend heavily on rice (devoid of carotene). Many are landless and this means they have to purchase all their food and have no means to buy or grow their own vegetables. Urban slum dwellers are especially vulnerable, as are those subsisting in semi-deserts. Rapid social change, as in some Pacific islands, and civil strife, wars and ecologic destruction in much of Africa and elsewhere often precipitate VADD.

Risk factors for VADD

Age

Preschool age children are most commonly affected by VAD and develop the most severe degrees of deficiency. This may be due to a combination of factors such as rapid growth, adverse effect of infections and low vitamin A status at birth.

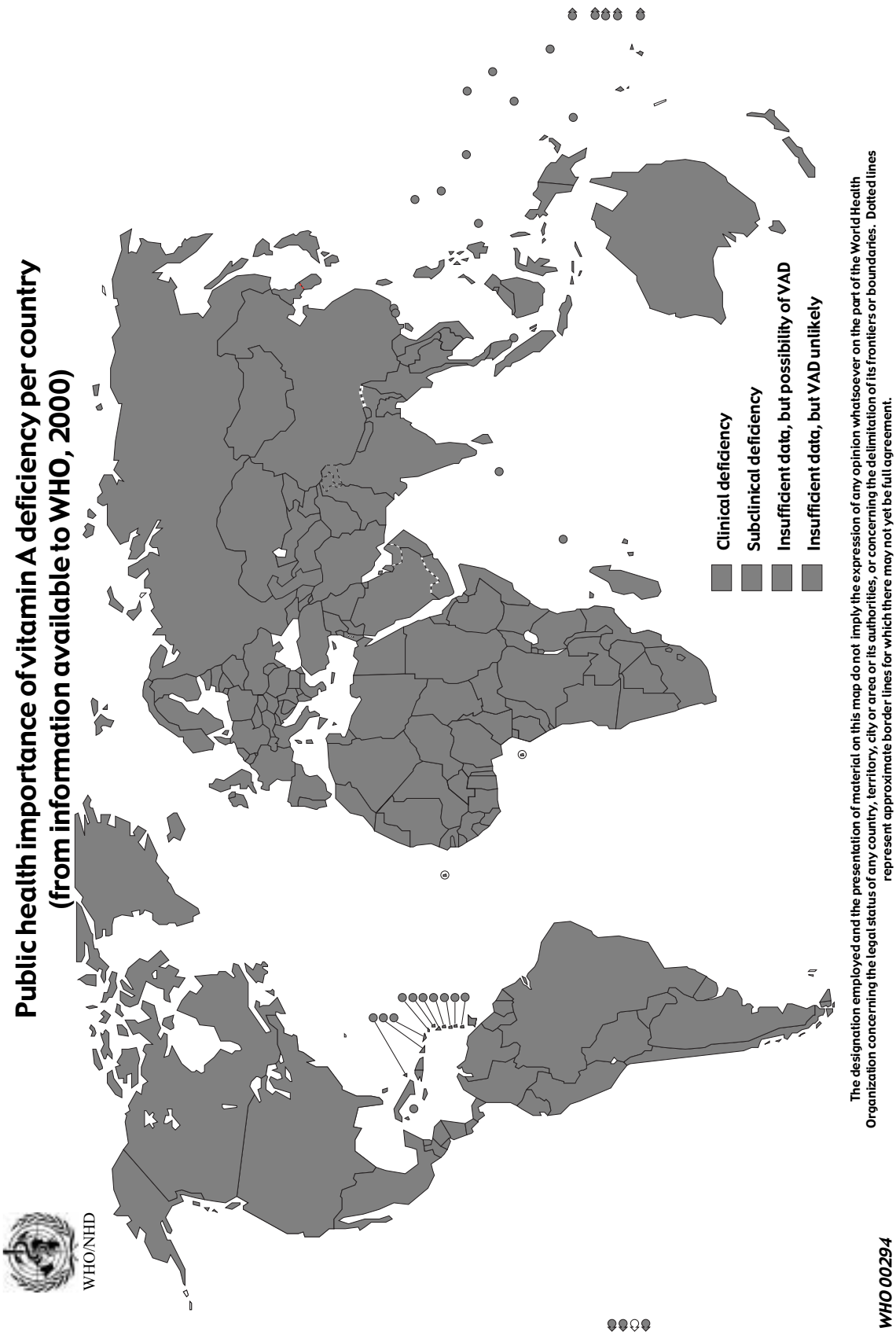


Figure 10. Global occurrence of vitamin A deficiency

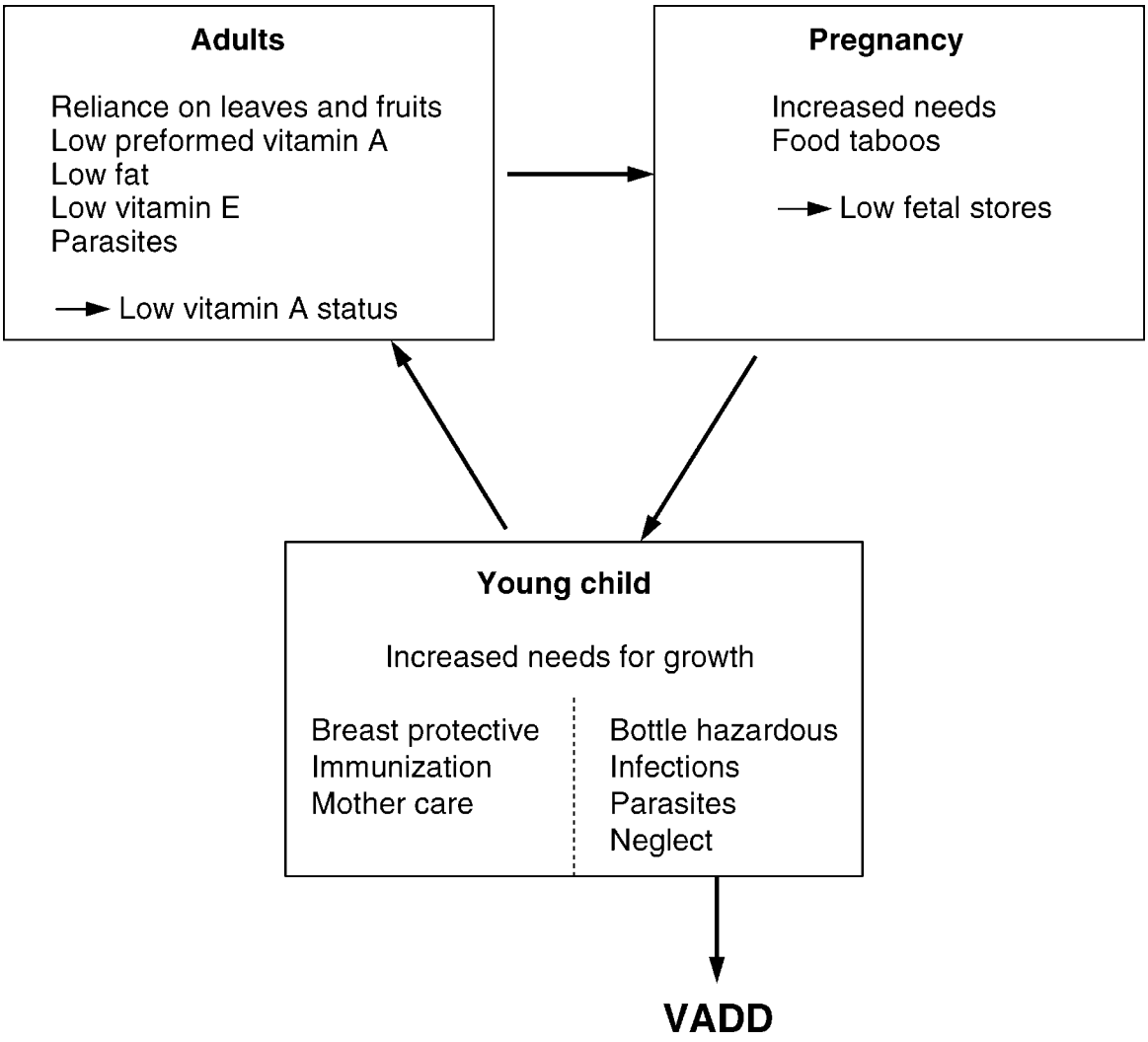


Figure 11. The VitaminA Deficiency Disorders (VADD) cycle.

Sex

It has been found that for all aspects of VAD males are more susceptible than females. The reasons have been much debated but are not fully understood.

Physiological status

Pregnant and lactating women have increased requirements for vitamin A and often develop night blindness or Bitot's spots. School children, perhaps

because of their adolescent growth spurt are also vulnerable.

Diet

Factors related to the diet were discussed previously, e.g. in Section 2.

Season

It is rare to find VAD occurring uniformly throughout the year. Much more commonly there is a marked seasonal pattern, usually together with infections which tend to precipitate VAD and other deficiencies in the rainy season. Lack of availability of vegetables and fruits in the dry season may also play a part. Nutritional surveys should take into account this important factor.

Breast-feeding

There is much evidence for the protective effect of breast-feeding. The regular supply of preformed vitamin A and decrease in infections probably play a part.

Cultural factors

Customs related to the spacing and limitation of the number of children are highly protective in a general way.

Infectious diseases

These often precipitate clinical VAD; the role of individual diseases was discussed earlier (see Section 6).

Figure 11 indicates how deficiency of vitamin A may develop and persist in a community.

Section 8

Vitamin A in general medicine

While VADD, as described here, are a problem to some degree in nearly all developing countries there are a number of aspects of the use and misuse of vitamin A that may affect us all.

Secondary VAD

Secondary, or endogenous, VAD occurs not because of lack of the vitamin in the diet but due to one of a variety of steps in its utilization by the body that goes wrong. Table 12 shows how this kind of deficiency may occur. Fortunately in most cases deficiency develops rather slowly and does not often proceed beyond the stage of night blindness or Bitot's spot, when treatment can be effective. However, it usually has to be continued throughout life unless the underlying disease can be cured.

Hypervitaminosis A

Vitamin A is stored in the body and if intake is excessive various systems can be damaged. Very large doses of vitamin A, especially in young children, may cause a rise in intracranial pressure that leads to headache, nausea and vomiting. Withdrawal of the vitamin results in a rapid return to normal without harmful long-term effects. More commonly a higher than normal intake of vitamin A over a period of months or even several years can result in a syndrome that may be very difficult to diagnose. Common symptoms are headache, vomiting, double vision, skin disease, bone and joint pain and liver damage. Once diagnosed and vitamin A intake reduced to normal, symptoms will gradually subside but damage to the liver and other organs may not be reversible.

Pharmacological use of synthetic retinoids

Large numbers of vitamin A-like compounds, retinoids, have been synthesized for use in treatment of various diseases, especially those that are due to abnormal differentiation of epithelial cells. These include acne, psoriasis and some other skin diseases and also some

Table 11. Secondary or endogenous causes of vitaminA deficiency

Diseases	Mechanisms
Coeliac disease, sprue, obstructive jaundice, ascariasis, giardiasis, partial or total gastrectomy	Impaired absorption of lipids, including vitaminA
Chronic pancreatitis	In some cases secondary to zinc deficiency
Chronic liver disease, especially cirrhosis	Storage impaired by damage to liver cells; zinc deficiency enhances the effect
Severe infection	Loss of RBP in urine
Cystic fibrosis	Excessive faecal loss, unrelated to degree of fat in stools
Enzyme defect	Failure to cleave β-carotene in small intestine
Heterozygotic reduction of plasma RBP	One case reported of keratomalacia due to reduced transport
Mutations in the gene for RBP	Biochemical but not clinical deficiency

cancers that affect epithelial tissues such as breast, skin, colon, and prostate. One form of leukaemia responds to retinoic acid.

Congenital malformations

Studies in various animal species have shown that both deficiency or excess of vitamin A during early fetal life may result in malformations in various systems of the body. In contrast to this in humans there is no firm evidence that malformations in the fetus are caused by either lack or excess of vitamin A. Nevertheless, restrictions are placed on the amount of vitamin A that can be safely administered during pregnancy and lactation (see page 35).

Synthetic retinoids that are being used to treat a number of skin and other diseases (see above) are known to be highly damaging to the fetus if continued during pregnancy.

Carotenoids and chronic diseases

This is a very rapidly growing field for research and can only be touched on here. It is probably the antioxidant and other effects of provitamin A and nonprovitamin A carotenoids in the body that are responsible for beneficial results. These have been reported in such major diseases as coronary heart disease, some cancers, and the eye diseases cataract and macular degeneration.

Section 9

What is being done to control VADD

There are three main types of intervention that are being carried out. Each has been researched and practised over the past several decades in many parts of the world. Each has its own particular characteristics, its disadvantages and its advantages. Frequently more than one intervention is being used at the same time. In addition, it must be remembered that human communities are not like laboratory animals, capable of strict control. Many unknown and uncontrollable variables exist. Improvement or deterioration of vitamin A status in these circumstances cannot be attributed directly or solely to an intervention.

Dietary modification

The vast majority of the world's peoples live in an environment that is capable of meeting all their nutritional requirements, including that of vitamin A, without artificial supplementation of any kind. In the case of vitamin A knowledge of its sources and the consequent ordering of family life should ensure normal vitamin A status. For example, home or school gardens can not only meet family vitamin A requirements but also provide additional nutrients and income and help to raise the status of women. Such programmes are difficult to start and to sustain. The doubt recently cast on the bioavailability of provitamin A carotenoids from dark green leaves and other sources suggests that some preformed vitamin A from animal sources may be needed.

Recently rice has been genetically modified to contain β-carotene. Intensive efforts are under way to make this "golden rice" widely available.

Supplementation

Large doses of vitamin A in capsule or liquid form (200,000 IU) have been administered prophylactically at 4–6 months intervals for many years in a number of countries. Table 12 shows the WHO-recommended schedule for

Table 12. Recommended xerophthalmia treatment schedule Ð oil-miscible oral vitamin A

	<1 Year of age	≥1 Year of age
Immediately	100,000 IU	200,000 IU
Next day	100,000 IU	200,000 IU
2–4 weeks later	100,000 IU	200,000 IU
Severe Protein-Energy Malnutrition (PEM)		
Monthly until PEM resolves	100,000 IU	200,000 IU

treatment of a patient with signs of VAD. In a sense this is also a preventive measure as the last dose is given with that aim in mind. Table 13 indicates the preventive schedule recommended by WHO. This should be a strictly emergency measure as it makes no contribution towards eradicating the problem. Although easy to initiate, experience has shown repeatedly that in a routine setting coverage falls dramatically to unacceptably low levels. It should not be considered in isolation, but thought should be given at the same time to other long-term measures. In recent years the national immunization days (NIDs) and other measures as part of the worldwide Expanded Programme of Immunization (EPI) of WHO has been utilized with good effect for the distribution of vitamin A capsules. It is not immune from the criticisms mentioned above.

Evidence of transiently raised intracranial pressure has occasionally been noted in vitamin A supplementation involving infants, but follow-up for 3 years has found no long-term ill effect. Mention was made (see page 32) of the possibility of large doses of vitamin A in early pregnancy causing malformations in the developing embryo. A number of studies have provided a consensus view that supplementation of vitamin A not exceeding 10,000 IU daily is perfectly safe.

Fortification

Addition of a nutrient to a food implies that a significant proportion of a population is unable to obtain their daily requirement from natural food alone. Recent evidence suggests that this may well be the case in many communities in the developing world. Foodstuffs used in developing countries which can be fortified include wheat, rice and other grain products, tea, dairy foods, margarine, edible oils, formula foods and speciality items. Other micronutrients such as iron and zinc are also being added. For a successful fortification programme to be initiated and maintained a great deal of cooperation is required. Several studies have shown that in a research setting it can significantly improve the vitamin A status of a whole population.

Table 13. Universal vitaminA distribution schedule for preschool children and lactating mothers

Children 1–6 years	200,000 IU of vitaminA orally every 3–6 months.
Infants 6–11 months	100,000 IU of vitaminA orally every 3–6 months. Immunization against measles provides a good opportunity to give one of these doses (see note).
Lactating mothers	200,000 IU of vitaminA orally once: at delivery or during the first 8 weeks postpartum if breast-feeding or during the first 6 weeks if not breast-feeding to protect the mother and raise breast milk vitamin A levels to help protect the breast-fed infant.

NOTE: When infants less than six months old are not being breast-fed, supplementation with 50,000 IU of vitaminA, as single dose or as divided doses of 25,000 IU, should be considered before they reach the age of six months.

Glossary

Acute-phase reaction (or response) (APR) A generalized reaction of the body to acute infection, inflammation and injury. Certain proteins, positive acute-phase proteins, increase in concentration in plasma. Other proteins, which include retinol-binding protein (RBP) and transferrin, decrease in concentration in plasma and are known as negative acute-phase proteins.

Bioavailability In general the term refers to the degree to which any substance in the diet is available after ingestion for utilization by the body. In the present context, bioavailability relates to the degree to which dietary provitamin A carotenoids are utilized after ingestion.

BitotÕs spot Heaping up of keratinized cells on bulbar conjunctiva. An advanced stage of conjunctival xerosis. The first description was attributed to a French physician of that name in the middle of the 19th century. Not all Bitot's spots are attributable to deficiency of vitamin A.

Carotenoids Yellow, orange, or red pigments occurring in nature. About 600 have been identified, of which less than 10 have provitamin A activity. They all have a basic C_{40} skeleton which is made up from successive additions of C_5 isoprene units.

Chlorophyll A green pigment that imparts its colour to the leaves of plants and many vegetables. It is mainly responsible for the process of photosynthesis, whereby in the presence of sunlight carbon dioxide from the atmosphere and water are converted to carbohydrate, and oxygen is given off.

Chloroplast This structure in leaves contains the chlorophyll and carotenoids, which act as catalysts in the process of photosynthesis.

Cis/trans See isomerization.

Conjunctiva The thin layer of tissue that overlies the white part of the front of the eye and also lines the inner part of the lids.

Conjunctival impression cytology (CIC) A technique whereby a cellulose acetate strip is applied gently to the surface of the bulbar conjunctiva of the eye. When the strip is removed the superficial layer of epithelial cells adheres to it. The strip with cells is processed and stained. The histological appearances are studied for evidence of early keratinization, suggestive of subclinical VAD.

Cornea The window in the front part of the eye through which we see.

Dark adaptation The ability of the rod cells of the retina of the eye to take over the function of vision under conditions of low illumination. This function is heavily dependent on an adequate vitamin A status.

Enzyme One of a large number of proteins whose function is to bring about a particular chemical reaction in the body.

Haemopoiesis The process in the bone marrow by which various kinds of blood cells are produced.

Hypervitaminosis A Vitamin A status in which there are an excessive concentration of retinol in plasma and symptoms and signs of toxicity.

Hypovitaminosis A This is synonymous with VAD.

Isomerization A change in the spatial orientation of a chemical molecule without any change in the basic chemical structure.

Keratinization A process characteristic of epithelial tissues. The tissues undergo a complex series of hardening and drying changes. Keratinization is normal in such tissues as skin, but is abnormal in many other epithelial tissues, including conjunctiva, cornea, and epithelial linings of lungs, gut, urinary tract etc. It is synonymous with the term xerosis.

Keratomalacia This term is applied to changes in the cornea in severe VAD. In addition to keratinization (see above) of the corneal epithelium there is softening of the stroma or underlying tissue.

Meta-analysis A statistical analysis applied to the data of a group of studies which all conform to a set of criteria to ensure similarity as far as possible. The larger numbers obtained in this way provide greater statistical power.

Night blindness The subjective sensation of difficulty to identify objects under conditions of low illumination.

Provitamin A Carotenoids, like β-carotene, capable of being converted to vitamin A in the animal body.

Recommended Dietary Allowance or Intake (RDA, RDI) This relates to the level of an essential nutrient considered to be adequate to meet the known nutritional needs of practically all healthy persons in a population.

Relative dose response (RDR) A biochemical test designed to assess vitamin A status by the indirect estimate of liver vitamin A stores.

Retinoids A class of compounds consisting of four isoprenoid units joined together in a head-to-tail manner and customarily containing five conjugated double bonds. The term vitamin A is used as a generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol.

Retinol equivalent (RE) This term was created to express both preformed vitamin A and provitamin A carotenoid equivalents as a single nutritive value. One RE is equal to 1 µg of all-*trans* retinol, or to 6 µg of all-*trans* β-carotene, or to 12 µg of other provitamin A carotenoids. It has recently been proposed that the previous RE values for provitamin A carotenoids be halved. This would make β-carotene 1/12 as active as retinol (up to now 1:6), and other provitamin A carotenoids 1/24 (up to now 1:12).

Vitamin The word originally meant "vital amine". Vitamins are vital in the sense that they are organic compounds that must be included in the diet in sufficient amount for health. Their chemical structure varies and they are not all amines as was first thought.

Vitamin A As might be expected this was the first vitamin to be discovered, in 1913. Chemically it is known as retinol. It is an alcohol with five carbon-carbon double bonds and a functional β-ionone ring.

Xerophthalmia A term that applies to all clinical stages of eye disease attributable to VAD.

Xerosis See keratinization.