REVIEW OF LITERATURE
HISTORICAL REVIEW

The history of xerophthalmia due to vitamin A deficiency can be traced as far back as the ancient Egyptian days. The Ebers Papyrus written in about 1600 B.C., referred to night blindness for which liver was recommended for treatment. A literal translation from the book reads: 'Another(prescription) for the eyes: liver of ox roasted and pressed, give for it. Very excellent' (Drummond and Wilbraham, 1939, Quoted by McLaren, 1963). At about the same time the physicians in China were giving liver, dung of the flying fox and tortoise shell for the cure of night blindness. At a later date Hippocrates with admirable clinical acumen prescribed the whole liver of an ox dipped in honey. The therapeutic values of liver was also known to subsequent Roman writers. Similar belief and therapeutic practices were widespread among the Hindus from very early times and in Europe during the middle ages. As far as the information goes, Celsus (25 B.C. - 50 A.D.) first used the term xerophthalmia (McLaren, 1963).

It would seem that night blindness was widespread in Europe about 5 centuries back. A 14th century poet in Holland, Jacob van Maerland, referred to the disease and its cure in this way (McLaren, 1963):
He who cannot see at night,
Must eat the liver of the goat,
Then he can see all right.

Bayly, who was once Queen Elizabeth's physician, wrote a book on eye diseases in which he recommended 'raw herbes' among which was 'eye bright'. References were made to mists and films over the eyes, but whether these were due to night blindness or early xerophthalmia, or even conditions not associated with malnutrition, is not clear (McLaren, 1963).

An accurate description of xerophthalmia was given by the French physician Jacques Guillemeau (1585), who also recommended for night blindness 'le foye de bouc resti, estant sale et le manger' (McLaren, 1963).

Bergen, 1754, (McLaren, 1963) seems to have the first to write about the relationship between dietary deficiency and night blindness. An English Naval Surgeon, Bampfield (1814), from his experience with lascars in East India Company distinguished two forms of night blindness; the first he called, 'idiopathic' and the second 'Scorbutic', because of its occurrence in patients with scurvy. The latter from did not disappear with lemon juice, but improved when a balanced diet was given (McLaren, 1963).

Francois Magendie (1783-1855) from France first proved experimentally in dogs, the role of nutrition on
ocular lesion(1816). Joseph Brown(1827) confirmed that the findings of Magendie on animal experiments tallied with his findings in human beings. He described the course of untreated keratomalacia, the important role of diet and the graveness of the general condition of the patients (Duke-Elder, 1965).

The Royal oculist in Scotland, William Mackenzie in his 'A practical treatise of the diseases of the eye'(1830), gave an account of xerophthalmia under the name of 'Conjuntivae arida' where he described the prolapse of the iris into the defect resulting from the rapid disintegration of the cornea in malnutritional keratomalacia as 'myocephon' i.e. head of a fly(McLaren, 1963). One of the best description in early literature, both of xerophthalmia and the dramatic sequelae of keratomalacia was given by Von Arlt in his 'Krankheiten des Auges(1851)', describing the condition as 'Malacie der Hornhaut' (Blegvad, 1924).

Though the first description on conjunctival xerosis was given by a Russian doctor, Hubbenet(1860) from his findings in soldiers and prisoners of war of Crimea, the real credit for the description of xerosis conjunctivae and conjunctival spot goes to the French physician, Bitot(1863); his description was based on 29 cases of xerosis conjunctivae which appeared together with hameralopia in children of larger growth in a foundling hospital in Bordeaux(McLaren, 1963).
The first minute description of the disease was given by Albrecht von Graefe in 1866. The disease was named, 'Hornhaut Verschwarung'. In the same year, Gama Lobo described keratomalacia in Negro children in Brazil. The origin of the disease, which Gama Lobo called, 'Ophthalmia Brasliana', was thought to be cellular atrophy due to bad nutrition. This was the first report from a tropical country (Blegvad, 1924). The next report from a tropical country came at the turn of the century from Indonesia (Ouwehand, 1900), where the disease has been still continuing to take tremendous toll of life and sight (Oomen, 1961).

In Petrograd, Blessig observed in 1866 numerous cases of xerosis conjunctivae in connection with hemeralopia and also, in more severe cases, keratomalacia. The disease appeared primarily during the long 'Lent Quadragesima' (Seven-week Lenten fasts) and was due, in Blessig's opinion, to the derangement of nutrition caused by the fasting (Blegvad, 1924).

The origin of the disease was for a time erroneously considered as infection with Corynaebacterium Xerosis bacillus, described in 1880 by Colomiatti, Kuschbert and Neisser, Schleich and Schulz, but later investigators came to the opinion that it was mostly due to a nutritional phenomena. Teuschar (1867) and de Gouvea (1883) reported keratomalacia in Negro children from the coffee plantation areas of Rio-de-Janerio, where nutritional status was very poor. Thalberg (1883), report-
ed keratomalacia in nurslings whose mothers on account of the Russian Lent Quadragesima, were in very poor nutritional status as their food consisted of rye bread, potatoes, porridge, cabbage, mushroom and onions (Blegvad, 1924).

The therapeutic value of Cod-liver oil in the cure of Bitot's spots and night blindness was claimed by Snell (1881), Kubli (1887) and Evetzki (1890), the last author described circumscribed epithelial xerosis of the conjunctiva in glass workers who did not complain of night blindness. Herbert (1897), reported from India pigmentation of the lower fornix and exposed conjunctiva. Stephenson (1898), demonstrated from Bitot's spot material, colonies of xerosis bacilli (McLaren, 1963).

Leber (1883), first described the pathological basis of keratinization and xerosis. He found thickening of the whole conjunctival and corneal epithelium, flattening of the superficial cells with disappearance of their nuclei and separation of the prickle cells in the deeper layers by leucocytes. The superficial cells were frequently arranged in irregular wavy bands staining diffusely as keratohyalin. Those immediately underneath showed granules of the same materials and in these respect these layers exactly resembled the stratum granulosum of the epidermis. In both superficial and deeper cells fatty globules staining deeply with osmic acid were common. A constant feature was the disquama-
tion of the degenerated superficial cells with intra- and extra-cellular xerosis bacillus (McLaren, 1963). 

Baer (1901), reported a case of xerophthalmia in a child nourished on oatmeal gruel, and after feeding with cows milk and lime water the condition improved. The year after, Hamburger described a similar case where the child was cured by the nurse’s milk (Blegvad, 1924).

From Denmark, Edmund Jensen, 1903. (Blegvad, 1924), reported nine cases of xerophthalmia occurring after prolonged intake of carbohydrate food and he was the first to prove that xerophthalmia could be cured by adequate diet. Blegvad, 1924, in his study of the prevalence of xerophthalmia in Denmark from 1909 to 1920 detected 434 cases of keratomalacia in children and 139 cases of keratomalacia in adults and 148 cases of xerosis conjunctivae without keratomalacia. He also observed seasonal variation of the disease.

In Japan, Mori observed in the years before 1904, 1511 cases of xerophthalmia among which 116 cases were keratomalacia, in children from 2 to 5 years of age. They called it 'Hikan' in their local language. Mori, and later on Ishihara (1913), were of the opinion that the disease was due to lack of fat-stuff in the foods which consisted of rice, farinaceous food and vegetables. On the coast where good sea fishes were available, 'hikan' was rarely observed (Blegvad, 1924).
Schiele (1907) observed many cases of keratomalacia in Kursk during the Lent Quadragesima and it was thought that it was due to lack of intake of food containing fat; those cases responded to cod-liver oil. At about the same time, Flemming mentioned 28 cases from Braslau and Stephen­son, 31 cases of keratomalacia from London; both considered that poor nutrition was the cause of the disease (Blegvad, 1924).

For a considerable time the malnutrition factor remained as a riddle and different authors put forward different views viz. absence of fat in the diet (Schiele, 1904), or of calcium (Straub, 1927). Almost hundred years after the pioneering work of Magendie (1816), the etiology of the condition was suggested to be due to absence of some unidentified fat soluble vitamin (Falta and Noeggerath, 1905; Knapp, 1909; McCollum and Davis, 1913—Quoted by Duke-Elder, 1965).

The association of xerophthalmia with an excessive intake of carbohydrate in the diet in infancy was recorded by many authors (Czerny & Keller, 1906; Brock & Aitret, 1952). Piper, Romahn, Peters, Brunning, Gille, Kapuschinski and Ronne in 1916 (Duke-Elder, 1965), denied the role of carbohydrate in producing xerophthalmia, but that the lack of milk or 'of some substance found in the milk', is the real cause of the disease. Since Czerny's days there has been a great number of other accounts in which ocular involvement has been
described (McLaren, 1958), providing good evidence for the contention that a deficiency of vitamin A is the most common of all deficiencies associated with Kwashiorkor or generalized protein deficiency (Venkataswamy, 1967).

The predilection of xerophthalmia to young children was recognized in the early part of the century especially in children whose mothers suffered from nutritional defects (Rumbaur, 1922; Maxwell, 1932; Gutheil, 1956 - Quoted by Duke-Elder, 1965). About 80% of cases, however, developed after the cessation of breast feeding; in these, xerosis sometimes in marked degree was frequent, appearing preferentially in the summer months and (curiously) mainly in males (Mori, 1904; Scullica, 1935; Oomen, 1957; El Sheikh, 1960; Chandra et al, 1960; Gopalan and Belvady, 1961; Venkataswamy, 1967 and Pereira & Begum, 1968). Reports from Europe also suggests that most of the children affected were below the age of one year (Blegvad, 1924).

There is a puzzling discrepancy between the age relationship of children brought to hospital with the milder signs of xerophthalmia and of children showing the same clinical signs but living in the community (Pirie, 1976). The peak age for children coming to hospital with XN (night blindness) or XI (conjunctival xerosis) is also near 2.5 years, but when the prevalence of xerophthalmia in the general community has been surveyed, ophthalmologist found in India
(Swaminathan, Susheela & Thimmayamma, 1970) and elsewhere a steady increase in these milder signs with age of children. In India it was 1.5% in the age group of 12 to 24 months and 16% in the age group of 48 to 60 months.

After the tenth year the gross changes of xerophthalmia are much rare, and when present, they usually suffer from severe debilitating diseases affecting the intestinal tract viz. acute and chronic diarrhoea or dysentery or cholera etc. and other illness e.g. typhoid, malaria, measles etc. (Ramalingaswamy, 1948; Vaughn, 1954; McGregor, 1954; Thygeson, 1959; Sinha, 1966; Baishya, 1971 & Sauter, 1974). The role of intestinal helminthiasis has also been reported in producing keratomalacia (El Sheikh, 1960; Tiwary, 1966 and Baishya, 1971).

The disease may affect the adult also to a less extent, often in epidemic form, when they are subjected to prolonged starvation due to any cause (Duke-Elder, 1965). The association of the incidence of xerosis with vitamin A deficiency has been studied by several authors. Abboud et al (1968), Oomen (1961), Dingle and Lucy (1965), Kuming & Politzer (1967), Baishya (1971) and Murugan et al (1977), showed that xerotic patients of all age groups and both sexes had significantly lower blood serum vitamin A levels than the corresponding normal groups. This finding was much
more pronounced in males than in females (Kuming & Politzer, 1967; Baishya, 1971) and they responded well to parenteral administration of vitamin A (Ram, 1953; Rodger, 1964). But many authors viz. Sie-Boen-Lian (1938) and Yourish (1953), denied the association of xerosis with vitamin A deficiency.
In 1913, E.V. McCollum isolated a fat-soluble factor necessary for growth and prevention of xerophthalmia in rats and he achieved full separation of vitamin A and D in 1922. Beta-carotene contains vitamin A activity (Steenbock, 1920).

Though the term vitamin A is used to refer to all the substances of related chemical structure having same biological activity, specific members of the group are referred to by their accepted chemical names. Retinol is the name which has got most therapeutic significance.

Retinol is a fat-soluble unsaturated isoprenoid alcohol (C\(_{20}\)H\(_{30}\)O) with five conjugated all-trans double bonds. The integrity of the basic carbon skeleton appears to be essential for specific biological activity. Cis-isomers are less active than all-trans isomers. Derivatives with functional groups other than an alcohol group appear to depend for their activity in most cases on the ease with which they are converted to the parent compound. Affinity for Retinol Binding Protein appears to be another measure of functional activity.

UNITS - As the absorption of vitamin A through the intestinal wall varies depending on whether it is a pre-formed vitamin A (Retinol) or pro-vitamin A carotenoids, the total...
vitamin A activity of a diet has to be qualified by indicating the percentage of the activity coming from retinol and pro-vitamins. Vitamin A activity in foods is expressed in international units (IU), 1 IU being equivalent to 0.3 micro-gm. of retinol, 0.344 micro-gm. of retinyl acetate, 0.55 micro-gm. of retinyl palmitate, 0.6 micro-gm. of beta-carotene or 1.2 micro-gm. of provitamin A carotenoids other than beta-carotene.

**Dietary Sources**

Dietary sources of vitamin A are of two kinds: 1) Pre-formed vitamin A from animal sources - vitamin A as such in the fat of milk and other milk products like butter or cream, in eggs, in very large amounts in liver fat especially in cod-liver oil and halibut-liver oil. 2) Provitamin A carotenoids - carotene is widely distributed in plant foods. Major sources are, alfa, beta, and gamma-carotene and several other related compounds. It is found chiefly in green leafy vegetables. Other useful sources are, yellow and red fruits and vegetables. All vegetable oils are devoid of vitamin A activity with the exception of red palm oil. Both retinol and carotene are stable to ordinary cooking method.

**Requirements**

(195 IU) per kg. body weight in children aged 4 months to 12 micro-gm. (36 IU) per kg. body weight in adults. They also calculated that 1 micro-gm. of beta-carotene is equivalent in biological activity to only 0.167 micro-gm. of retinol.

**METABOLISM**

Vitamin A is present in food mainly as the palmitate ester. In the upper small intestine the ester is largely hydrolysed to the free alcohol by a hydrolase in the pancreatic juice in the presence of bile salts. Together with the products of fat digestion, retinol is emulsified by bile salts and phospholipids and ultimately converted into a micellar form suitable for absorption. Normally more than 80% of the dietary vitamin A is absorbed from the intestine and the efficiency of absorption decreases only slowly as the dose increases. Under normal condition, about 70% of the beta-carotene are absorbed.

Dietary beta-carotene is converted into retinaldehyde fairly slowly by 'Beta-carotene dioxygenase' in the intestinal mucosa (Goodman et al, 1965 and Olson et al, 1965). Within epithelial cells of the gut, retinaldehyde is largely reduced to retinol (Fidge et al, 1968), which is re-esterified mainly with palmitic acid and incorporated into chylomicra. The latter products are transported via the lymph into the blood stream and are ultimately taken up mainly by the liver and stored for the most part as palmitate in fat-containing
30-40% of the absorbed vitamin A is usually stored in the liver. Two major reactions compete for the remainder: 1) Conjugation of retinol and retinoic acid with glucuronic acid in the liver followed by excretion of the conjugate in the bile and then into the faeces, and 2) Metabolism of retinol and retinoic acid mainly in the liver and kidney, followed by excretion of the degradation products in the urine (Fig. 1). Within a week after dosing, most of the retinol that is not stored is eliminated via these two routes.

During the mobilization from the liver, the retinol combines with a special type of protein called, 'Retinol Binding Protein (RBP)' and the biological activity of the former depend on the latter. The RBP is synthesized in the liver. Normal concentration of the RBP and Retinol are about 40-60 micro-gm./ml. and 40-60 micro-gm./100 ml. of plasma respectively. In the plasma the RBP-Retinol complex is largely associated with an acidic protein called, 'tryptophan-
rich prealbumin (TRPA). RBP is degraded mainly in the kidney. Under normal condition the plasma concentration of vitamin A is largely controlled by the finely balanced interaction of RBP synthesis, release and degradation.

**FUNCTION OF VITAMIN A**

Our thinking about the role of any vitamin is usually influenced by historical perspective, that is, by the effects of its deficiency on growth, on the disruption of physiological processes and changes in biological structure. In vitamin A deficiency a vast array of symptoms appear which ultimately involve almost all tissues of the body as shown below:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cause and tissue involved</th>
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<tbody>
<tr>
<td>Loss of appetite</td>
<td>Taste bud degeneration.</td>
</tr>
<tr>
<td>Retardation of growth</td>
<td>Inadequate intake and utilization of food, intestinal obstruction etc.</td>
</tr>
<tr>
<td>Nervous disorders</td>
<td>Defective myelination, abnormal growth of bone.</td>
</tr>
<tr>
<td>Follicular hyperkeratosis</td>
<td>Epithelial keratinization.</td>
</tr>
<tr>
<td>Defective reproduction</td>
<td>Testicular degeneration, foetal resorption, hormonal abnormalities.</td>
</tr>
<tr>
<td>Night blindness</td>
<td>Loss of rhodopsin.</td>
</tr>
<tr>
<td>Xerophthalmia</td>
<td>Defects in corneal epithelium, tear duct obstruction, infection.</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Cause and tissue involved</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Blindness</td>
<td>Rod and cone cell destruction, corneal rupture, etc.</td>
</tr>
<tr>
<td>Generalized infection</td>
<td>Immunological defects, reduced mucus secretion, keratinization of larynx and trachea.</td>
</tr>
<tr>
<td>Death</td>
<td>Infection, volvulus, urinary blockage.</td>
</tr>
</tbody>
</table>

Olson, 1971.

1. Vision - Only one function of vitamin A has been well defined biochemically, namely, its interaction with various opsins of the retina to form visual pigments. Resynthesis of rhodopsin from retinine and protein must keep pace with its photochemical breakdown under the influence of light in order to maintain normal vision of dim light. Vitamin A, which is a component of visual purple is found in the walls of the rods. The eye contains little vitamin A after exposure to bright light, and it has got to be reformed before it can be utilized by the rods for vision in dim light. The dark adaptation depends upon the rapidity of formation of visual purple. Since vitamin A is an essential ingredient of visual purple, inadequacy of vitamin A causes delay in formation of visual purple and hence retards dark adaptation. This, in extreme cases results in night blindness. Approximately 30 minutes is required for complete regeneration of rhodopsin.
A similar series of events occur in the cone visual pigments, but here the regeneration time is much shorter, which is virtually completed within few minutes.

2. **Growth** - Retinoic acid, a metabolite of vitamin A, supports normal growth and tissue maintenance. Deficiency of vitamin A leads to faulty modelling with the production of thick, cancellous bones instead of thinner more compact bone and there is increased cerebrospinal fluid pressure which may develop independently or in association with malformed skull bone (Moore, 1967). Even death may occur before typical deficiency symptoms develop.

3. **Epithelial tissue** - Of various tissue of the body affected by vitamin A deficiency, epithelial tissues show the most extensive and consistent changes. Vitamin A seems to control in some cases the differentiation of epithelial tissues, particularly of the skin, salivary glands, goblet cells of the gut, and the testes. Although the exact mechanism is not known, it is seen that in the absence of vitamin A the fraction of squamous and keratinized cell rises and conversely in its presence, the relative number of mucus-secreting and columnar or cuboidal cells increases (Fell et al, 1953; Kahn, 1954; Lawrence et al, 1960). Vitamin A may also cause hyperplasia of epithelial tissue and an increase in the mitotic index (Sherman, 1961).

As epithelial tissues are prone to infection due to
its loss of integrity caused by vitamin A deficiency, this vitamin has also been known as 'Anti-infective vitamin'.

Some epithelial tissue affected by vitamin A deficiency.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea</td>
<td>Keratinization.</td>
</tr>
<tr>
<td>Epidermis</td>
<td>Keratinization.</td>
</tr>
<tr>
<td>Trachea</td>
<td>Squamous metaplasia and keratinization.</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Squamous metaplasia and keratinization.</td>
</tr>
<tr>
<td>Vagina</td>
<td>Cornification.</td>
</tr>
<tr>
<td>Sebaceous gland</td>
<td>Cystic atrophy.</td>
</tr>
<tr>
<td>Hair follicle</td>
<td>Cystic atrophy, hyperkeratosis.</td>
</tr>
<tr>
<td>Salivary glands and duct</td>
<td>Squamous metaplasia.</td>
</tr>
<tr>
<td>Intestinal mucosa</td>
<td>Goblet cell decrease.</td>
</tr>
<tr>
<td>Testes</td>
<td>Degeneration of germinal epithelium.</td>
</tr>
<tr>
<td>Pancreatic ducts</td>
<td>Squamous metaplasia.</td>
</tr>
</tbody>
</table>

Since mucus serves as a wetting agent under normal condition and thereby preserves a tear film over the cornea, tear film that is deficient in mucus allows dry spot to form; these lead to damage of epithelial cell and its reduced resistance to bacterial infection.
Although various theories and hypothesis relating to vitamin A action have been put forward, for example, Membrane-lysosome concept (Lucy, 1969; Fell, 1970), Muco-polysaccharide Stimulatory concept (Rogers, 1969; Kean, 1970) and possible co-enzymic role of vitamin A (Olson, 1971), these seem to explain only a portion of the observed effects of vitamin A action. Only one generalized theory for the action of vitamin A on cells has been accepted, namely, the Interrupted Differentiation Model of Hayes (1969). Fig. 2:

Fig. 2.

Epithelial undifferentiated cell

\[ \text{Squamous (keratin)} \]
\[ \text{Ciliated and goblet cells} \]
\[ \text{Epithelial Fibrocytes} \]

Mesenchymal undifferentiated cell

\[ \text{Fibroblast} \]
\[ \text{Fibrocyte} \]
\[ \text{Chondroblast} \]
\[ \text{Chondrocyte} \]
\[ \text{Osteoclast} \]
\[ \text{Osteocyte} \]

The interrupted differentiation model of Hayes. In vitamin A deficiency the underlined cells tend to increase with respect to more mature forms (Olson, 1971).

The idea is that vitamin A deficient epithelial cells are arrested at the squamous cell stage so that few ciliated and goblet cells are formed, where as mesenchymal cells differentiate mainly to the blast stage. The hypothesis explains the cause of bone over growth, causes of incre-
ase or decreased mucous secretion by the cells, arrest of cellular differentiation in the adrenal cortex and primary sex glands due to vitamin A deficiency; but it does not explain the mechanism by which differentiation is arrested nor indeed why the differentiation of epithelial cells involves branching whereas that of mesenchymal cells are linear.

4. Anti-infective role of vitamin A — The interrelationship of vitamin A deficiency and infection has long been known. Until now, retinol appears to be the only naturally occurring enhancer of the humoral immune response (Dresser, 1968). Vitamin A may act as an adjuvant through its effect in damaging lysosomal membrane, in this way stimulating cell division; possibly this stimulation of cell division at the time when antigen is available in the cell, leads to the induction of immunity, and not paralysis. Moreover, retinol has been shown to suppress induced tolerance (Major et al., 1969).

5. Other functions — Vitamin A or carotenoids, may be concerned in the receptor system of olfaction and taste (Dingle & Lucy, 1968). Vitamin A deficiency has been reported to cause loss of appetite (Barnard & Halpern, 1968), which is thought to be due to changes in plasma amino-acid pattern.

There are ample evidence to suggest that for the
normal functioning of the nervous system vitamin A is necessary, and in its absence, widespread degeneration of medullary sheath of nerves occurs.

**VITAMIN A STATUS** - The nutritional wellbeing of an individual with respect to vitamin A can be expressed in terms of his 'Vitamin A status'; which can vary from 'excessive' (Hypervitaminosis) through 'acceptable' and 'marginal' to 'poor' (Hypovitaminosis) as shown below:

**VITAMIN A STATUS OF INDIVIDUALS.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical signs</th>
<th>Biochemical, dietary, and biophysical indicators.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>Xerophthalmia including night blindness;</td>
<td>Low plasma vitamin A levels; very low liver stores of vitamin A; impaired dark adaptation; very low dietary intake of carotene and vitamin A.</td>
</tr>
<tr>
<td></td>
<td>common association with PEM and infection</td>
<td></td>
</tr>
<tr>
<td>Marginal</td>
<td>None</td>
<td>Inadequate liver reserves of vitamin A; low to normal plasma vitamin A; low dietary intake of carotene and vitamin A.</td>
</tr>
<tr>
<td>Acceptable</td>
<td>None</td>
<td>Normal plasma and liver concentration of vitamin A; adequate dietary intake of carotene and vitamin A.</td>
</tr>
<tr>
<td>Excessive</td>
<td>Headache, vomiting, restlessness, bulging of fontanelle in infants</td>
<td>Abnormally high plasma vitamin A levels; ingestion of excessively large doses of vitamin A, either acutely or chronically.</td>
</tr>
</tbody>
</table>

An 'acceptable' vitamin A status is defined in terms of a 'protection period' during which an individual might function normally on a vitamin A deficient diet without showing any signs of vitamin A deficiency. Depending on the liver reserve of vitamin A, protection period varies from person to person.
CONJUNCTIVA
XEROSIS
BITOT'S SPOT

CORNEA
XEROSIS
ULCER
KERATOMALACIA

RETINA
NIGHT BLINDNESS

DIAGRAM INDICATING SITES AFFECTED BY XEROPHTHALMIA

XEROSIS
BITOT SPOT
ULCER
KERATOMALACIA

DIAGRAMMATIC REPRESENTATION OF XEROPHTHALMIA LESIONS

SOMMER, A.; 1978
OCULAR LESIONS DUE TO VITAMIN A DEFICIENCY

For many years there has been a need for the classification of the ocular lesions produced by vitamin A deficiency and in the last decades many workers have put forward their classifications with its merits and demerits (Vaughn, 1954; Sen, 1954; McLaren, 1963; Teng, 1967 and Doesschate, 1971). But, the classification adopted in WHO/USAID Meeting, held in Jakarta in 1974, is the well accepted one(Tjakrasudjatma, in Bandung, 1974; Toureau, & Sommer et al in Haiti, 1974-75; Sommer et al in El Salvador,1973; Pirie,1976 and etc.). The classification is as follows:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Signs - Primary</th>
</tr>
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<tbody>
<tr>
<td>X1A</td>
<td>Conjunctival xerosis</td>
</tr>
<tr>
<td>X1B</td>
<td>Bitot's spot with conjunctival xerosis</td>
</tr>
<tr>
<td>X2</td>
<td>Corneal xerosis</td>
</tr>
<tr>
<td>X3A</td>
<td>Corneal ulceration with xerosis</td>
</tr>
<tr>
<td>X3B</td>
<td>Keratomalacia</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Signs - Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>XN</td>
<td>Night blindness</td>
</tr>
<tr>
<td>XF</td>
<td>Xerophthalnia fundus</td>
</tr>
<tr>
<td>XS</td>
<td>Corneal scars</td>
</tr>
</tbody>
</table>

Description of the ocular lesions :

**Anterior Segment Ocular Lesions**

**X1A-Conjunctival xerosis**: The changes characteristics of vitamin A deficiency are usually confined to bulbar conjunctiva, but occasionally in long standing cases the conjunctiva
of the lower fornix and lid may also be involved. This change may be generalised or localised. A single characteristic or even several characteristics together, does not constitute the proof of the presence of conjunctival xerosis due to vitamin A deficiency, but the presence of most or all of them is highly suggestive of such a diagnosis. In these cases the estimation of serum vitamin A and Retinol Binding Protein (RBP) level, night vision testing are highly essential for proper diagnosis (McLaren, 1963). It is for this reason that night blindness and conjunctival xerosis are not recommended as criteria for community diagnosis of xerophthalmia.

In the pre-school children the position is rather different. Here, there have not yet been the long years of exposure to local trauma and external factors to affect the bulbar conjunctiva; so if it shows a dry, wrinkled, thickened and muddy appearance, then xerophthalmia is by far the most likely cause. Because of all these difficulties, in correct interpretation of vitamin A deficiency strict adherence to the principles stated here is most important for accurate diagnosis.

a) Dryness - Dryness is judged by lack of the normal lustre or brilliance of the bulbar conjunctiva. The appearance has been likened to that of wax or dry paint.

b) Unwettability - Oomen (1961) has emphasized that xerotic bulbar conjunctiva is not wetted by tears and this is an important sign. Patches of xerosis emerge from their
surroundings, like 'sand banks at receding tide', when the child stops crying. This probably results from the disruption of the continuity of the pre-conjunctival film by the xerotic process in the epithelium with degeneration of the goblet cells.

c) **Loss of transparency** - The ability of the conjunctiva to transmit light is impaired, leading to decreased visibility of the conjunctival vessels. The translucent conjunctiva which normally looks clear ('like an aquarium') and is crossed by blood vessels, appears milky owing to the presence of fine droplets. Soon, the vascular pattern apart from the large arteriols, becomes obscured.

d) **Thickening** - There is a tendency to generalized thickening and stiffness of the conjunctiva.

e) **Wrinkling** - There are small, more or less vertical folds in the conjunctiva which are best demonstrated in the temporal conjunctiva on lateral movement of the eyeball.

f) **Pigmentation** - In prolonged xerosis, the lower fornix first becomes yellowish, then light grey, and finally dark brown owing to the presence of chromatophores in the basal cell layer of the epithelium. The changes are most marked in the exposed interpalpebral fissure.

Considerable prominence was given to conjunctival pigmentation as a sign of vitamin A deficiency by
Pillat (1933-39). But, some authors (Kuming et al, 1967) do not consider it as a sign of hypovitaminosis A, as it is seen in normal subjects also due to prolonged exposure to dust, smoke, infection and ultra-violet rays. Again, it should not be confused with the patchy and coarser pigmentation that is frequently seen in healthy subjects of dark skinned races.

g) Accumulation of debris - In some cases of advanced xerosis debris accumulates on the surface of the bulbar conjunctiva and spread on to the adjacent part of the cornea. This material is creamy white, glistening and non-foamy and it easily becomes detached to lie in the canthi, the lower fornix, or the borders of eyelids.

XIV-Bitot's spot: The French physician Bitot in 1863, gave the first account of these spots which are triangular with the apex laterally placed and the base adjacent to the cornea. Sometimes it is circular or oval and sometimes singly linear. Most often the particles which compose it are conglomerated to produce a punctate, granular surface; at other types these particles are arranged in series of wavy parallel lines, which give the lesion the appearance of an undulating or rippled surface (McLaren, 1963).

A Bitot's spot usually has the form of a small plaque with a silvery grey hue and a foamy surface. It is quite superficial and is raised above the general level of
the conjunctiva. The spot is more or less readily removed by manipulation of the lids or direct wiping, when a xerotic conjunctival bed with a rough surface is exposed. A Bitot's spot is invariably situated on the bulbar conjunctiva; it is frequently bilateral and temporal and less commonly nasal, and is confined to the interpalpebral fissure close to the limbus. The characteristic location of the spot close to the protuding limbus would seem to be explained by the protection of the material by the restricted movements of the lids.

Exceptionally, the following variations may be found:

1) One or two bubbles of foam may sometimes seen under magnification in subjects who would otherwise be passed as normal. 2) Bitot's spot material may be scattered widely over the conjunctiva, sometimes arranged in vertical corrugations. 3) Not all Bitot's spots are foamy; some have a cheese-like or grease-like surface; some accumulations are quite exuberant.

If an unusual part of the conjunctiva is permanently exposed as in strabismus, coloboma of the eyelid or ectropion, a Bitot's spot may develop in relation to such an area, illustrating thereby the aetiological importance of exposure. Many workers have reported the presence of Corynabacterium Xerosis bacillus in the Bitot's spot material and the suggestion that it has an aetiological role, was short lived.

Histologically, there is keratinization of the epithe-
lium, meibomian glands and oedema of the mucosa and submucosa. The whole epithelium is thickened and superficial cells are flattened with disappearance of the nuclei. Superficial cells are lined by lamellae of keratohyaline of varying thickness.

Sometimes, there is a prominent vessel running to the area of the conjunctiva beneath the Bitot's spot and frequently there is a stippling of melanin pigment around the spot.

The classification of Bitot's spots are:
1. Those with foamy appearance - chronic type.
2. Those without foamy appearance - acute type.

Palmer, 1936 (Baishya, 1971), described three clinical types of Bitot's spots:

a. As if a fine powder has been dusted into the eye and adhered on each side of the cornea,
b. With a sort of white foam, and
c. Wrinkling of the conjunctiva on lateral movement of the eyeball with an appearance comparable with the belly of a 'Sardine' (a small fish).

The aetiology of Bitot's spot has excited considerable controversy. Collins (1930), Aykroyd and Rajgopal (1936), May and Worth (1938) and Nicholls and Nimalsuriya (1938), confirmed this sign to be a manifestation of vitamin A deficiency. Roels et al (1958), Ascher (1954), Bagchi et al (1959)
and Sood et al (1967) also found a positive correlation between low serum vitamin A levels and incidence of Bitot's spot.

Sie-Boen-Lian (1938), was the first to bring evidence of the absence of vitamin A deficiency in patients with Bitot's spot. Later on Basu and Dey (1941), Rodger (1958), Paton and McLaren (1960), Dhanda (1966), Darby et al (1960), obtained similar results. Dhir et al (1968) got mixed results when treating Bitot's spots with vitamin A alone or along with protein.

In view of these controversies it is very important to make distinction between whether the Bitot's spots are due to vitamin A deficiency or some other cause. It is because the Bitot's spots associated with vitamin A deficiency are almost invariably accompanied by conjunctival xerosis and almost invariably found only in young (pre-school) children, that these characteristics have been chosen to designate those spots that alone should be included in classification of X1B. However, it should be stressed that serious eye lesions due to vitamin A deficiency may develop without appearance of Bitot's spot.

X2-Corneal xerosis - This usually follows upon conjunctival xerosis. By the time the cornea has become hazy the conjunctiva usually shows marked xerosis. In the young infant, however, in whom the deficiency tends to progress rapidly, the cornea may become involved early with the development of keratomalacia.
When corneal xerosis develops, the corneal surface has a rough, fine 'pebbly' appearance and lacks lusture. The 'Breaking-Up-Time (BUT)' of the tear film is shortened (to less than the normal 10 seconds between the last blink and the occurrence of gap in the pre-corneal film). When the eye is kept open for about 10 seconds without allowing the child to blink, the cornea becomes dry and no longer reflects a sharp image. Slit-lamp examination in its early stage may reveal an increase of fine pigment in the para-limbal portion of the cornea; but it must be remembered that pigment in this area is common in healthy individuals of dark skinned races. There may also be loss of continuity of the surface epithelium and diminished tactile sensitivity. Later, cellular infiltration of corneal stroma contributes to the intensity of the haziness of the cornea, which frequently has a bluish, milky appearance and is usually most marked in the lower central part. In some cases even hypopyon may develop.

**X3A-Corneal ulceration with xerosis** - This is the earliest change in which an irreversible damage can occur with some visual defect. Minimal denudation of the epithelial surface (erosion) without transgression of the Bowman's membrane leaves no permanent damage. But when the ulcer invades the deeper part of the cornea, descemetocele or complete perforation with iris prolapse may occur.
**Keratomalacia** - This consists of a characteristic softening (colliquative necrosis) of the entire thickness of a part (Localized keratomalacia) or more often the whole of the cornea (Generalized keratomalacia) invariably leading to deformation or destruction of the eyeball. In these cases serum vitamin A and serum protein level are usually very low (Oomen, 1958). Keratomalacia may or may not be preceded by corneal xerosis. The process is a rapid one.

The two main factors commonly associated with keratomalacia are protein deficiency and local infection. Protein Energy Malnutrition (PEM) of both the kwashiorkor and marasmic type are commonly associated with vitamin A deficiency. The general nutrition of the child is affected pari passu with the ocular manifestation. This should not, however, be taken as evidence that the one is causing the other. The eyes are affected frequently to different degrees, suggesting thereby that local factors probably play a part in keratomalacia. Recent works suggests that lack of mucus in the tear film results in dryness of the cornea which leads to epithelial damage and corneal ulceration (Dohlman et al, 1971).

The initial step in keratomalacia is damage to the epithelium. Release of collagenase and other proteases then occurs and these enzymes attack the exposed stroma and/or invite secondary infection. The stroma is abnormally susceptible to enzymatic action as has been seen in cases of alkali
burn (Gnadinger et al, 1969). It is possible that the corneal stroma in keratomalacia (which usually occurs associated with severe protein deficiency) has lost normal defenses against enzymatic invasion. Serum is known to contain powerful collagenase inhibitors - alfa 2- macroglobulin and alfa 1- antitrypsin (Eisen et al, 1970) and such natural inhibitors may possibly diffuse into the stroma and normally protect it from auto-digestion. In severe protein deficiency inhibitor level may go down and expose the stroma to the destructive enzymes. The precise patho-physiology of keratomalacia is still unknown. A tentative flow chart for possible events in xerophthalmia and keratomalacia is presented below:

Hypovitaminosis A

Disappearance of conjunctival Goblet cells; keratinization

Lack of mucus on epithelium

Poor stability of Tear-Film-Break-Up

Evaporative Damage to epithelium

Irregular surface; Epithelial and stromal opacity; susceptibility to infection (Xerophthalmia)

Release of proteolytic Enzymes from altered epithelial cells (in protein deficiency)

Ulceration of the stroma (Keratomalacia)

Flow - Sheet of possible patho-physiological events leading to xerophthalmia and keratomalacia (Dohlman and Kalevar, 1971).
**XS-Corneal Scars**

Corneal scars result from the healing of the irreversible corneal changes that occur in keratomalacia. If the iris prolapses through the perforated corneal ulcer, leucoma adherens with distortion of the pupil will develop. Severe keratomalacia, on healing usually results in an anterior staphyloma. If the damaged cornea ruptures, the contents of the eyeball are extruded leading to the development of phthisis bulbi.

**OTHER SIGNS**

Eye lashes are often very long, stiff, sparse and irregular which is probably due to protein deficiency. Lanugo hairs on the forehead and in front of the ears may be seen. The periorbital skin and that of the lid is sometimes abnormally keratinized, dry and rough. There may be a mild heaping of keratinized cells between the lash follicles. The pores of the meibomian glands may be enlarged and protuding (Oomen, 1961). Some authors report the inability to open the eye lids in the morning, after getting up from sleep, to be the earlist symptom when other signs and symptoms donot appear (Nichellato et al, 1947).

**Posterior Segment Ocular Lesion**

**XN-Night blindness**

Diminution in the supply of vitamin A to the rod cells of the retina results in impairment in the function of dark adaptation. In the earliest stage without any symptom of night blindness this may be detected by
rod scotometry, dark adaptometry and electroretinography. But as the children of the susceptible age group i.e. pre-school children are not co-operative and responsive, none of the above methods are applicable specially for field study. The development of a simple and suitable but sensitive objective biophysical test of rod function, applicable to all age groups is not available so far. Dr. Sauter in Kenya (1974), introduced a simple technique for measuring night blindness. It was estimated in suitable children by having them enter a darkened room and finding out whether the child could locate his 'silent' mother at once (Xerophthalmia Club Bull. No. 10, June, 1976).

The presence of night blindness should always suggest the possibility of vitamin A deficiency, but it may also, though rarely, result from non-nutritional causes. Mothers are usually quick to recognise the problem of night blindness; the child no longer move about in the house or in the village after dusk, but prefers to sit in a secured corner, often unable to find their food or toys. In some cultures specific term exists to describe the condition, such as 'chicken eyes' ('Kukuri kana' in Assamese and 'Ratundi' in Hindi).

The significance and reliability of night blindness as a sign of vitamin A deficiency has been re-recognised by some recent workers. Sommer, A., from his study in Indonesia, prefers to place night blindness as a primary sign rather than

XP-Xerophthalmia Fundus - Though, it is thought that the fundus changes were first described by Uyemura (1928) in Japan, it was Mikamo of Japan, who first detected this sign (Elliot, 1920, quoted by McLaren, 1963). The fundus changes consist of white or yellowish spots scattered profusely along the course of the vessels. They are usually in the periphery of the fundus, the macula remaining free. The older children are usually affected, often complaining of night blindness and having xerosis conjunctivae and Bitot's spots. Spots are never seen on top of a vessel, but a vessel may run over them. Both eyes are always affected but not necessarily to the same extent. These changes have been documented by fundus photograph, from Indonesia (Teng-khoen-Hing, 1959; Sie-Boen-Lian, 1960). Confirmatory reports have also come from Japan (Imai, 1930; Kuwahara, 1935), from China (Pillat, 1940). Pillat, 1940, observed 'small glomerulation in the external strata' of the retina in vitamin A deficiency and that would seem to be at present the only histological evidence of such an eye. However, the evidence that they are actually caused by vitamin A deficiency is not entirely convincing.
ECOLOGY OF XEROPHTHALMIA

The etiology of xerophthalmia like that of any other disease can be understood by consideration of the interrelationships among host, environment and causal factors.

HOST FACTORS:

1. Age - Age plays a very significant role in determining the incidence and nature of the eye manifestations of vitamin A deficiency (McLaren, 1963). Young children constitute the most vulnerable age group, because vitamin A requirement is directly related to the rate of growth. Childhood infection and general malnutrition like PEM are common precipitating causes of vitamin A deficiency in this age group.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>PATHOGENIC FACTORS</th>
<th>MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Basic diet low in vitamin A (mostly carotene), Increased requirements, Food taboos, Strain of repeated pregnancy.</td>
<td>Low plasma vitamin A, Low liver stores, Bitot's spot (occasional), Xerophthalmia (rare).</td>
</tr>
<tr>
<td>Foetus</td>
<td>-</td>
<td>Low liver stores, Xerophthalmia (rare)</td>
</tr>
<tr>
<td>STAGE</td>
<td>PATHOGENIC FACTORS</td>
<td>MANIFESTATIONS</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Adult</td>
<td>As above plus special privation (famine, prison)</td>
<td>Night blindness predominant. Bitot's spot (Occasional) Keratomalacia (rare).</td>
</tr>
</tbody>
</table>


2. *Sex* — There is evidence that males are more susceptible to xerophthalmia. It has been established that there is quantitative difference in the metabolism of vitamin A and carotenoids between the two sexes (Moore et al, 1960). Oomen (1957), found that there is a low ratio (1.4 male : 1.0 female) in preschool children than to a much higher one after the age of 10 years or so (6.0 male : 1.0 female). These findings are supported by other workers like Mori (1904), Blegvad (1924), Kuning et al (1967), Darby et al (1960), Tiwary (1962), Krishnamoorthy (1966), Abboud et al (1968), Baisyha et al (1971) and Desai et al (1977). But Sheikh et al (1961) found the incidence to be more in females.

It has been reported (Teng, 1965; Baishya, 1971) that blood level of vitamin A is more in normal boy than in girls and there is an increase in Retinol Binding Protein (RBP) level in infants than in adults. The known high correlation between
RBP and plasma retinol is consistent with, and could at least in part explain the above-mentioned observations.

3. **Secondary or Endogenous vitamin A deficiency** – A disease that interferes with digestion, absorption (or in cases of carotene, conversion), transport, storage or metabolism, or leads to increased elimination or requirements may precipitate a nutritional deficiency. Prominent among those known to precipitate vitamin A deficiency, and occasionally severe enough to cause keratomalacia, are the various causes of fat malabsorption syndromes (coeliac disease, cystic fibrosis, sprue, lymphoma and etc.), interference with transport (alfa-and beta-lipoproteinemia), storage (cirrhosis, hepatitis), metabolic defects (diabetes mellitus, enzyme deficiency) and increase requirements (thyrotoxicosis, pyrexia, etc.).

**AGENT FACTORS**

1. **Rice** – Xerophthalmia is most prevalent in the underdeveloped countries of Asia, Latin America and Africa. Poverty is the basis of this global distribution. But poverty is made worse by disease and lack of understanding of the finer points of nutrition. In most of these countries rice is the staple food; 'rice is food; if all fails, rice will still fill the belly' (Pirie, 1976). But rice is devoid of carotene and does not constitute a complete diet. The danger of complete dependency on rice is great. It is common to find 'poverty in the midst of plenty'.
2. **Breast feeding and artificial feeding** - Breast feeding usually provides considerable protection against the development of xerophthalmia unless the mother herself has a very low vitamin A status and her milk is deficient in the vitamin. Even the relatively low vitamin A content of normal milk is adequately protective (WHO Tech. Report Series, 362, 1967). The tendency towards early weaning and artificial feeding from birth, is now considered to be nutritionally disastrous for the children of the underprivileged communities in all parts of the world.

The important role of breast feeding has been illustrated by the example of Uganda, where until recently the breast feeding was prolonged and though their staple food is 'Motoke', a steam plantation, which is very poor in carotene, keratomalacia has been rare.

3. **Skimmed milk** - Epidemics of xerophthalmia have occurred in association with food donation programmes in which preparation of skimmed milk without fortification with vitamin A has been used (WHO Tech. Report Series, 590: p. 35, 1976).

4. **Other dietary factors**

   **Fat** - Most dietaries are low in vitamins, proteins and fat. Fat is necessary for utilization of dietary carotene (Roels et al., 1958; Andri & Ganzin, 1954).

   **Vitamin E** - Vitamin A and E are intimately related in several aspects of their metabolism as proved by animal
experiments. Probably vitamin E has an antioxidative or other protective effects. However, in human experiments the role of vitamin E in vitamin A metabolism has not been definitely proved (Kusin et al., 1974). Nevertheless, it is advisable to add 10-40 I.U. of vitamin E in capsules containing 200,000 I.U. of vitamin A for dosing (Kusin et al., 1974).

**Protein and Energy** :- The relationship of hypoproteinaemia with avitaminosis has been observed by different workers (Kremer et al., 1958; Deshmukh et al., 1964; Baishya, 1971). The frank signs of either may, however, exist without those of the other. The concept of Retinol Binding Protein (RBP) and of pre-albumin, the transport protein for vitamin A in the serum, is now familiar from the fascinating works of Goodman, Vahlquist and their associates (Pirie, 1976). Their findings suggest that the low levels of vitamin A in kwashiorkor and protein-energy malnutrition (PEM) largely reflect a functional impairment in the hepatic release of vitamin A rather than vitamin A deficiency 'per se'. Hepatic release of vitamin A is apparently impaired because of defective production of RBP in the liver, due to limited supply of substrate for protein synthesis. In these cases even the vitamin A therapy does not increase the serum vitamin A level as it is not released from the liver due to defective production of RBP. When substrate is provided by dietary calories and proteins, the hepatic production of plasma protein increases, plasma RBP and pre-albumin rise and hence
plasma vitamin A concentration increases. So, in treating xerophthalmia it is advisable to supplement vitamin A therapy with dietary protein.

ENVIRONMENTAL FACTORS:

1. Season: The annual periodicity in the fluctuations of dietary intake of vitamin A and carotene, of plasma levels of vitamin A and of occurrence of xerophthalmia, are all well documented in various parts of the world. Blegvad (1924) from his study in Denmark, observed the maximum occurrence of xerophthalmia in April, then a sudden fall in June and July and very few cases in August, September and October. It was thought that in the month of May and June the cows eat grass rich in fat soluble vitamin A and hence the milk also contained more vitamin A. In a study carried out by Singha and Bang (1973), in rural West Bengal, found two definite peaks of vitamin A deficiency—one in November to December and the other in May and June. They thought that possibly this variation was associated with seasonal variation in growth and total food intake. Nguyen-Van-Ba (1956) from Hanoi, mentioned two distinct peaks in the incidence of xerophthalmia in every year, one in the hot months (from April to August) and a second in chilly season (October to December). Oomen et al (1964), mentioned a predilection for hot summer months in North Africa and the Near East. Blankhart (1967) in Indonesia, found that most of the cases occurred in the last five months of the year, at the end of the dry and beginning of the rainy season. Study from Jordan (Patwardhan, 1969) also showed
a seasonal variation especially when other precipitating factor like prolonged drought occurred. Gopalan et al (1960) in their studies in Coonoor and Hyderabad, South India, failed to reveal any definite trends in both the places in a five year period.

2. Rural and Urban Environments - It is difficult to generalise about the effect of urban and rural environments on vitamin A deficiency. In areas of high xerophthalmia endemicity, such as parts of Indonesia, the available evidence suggests that children in the lower socioeconomic classes are everywhere equally at risk. An attempt is made in the table below

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>RURAL ENVIRONMENT</th>
<th>URBAN ENVIRONMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Services</td>
<td>-</td>
<td>better</td>
</tr>
<tr>
<td>Carotene sources</td>
<td>more</td>
<td>-</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>Equally common but different.</td>
<td>More parasitic infection.</td>
</tr>
<tr>
<td></td>
<td>infection.</td>
<td>Measles equally common</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>More frequent and for a longer time</td>
<td>-</td>
</tr>
<tr>
<td>PEM</td>
<td>Kwashiorkor</td>
<td>Marasmus</td>
</tr>
<tr>
<td>Rice dependent diet</td>
<td>Little variety of foods.</td>
<td>Greater variety of foods available</td>
</tr>
<tr>
<td>Money consuming distractions</td>
<td>Few</td>
<td>More numerous</td>
</tr>
</tbody>
</table>

to indicate some possible difference and similarities in the
two kinds of environments in this respect.

3. Infections and Infestations - The influence of illness
on vitamin A metabolism and its defective absorption has been
reported by many investigators. Diseases depress the absorp-
tion of vitamin A and carotene from intestine and disorganise
metabolism of vitamin A in the body. In all fevers, for ex-
ample, Pnumonia, Pertusis, Malaria, Measles, the level of
vitamin A in the blood falls sharply (Lawria et al, 1941 ;
Moore, 1937; Thygeson,1959; Sauter, 1974). The association of
measles with xerophthalmia is however known to be of major
importance Sauter (1974). Because, it can trigger off a dis-
aster in children who have got marginal vitamin A level in
the body. Above all, measles must be implicated in the ocular
lesion associated with vitamin A deficiency when the two are
found together, because measles is invariably an eye disease
to some extent (Thygeson, 1959 ).

Gastrointestinal disorders (like diorhooea and dysen-
tary ) play a key role in the etiopathogenesis of xerophthalmia ( Ramalingaswami, 1948 ; Vaughan, 1954 ; Sinha, 1966 ;
Baishya, 1971 ). Baishya,1971, found that gastrointenstinal
disease was present in 87.5% of the cases with ocular mani-
festations of hypovitaminosis A.

The coincidence of keratomalacia induced by intes-
tinal helminthiases has been reported and it has been sugges-
ted that ocular manifestation of hypovitaminosis A is
accelerated by metabolic - toxic disturbances induced by these worms (Tiwary, 1966; Sivakumar et al, 1975).

Baishya (1971) found that 78.1% of the children with xerophthalmia were suffering from intestinal helminthiasis.

4. Toxins - It has been reported (Sikes et al, 1952) that toxic food ingredients like naphthalene, aspergillus niger etc. cause great decrease of vitamin A level in the blood.
GLOBAL OCCURRENCE OF HUMAN VITAMIN A DEFICIENCY
(MALNUTRITION AND THE EYE, BY- MCLAREN, D.S.; 1963, P.217)
GLOBAL PREVALENCE OF XEROPHTHALMIA

A global survey of xerophthalmia carried out by Oomen et al., 1962-63, revealed that this was the most important cause of blindness in children. He compiled his data mainly from hospital records, impressions of physicians and observations made by visiting consultants. Such impressions, though, do not provide the evidence of true prevalence, may indicate the frequency of occurrence in general. Schrimshaw (1959) and McLaren (1963), are of the opinion that vitamin A deficiency is one of the main nutritional problems in tropical and subtropical countries of the world. Patwardhan (1960), Kuming et al. (1967), Kamel (1973) and Sauter (1974) have collected data on vitamin A deficiency from a number of countries basing on dietary intake, level of plasma vitamin A and carotene along with the associated clinical picture of ocular involvement, though, they faced numerous difficulties in collection, standardization and interpretations of serum vitamin A and carotene levels. Recently, well controlled studies of xerophthalmia have been conducted in El Salvador (1973), Indonesia (1973 & 1977-78), Phillipines (1976), Haiti (1975) and Kenya (1974-75).

Global distribution of vitamin A deficiency can be divided into:

1) Technologically developed countries where there is no xerophthalmia problem but some hypovitaminosis A may exist;
2) Some rice dependent developing countries of Asia where it is a problem of public health importance;

3) The rest of the world including Africa, Latin America and the Middle East where the problem is not so extensive.

**ASIA**

**INDIA** - The Indian subcontinent bears lakhs of blind children who are the victims of keratomalacia. Records are made available about the prevalence of xerophthalmia during the centuries from different sources. Bishop Reginald Heber, Lord Bishop of Calcutta, in his 'Narrative of a Journey through the Upper Provinces of India', on the occasion of his visit to Chittore, February 22, 1826 (Quoted by McLaren, 1963), reported that 'Ratunda' (means night blindness) was very common amongst the illnourished people mainly living on poor quality of rice.

Major Robert E. Wright (1922) in his report mentioned the frequency of keratomalacia in South India and suggested that children in the weaning period were affected heavily. Kirwan, Sen and Bose (1943) described many cases of keratomalacia in young Bengali children who were often emaciated, with distended abdomen, dry, brittle and scanty hair and with loose, dry and darkened skin (McLaren, 1963). Holmes reported that he saw several hundred cases of keratomalacia during his visit to India in 1952. McLaren (1956), in the province of Orissa, encountered racial difference in the incidence of infantile keratomalacia. He also, quoted the reports of Achar (1950),
Khalap (1956) and Rambo (1958), seeing large numbers of cases of keratomalacia in Madras, Poona and Madhya Pradesh respectively.

In the wheat eating zone of North India, xerophthalmia is less frequent (Chatterjee, 1971). Of the 200 hundred children suffering from malnutrition, studied by Manchanda and Gupta (1958, quoted by McLaren, 1963) in Amritsar, only 4 had keratomalacia. Madan Mohan et al (1966), in their study of the children in Residential Blind Schools, of Delhi found that amongst 237 students admitted, keratomalacia was the cause of blindness in 4 children. In the following years numerous reports have been published signifying the prevalence of xerophthalmia in North India (Sood and Ratnaraj, 1967; Dhir et al, 1968; Dhar, Gupta & Agarwal, 1969; Chouhan, 1971; Vijoykumar et al, 1975 and Desai et al, 1977).

Gilroy in 1951, observed xerophthalmia in 250 out of 4191 children examined in 44 tea gardens in Assam. Preliminary studies made by Dutta (1962), amongst the 2462 children attending the eye Deptt. of Assam Medical College Hospital, Dibrugarh, from 1951 to 1960, revealed that hypovitaminosis A manifestation constituted 11.41% of all eye diseases.

Sinha and Bang (1973), found in rural Bengal 11.25% of children below 9 years, either had night blindness or Bitot's spots. He also noticed a seasonal variation of the disease. Sundarajan (1963), observed xerophthalmia in 30-45% of school children in Calcutta. Bhattacharyya (1975) reported that children attending a Calcutta hospital, showed 20%
prevalence of xerophthalmia in them.

Rao, Swaminathan, Swarup and Patwardhan (1959), observed 2-5 cases of vitamin A deficiency for every kwashiorkor in South India. In a survey of the states of Kerala, Madras and Andhra Pradesh, Rao et al (1959), found 7% of children having signs of deficiency of vitamin A and B-complex. Chandra et al (1960), reported that out of 14,563 children examined in 5 years period 2,245 showed malnutrition and 551 vitamin A deficiency and 157 keratomalacia. In the Eye Department of Madurai Medical College, 250-350 keratomalacia cases are seen among 48,000 new patients a year (Venkataswamy, 1971). A survey of children in public schools in Tamilnadu State, showed that 20-25% had signs of xerophthalmia. According to Venkataswamy (1971), amongst all the blind people in Tamilnadu, keratomalacia is the cause of blindness in 50% of them. The total number of keratomalacia cases from 1968-72 in four hospitals of Kerala, Mysore, Tamilnadu and Andhra Pradesh were 2319 (Xeroph Club Bull. No. 3, May, 1973 - Table - A). Rao, Ahmed and Reddy et al (1974), found the prevalence of xerophthalmia to be 4.2% in the twin cities of Hyderabad and Secunderabad. Muruyan et al (1977) and Kuruvilla et al (1978) observed that prevalence of xerophthalmia is quite significant in school children, Hyderabad and rural coastal areas of Karnataka.

BANGLADESH - Individual reports from Bangladesh refer to a massive problem of xerophthalmia in that country; large numbers of cases of keratomalacia have been reported from Dacca and
other large urban centers. Initial examinations of 21,000 children for a prevention programme showed about 32% prevalence of xerophthalmia in the country (WHO Tech. Report Series, 580: p.43, 1976, Table - C).

Table - A

Number of cases of keratomalacia seen at various hospitals in India, 1968-72. The total number of cases of keratomalacia seen at these four hospitals in 1968-71 inclusive was 8,319 (Xeroph. Club Bull. No.3, May, 1973; and WHO Tech. Report Series, 590: p.43, 1976).

<table>
<thead>
<tr>
<th>Place</th>
<th>Total no. of out patients</th>
<th>Total no. of keratomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govt. hosp. Trivandrum, Kerala</td>
<td>34482</td>
<td>37473</td>
</tr>
<tr>
<td>Minto Oph. hosp., Bangalore, Mysore</td>
<td>1072</td>
<td>100544</td>
</tr>
<tr>
<td>Govt. Ers. hosp., Madurai, Tamilnadu</td>
<td>39416</td>
<td>39026</td>
</tr>
<tr>
<td>Sarojini Devi hosp., Hyderabad, Andhra Pradesh</td>
<td>67341</td>
<td>60008</td>
</tr>
</tbody>
</table>

Active keratomalacia

<table>
<thead>
<tr>
<th>Place</th>
<th>Total no. of out patients</th>
<th>Total no. of keratomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govt. Ers. hosp., Madurai, Tamilnadu</td>
<td>39416</td>
<td>39026</td>
</tr>
<tr>
<td>Sarojini Devi hosp., Hyderabad, Andhra Pradesh</td>
<td>67341</td>
<td>60008</td>
</tr>
</tbody>
</table>

Burnt-out keratomalacia

SRI LANKA - Reports from Sri Lanka (Wickremesinghe, 1942 & Sivasubramaniam, 1958), suggest that keratomalacia is the major cause of blindness in that country (Quoted by McLaren, 1963).
### Table - B


<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of children</th>
<th>Conjunctival xerosis (%)</th>
<th>Bitot's spots (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 3 yrs.</td>
<td>947</td>
<td>2.6</td>
<td>1.3</td>
<td>3.9</td>
</tr>
<tr>
<td>3 - 5 yrs.</td>
<td>633</td>
<td>6.5</td>
<td>6.2</td>
<td>12.7</td>
</tr>
<tr>
<td>Total</td>
<td>1580</td>
<td>4.2</td>
<td>3.2</td>
<td>7.4</td>
</tr>
</tbody>
</table>

### Table - C


<table>
<thead>
<tr>
<th>Xeroph. classification</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1A</td>
<td>...</td>
<td>6778</td>
</tr>
<tr>
<td>X1B</td>
<td>...</td>
<td>140</td>
</tr>
<tr>
<td>X2</td>
<td>...</td>
<td>84</td>
</tr>
<tr>
<td>X3</td>
<td>...</td>
<td>13</td>
</tr>
<tr>
<td>XN</td>
<td>...</td>
<td>213</td>
</tr>
<tr>
<td>XS</td>
<td>...</td>
<td>39</td>
</tr>
</tbody>
</table>

**PAKISTAN, NEPAL, AFGHANISTAN** - Pakistan has relatively few cases of xerophthalmia compared to the neighbouring rice eating countries. It is reported that cases of xerophthalmia are seen frequently in hospitals in both Afghanistan and Nepal. (WHO Tech. Report Series, 590: 41, 1976).

**CHINA** - Things have changed a lot since the communist
regime came into power in China; about 30-40 years earlier, things were quite different. At that time (McLaren, 1963) there were many cases of xerophthalmia, frequently associated with protein malnutrition (Pillat, 1930-31 & 1939; Sareet and Yang, 1935; Chen, 1942).

SOUTH EAST ASIA - In this part of the world several hundred million people live and the density of population is greater than anywhere else of comparable size. Rice is their staple food and is universally employed to supplement breast feeding. So, it is little wonder that infant keratomalacia is so common in this part.

From Indonesia, several reports have been published on the prevalence of xerophthalmia and its close relationship to kwashiorkor (Oomen, 1953-55; Yap-Kie-Tieng, 1956; Darby and McLaren, 1957). In 1973, The Ministry of Health, Indonesia, found the prevalence of xerophthalmia to be 4.7% in children aged 12-48 months residing in 7 urban 'Kampongs' and 5 rural villages. Other investigators (Teng, 1975; Tjakrasudjatma, 1975), put the incidence in the range of 3-14% in children of 0-16 years age group (Xeroph. Club Bull. No.8, June, 1975). The percentage of xerophthalmia cases with involvement of the cornea has decreased tremendously in the following years, as is suggested by the reports of Teng (1975), table - D.

Xerophthalmia has virtually disappeared from HONGKONG and SINGAPORE (WHO Tech. Report Series, 590; p.40, 1976).
Xerophthalmia exists in Thailand, Burma and Borneo, though it is not a problem of major public health importance (McLaren, 1963). In Thailand, the United States Interdepartmental Committee on Nutrition for National Defence Survey in 1962, reported 0.2% prevalence of xerophthalmia in a general randomized sample of over 5000 persons of all ages (McLaren, 1963).

In Vietnam also, it is not a major health problem. The problem of xerophthalmia has been recognised for sometime in Malaya (Nguyen Dinh Cat, 1958; quoted by McLaren, 1963).

In the Philippines, keratomalacia frequently accompanies kwashiorkor (McLaren, 1963). A recent investigation by Solon et al, found that 40% of the children had both low serum vitamin A levels and clinical signs of xerophthalmia which was most common in 4-6 years old age group (Xeroph.Club Bull.No.7, Feb., 1975).

---

**Table - D**

Percentage of the three stages of xerophthalmia in children aged 0-6 years at the out patients department of 'Cicendo' Eye hospital, Bandung (Teng, K.H., Xeroph.Club Bull. No. 8, 1975).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Without corneal involvement</td>
<td>64.8%</td>
<td>79.9%</td>
</tr>
<tr>
<td>With corneal xerosis</td>
<td>19.9%</td>
<td>7.2%</td>
</tr>
<tr>
<td>With irreversible active corneal changes</td>
<td>15.3%</td>
<td>12.3%</td>
</tr>
<tr>
<td>Total xerophthalmia cases</td>
<td>7596</td>
<td>1484</td>
</tr>
</tbody>
</table>
Reports from Korea and Taiwan, also show that xerophthalmia is quite a problem there especially in the former McLaren, 1963).

JAPAN — The accounts of 'Hikan' by Mori (1904) and Ishihara (1913), have now become the story of the past. Majima et al (1960), found not a single case of xerophthalmia in a detailed ophthalmic examination done on 3033 school children aged 6-10 years. According to recent report, only a few aged blind remain as a relic of the past, long forgotten, endemic (WHO Tech. Report Series, 590: p. 40, 1976).

THE MIDDLE EAST — In the past decade, the living conditions generally have improved almost everywhere in the Middle East. So, xerophthalmia had declined throughout the region. In the Gezira area of Sudan, for example, hundreds of cases were reported in 1962, but few are now seen. Cases of xerophthalmia are seen occasionally in Iraq, Jardan and Syria - all previously endemic areas (Patwardhan, 1969).

Tobgy and Wilson (1933), Dugan (1955), described night blindness and xerophthalmia in Egypt to be a frequent finding, although keratomalacia was found to be rare (Quoted by McLaren, 1963). Awaad, Khalifa et al (1975), reported vitamin A deficiency in the form of keratomalacia or Bitot's spots in 15.1% of children examined between 3 to 12 years of age in a village of Egypt.
Traditionally, Africa, South of the Sahara, has not been considered to have serious xerophthalmia problem because of the availability of carotene-rich red-palm oil. The drier Northern part of the Sahara, are highly susceptible to xerophthalmia. In the rapidly growing urban areas of Africa, amongst the casual and poorly paid workers, protein malnutrition accompanied by xerophthalmia is quite common (McLaren, 1963). Scragg and Rubidge (1960) found that 0.9% of the children in Durban, suffered from xerophthalmia. Rodger, 1958, reported that in Ghana, Nigeria and Cameroons, vitamin A deficiency cases are detected quite frequently.

A recent account from the Blue Nile Province of Sudan (Seikh, M. El, 1960) shows that keratomalacia is common there in young children. Balleto (1954) and McLaren (1963) observed that, in Tanganyika, about 10% of all children had xerosis conjunctivae and nearly 1% had permanent damage to the eye sight from xerophthalmia. Low serum vitamin A levels and xerophthalmia have been reported in a recent study of African children in Northern Rhodesia (Friis-Hansen & McCullough, 1963, quoted by McLaren, 1963). There is no endemic xerophthalmia in Uganda today (McLaren, 1963). Kuming and Politzer (1967), detected xerophthalmia in 9.7% of Bantu children in South Africa. Recent data from Upper Volta shows that the incidence of night blindness and xerophthalmia is quite high there (WHO Tech. Report Series, 590, 1976).
In the past 10 years, reports of xerophthalmia have been coming from parts of Africa where previously it was not known to be common. These places are - Addis Ababa, Ethiopia (Paton & McLaren, 1960), South Rhodesia (MacManus, 1967), Luapula Valley of Zambia (Awdry et al, 1967), Kenya (Sauter, 1974), East Africa (Franken, 1974), Malawi (Ben-Sira et al, 1972), Nigeria (1971) and Rwanda (Yassur et al, 1972).

**LATIN AMERICA AND WEST INDIES**

Brazil was the first, more or less, tropical country from where xerophthalmia was first reported in the 19th. century (Gama Lobo, 1865, 'Ophthalmia Brasiliiana'). Xerophthalmia is still a national problem in Brazil; it is mentioned that, in Brazil, 17-32% of those under 15 have very low serum vitamin A level and signs of xerophthalmia (Simmons: Xeroph. Club Bull. No.7, Feb., 1975).

Night blindness used to be common among the fishing communities of New Foundland and Labrador (Aykroyd, 1930; Steven & Wald, 1941). Several reports have been published highlighting the prevalence of xerophthalmia from Central American Countries (Autret abd Behr, 1954), Guatemala and El Salvador (McLaren, 1960; Sommer et al, 1973), Mexico (Gil, 1934; Pagola, 1948), Cuba (Castellanes, 1935 & 1937), Honduras (Vidal, 1938), Venezuela (Vander Sar, 1951) and Santiago, Chile (Menghello et al, 1950). In Peru, Uruguay and Colombia, it is less frequent.

**EUROPE**

Endemic form of xerophthalmia occurs only in few parts of Europe. Biotti (1940), Frontali (1948) had reported the occurrence of keratomalacia in Italy (McLaren, 1963). Quite recently 17 cases of xerophthalmia and keratomalacia have been reported from Poland (Juzwa, 1958 - quoted by McLaren, 1963). There is no report of xerophthalmia from Spain (McLaren, 1963). The last case reported from Great Britain was in 1938 (Pirie, 1976).

**AUSTRALIA**

According to Ida Mann (1959), nutritional eye diseases do not occur among the nomadic hunting aborigins living in the interior of Australia; but in Fiji it has been reported to be prevalent among young children (Thompson, 1949) and is occasionally associated with kwashiorkor (Manson-Bahr, 1951 - McLaren, 1963).
TREATMENT OF XEROPHTHALMIA

'The physician who finds himself with the responsibility of treating cases of xerophthalmia will probably be subjected to a wide range of emotional feelings. On the one hand he will feel gratified with dramatic response made by even quite advanced cases of xerosis corneae and frequently even when there is residual scaring, a useful vision may be preserved. Nevertheless, there will be occasions, when one glance at the screwed up soggy eyelids and the underlying disorganised globe will suggest that all is already lost' (McLaren, 1963). Once the clinical signs of structural damage of the eye has been started, things proceed with alarming rapidity. The corneal stage, like an intestinal perforation, should be considered as an emergency. Delay for even one day at stages X2 or X3A, when changes still can be reversible, may make all the difference between sight and blindness for the patient.

The Joint WHO/USAID Meeting held in Jakarta in 1974 (WHO Tech. Report Series, No.590) recommended the following treatment schedule for xerophthalmia:

Treatment Schedule for Xerophthalmia

- Immediately on diagnosis ... 100000 I.U.; water miscible preparation; intramuscular
- Second day ... 100000 I.U.; oil soln., oral
- Prior to discharge - Patient under 1 yr. of age ... 100000 I.U.; oil soln., oral
- Patient over 1 yr. of age ... 200000 I.U.; oil soln., oral
Explanatory notes:

1) Retinyl palmitate is the preferred active form of vitamin A in water-miscible formulations for intramuscular injection.

2) Upon diagnosis, an oil solution of vitamin A (100,000 I.U.) should be substituted only if an intramuscular preparation is not available. Hospitals in areas where xerophthalmia is endemic should keep water-miscible intramuscular preparations of vitamin A on hand at all times.

3) Oral water-miscible preparations of vitamin A may be substituted for oil solutions; vitamin A acetate may be used in place of retinyl palmitate in oil solutions for oral use.

4) Oil solutions of vitamin A should never be injected intramuscularly, because they are relatively ineffective, the vitamin being liberated extremely slowly, if at all, from the injection site.

It is very important that underlying conditions receive vigorous treatment. The conditions include PEM and other nutritional disorders, gastroenteritis, dehydrations and electrolyte imbalance, infections (especially measles), parasitic infections. An specially dangerous, not infrequent, situation is the omissions of vitamin A therapy in the treatment of cases of PEM without obvious eye lesions. Xerophthalmia may be precipitated when growth is stimulated and vitamin A requirements are consequently increased (Gopalan et al, 1960).
A vitamin A control and preventive programme can be directed towards improving the vitamin A status of a population, eliminating blindness related to vitamin A deficiency, or to an intermediate objective. Certain countries that have the necessary resources and motivation may, however, decide to introduce a comprehensive control programme in order to improve vitamin A intakes, even in the absence of a xerophthalmia problem. Among the available strategies to prevent and control vitamin A deficiency and xerophthalmia are the followings:

1) **Periodic massive dose programme** - In these programmes the generally recommended method is to provide 100,000 I.U. of vitamin A to children under 1 year of age and 200,000 I.U. of vitamin A with vitamin E to children 1 to 6 years of age every 6 months. A delivery system has to be devised that will as far as possible ensure that children at the greatest risk receive these doses.

2) **Fortification of Foods** - Fortification of foods with appropriate amounts of vitamin A has the advantage of reaching all those who consume the fortified food and requires neither the active participation of the population nor an elaborate and costly delivery system. An ideal food vehicle for fortification should be one which is widely consumed, especially by children at risk and shows little variation in per capita consumption.
In addition, the selected food product should be stable. At present in various parts of the world where vitamin A deficiency and xerophthalmia are considered to be serious problems, dried milk and cereals grain products, sugar, tea and monosodium glutamate are fortified with vitamin A.

3) **Public health measures** - Health services need to be in a position to detect the presence of vitamin A deficiency and xerophthalmia in the community to estimate the prevalence of the condition to provide some indications of their epidemiology and to have the staff and facilities to ensure early treatment of patients and carry out preventive measures in the community. All health units, even in the most remote locations, should keep a ready stocks of vitamin A for treatment and 'prophylaxis'. In high risk areas where massive dose programmes or food fortification measures are not in operation, regular routine dosing with vitamin A of all children and pregnant and lactating mothers attending hospitals, maternal and child health clinics and other health units, should be considered.

The control of diseases, such as measles, diarrhoea and Protein Energy Malnutrition (PEM), known to be related to xerophthalmia should be undertaken.

4) **Horticultural and Food production activities** - Efforts to increase production and consumption of foods containing carotenoids should be a feature of most of these programmes designed to reduce the incidence of xerophthalmia. The richest
sources of carotene (other than red palm oil) are vegetables like carrot and the green leafy vegetables and fruits like mango, papaya, etc. Some staple food-stuffs such as yellow corn also provide some carotene.

5) **Nutrition education** - Use of educational methods, including the mass media of communication (radio, television etc.), should be an integral part of all vitamin A programmes.

**Evaluation**

It is important to evaluate all programmes for preventions and control of xerophthalmia. Evaluation should cover the operation of the programme as well as its effectiveness in reducing the prevalence of xerophthalmia due to vitamin A deficiency.