FEDERAL UNIVERSITY OF TECHNOLOGY MINNA

RETINOL : THE VITAMIN OF LIFE

By

Helmina Olufunmilayo Akanya

Inaugural Lecture Series No. 5

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Inaugural Lecture delivered at the
Federal University Of Technology, Minna,
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Ladies and Gentlemen

It is with humility and joy that I stand before you this day to deliver this inaugural lecture titled "Retinol, The Vitamin of Life".

I do understand that inaugural lectures afford one the opportunity to bring 'town and gown' together in a celebration of academic excellence, discussing one's contributions to knowledge in a language which is informative and can be understood by ordinary person who is neither a biochemist or a scientist. Therefore, I intend to make my presentation as simple as possible. Vice Chancellor Sir, I am of the opinion that precision is a true mark of scholarship, I hereby crave your indulgence to permit me to delve into the issue of the day.

RETINOL

HISTORICAL INTRODUCTION

In the 16th Century BC night blindness and eye disorders, which were well recognized in ancient Egypt, were treated by the topical application of juice squeezed from raw liver or by prescribing liver in the diet (Wolf, 1996). Also fishermen from Newfoundland have known for a long time that they navigate better at night if they eat cod liver. This

medical folklore was lost over the centuries and night blindness plagued armies throughout the world in the 19th Century BC. In 1913 the researchers found a substance that made one grow and see better. McCollumn and Davis,(1913) described the substance as fat 'Soluble A'. Later, they gave the substance the name vitamin A. Another growth promoting factor, vitamin A_2 (3-dehydro retinol) was also detected from fresh water fish liver oils. Since then researchers have continued to unravel the biochemical importance of this unique substance in metabolism.

The structure of Vitamin A was elucidated in 1930 by Karer *et al.* The biological conversion of ß-carotene into vitamin A was also demonstrated in the same year.

THE STRUCTURE OF RETINOL

The parent compound in the vitamin A group is called all-trans retinol. Retinol is the immediate precursor to two important active metabolites: retinal, which plays a critical role in vision, and retinoic acid, which serves as an intracellular messenger that affects transcription of a number of genes. ß-carotene is the major carotenoid that can be converted to vitamin A within the intestine and other tissues (Olson *et al.*, 2000). The structures of these compounds are presented in Figure 1.

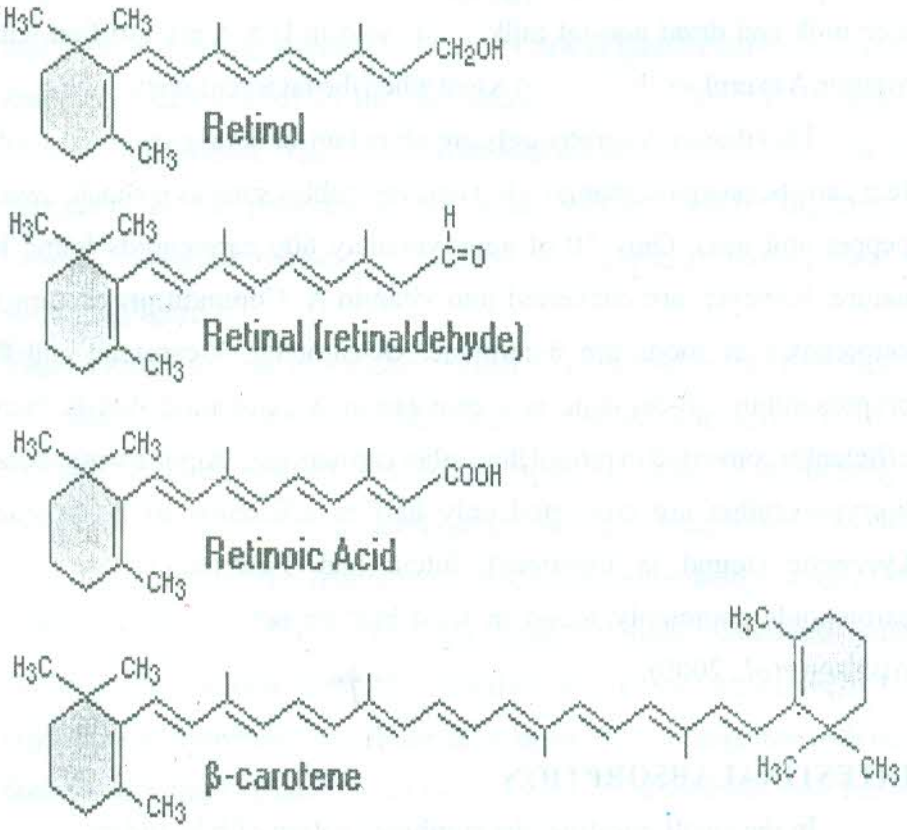


Figure 1. Structure of some vitamin A compounds.

SOURCES OF RETINOL

Retinol is often called preformed vitamin A while the carotenoids are the provitamin A.

Pre-formed vitamin A is found in animal foods such as whole eggs, cheese, whole milk and liver (Sebrell and Harris, 1967). Fortified

foods such as fortified breakfast cereals also provide vitamin A. Most fat-free milk and dried non-fat milk solids sold in U.S.A are fortified with vitamin A to replace the vitamin A lost when the fat is removed.

Provitamin A carotenoids are abundant in darkly coloured fruits (e.g carrots, pawpaw, mango, etc.) and vegetables such as spinach, sweet pepper and peas. Only 50 of approximately 600 carotenoids found in nature, however, are converted into vitamin A. Common provitamin A carotenoids in foods are ß-carotene, ∝-carotene, ϒ-carotene and ß-cryptoxanthin. ß-carotene is a provitamin A carotenoid that is more efficiently converted to retinol than other carotenoids. Alpha carotene and ß-cryptoxanthin are converted only half as efficiently as ß-carotene. Lycopene (found in tomatoes), lutein and 3-zeaxanthin are other carotenoids commonly found in food but are not sources of vitamin A(Olson *et al.*, 2000).

INTESTINAL ABSORPTION

In the small intestine, the combined action of bile and pancreatic esterases hydrolyses the esters of retinol. Retinol is then actively transported in micellar form across the membrane of epithelial cells of the intestinal villus (Ong, 1994). The absorption efficiency of dietary vitamin A in healthy person who ingest significant amounts of fat is >80%. The absorption efficiency, or bioavailability, of dietary carotenoids can vary from approximately 50% to <5% depending on the specific carotenoid, its isomeric form, the amount ingested, the presence of accompanying fat, cooking practice, the particle size of the ingested food and the integrity of the gut (de Pee and West, 1996). The absorption efficiency is best with

relatively small amounts of all-trans ß-carotene in oil, such as red palm oil, and poorest in whole vegetables, whether raw or rapidly stir-fried. As the amount of carotenoids in the diet increases, however, the absorption efficiency decreases. The intestinal absorption of carotenoids is critically dependent on the presence of bile acids (Olson, 1994). Ingested ß-carotenes may be oxidatively cleaved by ß-carotene dioxygenase as shown in Figure 2.

This cleavage utilizes molecular oxygen, is enhanced by the presence of bile salts, and generates two molecules of retinaldehyde (retinal). In the intestinal mucosa, retinal is reduced to retinol by a specific retinaldehyde reductase utilizing reduced nicotinamide adenine dinucleotide (NADH). A small fraction of the retinal is oxidized to retinoic acid. Most of the retinol is esterified with saturated fatty acids and incorporated into lymph chylomicrons, which enter the bloodstream. These are converted to chylomicrons remnants, which are taken up by the liver together with their content of retinol (Blaner and Olson, 1994). Carotenoids may escape some of these processes and pass directly into the chylomicrons.

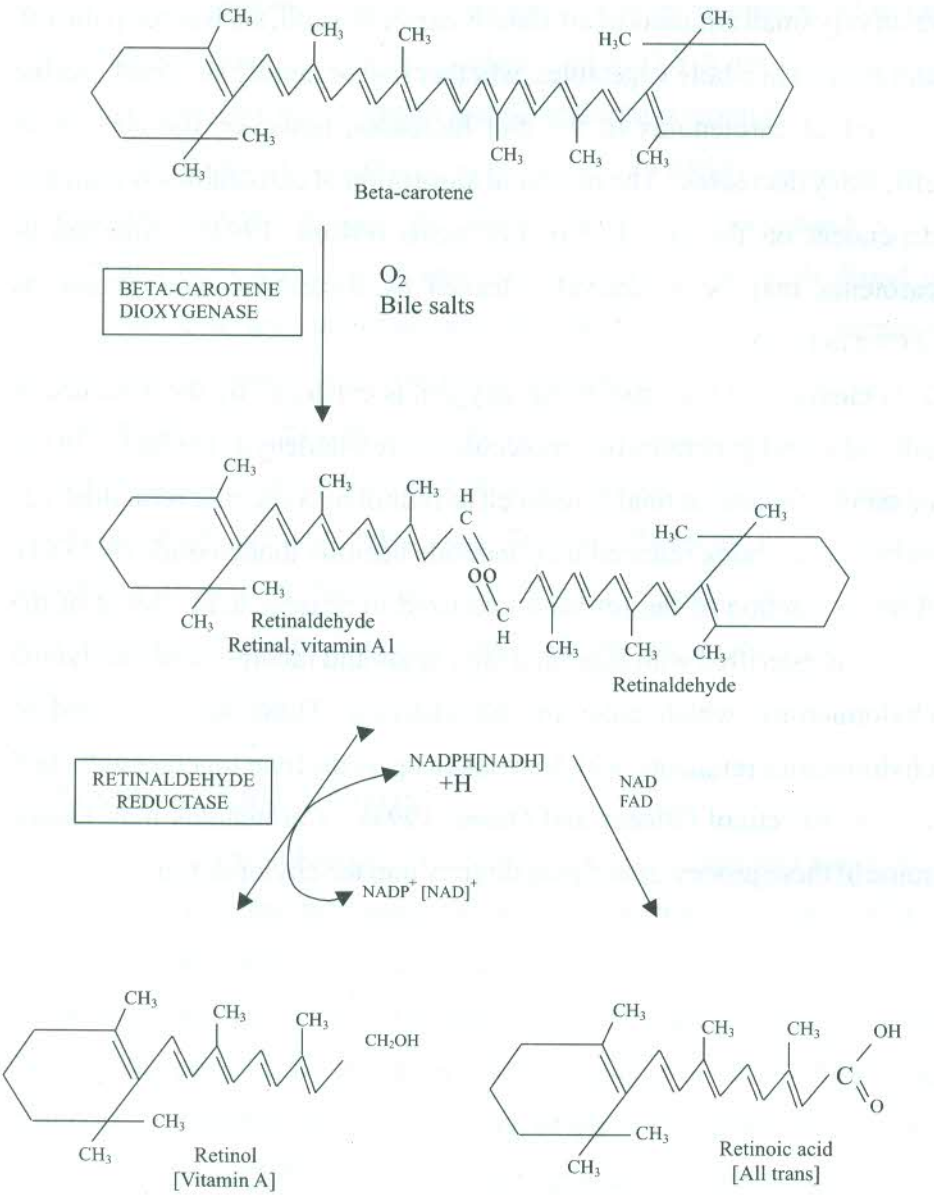


Fig 2. Conversion of ß-carotene to Retinol.

STORAGE OF RETINOL IN THE BODY

Hepatic vitamin A in a well-nourished individual normally represents over 90% of the total reserve of vitamin A in the body (Goodman, 1984). The parenchyma cells, the predominant cell type in the liver, contain small amounts of retinol and significant amounts of retinyl ester. These cells take up and process chylomicron remnants as well as synthesizing and releasing plasma retinol - binding protein (pRBP) (Blaner and Olson, 1994). Ingested vitamin A is therefore, transferred from parenchyma cells to stellate cells in the form of retinol, is then re-esterified, and stored there as a lipoglycoprotein complex. For its utilization, retinyl ester is hydrolysed to retinol, which is bound to apo-retinol binding protein (RBP) before it is released into the plasma.

Other important organs for vitamin A storage are the adrenals and the kidney. The adrenals contain stellate type cells similar to the liver. The kidney might not be a true storage organ since it is mainly involved in the metabolism of serum pRBP and the conservation of the retinol ligand. Another subsidiary storage site for retinol is the pigment epithelium of the retina in the eye. The retinol arrives from circulation as holo-retinol-binding protein (holo-RBP) and becomes esterified and stored in pigment epithelium in lipid droplets (Blaner and Olson, 1994).

TRANSPORT OF RETINOL IN THE PLASMA

Vitamin A must be transported to target tissues, since retinol is a fat-soluble molecule and is not readily soluble in aqueous environment. In addition, the polyunsaturated nature of the molecule makes it susceptible to oxidation. With its polar end and non-polar groups it is also easily

adsorbed onto membrane interfaces. Hence, a binding protein is required to solubilise retinol in the aqueous plasma and intracellular fluids, thus enabling the vitamin to reach tissue cells while at the same time affording some protection against oxidation.

Vitamin A is mobilized from liver stores and transported in plasma as retinol bound to retinol-binding protein (Chen *et al.,* 1986). In humans, retinol-binding protein is a single polypeptide chain with a molecular weight close to 21,000 daltons and with one binding site for one molecule of retinol (Kanai *et al.,* 1968). In plasma, most of the normally circulating pRBP is saturated with retinol and is referred to as holo-RBP. The protein moiety also has a binding site for attachment of the molecule to receptors on the target tissues such as pigment epithelia in the eye, epithelial cells of the skin and cells of the reproductive tissues. The protein, however, is small enough to be susceptible to glomerular filtration in the kidney and thus loss of retinol in circulation. Holo-RBP, however, is combined with prealbumin (transthyretin) also in 1:1 mole ratio raising the complex to approximately 75,000 daltons and thus preventing glomerular filtration in the kidney (Kanai et al., 1968).

The combination of retinol and pRBP protects and stabilizes the vitamin, makes it soluble and transportable in plasma and protects tissues from the toxicity of free retinol. The combination of prealbumin with holo-RBP further confers stability on the holo-RBP.

THE CONCENTRATION OF RETINOL-BINDING PROTEIN IN PLASMA.

The concentration of retinol in plasma is 30μg/100ml for normal

subjects (IVACG, 1976). Below this, there may be symptoms of deficiency though the normal level may vary depending on age and sex.

Plasma concentration of retinol-binding protein and prealbumin in normal subjects are 50-50μg/ml and 20-300μg/ml respectively (Smith *et al.*, 1970); Goodman, 1974). The younger the child the lower the pRBP. In Indian children (2-10 years old), the normal level is 30-40μg/ml and prealbumin is 160μg/ml (Pirie, 1978). In Northern Nigerian children, the pRBP level ranged between 25μg/ml and 35μg/ml (James *et al.*, 1984).

INTRACELLULAR TRANSPORT OF RETINOL

A number of tissues in rats, humans and other species contain a soluble intracellular protein with binding specificity for retinol. Cellular retinol-binding protein has been purified from rat liver, testes and retina (Bashor *et al.*, 1973; Ong and Chytil, 1975a) chick liver (James and Glover, 1986) and human liver (Fex and Johannesson, 1984). cRBP has a molecular weight of 14,600 daltons (James and Glover, 1986, Ong and Chytil, 1975a) different from that of pRBP with a molecular weight of 21,000 daltons. Another interesting distinction between the plasma RBP and the cellular RBP is that pRBP is highly specific for the cylohexene ring and the conjugated side chain and therefore can bind retinol, retinal, retinyl acetate, retinoic acid (Horwitz and Heller, 1973), whereas, cRBP on the other hand, is highly specific for the polar end groups but can accept modification of the cyclohexene ring (Ong and Chytil, 1975b). Cellular RBP is also immunologically distinct from plasma RBP (Bashor and Chytil, 1975, James *et al.*, 1986).

It has been shown that 88-91% of the total liver cRBP appeared to be

located in cytosol (Adachi *et al.*, 1981, Akanya,1993). This is different in the case of pRBP which is almost entirely particulate i.e mainly in the microsomal and golgi fractions (Glover *et al.*, 1974).

One main function of cellular retinol binding protein is belived to be the transport of retinol in the cytoplasm, a function analogues to intracellular receptors for steroid hormones. Cellular RBP may play a part in the biological expression of retinol activity and facilitate specific interaction of retinol with nuclear binding sites (Takasse *et al.*, 1979).

OTHER TRANSPORT PROTEINS FOR RETINOL METABOLITES

In addition to cRBP within functional cells there are other proteins for the transport of retinoic acid and retinyaldehyde. Cellular retinoic acid-binding protein was first detected in the supernatant fraction from rat testicular homogenates by Ong and Chytil (1975a) and isolated as a single polypeptide of 14,600 daltons (Ong and Chytil, 1978, Ross *et al.*, 1980). It is immunologically different from cRBP, although there is partial homology between the two. It has one binding site for retinoic acid but as with cRBP its specificity resides mainly in the terminal carboxyl group and does not require the ligands to have a ß-ionone ring (Muto *et al,* 1982. The organs containing it in high concentration include the eye, ovary, pituitary, prostate, testes and uterus. Its role in the cell for transporting retinoic acid probably corresponds to that of cRBP for retinol. A specific carrier for 11cis-retinaldehyde has been detected in both retina pigment epithelium and retina (Futterman *et al,* 1977,Saari *et al.*,1982). It has an Mr of 33,000 daltons and is called cellular retinaldehyde-binding protein.

RECOMMENDED DIETARY ALLOWANCE OF VITAMIN A FOR ADULTS AND CHILDREN.

Recommended Dietary Allowance (RDA), is the average daily dietary intake level sufficient to meet the nutrient requirement of nearly all (97-98%) healthy individuals in each age and gender group. In Table 1 RDAs for vitamin A are listed as Retinol Activity Equivalents (RAE) to account for the different activities of retinol and provitamin A carotenoids.

Also, RDAs are also listed in International Units (IU) because food and some supplement labels list vitamin A content in International Units (IRAE) in micrograms (μg = 3.3 IU).

The RDAs for adults and children in μg RAE and IU (Alaimo *et al.*, 1994) are as in Tables 1 and 2. There is no RDA for ß-carotene or other provitamin A carotenoids. There has been a suggestion that consuming 3 to 6mg of ß-carotene daily will maintain plasma ß-carotene blood levels in the range associated with a lower risk of diseases.

Table 1: Recommended Dietary Allowances for Vitamin A in micrograms (µg), Retinol Activity Equivalents (RAE) and International Units (IUS) for Children and Adults.

Age (Years)	Children	Men	Women	Pregnancy	Lactation
1-3	300µg or 1000 IU				
4-8	400 µg or 1333 IU				
9-13	600µg or 2000 IU				
14-18		900µg or 3000 IU	700µg or 2330 IU	750µg or1 2500 IU	1,200µg or 4000 IU
19+		900µg or 3000 IU	7000µg or 2330 IU	770µg or 2565 IU	1300µg or 4335 IU

There is insufficient information to establish a RDA for Vitamin A for infants. An adequate intake (AI) has been established that is based on the amount of vitamin A consumed by healthy infants who are fed breast milk.

Table 2: Adequate Intake for Vitamin A in micrograms (µg) and International Units (IU) for infants.

Age (Months)	Males and Female
0 - 6	400µg or 1330 IU
7 - 12	500µg or 1665 IU

VITAMIN A AND REPRODUCTION IN ANIMALS

The requirement of vitamin A for reproduction functions in higher animals has been documented. In studies with animals restricted to vitamin A deficient diets and repleted with various active forms of vitamin A Thompson *et al* (1964), established a dichotomy of vitamin A function. While retinoic acid maintained somatic epithelial function in testes, it did not maintain germinal epithelium or spermatogenesis. The reduced forms of vitamin A, retinol or retinal, are required for these functions.

In addition to its general somatic role in epithelial maintenance, retinoic acid does have a specific function in testes, in that it supports testosterone biosynthesis in Leydig (interstitial) cells (Appling and Chytil, 1981). Both retinol and retinoic acid alone can support spermatogenesis and oogenesis in birds (Thompson *et al.*, 1969).

The mechanism of action of vitamin A proposed for maintenance of growth and differentiation have also been suggested for the function of vitamin A in reproduction. Extensive studies with testicular retinol and retinoic - acid specific binding proteins have strengthened the view that the action of vitamin A compounds in reproduction is mediated by specific intracellular carrier proteins and that vitamin A exerts its effect on reproduction at the gene level via a nuclear receptor.

THE ROLE OF VITAMIN A IN CELL DIFFERENTIATION AND GROWTH

The various forms of vitamin A capable of supporting somatic functions include retinal, retinyl esters, retinal and retinoic acid. Early histological studies have clearly shown that when animals become vitamin A deficient, various epithelial tissues loose the ability to maintain differentiation (Wolbach and Howe, 1925). Depending upon the severity of the deficiency, normal epithelium disappears and is replaced by keratinized epithelium. In the testis, spermatogenesis becomes atrophied (Wolbach and Howe, 1933). A general observation of the effect of vitamin A upon differentiation is that the vitamin most certainly exerts its action upon biopotential cells (cells that have retained their differentiating ability in the growing and mature animal and can differentiate in more than one direction). Vitamin A deficiency at the cellular level is most readily seen in the differentiating tissues that have a rapid turnover rate, such as epithelial of the oral cavity, respiratory tract, urinary tract and ducts of various secretary glands.

In an attempt to elucidate the mode of action of vitamin A, a working hypothesis was developed by Bashor and Chytil (1975), that the nucleus is responsible for the molecular mechanism underlying vitamin A-dependent cellular differentiation.

In the search for the manner in which retinol and retinoic acid communicate with the nucleus, two intracellular Vitamin A-binding proteins have been discovered and characterized, cellular retinol-binding protein (cRBP) and cellular retinoic acid - binding protein (cRABP). The exact nature of the interaction of these proteins with the nucleus is not

known but there is evidence that cRBP can indeed transfer retinol specifically into the cell nucleus, where retinol, but not its binding proteins, becomes bound to the chromatin in the nucleus (Liau *et al.*, 1981).

The striking morphological changes in certain epithelial tissues that are the result of alterations in vitamin A nutrition are often accompanied by altered nucleus secretion, thus a role of vitamin A in glycoprotein metabolism has been suggested to explain its effect on differentiation (Thompson *et al.*, 1964, De Luca, 1977). De Luca in 1977 proposed a coenzyme role for vitamin A where retinol as retinyl-phosphate-sugar complex functions in membranes in post-translational transfer of monosaccharides to an acceptor protein, resulting in synthesis of a specific glycoprotein that may affect differentiation. The demonstration that retinoic acid can regulate release of the glycoprotein, fibronectin, in an enucleated cell (Bolmer and Wolf, 1982) indicates that cytoplasmic function may be another molecular mechanism for vitamin A. Retinoic acid has been found to attach to special receptor proteins in the nuclei of cells to help regulate the cell cycle. These retinoic acid nuclear receptors are in a special super family of nuclear receptors that mediate the activity of steroid and thyroid hormones, vitamin D, prostaglandins, and certain drugs that induce specific kinds of cell proliferation (Kato, 2000). Specifically, retinoic acid receptors activate certain transcription factors that regulate gene expression involving growth, differentiation and apoptosis (cell death) (Hashimoto and Shudo 1991, Meier, 1997) (Fig 3.0)

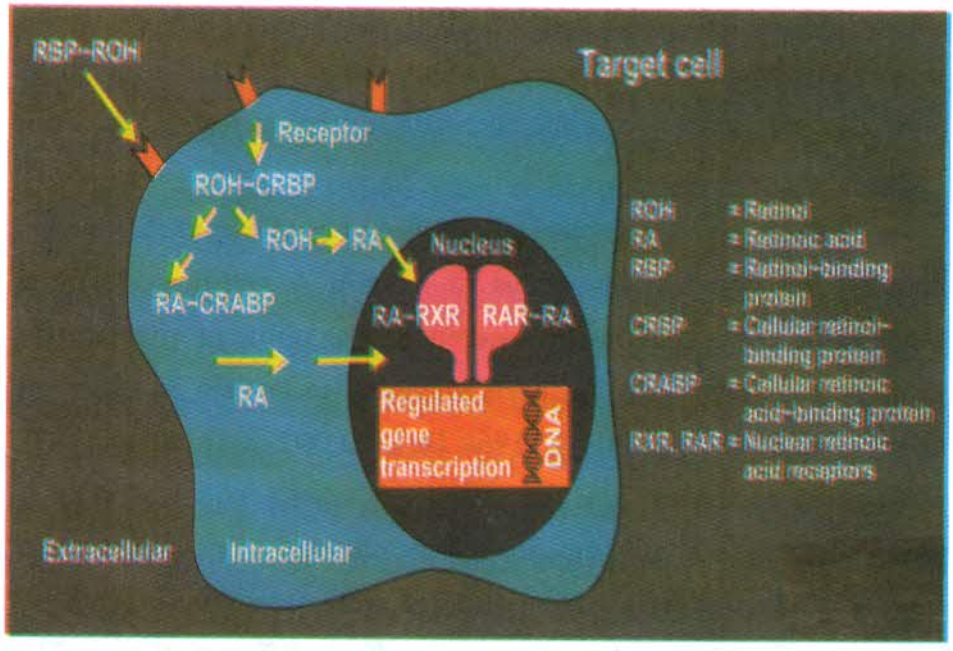


Fig. 3. Interaction of Vitamin A with Nucleus.

RETINOIDS IN CANCER

Several lines of evidence suggest that important relations exist between retinoids and cancer (Bollag, 1983). As discussed above, retinoids have powerful effects on cell differentiation and proliferation. These effects have been demonstrated with both normal and neoplastic cells (Goodman, 1984). Since carcinogenesis is fundamentally a disorder of cell differentiation, it is possible that the retinoid status of a cell influences its potential for cancer development. Secondly, there is evidence from epidemiologic studies that a person's retinoid (vitamin A) status may be an important determinant of the risk that cancer will develop (*Wald et al.*, 1980, Kark *et al.*, 1981).

In addition, synthetic retinoids have been shown to be useful and

effective in the prevention of carcinogenesis in laboratory animals. These studies suggest the potential utility of retinoids as pharmacologic agents for prevention of cancer in high-risk persons, as well as their use in the treatment of certain pre-cancerous and cancerous lesions (Goodman, 1984). However, there is no proof that these supplements can help prevent or treat cancer in people. In fact, some evidence suggests that ß-carotene and, possibly, vitamin A may put people at increased risk of lung cancer, particularly smokers. Preliminary evidence suggests that a topical form of vitamin A, applied to the cervix with sponges or cervical caps shows promise for the treatment of cervical cancer. More research is needed before conclusions can be drawn about use of vitamin A to treat or prevent cervical cancer or cervical dysplasia (French *et al.*, 2000).

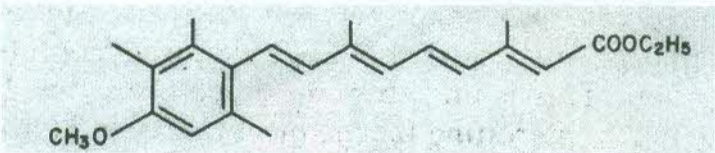
Similarly, use of synthetic retinoids for skin cancer is currently under scientific investigation. Vitamin A and ß-carotene levels in the blood tend to be lower in people with certain types of skin cancer. (Frieling *et al.*, 2000).

DERMATOLOGICAL IMPLICATIONS OF RETINOIDS

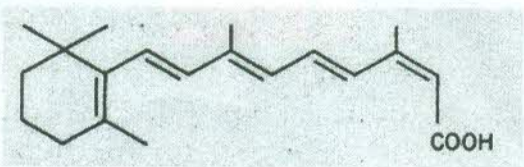
The search for new retinoids has identified a number of compounds with greatly increased therapeutic index (i.e the ratio between biologic activity and toxic side effects), as compared with the indexes of naturally occurring retinoids (Bollag 1979 and 1983). Extensive clinical testing of two of these retinoids, 13-cis-retinoic acid and the aromatic analogue etretinate (Fig. 4) has led to their clinical use in skill disorders.

The use of retinoids in dermatology followed normally from knowledge of the powerful effects of retinoids and of retinoid deficiency

or excess on skin. In Europe, etretinate is used, either alone or in combination with other agents, for the treatment of psoriasis and related disorders of keratinization (Ehman *et al.*, 1982, Strauss *et al.*, 1982).



(a)



(b)

Fig. 4. Structure of (a): 13-cisretinoic acid (b): etretinate

VITAMIN A AND THE IMMUNE SYSTEM

Vitamin A was early termed the 'anti-infective' vitamin based on the increased number of infections noted in vitamin A - deficient animals and humans (Sommer and West, 1996). In vitamin A deficiency, both specific and non-specific protective mechanisms are impaired, namely the humoral response to bacteria, parasitic and viral infections, cell-mediated immunity, mucosal immunity, natural killer cell activity, and phagocytosis. The immune responses to certain antigens in vitamin A - depleted children are enhanced by vitamin A supplementation (Ross and Hammering, 1994).

The primary immune response to protein antigens, but not to bacterial lipopolysaccharides, is markedly reduced in vitamin A

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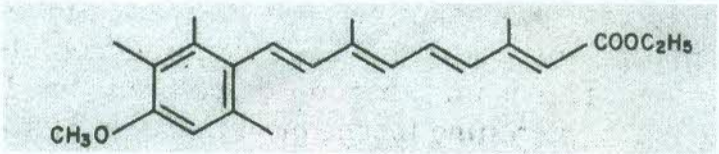

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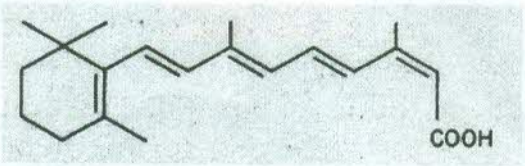

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The primary immune response to protein antigens, but not to bacterial lipopolysaccharides, is markedly reduced in vitamin A

deficiency. On the other hand the process of immunological memory, essential for a marked secondary response, does not seem to be adversely affected. The T-helper cell is a major site of vitamin A action in the immune response. Retinol, probably via 14-hydroxyl retinol (HRR), is also involved in the proliferation of normal B cells and T cells (Ross and Hammering, 1994).

Some carotenoids, in addition to serving as a source of vitamin A, have been shown to serve as singlet oxygen quenchers and function as antioxidants in laboratory tests. However, this role has not been consistently demonstrated in humans. Antioxidants protect cells from radicals, which are potentially damaging byproducts of oxygen metabolism that may contribute to the development of some diseases. Because of these chemical properties carotenoids may play additional roles in health and diseases, (Olson *et al.*, 2000).

THE ROLE OF VITAMIN A IN VISION

In 1968, Wald demonstrated the importance of vitamin A in vision. Retinal is needed to maintain the visual process because it is the precursor for the 11-cis retinal prosthetic group of the visual pigments (Simon *et al.*, 1996). Consequently, retinoids must be supplied to the eye by circulation, transported between its layers and within its cells and stored in its tissues as a reserve against dietary deprivation. 11-cis-retinal combines with a specific lysine group in the membrane bound protein, opsin, in the eye to form rhodopsin, a conjugated protein (Saari, 1994). When rhodopsin is exposed to light, it dissociates as it bleaches and forms all-trans-retinal and opsin. This reaction is accompanied by a conformational change that

induces change in permeability to cations, increased polarization of the membrane, and triggering of a nerve impulse. In the reaction also, the all-trans-retinal is reduced to all-trans-retinol by an NADP-dependent, membrane-bound retinol dehydrogenase (Bridges, 1976 and Futterman, 1977). The retinol lost to the pigment epithelium in the light must be restored by a reversed flow during rhodopsin regeneration (Fig. 5.0).

Rhodopsin is required for low light vision while iodopsin is required for day light vision. Iodopsin consists of cone protein and also 11-cis-retinal. The requirement for retinol in vision is absolute, retinoic acid cannot replace retinol, since it cannot act as a precursor to retinal. Dowling and Wald in 1960 showed that rats given a vitamin A - free diet supplemented with retinoic acid grew well but gradually became irreversibly blind.

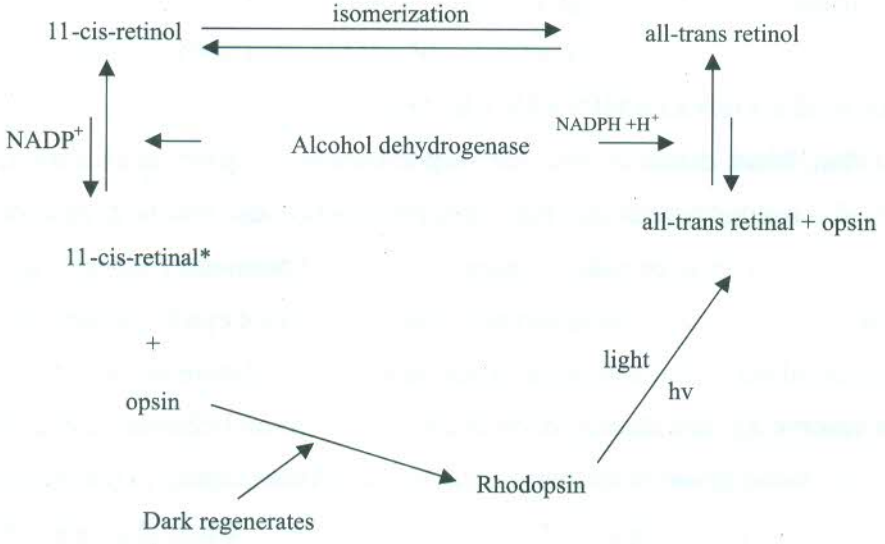

Fig. 5. Retinol in Visual Cycle

* Indicates the active form .

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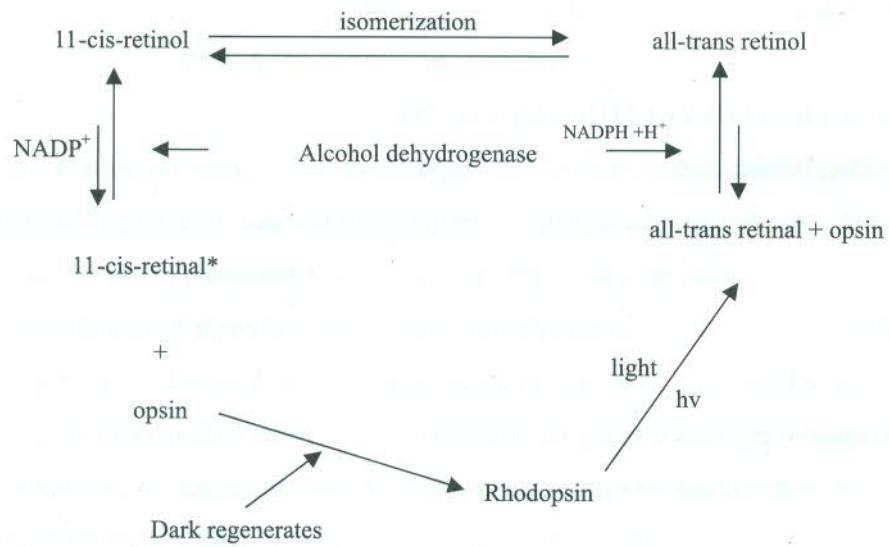

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VITAMIN A DEFICIENCY (VAD) AND VITAMIN A DEFICIENCY DISORDERS (VADD)

Vitamin A deficiency (VAD) occurs where diets contain insufficient vitamin A for meeting the needs associated with growth and development, physiological functions, and periods of added stress due to illness. Vitamin A deficiency is a major public health problem in the developing world. Vitamin A deficiency, although affecting many tissues of the body, is clinically most severe in its ability to damage the cornea of the eye. The surface of the cornea becomes dry and rough and ultimately breaks down partially or completely leading to permanent scarring and irreversible partial or total loss of sight.

FACTORS THAT CAN PRECIPITATE VITAMIN A DEFICIENCY

Vitamin A deficiency can occur :

* through an overall inadequate intake of vitamin A as is often seen in malnutrition.
* through an inadequate intake of protein and zinc. These nutrients are needed to make retinol binding protein (pRBP) which is essential for mobilizing vitamin A from liver and transporting vitamin A to general circulation
* when vitamin A is lost through chronic diarrhoea.
* iron deficiency which can limit the metabolism of vitamin A, and iron supplements provided to iron deficient individuals may improve vitamin A nutriture as well as iron status.
* excess alcohol intake, which depletes vitamin A stores. Also, diets high in alcohol usually do not provide recommended amounts of

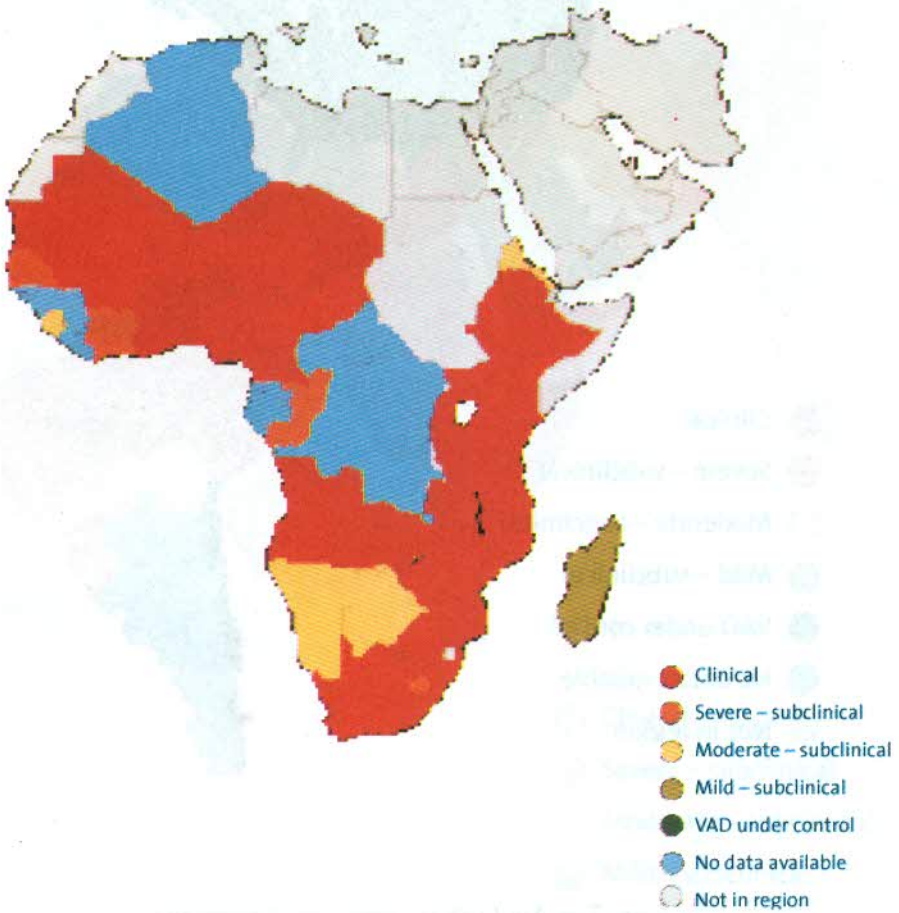

Fig. 6. VAD Prevalence in African Region

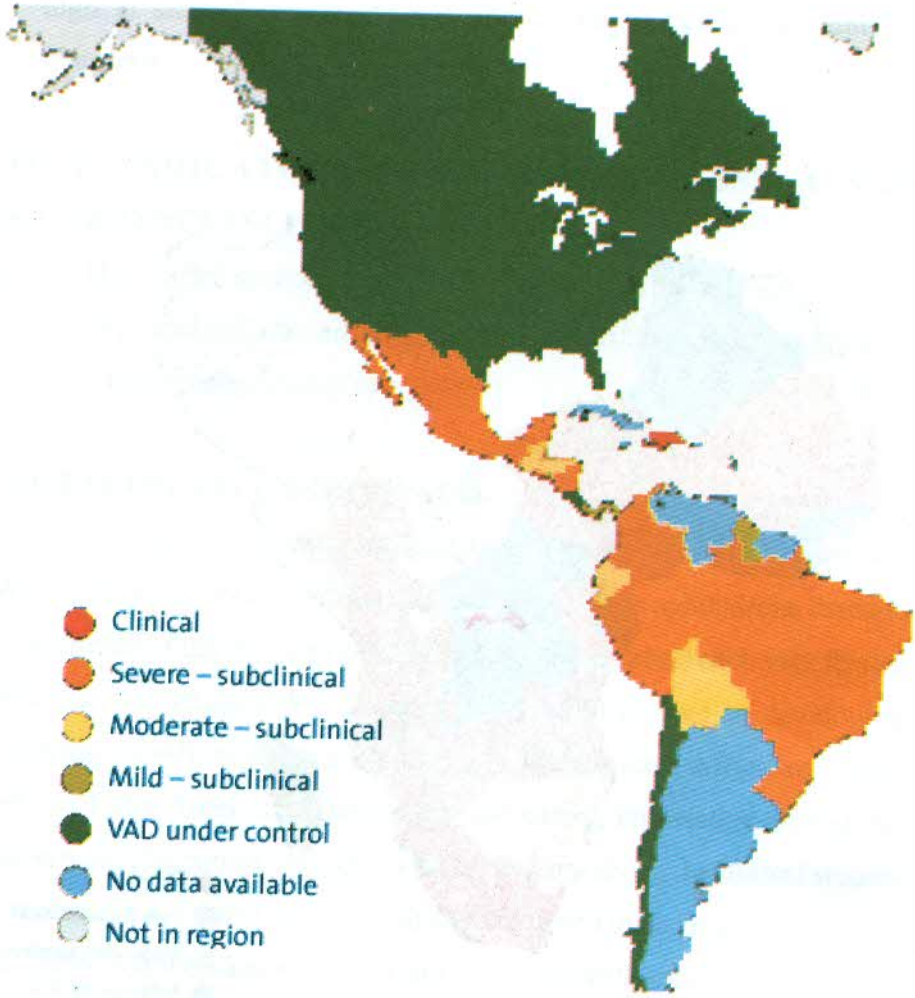

Fig. 7 VAD Prevalence in Americas

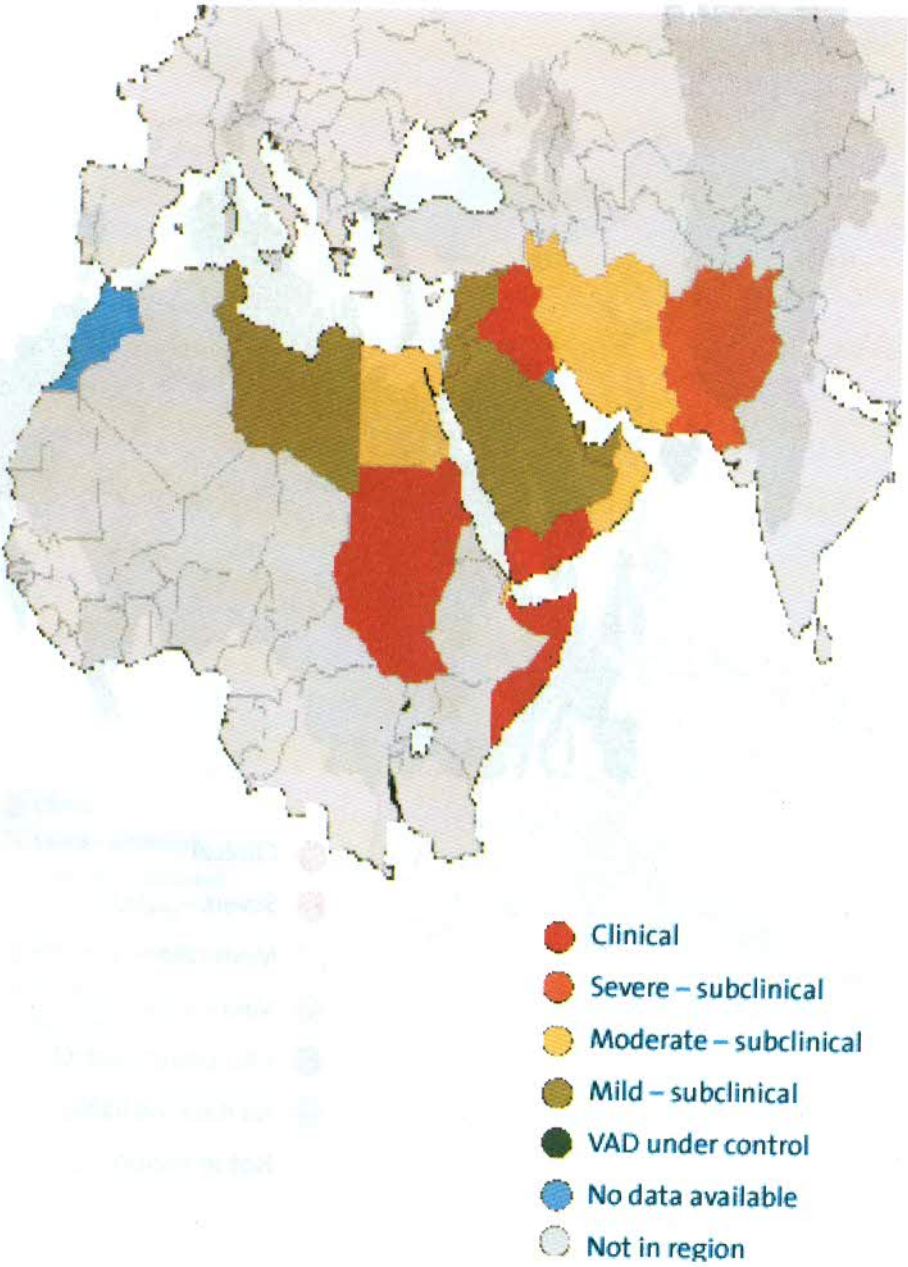

Fig. 8 VAD Prevalence in Eastern Mediterranean Region

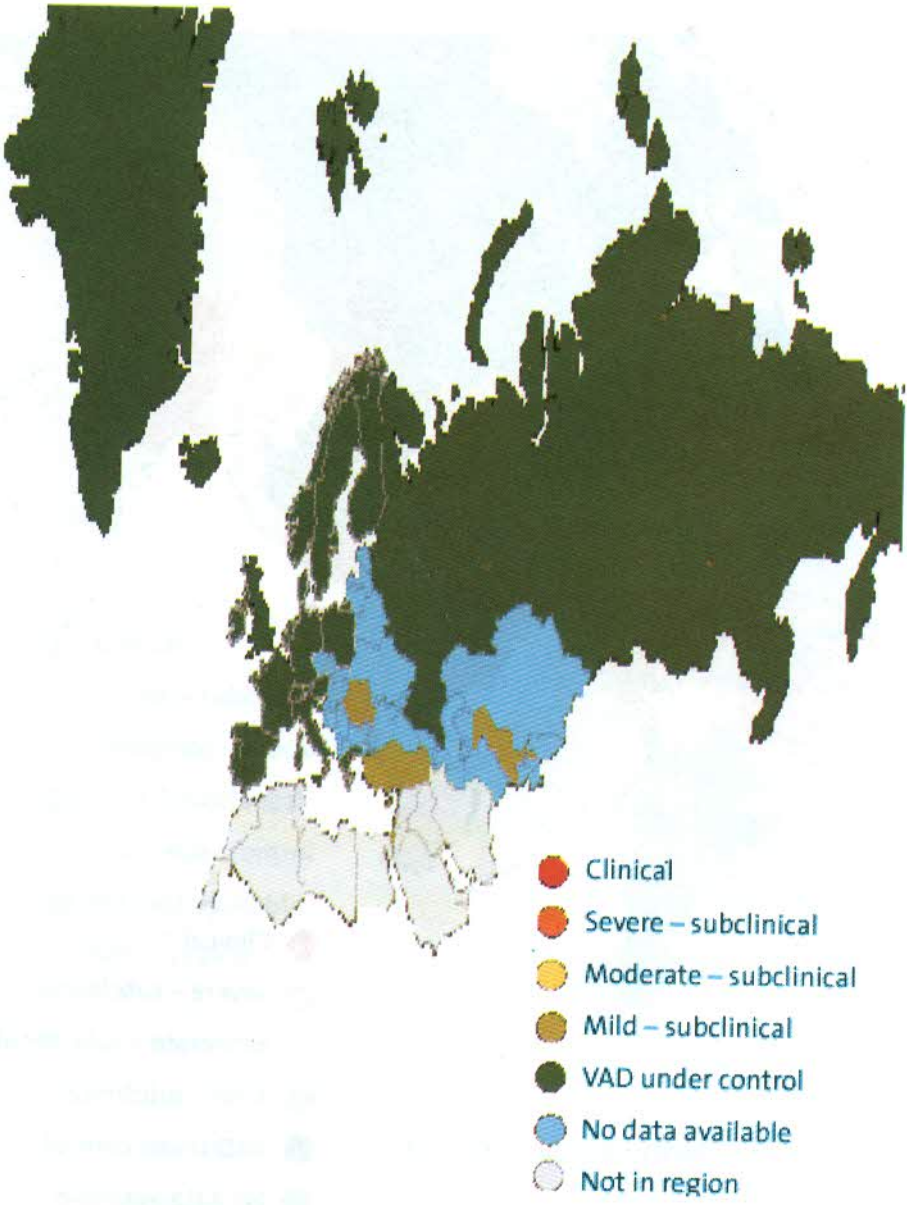

Fig. 9. VAD Prevalence in European Region

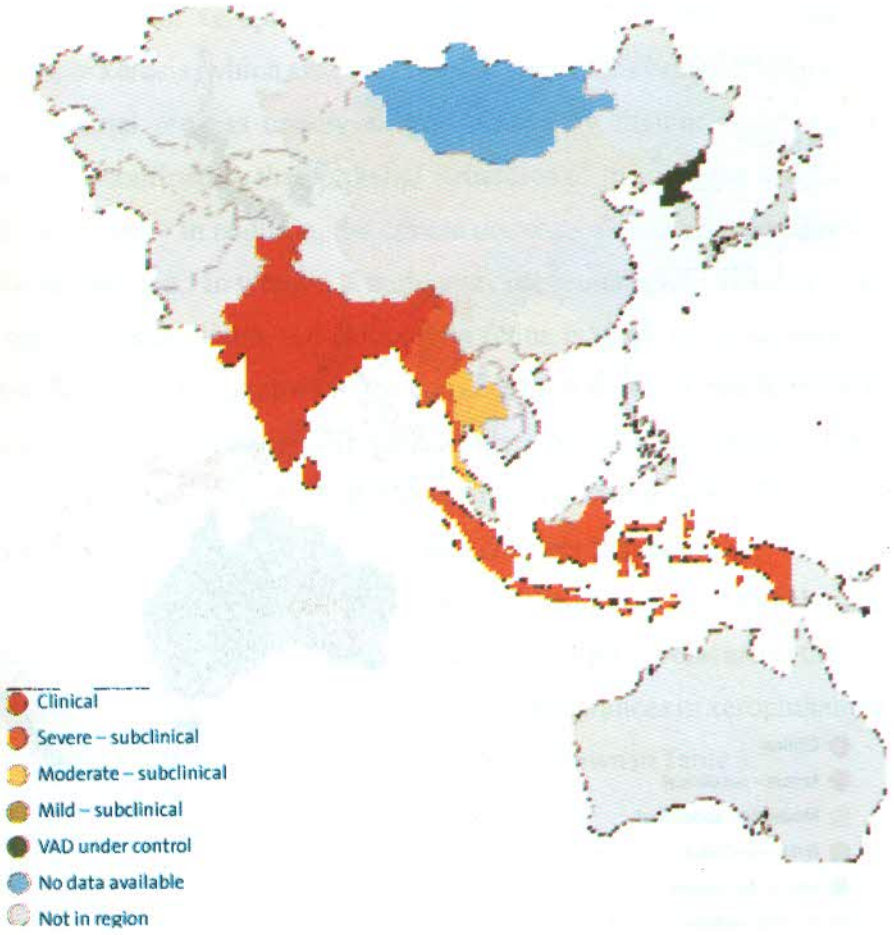

Fig. 10. VAD Prevalence in Southeast Asian Region

Fig. 11. VAD Prevalence in Western Pacific Region

XEROPHTHALMIA

The term xerophthalmia literally means "dry eye". However, dryness or xerosis, which also affects other parts of the body, is only part of the abnormal process undergone by the eye in vitamin A deficiency. Xerosis is confined to the epithelial structures of the eye, the conjuctiva and the cornea. In addition, the cornea undergoes other changes, known as keratomalacia. In vitamin A deficiency the retina is also affected. The rhodopsin system in the rod cells of the retina is much more sensitive to deficiency than the iodopsin in the cone cells. As a result, rod function is impaired early on, resulting in sufficiently marked impairment of night vision. Figures 12 and 13 are diagrams indicating sites affected by vitamin A deficiency. All of these eye changes that occur in vitamin A deficiency are included in the term xerophthalmia i.e xerophthalmia is synonymous with all of the clinical signs and symptoms that affect the eye in vitamin A deficiency. The various ocular appearances in xerophthalmia as classified by WHO Expert Group in 1982 is shown in Table 3.

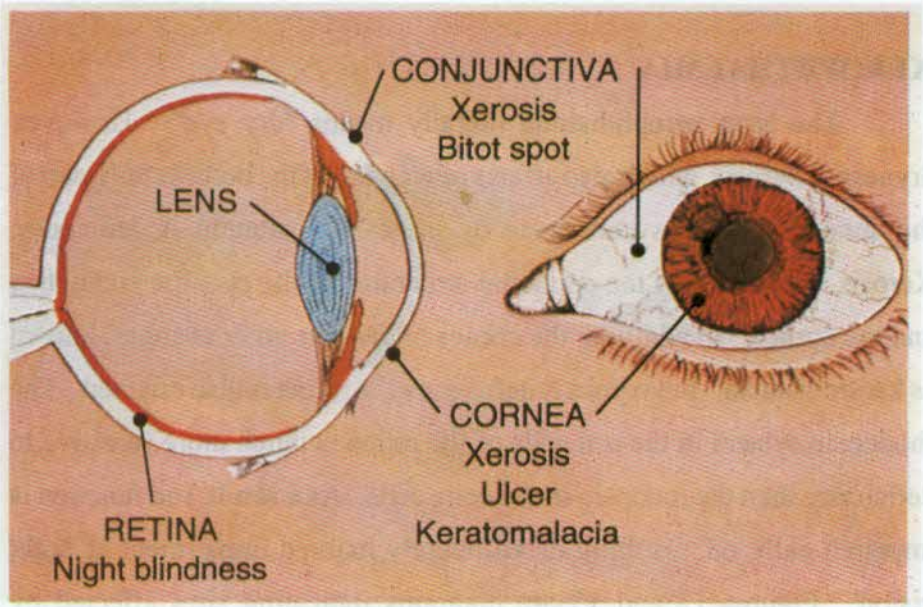

Fig 12. Site of the eye affected by Xerophthalmia

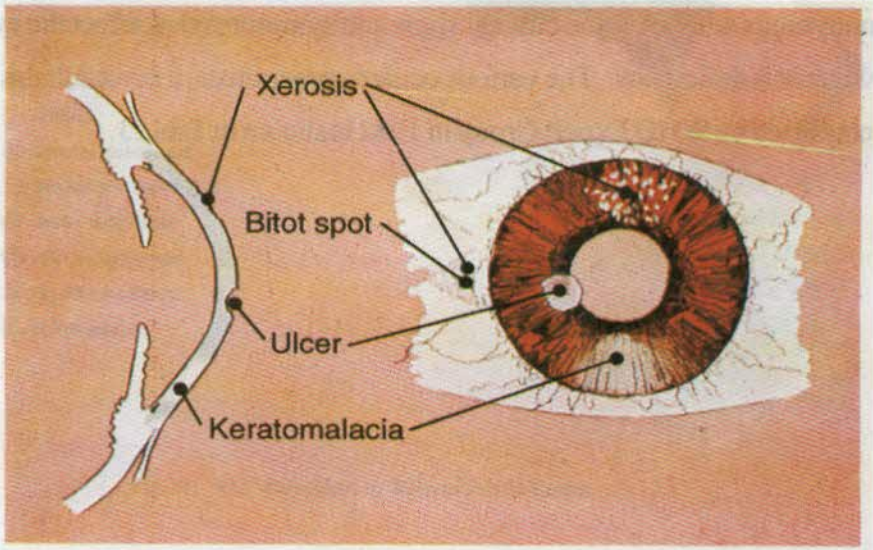

Fig 13. Diagrammatic representation of Xerophthalmia lesions.

Table 3 Xerophthalmia classification by Ocular signs (WHO, 1982)

Night blindness	XN
Conjunctival xerosis	X1A
Bitot's spot	X1B
Corneal xerosis	X2
Corneal ulceration (< 1/3 of corneal surface)	X3A
Keratomalacia (⩾1/3 of corneal surface)	X3B
Corneal scar	XS
Xerophthalmic fundus	XF

NIGHT BLINDNESS (XN)

Night blindness is one of the first signs of vitamin A deficiency. It is retina dysfunction that is sufficiently severe to cause subjective impairment of vision at night. It is often used as indicator of vitamin A deficiency disorder (VADD) (McLaren and Frigg, 2001). The occurrence of names for night blindness in local languages suggests that this rather distinctive phenomenon is occurring with some regularity in a community. The commonest terms used are "night eyes" and "chicken eyes" (chicken has no rods and are therefore night blind). Night blindness is frequently the most prevalent form of xerophthalmia.

CONJUNCTIVAL XEROSIS (XIA)

The term conjunctival xerosis could apply to any stage of xerotic change in the conjunctiva. (Fig 14). This would range from abnormal impression cytology, through dryness of the conjunctiva to keratinization and heaping up of material as in Bitot's spot (XIB).

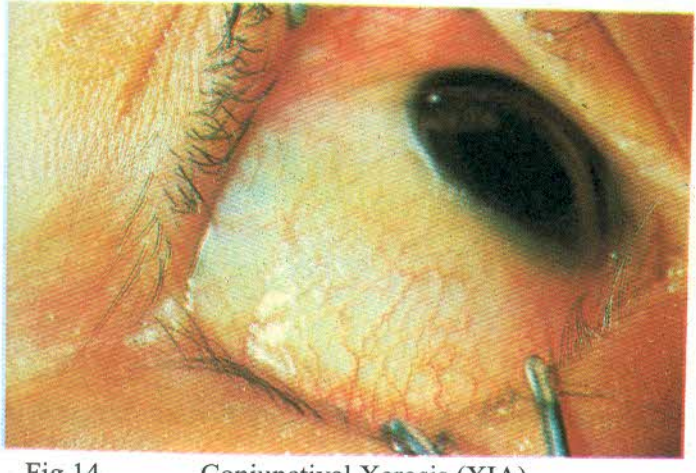

Fig 14. Conjunctival Xerosis (XIA)

BITOT'S SPOT (XIB)

Bitot's spot is the final part of the process of xerosis affecting the bulbar conjunctiva. The typical Bitot's spot occurs in the exposed part of the conjunctiva. Bitot's spot varies considerably in size and shape (Fig 15 and 16). (Sommer, 1995). The areas of conjunctiva affected may be multiple but more usually there is a single spot to an eye. A Bitot's spot consists of a heaping up of desquamated, keratinized epithelial cells which form a slightly raised area that may be readily wiped away. This leaves an uneven, eroded base in the superficial epithelium on which more abnormal cells may accumulate over a few days. The transient nature of Bitot's spot creates a problem over their use in surveys. A subject may "remove" a spot by vigorously rubbing their own eyelids. Broadly speaking the appearance of Bitot's spots has been likened either to foam or cheese (McLaren, 1980).

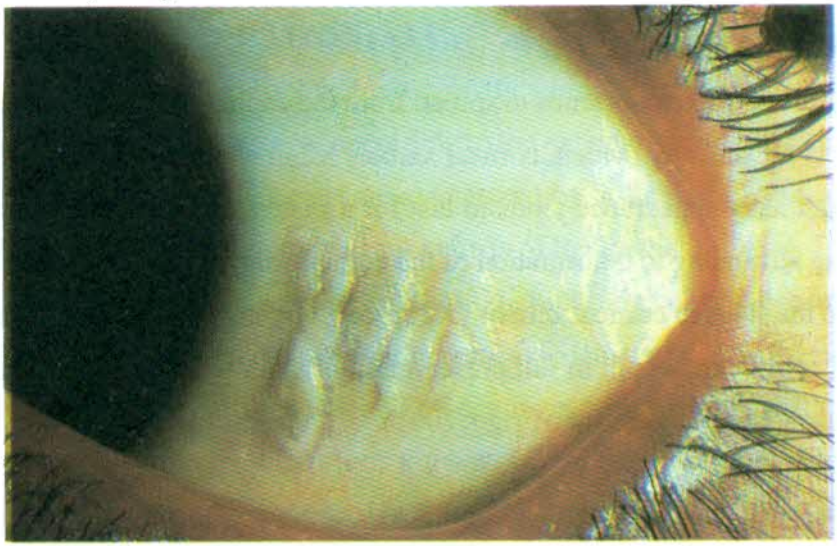

Fig 15 Bitot's spot (XIB) - "Cheesy"

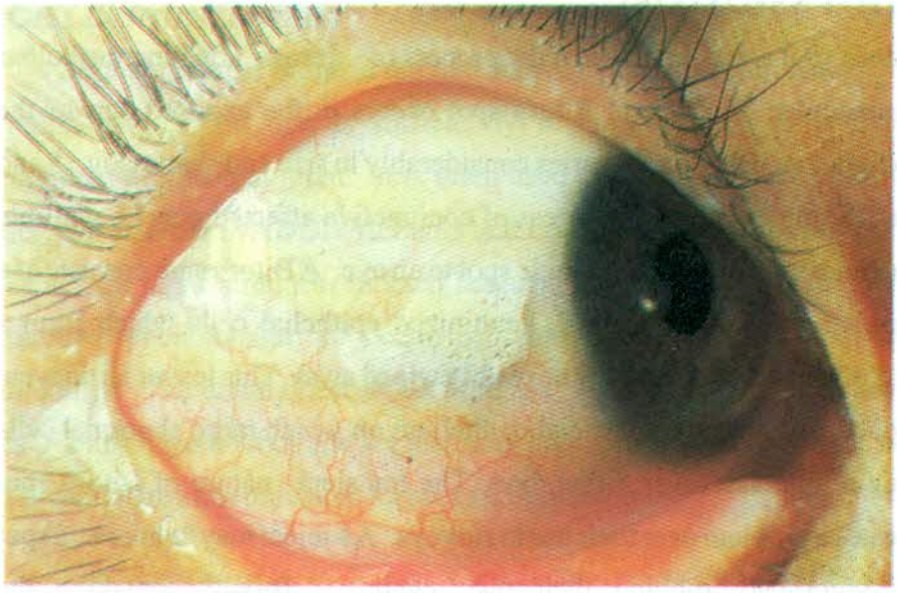

Fig 16 Bitot's spot (XIB) - "Foamy"

CORNEAL XEROSIS (X2)

The process of xerosis tends to spread from the conjunctiva to the cornea (Fig 17). Clinically evident corneal xerosis X2 in which the cornea has a distinct hazy appearance tends to last for a matter of only a day or two before advancing to deformation of the cornea, known as keratomalacia. Up to the stage of corneal xerosis (X2) prompt treatment with large doses of vitamin A can result in full preservation of sight without any residual impairment. (McLaren and Frigg, 2001).

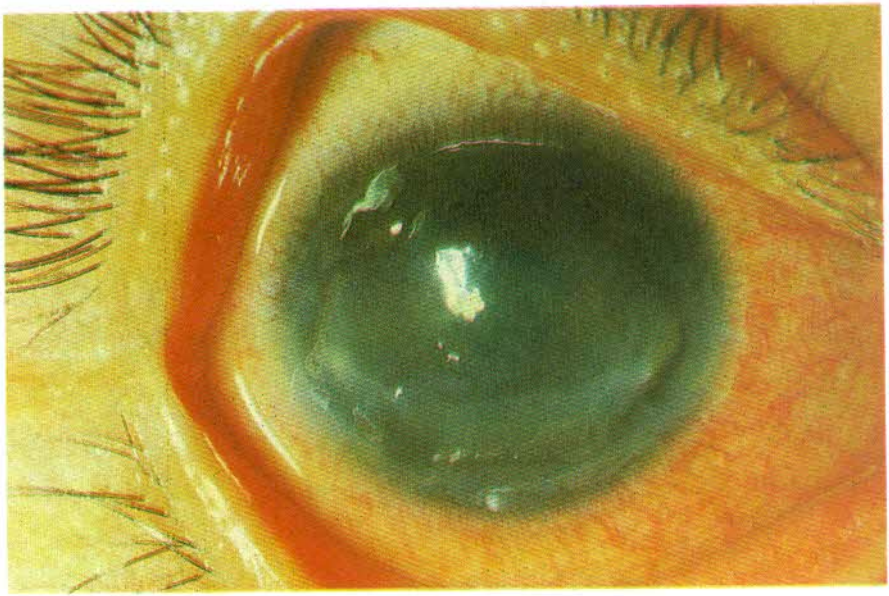

Fig 17. Corneal Xerosis (X2)

CORNEAL ULCERATION (X3A), (X3B)

In the 1982 WHO xerophthalmia classification, corneal ulceration has been divided into two stages according to the extent of the involvement of the cornea. Keratomalacia is characterized by softening of the cornea substance in addition to increasing xerosis of the epithelium (Fig. 18 and 19). Corneal softening is due to a unique pathological process termed colliquative necrosis. The stroma becomes oedematous. It is suspected that activation of collagenases and other enzymes may be responsible but the precise pathogenesis is not known. In corneal ulceration there is usually only one ulcer per eye. In about 20% cases both are affected and the characteristics tend to be similar (McLaren and Frigg, 2001).

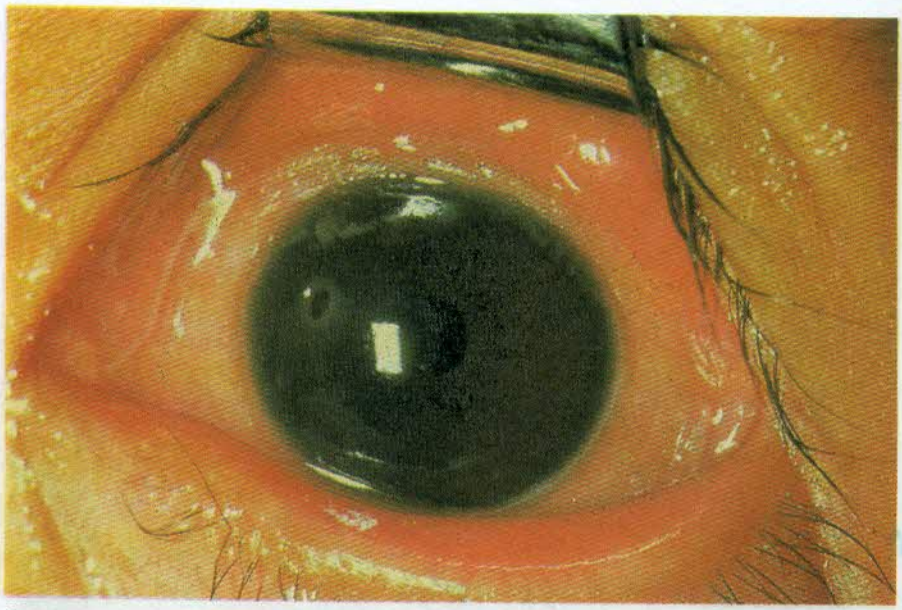

Fig 18. Corneal Ulceration (X3A)

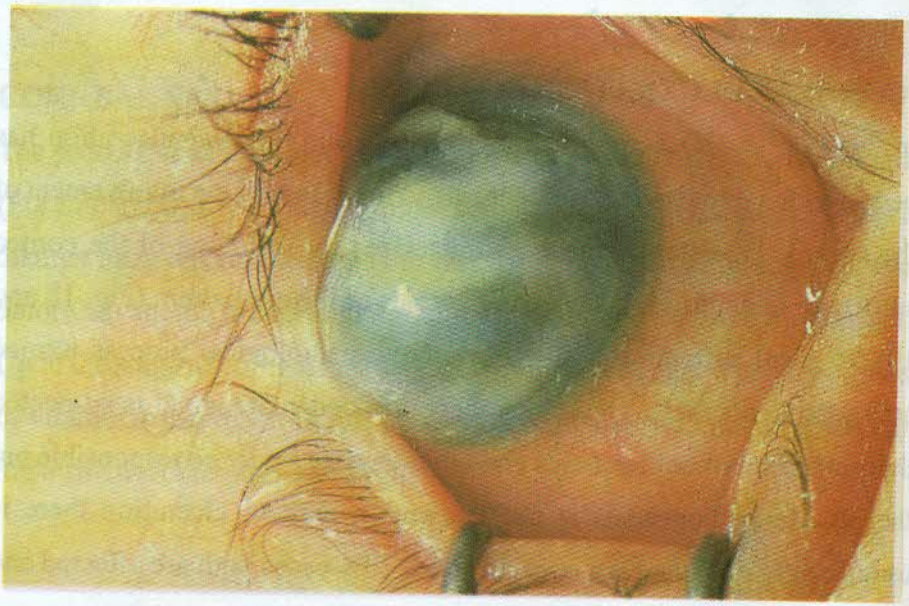

Fig 19. Keramatomalacia (X3B)

CORNEAL SCAR (XS)

After recovery from acute vitamin A deficiency that affects more than just the most superficial layer of the cornea, scars of varying extent and depth remain (XS). Scarring of the cornea may result from a wide variety of diseases affecting the eye. Visual impairment is inevitable, its degree depends on the location and the density of the scar. Damage that is confined to the cornea may be overcomed by sugery. This is not possible when internal structures are involved, usually as a result of accompanying infection (Fig 20).

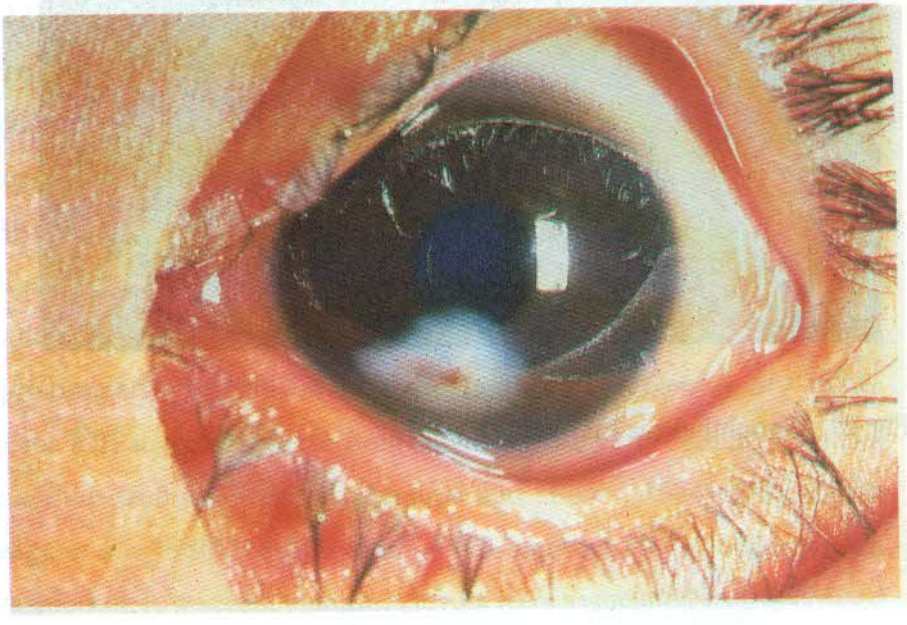

Fig 20 Corneal scar (XS)

XEROPHTHALMIC FUNDUS (XF)

Xerophthalmic fundus appears to result from prolonged deficiency of vitamin A in which impairment of rod function is succeeded by structural damage to retina (Fig 21). This rare condition has been described in school age children or young adults in Southeast Asia. (Sommer *et al.*, 1995).

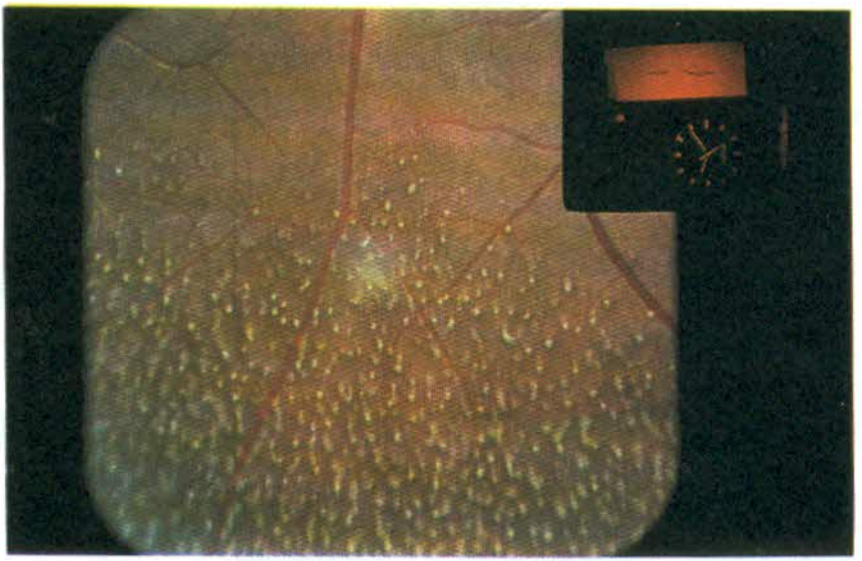

Fig 21 Xerophthalmic Fundus (XF)

VITAMIN A DEFICIENCY AND PROTEIN ENERGY MALNUTRITION (PEM)

Protein-energy malnutrition (PEM) manifests itself in two forms; kwashiorkor and marasmus. Kwashiorkor is due to protein deficiency, and marasmus is the result of energy deficiency (Laditan and Reeds, 1976) (Figs 22 and 23). Protein-energy malnutrition and vitamin A deficiency are the two most frequently encountered diseases among children in many developing countries. Ocular signs of vitamin A deficiency are seen in 30-40% of the children suffering from kwashiorkor (Chandra *et al.*, 1960). Levels of serum vitamin A are low in children with PEM whether or not they exhibit clinical signs of vitamin A deficiency (James *et al.*, 1984). Studies have suggested that retinol transport system is defective in this condition (Smith *et al.*, 1973). Just as pRBP cannot be released from the liver without retinol and the level of circulating holo-RBP declines in vitamin A deficiency, so pRBP cannot be synthesized and released if dietary protein is lacking; even if vitamin A is present. This would be expected of a protein that turns over rapidly (turnover time is approximately 7hr both in rats and humans; Peterson *et al.*, 1974). Plasma RBP level depends on both quantity and quality of dietary protein. This holds true for both rats (Muhilal and Glover, 1974) and children (Large *et al.*, 1980). Smith *et al.*, 1973 reported that in children with kwashiorkor, low serum vitamin A levels were associated with decreased concentration of plasma retinol-binding protein (pRBP) and pre-albumin. Treatment with calories and protein without supplemental vitamin A resulted in a significant increase in the concentration of all the three

components. It was therefore, suggested that low levels of serum vitamin A may reflect a defective hepatic production of the carrier protein rather than vitamin A deficiency per se. However, some children with kwashiorkor have associated vitamin A deficiency. A significant drop in the level of cRBP was also observed in protein deficient Japanese quails (Couturnix counturnix japonica). This probably is as a result of general low protein synthesis (James, 1986).

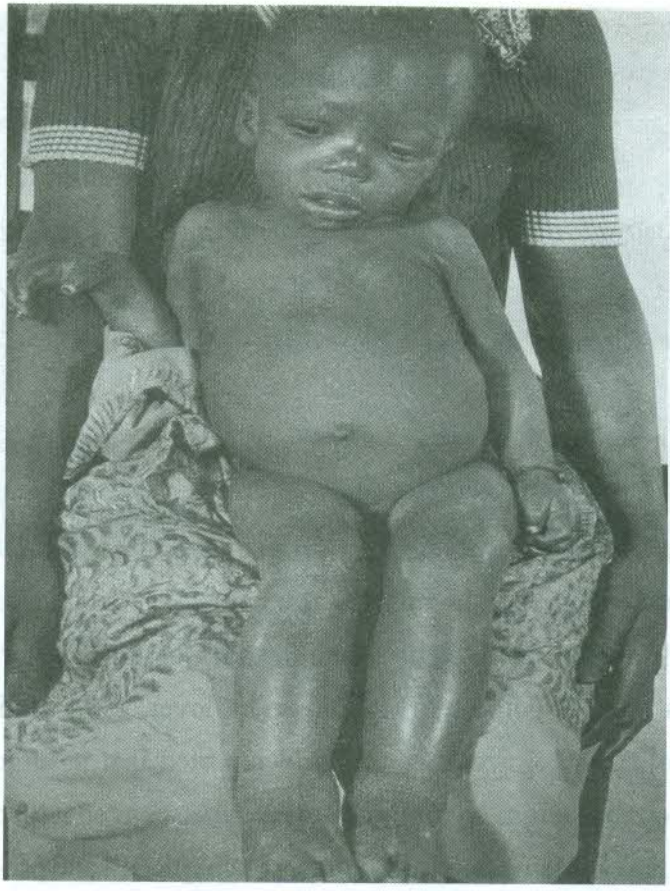

Fig 22 A two year old male child with Kwashiokor

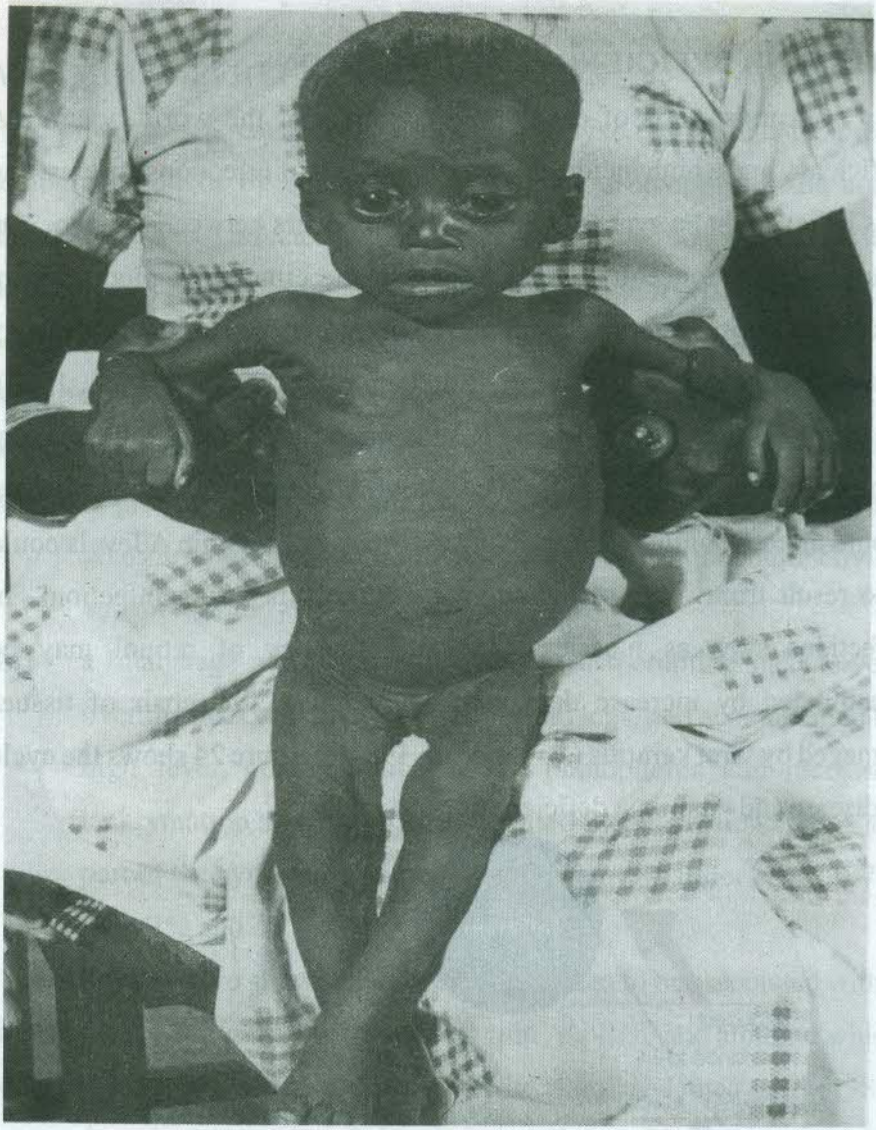

Fig 23 A two year old female child with marasmus

VITAMIN A DEFICIENCY AND INFECTIONS

In most parts of developing countries of the world, vitamin A deficiency and a high incidence of various types of infections co-exist and it is believed that a synergistic relationship occurs between the two. On one hand, the concentration of retinol in the circulating blood stream decreases during infections and on the other hand vitamin A deficiency results in a greater susceptibility to infections (Scrimshaw *et al.*, 1968). As synthesis and metabolism of RBP is intimately linked to the general protein metabolism, any disease condition affecting protein metabolism would affect vitamin A transport. The decrease of vitamin A levels could also result from increased vitamin A metabolism during infection. In infections such as measles, a local deficiency of retinol may be precipitated by increase demand for vitamin A for repair of tissues damaged by viral keratitis (James *et al.*, 1984). Figure 24 shows the cycle of disease and vitamin A deficiency.

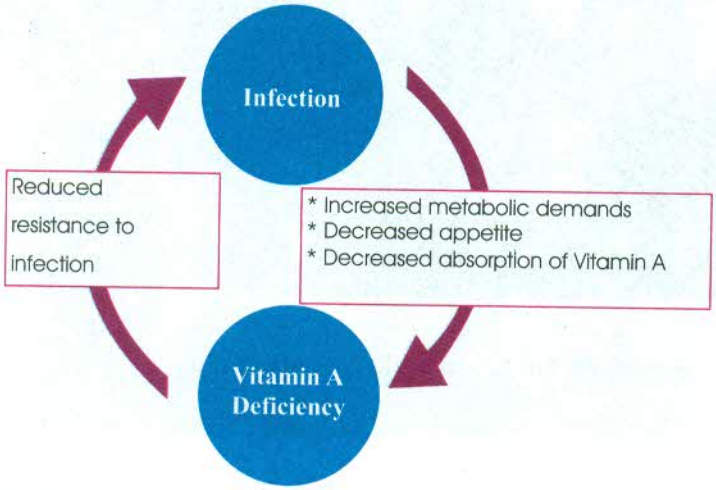

Fig 24. Cycle of disease and vitamin A deficiency

VITAMIN A DEFICIENCY AND MEASLES

Measles is caused by a virus (paramyxo virus) that is spread through the air or by contact with infectious droplets from the nose, mouth, or throat of infected person. The disease is so contagious that it is possible to contact it by merely living in the same room as an infected person. Most people get measles because they were never immunized. It is characterized by three stages:

(i) an incubation stage of approximately 10-12 days

(ii) a prodomal stage with Koplik's spots on the buccal and pharyngeal mucosa, mild to moderate fever, slight conjunctivitis and increasingly severe cough, and

(iii) a final stage with a maculo - papular rash erupting successively over the neck and face, body, arms and legs, and accompanied by high fever, conjunctival redness, photophobia and increased lackrymation sometimes accompanied by punctuate keratitis are part of the symptoms of measles infection (Dossetor *et al.*, 1977) (Fig. 25a and 25b).

Studies have shown that measles was seen to be associated with a significant lowering of both plasma vitamin A, pRBP and albumin which persisted long after the acute phase of the illness. James *et al* (1984) demonstrated that parenteral administration of a water soluble preparation of retinyl palmitate produced a sharp increase in plasma RBP - bound retinol in both well- nourished and malnourished children with acute measles. This indicates that measles does not affect the ability of the liver to take up retinyl esters and to release retinol bound to pRBP and

prealbumin; and accords with the concept of measles as a disease affecting mainly epithelial tissues of the body, including the mucosa of the gut. A more marked fall in plasma concentration of vitamin A was seen in association with measles than in malnutrition alone, despite a less dramatic decline in plasma albumin concentration (Inua *et al.*, 1983). Depressed levels of retinol and pRBP have been reported during the course of childhood varicella (chickenpox) together with slightly depressed levels of albumin (Arroyave and Calcano, 1979). Thus, it is tempting to suggest that febrile illness such as measles and varicella depress the concentration of vitamin A by increasing its rate of excretion, while measles, in addition, interferes with intestinal absorption and also increases tissue requirements for repair of desquamated epithelia.

In areas of the world where vitamin A deficiency is widespread or where at least 1% of those with measles die, experts (including the WHO) recommend giving high doses of vitamin A supplements to children with the infection (Coutsoudis *et al.*, 1991).

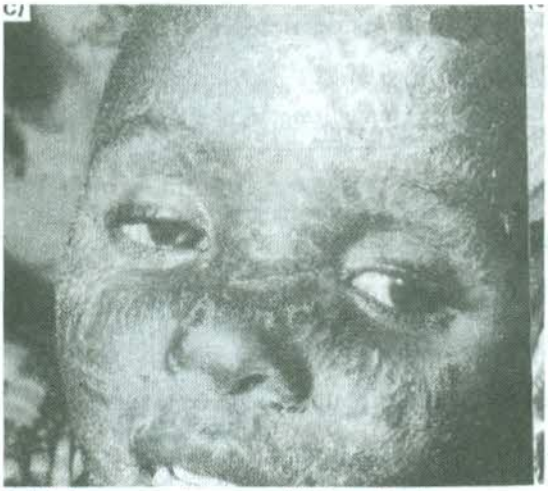

Fig 25a. Child in second year of life with desquamating measles rash and unilateral right side corneal ulcer (X3A)

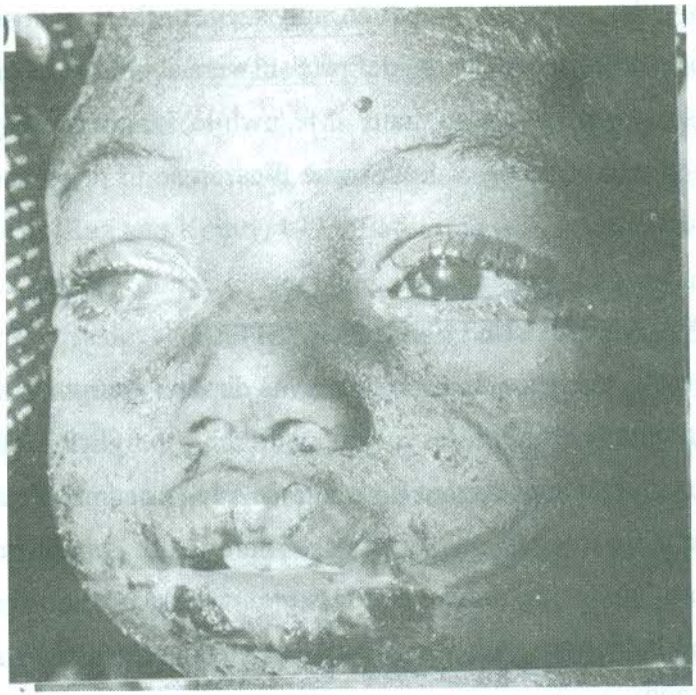

Fig 25b. Child in the third year of life with desquamating measles rash and unilateral right side corneal ulcer (X3B)

VITAMIN A DEFICIENCY AND HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Vitamin A deficiency is fairly common with HIV. A study of HIV positive intravenous drug users found that those with a vitamin A deficiency (about 15% of the HIV positive persons studied) had a death rate several times as high as those who did not have a vitamin A deficiency. (Semba *et al.*, 1992). While this study does not prove that correcting the

deficiency will improve survival, it strongly suggests that conclusion.

The studies needed to get definite answers about use of vitamin A in HIV disease have not been done. Meanwhile, it appears that people with HIV should be using at least some ß-carotene to prevent possible vitamin A deficiency.

VITAMIN A AND INTESTINAL PARASITES

There is evidence that round worms deplete vitamin A stores in people, particularly children, leaving them less able to fight off infections. At the same time, it appears that low vitamin A levels can make a person more susceptible to intestinal parasites. There is not enough scientific evidence at this point, however, to suggest that taking vitamin A supplements helps prevents or treat intestinal parasites. (Jalal *et al.*, 1998, Rai *et al.*, 2000).

VITAMIN A AND WOUNDS AND BURNS

The body needs vitamin A, along with several other nutrients, in order to form new tissue and skin. The body's levels of vitamin A are low immediately after burn injuries. Supplementation with ß-carotene helps the body replenish vitamin A stores, strengthen the immune system, relieve oxidative stress caused by the injury, and aid the body in forming new tissue. (Rock *et al.*, 1997, De-Souza and Greene, 1998).

VITAMIN A DEFICIENCY AND PREGNANCY

Good vitamin A status during pregnancy is essential for normal

fetal development and the health of the mother. Low maternal serum vitamin A is strongly associated with higher rates of infant and maternal mortality and morbidity. VAD may result in various embryonic abnormalities such as renal malformations, and eye and hearing impairment (Raz and Kelley, 1999, Batourina *et al.*, 2001). Lower birth weights, growth delays, poor immunity manifesting in respiratory infections, measles, and diarrhea are more common in infants born to mothers deficient in vitamin A (Azais-Braesco and Pascal, 2000).

HIV infected mothers who are vitamin A deficient may have a significantly higher risk of perinatal transmission of HIV (Semba, 1997; Greenberg *et al.*, 1997). Sloan-Kettering's studies found 70% of the children congenitally exposed to HIV were vitamin A deficient in the first months of life (Cunningham-Rundles *et al.*, 1996). Cervical shedding and transmission of herpes virus in HIV positive women has been linked to low vitamin A status as well (Mostad *et al.*, 2000).

CONTROL OF VITAMIN A DEFICIENCY (VAD)

At the 1990 world summit for children, WHO, UNICEF and governments of the various countries of the world committed themselves to eliminate VAD as a public health problem by the year 2000. However, it is currently estimated that only 35 countries are 'on track' for reaching the goal of VAD elimination on time.

The elimination of VAD can best be achieved through a comprehensive approach that combines strategies. There are four main types of intervention for VAD. These are:

- Periodic supplementation

- Food fortification
- Dietary diversification
- Infection control.

SUPPLEMENTATION

Because vitamin A is well absorbed from the intestine, well stored in the body, and catabolized at a relatively slow rate, large oral doses can be used to protect children at risk of deficiency for periods of 4 months to a year. This so-called "massive dose" approach has now been adopted in many countries in which vitamin A deficiency is a public health problem (Sommer and West, 1996). Such a programme may be targeted to high-risk groups (patients with measles or other serious infections or PEM, or babies and their mothers).

Periodic dosing is ideally suited to an emergency situation, but it fails to address the underlying cause and after it has been in place for some time, efficiency falls significantly. It also tends to direct attention away from the need to seek long-term solutions.

FOOD FORTIFICATION

The objective is to provide to a high proportion of a susceptible population an amount of vitamin A in addition to the customary dietary intake that would ensure adequate vitamin A status to the large majority of the population without any risk of an excessive intake by some. Once implementation and monitoring procedures are in place the programme should be sustainable on a long term.

Many food items are being fortified at the recent time in many countries. The chosen vehicle must be:

- Consumed regularly by a high proportion of the target population.
- It must also be processed at a limited number of central sites so that fortification may be carefully implemented and monitored.
- The added vitamin should be inexpensive stable and virtually undetectable.
- The food properties should not be interfered with.

In the Philippines, monosodium glutamate and margarine have been the preferred vehicle for vitamin A (Solon *et al.,* 1996). In Brazil, sugar has been used for vitamin A fortification (Xerophthalmia Club Bulletin, 1979).

DIETARY DIVERSIFICATION

Cultural beliefs play an important role. Spinach and other dark green leaves are often regarded as "poor man's food" or "only fit for animals", "Greens" are universally unpopular with young children. Yellow fruits are popular but have short seasons. Parents need to be educated and persuaded by all appropriate media that plant sources of the vitamin are essential for the health of the young child. These foods are often readily available in the surrounding environment, can be grown easily, and if they must be purchased they are cheap. They also provide other micronutrients and fibre. If produced in excess to the requirements of the family they can generate additional income. For vulnerable rural families in India, growing fruits and vegetables in home gardens complements dietary diversification and fortification and contributes to

better lifelong health (Santosh, 2000).

Because the bioavailability of carotenoids depends on so many factors such as carotenoid species, concentration, food matrix, dietary fat and parasites attention must also be given to measures to promote the consumption of sources of preformed vitamin A, such as dairy products, liver, milk, eggs and cod liver oil.

INFECTION CONTROL

The synergistic relationship between infection and vitamin A deficiency is well documented (Scrimshaw *et al.*, 1968). For an effective vitamin A supplementation programme it is important that the environmental factors leading to subclinical infection in children be controlled. Large scale nutritional programmes for young children often fail to obtain maximum benefits, because of underlying disease or infestation. There should be development of general primary health care in villages and urban slums to control gastro-intestinal and infestations which precipitate nutritional blindness. Where measles is a serious disease as in Africa, measures for its control should be undertaken through effective immunization programmes.

MORTALITY RATE AND VITAMIN A SUPPLEMENTATION

Vitamin A deficiency is associated with blindness, diarrhoea, infectious diseases, and malnutrition, which are leading causes of more than half of all deaths in the world's children (Bohler and Wathne, 2000, Quadro *et al.*, 2000). Nearly 250 million children have subclinical VAD resulting in a 23% increase in childhood mortality (Craft *et al,* 2000). Less

than severe deficiencies increase the grimness of infectious morbidity, intensify iron deficiency anemia, retard growth, and results in 1-3 million childhood deaths each year (Sommer, 1998). Very young indigent children (<5 years of age) are most vulnerable to the consequences of a deficiency, with blindness and death significantly occurring (McLaren, 1999, Rumore, 1993, Fielder, 2000). Vitamin A therapy has been shown to significantly reduce the severity of diarrhoea, certain infections, and measles-associated morbidity and mortality in poor children (Molina and Patel 1996, Julien *et al.*, 1999). For this reason, health organizations have recently integrated vitamin A supplementation with immunization programme for many poor children around the world. In 1998, more than 94 million doses of vitamin A were administered in 41 countries, which helped avert appropriately 169,000 deaths. More than 97 million doses in 50 countries were delivered in 1999, which helped prevent an estimated 242,000 deaths. Control of VAD is currently a major health challenge and goal of both UNICEF and the World Health Organization (Sommer, 1998). Beneficial effects of vitamin A are further enhanced by good zinc status, and combined therapy is being encouraged by progressive healthcare providers (Christian and West, 1998).

VITAMIN A DEFICIENCY IN NIGERIA

Vitamin A deficiency (VAD) is a major contributory factor to the high infant, child and maternal mortality in Nigeria. Mortality is significantly higher among children with mild xerophthalmia. This high mortality rate among children with mild vitamin A deficiency has been attributed to the severity of accompanying systemic conditions,

particularly protein-energy malnutrition, respiratory infections and diarrhoea (FGN/UNICEF-2001).

The World Health Organization has classified Nigeria among the 34 countries in the world with serious problems of nutritional blindness and xerophthalmia. Available data from the Participatory Information Collection (PIC) survey showed that the prevalence of VAD in 1993 was 9.2% in children and 7.2% in mothers (FGN/UNICEF G-1994). It also showed that VAD is heavily concentrated in the North of the country, with rates of 17% in the Northwest and 12% in the Northeast for children under 6 years. This mirrors the wide regional disparities in under five mortality suggesting that VAD is one of the important determinants. The problem of VAD is not restricted to children only but also affects adults. Prevalence in mothers ranges from 2% in the Southwest to 15% in the Northwest (Fig. 26).

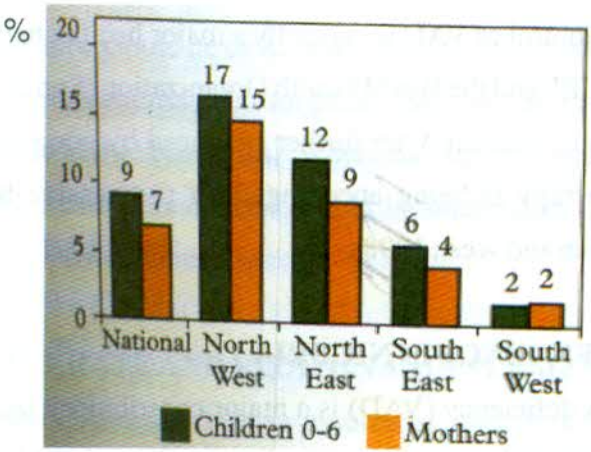

Fig 26. VAD prevalence in Nigeria (PIC 1993 {FGN/UNICEF G-1994})

Oomen (1972) commented that the spatial variation of the prevalence of VAD may be attributed to the lower dietary intake of red palm oil by people in the Northern Savannah area than by those living in the coastal rain forest where it has been assumed that the high carotene content of palm oil protects against xerophthalmia, except perhaps in the very young child.

STRATEGIES FOR VAD CONTROL IN NIGERIA

The strategies for VAD control are as outlined below:

(i) ***Supplementation***

This is the first strategy, which is short term and remedial in character. It focuses on large scale vitamin A supplementation using the opportunity of National Immunization Days (NIDS). In 2000, it was linked specifically with large-scale campaign against polio, which was aimed to reach nearly 39 million children between 6 months and 5 years of age with high potency doses of vitamin A in addition to polio vaccines. All vitamin A supplement has been imported with UNICEF assistance for procurement, through the Micronutrient Initiative (MI). The National Immunization Days in 2000 were expected to raise the coverage of vitamin A supplementation to close to 90%. Multiple Indicator Cluster Survey (MICS) data from 1999, however showed that less than a quarter of children between the ages of 6 and 59 months had received vitamin A supplement in the preceding 24 months. Furthermore, the data indicated that the regions with the most serious prevalence of VAD had received the least supplementation while the proportion of children receiving vitamin A supplement was as high as 47% in the southeast, it was only 16% in the

Northeast and 10% in the Northwest (Fig. 27). This shows that vitamin A supplementation is much more available in the urban areas than in the rural areas.

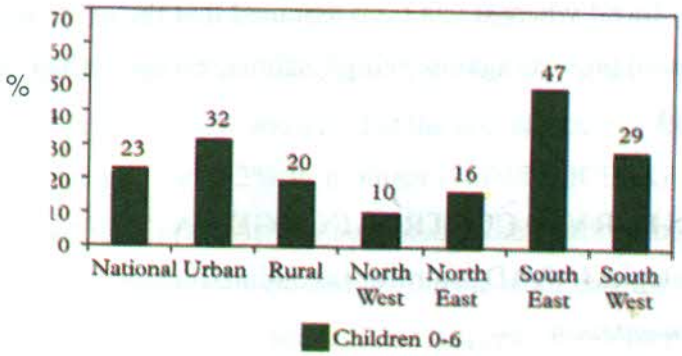

Fig 27.0 Vitamin A Supplementation (% receiving Vitamin A Supplement, 1999 {MICS, 1999} {FGN/UNICEF A-2001})

Supplementation is a feasible alternative in the short term, especially if the distribution mechanism is efficient, but the availability of the supplement is a constraint. Thus, this approach is unsustainable and not cost effective.

ii) Food Fortification

A Consultative forum established in 1993 by the National Committee on Food and Nutrition comprising the Standards Organization of Nigeria (SON), National Agency for Food and Drug Administration and Control (NAFDAC), Universities and Research Institutes as well as UNICEF and Micronutrient Initiative (MI) reviewed the available evidence and revised standards. Levels of fortification were recommended to a stakeholder's meeting involving the modern large-scale food

industries with efficient management structures, including quality assurance, and having market outlets that cover the entire country. SON giving the responsibility for setting standards produced a white paper for Government who then approved the standards with the levels for fortification of some food vehicles. In February 2000, the government enacted a law for mandatory fortification of wheat and maize flour, vegetable oil and sugar. These products were selected on the basis of their importance in the national food market and food consumption habits of the population. A major challenge will be to ensure the effective implementation of the law, by securing the involvement and support of the private sector, as well as adequate systems for monitoring compliance. Vitamin A fortification of wheat/maize flour as well as vegetable oil started in 2002 while the fortification of sugar started on April 1, 2004. Enforcement of compliance started in September 2002 but compliance has been extremely low. Survey conducted in October 2003 by NAFDAC sampling flour and vegetable oil products indicated only 5% compliance. Food fortification is the most cost effective option, it is technically feasible, and cost of fortification with vitamin A is marginal for the industries and consumers.

iii) Dietary Diversification

In the longer term, the challenge is to bring about dietary diversification using food based approaches, so that Nigerian children and women in all parts of the country can produce and consume foods naturally rich in vitamin A or its precursor (pro-vitamin A). This approach though slow, efforts have evolved to develop vegetable garden and fruit

cultivation in schools and communities, particularly in vitamin A deficient areas.

The use of biotechnology is now gaining greater importance as the International Institute of Tropical Agriculture (IITA) is undertaking research activities to identify maize varieties that could be biofortified with pro-vitamin A.

iv) Primary Health Care

The promotion of exclusive breast feeding during the first 6 months of the infants life and adequate complementary feeding with breast feeding has been an on-going programme in Nigeria since the mid 1990's.

Similarly, growth monitoring promotion, Integrated Management of Childhood Illnesses (IMCI), Malaria Control and Immunization have been part of the Primary Health care system in Nigeria. However, due to the general decline in health system these programmes have had limited impact. Nutrition education and public awareness campaigns are also on-going by civil society organizations e.g. Nutrition Society of Nigeria and Consumer Association amongst others.

IMPACT ASSESSMENT OF STRATEGIES FOR VITAMIN A CONTROL IN NIGERIA

To date there has been no impact assessment of the various strategies employed for VAD eradication. With food fortification just beginning, only the impact of supplementation and School/Community

gardens can be assessed at this stage, but the shortcomings in coverage of supplementation already highlighted, suggest the need for a critical reappraisal of the mechanisms for targeting beneficiaries.

Constraints to the effectiveness of fortification include socio-economic factors (ignorance, poverty and cultural taboos that preclude consumption of vitamin A - rich foods by some population groups). The expansion of the fortification programme in Nigeria to more vehicles identified would provide an opportunity to address and remove these barriers.

HYPERVITAMINOSIS A

This occurs at recurrent intakes of 10 times recommended dietary intake (RDI) (Armstrong *et al.*, 1994). Normally, Vitamin A in excess of the storage capacity of the liver results in a "spilling out' of retinyl esters into the blood stream attached to lipoproteins, enabling abnormally large amounts of vitamin A to reach the tissues. This causes toxicity. The most common cause of this disorder in both man and animals is excessive supplementation.

The major symptoms are found to be softening and fracturing of bones, widespread haemorrhaging, exophthalmia, mucous cell formation in keratinized membranes, temporary skin lesions have been found to be secondary to either membrane disruption or to the change from keratinized epithelial to mucous secreting epithelial (Fell and Mellanby, 1953), the opposite effect of deficiency on the epithelial. Excess retinol was found to cause rapid haemolysis of erythrocytes due to the

incorporation of the vitamin A into the membrane structure (Dingle and Lucy, 1965). Similar effects were shown in mitochondria and lysosomes which released degenerative enzymes leading to the destruction of bone and cartilage, such effects probably being the basis of many of the observed symptoms of hypervitaminosis A (Dingle and Lucy, 1965).

Daily tolerable upper levels (UL) of intake for vitamin A has been established by Institute of Medicine, Food and Nutrition Board, Washington DC (2001) to help prevent the risk of vitamin A toxicity (Table 4). The risk of adverse health effects increases at intakes greater than the UL.

Table 4.0 Tolerable Upper Intake Levels (Ul) of Intake for Preformed Vitamin A in Micrograms (mg) And International Units (IU) for Infants, Children And Adults.

Age	Children	Men	Women	Pregnancy	Lactation
0-11months	600µg or 2000 IU				
1-3years	600 µg or 2000 IU				
4-8years	900 µg or 3000 IU				
9-13years	1700 µg or 5665 IU				
14-18 years		2800 µg or 9335 IU	2800 µg or 9335 IU	2800 µg or 9335 IU	2800 µg or 9335 IU
19+years	3000 µg or 10,000	3000 µg or 10,000 IU	3000 µg or 10,000 IU		3000 µg or 10,000 IU

CONCLUSION

The occurrence of diseases associated with vitamin A deficiency is well established in developing countries. Vitamin A deficiency is clearly associated with blindness in children. Higher infant mortality rates and morbidity and mortality associated with infectious diseases have also been demonstrated in vitamin A deficient children. Xerophthalmia currently afflicts 2-3 million children each year in the developing world, of whom as many as 250,000 - 500,000 go needlessly and permanently blind and half of them dying within 12 months of loosing their sight. The right to see must be recognized as an important component of public health, and prevention of blindness is a socially relevant public health activity which requires massive support. In the developing countries, the blind child has a sad existence because he is unable to fend for himself in the absence of any organized social service programme. He is often abandoned by members of his family who themselves may be in abject poverty. A child in this situation has little to look forward to. The goodnews about blindness caused by vitamin A deficiency is that this human tragedy and economic burden on society can easily be averted by improving the intake of vitamin A by young children. Sir John Wilson, Director, Royal Common Wealth Society for the Blind in his address to the WHO Regional Conference on Curable Blindness, Hyderabad, India said "If we could take action against one of the world's major causes of blindness, the choice would have to be xerophthalmia. It occurs at the critical beginning of life and even the intimidating statistics of its present prevalence reveal only the smaller part of the human tragedy it involves or of the menacing prospect for the future. Experts agree that an adequate

technology already exists to achieve control- The need now is for action and the urgency of the task will require no emphasis to those who have seen those children flickering on the edge of life or, in impossible conditions, facing a lifetime blindness". Prevention action already discussed include supplementation, fortification, dietary diversification and infection control. Together, these strategies make the prevention of vitamin A deficiency achievable child health goal today and a wise government investment in terms of developing full human capacity in the 21st century. Ladies and Gentlemen what can be more important to life than sight.

ACKNOWLEDGMENT

MR Vice-Chacellor, Sir, Distinguished Ladies and Gentlemen, I would like to recognise at this juncture some of the notable people who have contributed to my success.

First, I wish to give honour and glory to Almighty God through our Lord Jesus Christ for sparing my life and giving me good health to witness this wonderful day and for granting me this rare opportunity to give this Inaugural Lecture.

My foremost thanks go to my late mother Madam Lydia Olubukola James (nee Bukola Eledie) who departed this world exactly five years ago. When I reflect back on her struggles to get me educated, I thank God for her courage. May her gentle soul rest in perfect peace.

I wish to thank God for my beloved husband, a loving and caring husband. He is indeed a selfless lover. I remember a particular day that he prophesied over my life and I quote "My wife Funmilayo you will be a professor". His prayers have been answered today. I rejoice with him. To my loving children, Ninmo, Mana, Wonci and Samuel I say thank you for bearing with me. I recollect the number of occasions I had to carry them to conferences and kept them alone in the vehicle until the conference was over.

I want to express my gratitude to every member of my extended family some of whom are here present for this occasion. I cannot forget the role my uncle Dr Ajagbonna played in assisting me in the University, may the good Lord reward him, Amen.

I also want to thank all my teachers, colleagues, friends, students and well wishers, too numerous to mention who have contributed in one

way or another to my success.

I cannot end this lecture without acknowledging the encouragement from the Acting Registrar of this University. He urged me to give this lecture at this time and not make it a valedictory lecture.

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