Control of vitamin A deficiency and xerophthalmia

Report of a Joint
WHO/UNICEF/USAID/Helen Keller
International/IVACG Meeting

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"If we could take action against only 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 of blindness".

Sir John Wilson

Director, Royal Commonwealth Society for the Blind
(From an address to the WHO Regional Conference on Curable Blindness, Hyderabad, India, October 1980)

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CONTROL OF VITAMIN A DEFICIENCY
AND XEROPHTHALMIA

Report of a Joint WHO/UNICEF/USAID/Helen Keller
International/IVACG Meeting

A Meeting on the Control of Vitamin A Deficiency and Xerophthalmia was convened jointly by the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), the US Agency for International Development (USAID), Helen Keller International (HIKI), and the International Vitamin A Consultative Group (IVACG) in Jakarta from 13 to 17 October 1980 at the invitation of the Government of the Republic of Indonesia. The purpose of the meeting was to review the progress that had been made in the institution of measures to control vitamin A deficiency and xerophthalmia since the previous meeting on this subject in 1974.

At the 1974 meeting, all available information on the metabolism of vitamin A (and the carotenoids) and the assessment of vitamin A status, as well as the ecology, occurrence and treatment of xerophthalmia, the control and prevention of this disease, and the needs for further research were extensively reviewed. For this basic information the report of this meeting, published in 1976 (1), and other publications (2, 3) should be consulted.

The present report focuses attention on recent developments in the control of vitamin A deficiency and xerophthalmia (see section 7), while sections 2–6 present information on recent advances in the understanding of the causes and in the recognition of problems relating to such control.

1. INTRODUCTION

Vitamin A deficiency and xerophthalmia are among the most widespread and serious nutritional disorders that affect mankind. For many years the problem remained unchecked and continued to exact a devastating, although uncertain, toll in blindness and death among young children. More recently there has been an increasing realization, by international, governmental and private agencies, of the enormity
of the problem and concerted efforts have been made in the areas of research, field surveys, action programmes and educational activities. As these measures are beginning to bear fruit and have already produced some degree of control of the problem, there is every reason to believe that their impact will increase if the momentum, now gained, is maintained and reinforced in the years ahead. Although the goal (4) of controlling the florid forms of severe malnutrition like kwashiorkor, marasmus, and keratomalacia by the turn of the century may be difficult to attain, it is not unrealistic as far as keratomalacia is concerned, provided that the knowledge now to hand is applied.

1.1 Definitions

A word of explanation is necessary concerning the use of the terms xerophthalmia, vitamin A deficiency, and vitamin A status in this report.

Xerophthalmia is a convenient term used here, as in the previous report (1), to cover all the ocular manifestations of vitamin A deficiency, including not only the structural changes affecting the conjunctiva, cornea and occasionally the retina, but also the biophysical disorders of retinal rod and cone function that are attributable to vitamin A deficiency (see section 4.1.1). Xerophthalmia, while clearly not synonymous with blindness resulting from vitamin A deficiency, does denote an advanced degree of vitamin A depletion which constitutes a potential threat to sight.

Vitamin A deficiency, of necessity, includes xerophthalmia but has much wider implications. It relates to any state in which the vitamin A status is subnormal. Although this is not capable of precise definition, it can be presumed to occur when the habitual intake of total vitamin A is markedly below the recommended dietary intake (RDI). There is evidence that the methodology in customary use for the determination of the provitamin A activity of foodstuffs has tended towards overestimations in some instances, and, considering the more precise techniques now available, there is need for reappraisal in this area.

Vitamin A status is defined in terms of the total body reserves of vitamin A, which can vary from excessive (hypervitaminosis), through acceptable and marginal, to poor or deficient (hypovitaminosis) (1). An acceptable vitamin A status is defined in terms of a protection period, which is the period of time during which an individual might
function normally on a vitamin-A-deficient diet. Since the liver usually contains 90% of the total body reserves of vitamin A, the concentration of this vitamin in the liver generally correlates well with the protection period. The plasma vitamin A concentration is a useful indicator of excessive, deficient, and possibly of marginal vitamin A status (see section 4.2). The liver concentration of vitamin A, in circumstances where autopsy samples can be obtained, yields information about the total body reserves (section 4.2). Other possible approaches require further exploration.

With the increased understanding in recent years of the importance of vitamin A in many extraocular processes (section 4.1.2), it may be expected that the attention given to aspects of vitamin A deficiency in other conditions than xerophthalmia will increase in the future.

2. RECENT ADVANCES IN THE BIOCHEMISTRY OF VITAMIN A AND CAROTENOIDS

2.1 The liver

After absorption, vitamin A (in the form of retinol esters associated with lymph chylomicrons) is almost entirely removed from the circulation by the liver. Hydrolysis takes place there, followed by re-esterification, mainly as palmitate. Most of the liver vitamin A is in the form of retinol ester and this is considered to be the storage form. Prior to mobilization, hydrolysis again takes place. Retinol palmitate hydrolase activity requires a bile salt for stimulation and shows an unusual subcellular distribution (5). It appears to be highly hydrophobic (6), which may be of considerable physiological importance.

The cellular site of vitamin A storage in the liver has received considerable attention recently. In an extensive review (7), convincing evidence is presented for the parasinusoidal stellate cell in the space of Disse (also called the Ito cell, lipocyte and storage cell) as the main site of storage under physiological conditions and in hypervitaminosis A when liver damage may result (8).

2.2 Control of retinol-binding protein (RBP) synthesis and release

In the hepatocyte, retinol, prior to release, forms a complex with retinol-binding protein (RBP), which is then known as holo-RBP. The precise subcellular locus of this interaction is not known (9).
After the secretion of holo-RBP into the plasma, it forms a complex with prealbumin which is secreted by the hepatocyte by an independently regulated process. Vitamin A deficiency blocks the secretion of RBP (10) and protein deficiency impairs its synthesis (11). A rise of plasma RBP in puberty and in seasonal breeding animals (12) suggests hormonal control at these times, but it is not known what affects the normal day-to-day synthesis and release of RBP.

2.3 Uptake of retinol by cells

Holo-RBP becomes attached to a specific receptor on the cell membrane, the retinol passing into the cell while the protein does not enter (13). The retinol released from bound RBP is presumed to diffuse across the cell membrane and is then bound by cellular retinol-binding protein (CRBP) (14), which differs from RBP, because its function is probably to transport retinol to its site of action within the cell. A cellular retinoic acid-binding protein (CRABP) has also been identified in a number of tissues (15), and a cellular retinaldehyde-binding protein has been isolated from the retina (16).

2.4 Vitamin A and glycoprotein synthesis

Vitamin A is necessary for the maintenance of normal differentiation and of mucus secretion of epithelial tissues. Glycoproteins are common constituents of membranes and are involved in a number of cellular functions which may be deranged in vitamin A deficiency. There is some evidence (17, 18) that mannosyl retinol phosphate may be an intermediate for specific glycosylation reactions, but additional studies to support this possibility are required.

2.5 Retinoids and cancer

Retinoids (compounds, either natural or synthetic, with a vitamin A-like structure or activity) are known to affect cellular differentiation, especially in epithelial tissues. Retinol, retinoic acid and a large range of synthetic analogues have been studied with isolated cells in culture (in vitro organ culture systems) and in intact animals and have been shown to be effective in preventing experimentally induced cancer in a number of tissues (19). Clinical studies on the effects of 13-cis-retinoic acid on the recurrence of human bladder cancer have been initiated.
2.6 Carotenoid determination in foodstuffs

More than 400 carotenoids have been described to date and between 50 and 60 of these are provitamin A carotenoids and apocarotenals (20). Some vegetables and fruits are the main dietary sources of provitamin A, the concentration varying with the species, the degree of maturation, storage conditions, and many other factors. The provitamin A activity of different active carotenoids varies considerably, but is not known with any degree of accuracy. It is customary to assume that 1 μg of retinol is equivalent to 6 μg of β-carotene and to 12 μg of mixed dietary carotenoids, and to express the total vitamin A activity in a diet in terms of retinol equivalents by applying these factors (21).

The recent application of reverse-phase high-pressure liquid chromatography (HPLC) for the separation of β-carotene, α-carotene, and lycopene from unidentified xanthophylls (22) has shown that previous methods, like the one used by the Association of Official Analytical Chemists (AOAC), resulted in considerable errors in the estimation of provitamin A activity. This study shows that only 7% of the “carotene” value in tomatoes estimated by the AOAC method was actually β-carotene or provitamin A. In another instance, the AOAC method overestimated the provitamin A content by tenfold. HPLC has also been applied to the determination of carotenoids in other fruits and vegetables (23).

In view of the fact that the long-term solution to the problem of vitamin A deficiency lies in the consumption of an adequate intake of provitamin A, more accurate estimates of the provitamin A activity of the major food sources throughout the world should be made.

3. INTERRELATIONSHIPS OF VITAMIN A DEFICIENCY, PROTEIN-ENERGY MALNUTRITION AND INFECTIONS

3.1 Vitamin A deficiency and PEM

It has long been recognized that vitamin A deficiency does not occur as an isolated problem, but is almost invariably accompanied by protein-energy malnutrition (PEM) and infections (I). Some recent studies have contributed towards a better understanding of the nature of these complex interrelationships, but certain aspects remain to be elucidated.
3.1.1 Absorption of preformed vitamin A and β-carotene

With a single oral dose of 900 μg of retinol palmitate and trace amounts of labelled vitamin, absorption was 95% in normal children and only a little less (90%) in children with kwashiorkor without active infection (24). Several studies have shown that small amounts of β-carotene are, in general, well absorbed by malnourished children, but additional fat in the diet considerably enhances carotene absorption (25).

3.1.2 Retinol transport in plasma

In kwashiorkor, low plasma retinol is associated with low RBP and prealbumin, and all components increase after a diet high in protein and energy but without added vitamin A (26). Low levels of retinol and RBP in plasma have been reported (27) to increase after giving vitamin A in man, which was also the case in experimental animals.

3.2 Vitamin A deficiency and infections

3.2.1 Vitamin A deficiency and the immune response

Although many aspects of the immune response have been shown to be depressed in experimental animals that had been made vitamin A deficient, the few preliminary reports in children are conflicting. This is probably related to the complexity of both the deficiency state and the immune response. The leukocyte lysozyme content was reported to be low (28); T lymphocytes were decreased in number but the response to phytohaemagglutinin (PHA) was normal (29); the phagocytic and bactericidal activity of the leukocytes was depressed, but the number of B lymphocytes, the immunoglobulin levels and the antibody titres following immunization were all normal (30). Brown et al. (31) reported no enhancement of antibody response to tetanus toxoid and to intradermal tests with tuberculin and *Monilia* extract, following the intramuscular injection of 110 mg (200 000 IU) of water-miscible retinol palmitate in children with low vitamin A status.¹

¹ The International Units (IU) for vitamin A and provitamin A were discontinued in 1954 and 1956 respectively. Owing to their continuing use, however, particularly in the labelling of capsules and injectable preparations, all intakes and dosages mentioned in this report are expressed both in micrograms (μg) or milligrams (mg) and in the former international units.
3.2.2 Association of vitamin A deficiency and infections

The frequent occurrence of a variety of common infections in children with xerophthalmia is well known (32) and a seasonal association has been observed (33, 34). In Indonesia (35, 36), it was found that children with xerophthalmia (in various stages) more frequently had a recent history of diarrhoea, respiratory disease, and passing of worms than their matched healthy controls. It is not entirely clear that the association is with vitamin A deficiency as such, since PEM is also usually accompanied by infections. In two studies of children suffering from severe PEM with or without xerophthalmia (37, 38), the infection rates did not differ significantly. Brown et al. (38) found significantly more bacteriuria in those with xerophthalmia but suggest that this may be a consequence of the known keratinizing effect of vitamin A deficiency on the urinary tract epithelia.

Many organisms have been identified in bacterial cultures of conjunctival and corneal swabs and scrapings (36). Potentially the most pathogenic organisms are Pseudomonas, coagulase-positive Staphylococcus aureus and Escherichia coli, but in this study there was no significant difference in the presence of positive cultures between normal and abnormal corneas, nor between ulcerated and nonulcerated eyes in the same patient. There is at present no convincing evidence to link any specific organism with the characteristic eye changes of xerophthalmia.

3.2.3 Effects of infections on vitamin A status

3.2.3.1 Absorption of vitamin A. Numerous studies have shown that a variety of infections impair absorption. Although inadequate intake of vitamin A is of primary importance in the development of deficiency, malabsorption is probably a major contributory factor that has to be considered when control measures are undertaken.

Malabsorption of vitamin A has been demonstrated in acute gastro-enteritis (39), ascariasis in adults (40) and children (41), giardiasis (42), severe hookworm infestation (43), and salmonellosis and schistosomiasis (44). Although vitamin A absorption is also impaired in children with respiratory infections (39), the mechanism is unclear. Vitamin A absorption studies in adults who had been infected with a variety of potential enteric pathogens gave results that varied with the agent and the severity of symptoms (45).
It has recently been shown that periods of steatorrhoea frequently follow acute attacks of even mild diarrhoea (46, 47). This could affect vitamin A absorption. However, adequate amounts of vitamin A in oral therapeutic doses are absorbed even by children with PEM, infections, and xerophthalmia, and in these circumstances the oral route has been shown to be as effective as intramuscular injection (48).

3.2.3.2 Retinol and RBP plasma concentration. There are numerous reports of a fall in plasma vitamin A concentration during febrile illnesses of various kinds, with a return towards normal during convalescence. Smith & Goodman (49) reported that vitamin A, retinol-binding protein (RBP) and prealbumin were markedly decreased during acute hepatitis, with increases as the disease improved.

Common childhood infections (such as diarrhoeal disease, upper respiratory infection, bronchitis and chickenpox) were associated with a fall in plasma vitamin A (retinol) of 0.35–1.05 μmol/l (10–30 μg/dl), as well as depression of RBP (50). In malnourished children with pre-existing low plasma vitamin A, this might lead to the precipitation of xerophthalmia.

3.2.3.3 Measles. Measles deserves separate consideration on several counts which have been reviewed recently (51). It tends to take an especially severe form in the child with PEM in whom immunocompetence is markedly impaired. Even in mild cases there is viral infection of the cornea, which is unique to measles among the common childhood infections. In the presence of vitamin A deficiency, such infection may facilitate the changes that lead to liquefaction.

Many reports from Africa document the serious nature of measles and the frequency of keratoconjunctivitis leading to blindness. In some of these, vitamin A deficiency has been recognized as a contributory factor but in others this has not been investigated. In a recent report from the north of Nigeria of 70 cases of measles-related corneal destruction seen in one year (52), herpes simplex virus was identified in a substantial proportion.

There is little information on involvement of the eye in measles in other developing regions. It is considered to be infrequent in India (53). In Indonesia (35, 36) a high proportion of blindness due to corneal destruction was associated with measles. Serum vitamin A was found to be extremely low in patients with active corneal disease and measles, in whom this was measured. There is clearly need for a thorough investigation of this important interrelationship.
A. CONJUNCTIVAL XEROSIS (X1A) *

Conjunctival xerosis in a 4-year-old child (Case No. 18121). Wrinkling and dryness can be seen in the lower part of the bulbar conjunctiva. Note especially that xerosis is not a conspicuous change; it is difficult to observe and to reproduce photographically. Plasma vitamin A: 9 µg/100 ml; liver vitamin A: 10 µg/g. Reproduced by courtesy of Dr D. S. McLaren.

B. BITOT'S SPOT (X1B) *

Numerous flakes of Bitot's spot material on the exposed part of the conjunctiva in a child aged 2 years (Case No. 15127). Plasma vitamin A: 8 µg/100 ml. It is important to be able to identify the less pronounced type of lesion shown here. For more classical examples, see McLaren et al (54). Reproduced by courtesy of Dr D. S. McLaren.
A. BITOT'S SPOT (X1B) WITH CONJUNCTIVAL XEROSIS

* Early Bitot's spot, the foam covering a patch of mild conjunctival xerosis. Five-year-old Indonesian boy with a 6-month history of night blindness. Reproduced by courtesy of Dr A. Sommer.

B. CONJUNCTIVAL AND CORNEAL XEROSIS (X2)

* Conjunctival and early corneal xerosis in a 2-year-old Indonesian boy. Both the conjunctiva and cornea have a coarse, dry, granular appearance in place of their normally smooth, shiny luster. Reproduced by courtesy of Dr A. Sommer.
A. CORNEAL ULCERATION (X3A) WITH XEROSIS

Marked conjunctival thickening and wrinkling and infiltration of the cornea with vascularization. Early ulceration is present. Child aged 2 years 3 months (Case No. 15437). Plasma vitamin A: 3 μg/100 ml; liver vitamin A: 0.0 μg/g. For a more pronounced example of X3A, see McLaren et al (54). Reproduced by courtesy of Dr D. S. McLaren.

B. KERATOMALACIA (X3B)

Child aged 14 months with colliquative necrosis affecting the greater part of the cornea (Case No. 17937). The relative sparing of the superior aspect is typical. Plasma vitamin A: 4 μg/100 ml; liver vitamin A: 3 μg/g. Reproduced by courtesy of Dr D. S. McLaren.
A. XEROPHTHALMIC FUNDUS (XF)*

* Fundus photograph showing typical seed-like, raised, whitish lesions scattered rather uniformly over the part of the fundus at the level of the optic disc. Reproduced by courtesy of Dr A. Sommer.

B. CORNEAL SCARS (XS)*

* Corneal scars (leucomata) of uncertain nature; their bilateral symmetry in a young malnourished child in an inferior position on the cornea is very suggestive of previous xerophthalmia. Reproduced by courtesy of Dr D. S. McLaren.
4. ASSESSMENT OF VITAMIN A STATUS

4.1 Clinical signs

4.1.1 Ocular signs

The xerophthalmia classification, introduced in the previous report (1), was modified at the present meeting in the light of subsequent experience (Table 1). The previous division into primary and second-

<table>
<thead>
<tr>
<th>Table 1. New xerophthalmia classification by ocular signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night blindness (XN)</td>
</tr>
<tr>
<td>Conjunctival xerosis (X1A)</td>
</tr>
<tr>
<td>Bilot's spot (X1B)</td>
</tr>
<tr>
<td>Corneal xerosis (X2)</td>
</tr>
<tr>
<td>Corneal ulceration/keratomalacia &lt; 1/2 corneal surface (X3A)</td>
</tr>
<tr>
<td>Corneal ulceration/keratomalacia ≥ 1/2 corneal surface (X3B)</td>
</tr>
<tr>
<td>Corneal scar (XS)</td>
</tr>
<tr>
<td>Xerophthalmic fundus (XF)</td>
</tr>
</tbody>
</table>

ary signs was considered unnecessary and was abolished. The division of X3 into X3A and X3B was modified to relate more closely to the degree of damage and the ultimate prognosis for vision. The ocular lesions have been pictured in colour in numerous publications (1, 36, 54, 55).

Night blindness (XN) in children, which has to be elicited by detailed history-taking from a guardian or relative, was shown in a study in Indonesia (56) to be a useful screening tool for xerophthalmia in that it correlated closely with other evidence of vitamin A deficiency. The serum levels of vitamin A were determined in 325 children who had xerphthalmic lesions of the conjunctiva or a history of night blindness. As shown in Table 2, twice as many had a history of night blindness, with or without conjunctival lesions, as had conjunctival lesions, with or without a history of night blindness. The mean serum levels of vitamin A (Table 3) and the proportion of cases with “adequate” levels of vitamin A were slightly higher among children with isolated night blindness than among children with either isolated conjunctival lesions or a combination of the two (P < 0.05 by
Table 2. Night blindness and Bitot’s spot as independent screening criteria for xerophthalmia

<table>
<thead>
<tr>
<th>Clinical statusa</th>
<th>No. of cases</th>
<th>Mean serum vitamin A in µmol/l</th>
<th>Standard error</th>
<th>Proportion of total number of cases identified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XN</td>
<td>273</td>
<td>0.47 (13.4)</td>
<td>0.35</td>
<td>84</td>
</tr>
<tr>
<td>X1B</td>
<td>132</td>
<td>0.44 (12.6)</td>
<td>0.46</td>
<td>41</td>
</tr>
<tr>
<td>XN and/or X1B</td>
<td>325</td>
<td>0.47 (13.4)</td>
<td>0.31</td>
<td>100</td>
</tr>
</tbody>
</table>

a Based on data from A. Sommer et al. (56).
b XN includes cases with and without conjunctival xerosis (X1A), Bitot’s spots, or X1B.
c X1B includes cases with and without night blindness (XN).

Serum vitamin A values were not available for 3 of the 273 cases of night blindness (XN), 2 of the 132 cases of conjunctival xerosis with Bitot’s spots (X1B), and 4 of the 325 cases with either.

Table 3. Serum vitamin A level by clinical status

<table>
<thead>
<tr>
<th>Clinical statusb</th>
<th>No. of cases</th>
<th>Mean (µg/dl)</th>
<th>Deficient (&lt;10 µg/dl) (µmol/l)</th>
<th>Low (10-20 µg/dl) (0.35-0.7 µmol/l)</th>
<th>Adequate (&gt;20 µg/dl) (&gt;0.7 µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XN(+), X1B(−)</td>
<td>174</td>
<td>13.9</td>
<td>27</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>Controls</td>
<td>161</td>
<td>17.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XN(−), X1B(+)</td>
<td>51</td>
<td>13.4</td>
<td>31</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Controls</td>
<td>45</td>
<td>17.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XN(+), X1B(+)</td>
<td>79</td>
<td>12.1</td>
<td>38</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Controls</td>
<td>76</td>
<td>18.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sample</td>
<td>268</td>
<td>20.0</td>
<td>9</td>
<td>36</td>
<td>53</td>
</tr>
</tbody>
</table>

b Based on data from A. Sommer et al. (56).
c XN = night blindness; X1B = conjunctival xerosis with Bitot’s spot; XN(−), X1B(+) = XN and X1B coexist in the same child. The mean serum vitamin A level and the proportion of cases with “adequate” levels were higher in the less severe lesion XN(−), X1B(+) > XN(−), X1B(+) > XN(+), X1B(+/−). P <0.05 by linear trend.

linear trend). The serum levels of vitamin A among normal, matched controls in the neighbourhood and those in a random subsample were substantially higher. The value of this method will depend upon the care with which questions are presented and answers sought, and upon the degree to which the phenomenon of night blindness is recognized by a community.

Conjunctival xerosis (X1A) consists of one or more patches of dry, nonwettable conjunctiva, which has been well described as “emerging like sand banks at receding tide” when the child ceases to cry. Usually best seen on oblique illumination, these patches almost
always involve the interpalpebral area of the temporal quadrants and often the nasal quadrants as well. In more advanced disease the entire bulbar conjunctiva may be affected. In exceptional cases, advanced corneal changes may develop very rapidly, without being accompanied by conjunctival xerosis. Typical xerosis may be associated with various degrees of conjunctival thickening, wrinkling and pigmentation. These latter signs are, however, poorly reproducible, highly variable, and nonspecific. They should not be used in isolation in making a diagnosis of conjunctival xerosis, as has sometimes been done in the past.

Bitot's spot (X1B) is no more than an extension of the same xerotic process as in the X1A cases. For clinical purposes it is considered useful to record the stages separately (as X1A or X1B), but to record only X1B in prevalence field surveys in order to avoid over-diagnosis from the inclusion of doubtful cases with minimal degrees of conjunctival xerosis (X1A). Lesions of identical appearance are sometimes found in individuals in whom the vitamin A status is normal. The subjects are usually older children or young adults and the lesions do not respond to vitamin A. Some of these lesions are probably sequelae of old, corrected vitamin A deficiency, though some other factors may be important. Although the only definite way of distinguishing between these two types of Bitot's spot is by their response to therapy, other, more immediate, clues exist. Thus, when Bitot's spot or classical conjunctival xerosis occurs in both the nasal and temporal sides or when night blindness is present, the lesions are almost certainly associated with active vitamin A deficiency (57). Not in all active cases are lesions present on both the nasal and temporal sides of the cornea, or is it recognized that dark adaptation is impaired; so the presence of these clues is far more helpful than their absence.

The characteristics of conjunctival xerosis and Bitot's spots that are responsive and unresponsive to vitamin A have been considerably clarified in a recent study (57). The responsive lesions almost invariably began to disappear within one week after treatment was commenced (Table 4). Lissamine green or rose Bengal staining, which was advocated for identification of early conjunctival xerosis (58), has been shown in subsequent studies (59, 60, 61) to lack both specificity and sensitivity and is not recommended.

The earliest change in the cornea is punctate keratopathy which begins in the lower nasal quadrant (62). It is present, on slit-lamp examination of the fluorescein-stained eye, in a majority of children with night blindness and/or conjunctival xerosis whose corneas appear normal on headlight examination (Table 5).
Table 4. Speed of improvement in cases of conjunctival xerosis that responded to treatment\(^a\)

<table>
<thead>
<tr>
<th>No. of days since therapy</th>
<th>No. of cases examined(^b)</th>
<th>Cases improved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-4</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>5-7</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>8-14</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>15-21</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>22-31</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>32-62</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\) Based on data from A. Sommer et al. (57).
\(^b\) Excludes cases already improved at an earlier examination.

Table 5. Fluorescein-positive punctate keratopathy\(^a\)

<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>Number of eyes</th>
<th>Percentage positive</th>
<th>Average extent(^b)</th>
<th>Average density(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>58</td>
<td>7</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>XN: history positive,</td>
<td>18</td>
<td>22</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>exam. negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XN: history positive,</td>
<td>10</td>
<td>60</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>exam. positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X1A, 1B</td>
<td>63</td>
<td>75</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>X2</td>
<td>47</td>
<td>100</td>
<td>3.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

\(^a\) Based on data from A. Sommer et al. (62).
\(^b\) Graded: 1 = infero-nasal quadrant; 2 = inferior 1/2 of cornea; 3 = inferior 3/4 of cornea; 4 = entire corneal surface.
\(^c\) Graded: 1 = mild; 2 = moderate; 3 = heavy.

Corneal xerosis (X2) is present once haziness and/or a granular, pebbly dryness are apparent on routine headlight examination. These changes begin in the inferior portion of the eye and denote increased density and extent of punctate keratopathy and accompanying stromal oedema (63).

Stromal defects take several forms (63). Small (1–3 mm) “ulcers” occur peripherally; they are characteristically circular, with steep margins and are sharply demarcated, as if a cork borer had been applied to the cornea. Large “ulcers” and areas of necrosis may extend centrally or involve the entire cornea. If appropriate therapy is immediately instituted, stromal defects involving less than one-third of the corneal surface (X3A) usually heal, leaving some useful vision; larger stromal defects (X3B) commonly result in blindness.

Vitamin A is necessary for photopic and colour vision as well as scotopic vision. Attention has recently been drawn to the possibility of using the detection of impairment of hue discrimination as a screening test in the field and this merits further investigation.
4.1.2 *Extraocular effects*

It has long been recognized that anorexia and growth retardation are early signs of vitamin A deficiency in experimental animals. In children with inadequate vitamin A status, accompanying infections and other deficiencies also impair the appetite and retard growth, and have hitherto precluded the demonstration of such an effect of vitamin A deficiency *per se*. Follicular hyperkeratosis has been observed in depletion studies on adults (65), but it is a nonspecific sign and rare in young children. In this study, abnormalities were also observed in taste, smell, vestibular function and cerebrospinal fluid pressure; these have been well documented in experimental animals. Sterility, congenital malformations and other disturbances of the reproductive system have hitherto been substantiated in experimental animals and not in man. Anaemia is frequently associated with vitamin A deficiency in human populations, and animal studies suggest that there may be a disturbance of iron metabolism (66). Impairment of the immune response and increased susceptibility to infection have been previously discussed (see sections 3.2.1 and 3.2.2).

4.2 *Biochemical data*

The methods for the determination of vitamin A (retinol) and retinol-binding protein (RBP) levels and the interpretation of vitamin A concentrations in plasma and liver were discussed in the previous report (7). Since then, high-pressure liquid chromatography (HPLC) has been introduced and shown to be an accurate, rapid and reproducible method for the estimation separately of vitamin A compounds; it is likely to become the method of choice.

Plasma vitamin A values in excess of 0.7 μmol/l (20 μg/dl) are not associated with the deficiency state, but the lower the value is below 0.7 μmol/l the more severe is the deficiency (7). Plasma values in excess of 1.75 μmol/l (50 μg/dl) have frequently been reported in healthy adults (64). There is no clear evidence as to what plasma values are indicative of hypervitaminosis A, but they are probably in excess of 3.5 μmol/l (100 μg/dl).

Determination of vitamin A concentration in autopsy liver samples has recently received attention as a method of assessing the vitamin A status of a population. There is considerable variation in the values obtained from different sites (67). With an appropriate sampling technique, a single sample may be used for assessing the vitamin A status (68).
As part of a preliminary assessment of the vitamin A status of a population (see section 4.4), the determination of vitamin A concentration in autopsy liver material may yield valuable information. A vitamin A deficiency problem of public health magnitude may exist where 5% or more of such samples from 1–5-year-old children have a vitamin A (retinol palmitate) concentration of below 5 μg/g fresh liver. Autopsy liver samples have been used as part of the evaluation of a vitamin A fortification programme (see page 43).

Recently an indirect approach to the assessment of liver retinol concentration, by observing the response of plasma retinol to oral doses of retinol acetate in experimental animals, has been proposed (69) and evaluation in humans is under consideration.

4.3 Dietary data

The techniques in general use for the estimation of dietary intake of vitamin A and carotenoids have not changed since the previous report (1). It is extremely difficult and time-consuming to determine the intake of individual young children. Although a clustering effect of vitamin A deficiency has been demonstrated within families and communities (56, 70), household consumption data do not necessarily reflect the intake of the young child. Other difficulties arise from (1) methodological inaccuracies in the chemical determination of carotenoids, and (2) differences between the content of vitamin A and carotenoids in the foods actually ingested and the values given in food composition tables.

4.4 Preliminary assessment

When it is suspected that a vitamin A deficiency or xerophthalmia problem may exist in a region, information of a qualitative and preliminary nature should be obtained before starting on a prevalence survey, which will require considerable effort, expertise and expense. Such information may be obtained by local personnel from existing records of household food consumption data, nutritional surveys, hospital admissions and clinic attendances. If these data suggest the existence of a problem, more information may be obtained through the planned visit of a consultant. The consultant can collate and evaluate the existing data and obtain additional information by discussions with health personnel and visits to hospitals and clinics in the region. Further collection of appropriate data in relation to the
occurrence of eye signs of xerophthalmia and dietary intake of vitamin A, and where possible the collection of autopsy liver material for vitamin A analysis as previously mentioned (section 4.2), may be instituted on a continuing basis. It is also important to assess the potential support from lay officials and decision-makers.

### 4.5 Prevalence surveys

Regional or countrywide probability surveys are the only unbiased means of determining the frequency (prevalence) and severity of vitamin A deficiency and xerophthalmia in a population. These surveys should include both clinical and biochemical determinations, whenever possible. Due attention must be paid to the statistical aspects of choice of sample size, sites and season, the training and supervision of personnel, logistics of field activities, and the methods of data analysis (2, 55).

### 4.6 Prevalence criteria determining a vitamin A deficiency or xerophthalmia problem of public health significance

The previous report (1) suggested certain prevalence criteria indicative of significant vitamin A deficiency or a xerophthalmia problem among the “at-risk” group of children aged 0–5 years. These criteria were then applied in a number of countries (35, 36, 71–73). As the reference rates of active corneal disease (X2 + X3A + X3B) correlated with much lower prevalence rates of Bitot’s spot (X1B) and corneal scar (XS) than originally anticipated (35, 36), the new criteria relating to the latter have been reduced accordingly (Table 6). Since a properly elicited history of night blindness (XN) in preschool-age children has been found to be reasonably specific in indicating active vitamin A deficiency (see pages 13–14), it has been added to the prevalence criteria (Table 6). In accordance with Indonesian (56) and other data, the overall prevalence criterion for night blindness (among preschool-age children, with or without other signs of xerophthalmia) has been fixed at 1% or twice that for Bitot’s spot.

In a vulnerable population, the presence of any one of the above four clinical criteria should be considered as evidence of a xerophthalmia problem. The biochemical criterion (plasma vitamin A level of less than 100 μg/litre in more than 5% of the population at risk) indicates significant vitamin A deficiency and may be used alone if
the objective is to improve vitamin A status. The value of having corroborative evidence from more than one indicator must be stressed.

Bitot’s spots that are unrelated to active vitamin A deficiency usually occur in older children and young adults, and their exclusion on the basis of age from the study population will ensure as far as possible that all lesions recorded are Bitot’s spots (X1B) due to vitamin A deficiency.

The specificity of night blindness (XN) is increased if local terms for the condition are available and are used during history-taking (see page 13).

Corneal scar (XS), with the required characteristics, differs in significance from the other clinical criteria. It is indicative not of active vitamin A deficiency, but of a deficiency some time in the past.

### 4.7 Surveillance

Surveillance is an activity of periodic (or continuous) collection and analysis of data that provide information on changes in the epidemiological characteristics and magnitude of a problem and on those factors that influence it (74). Surveillance is necessary for the management and evaluation of an intervention programme, and should be initiated before launching the programme.

Surveillance will ideally be based on a prevalence survey, conducted as previously mentioned (section 4.5). The complexity and cost of such surveys militate against their being repeated at frequent intervals. One approach is to select a limited number of “sentinel” clinics, located in areas in which xerophthalmia is known to be a serious problem. Simplified reporting procedures have also been drawn up (55).
5. GLOBAL OCCURRENCE OF VITAMIN A DEFICIENCY AND XEROPHTHALMIA

The worldwide situation in the early 1970s was reviewed in the previous report (1). At that time, the estimated annual incidence of cases of xerophthalmia blindness throughout the world was 100 000, based on a WHO global survey (32) and a detailed notification system in Jordan (75).

Since then, surveys have been conducted in several countries, most notably the nationwide prevalence survey in populous Indonesia (35, 36). On the basis of this last survey, an estimate of 250 000 cases as the annual incidence of xerophthalmia blindness in four major Asian countries has been made (76); the figure for noncorneal xerophthalmia is much higher: 8–9 million. As these estimated figures do not take account of the quite unknown number of cases occurring in other countries, they may be taken as a conservative estimate on a global basis. Despite the tentative nature of these estimates and the numerous gaps in knowledge, it may be noted that the information now available on the global occurrence of xerophthalmia is more precise than that for any other nutritional disease.

In 1976 a map was published (77), based on a list of 73 countries and territories where vitamin A deficiency was considered to be a public health problem. Since the previous report (1) was written, reports from a number of countries have been published that provide a more detailed, although still far from complete, picture of the global occurrence of the problem. In some of the countries where it is already recognized that a serious problem exists, efforts have been concentrated on control measures and these are referred to below (see section 7.2).

5.1 Asia

5.1.1 Bangladesh

The Blindness Prevention Programme, in operation since 1973, has recently estimated that at least 17 000 children aged 0–6 years go blind every year from xerophthalmia.

5.1.2 China

Very little information has been available outside the country concerning this problem since 1948. Dr Cheng Hu (Department of

21
Table 7. Vitamin A deficiency in China

<table>
<thead>
<tr>
<th>Location</th>
<th>Author</th>
<th>Year</th>
<th>Total No. of persons examined</th>
<th>Vitamin A deficiency (%)</th>
<th>Blindness due to vitamin A deficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shanghai</td>
<td>Chen</td>
<td>1946-49</td>
<td>14,347(^a)</td>
<td>0.20</td>
<td>2.22</td>
</tr>
<tr>
<td>Tianjin</td>
<td>Yan</td>
<td>1947-48</td>
<td>7,925(^a)</td>
<td>0.45</td>
<td>2.9</td>
</tr>
<tr>
<td>Hankou</td>
<td>Sun</td>
<td>1946-51</td>
<td>3,344(^a)</td>
<td>1.45</td>
<td>6.21</td>
</tr>
<tr>
<td>Xiamen (Amoy)</td>
<td>Wei</td>
<td>1945-51</td>
<td>3,822(^a)</td>
<td>0.44</td>
<td>2.25</td>
</tr>
<tr>
<td>Chengdu</td>
<td>Xu</td>
<td>1949-51</td>
<td>–</td>
<td>–</td>
<td>7.8</td>
</tr>
<tr>
<td>Beijing</td>
<td>Liu</td>
<td>1949-52</td>
<td>21,526(^a)</td>
<td>0.83</td>
<td>8.57</td>
</tr>
<tr>
<td>Guangzhou</td>
<td>Tu</td>
<td>1949-52</td>
<td>11,776(^a)</td>
<td>0.67</td>
<td>8.76</td>
</tr>
<tr>
<td>Sian</td>
<td>Ren</td>
<td>1953</td>
<td>2,650(^a)</td>
<td>0.60</td>
<td>3.56</td>
</tr>
<tr>
<td>Shanxi</td>
<td>Medical College</td>
<td>1953-54</td>
<td>11,480(^a)</td>
<td>0.17</td>
<td>1.10</td>
</tr>
<tr>
<td>Changchun</td>
<td>Chang</td>
<td>1953-54</td>
<td>24,943(^a)</td>
<td>0.09</td>
<td>1.30</td>
</tr>
<tr>
<td>Canzhou</td>
<td>Li</td>
<td>1954-55</td>
<td>1,654(^b)</td>
<td>0.15</td>
<td>3.90</td>
</tr>
<tr>
<td>Jinlin</td>
<td>Dang</td>
<td>1954</td>
<td>2,123(^a)</td>
<td>4.71</td>
<td>6.50</td>
</tr>
<tr>
<td>Jilin</td>
<td>Sun</td>
<td>1951-55</td>
<td>19,370(^a)</td>
<td>0.03</td>
<td>0.21</td>
</tr>
<tr>
<td>Shanghai</td>
<td>Lei</td>
<td>1953-57</td>
<td>201,645(^a)</td>
<td>0.14</td>
<td>1.25</td>
</tr>
<tr>
<td>Guilin</td>
<td>Guangxi Medical College</td>
<td>1951-56</td>
<td>9,291(^a)</td>
<td>1.68</td>
<td>5.86</td>
</tr>
<tr>
<td>Shanghai</td>
<td>Yang</td>
<td>1959</td>
<td>12,500(^b)</td>
<td>0.016</td>
<td>0.31</td>
</tr>
<tr>
<td>Inner Mongolia</td>
<td>Yang</td>
<td>1960-76</td>
<td>147,954(^b)</td>
<td>0.05</td>
<td>0.68</td>
</tr>
<tr>
<td>Henan</td>
<td>Henan Medical team</td>
<td>1963-64</td>
<td>3,817(^a)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Henan</td>
<td>Henan medical team</td>
<td>1974-79</td>
<td>213,725(^b)</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Shanxi</td>
<td>Shanxi Postgraduate School</td>
<td>1976-77</td>
<td>104,837(^b)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Dunhuang</td>
<td>Hu</td>
<td>1974-75</td>
<td>8,782(^b)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Anhui</td>
<td>Chan</td>
<td>1978</td>
<td>17,348(^b)</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Total number of patients seen in the outpatient department.  
\(^b\) Total number of persons screened in the region.

Ophthalmology, Capital Hospital, Chinese Academy of Medical Sciences, Beijing) was unable to attend the present meeting but prepared a table of information obtained from many parts of China over the past 30 years. This information is of considerable interest and is reproduced in full (Table 7). Dr Cheng Hu also reported that the disease often occurs in winter, when green vegetables are in short supply and the incidence of measles is high.

5.1.3 India

It has recently been estimated that among the 92 million children aged 1–5 years, 7.4 million have noncorneal and 0.22 million have corneal xerophthalmia at any one time (78). This particular author estimated that 52,500 children become blind and between 110,000 and 132,000 become partially blind in India every year. The prevalence of vitamin A deficiency is high in all states except the northern
Table 8. Point-prevalence rates of xerophthalmia in the ICDS (Integrated Child Development Scheme) survey in India, 1977a

<table>
<thead>
<tr>
<th>Projects grouped together</th>
<th>% of children with signs of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X1A</td>
</tr>
<tr>
<td>Urban slums</td>
<td>17.6</td>
</tr>
<tr>
<td>Tribal villages</td>
<td>12.0</td>
</tr>
<tr>
<td>Other villages</td>
<td>13.3</td>
</tr>
</tbody>
</table>

* Based on data from P. M. Shal. (78).

states of Haryana, Punjab, Himachal Pradesh, Jammu and Kashmir, and Delhi. The figures vary considerably within states, and the rates have been especially high in some of the remote tribal and rural areas that have been surveyed.

In general, data are lacking for urban slum areas, and it is to be noted that these sections of the populations are not covered at present by the national periodic dosing programme. The Integrated Child Development Scheme (ICDS) carried out a survey on 24,530 preschool-age children living in areas where the ICDS projects operate in 15 states. Although the point-prevalence figures shown in Table 8 are in no way representative of the country as a whole, since the ICDS projects focus on the more deprived areas, they do suggest a higher rate of serious lesions in urban slums and this requires further investigation.

5.1.4 Indonesia

Reference has already been made to some of the results obtained in the Nutritional Blindness Prevention Project (35, 36, 48, 56, 57, 61–63, 76). This project, based in Bandung, West Java, included a point-prevalence survey of more than 27,000 rural and 9,000 urban preschool-age children in more than 250 sample sites. In 11 out of 23 provinces, the criteria (given in the previous report (1, pp. 30–32)) for a public health problem were exceeded. In a longitudinal, prospective study, about 5000 rural preschool-age children were examined every 3 or 4 months for nearly 2 years. The risk of contracting corneal xerophthalmia before the fifth birthday was 2% and of noncorneal xerophthalmia was 52%, the former carrying a mortality of 50–80%. As would therefore be expected, the prevalence of corneal scars was negligible.
5.1.5 Sri Lanka

A survey of 13,450 children, aged 6 months to 6 years, revealed a public health problem, based on the above-mentioned criteria, in only 2 out of 15 health areas (79).

5.2 The Middle East

There is still a dearth of information from this region. It should be noted that xerophthalmia tends to be overlooked in countries such as those where communicable ophthalmia, particularly trachoma, is endemic (80).

5.3 Africa

Because of the lack of information from many parts of this region, WHO and USAID have jointly conducted preliminary assessments in collaboration with the governments of the following countries: Benin, Ethiopia, Malawi, Mali, Somalia, Sudan, United Republic of Cameroon, Upper Volta, and Zambia. Much useful background information has been provided in the reports of these preliminary assessments and it is possible here to present only a few salient details. Several general features emerge as being common to all the reports. Previously attention has mainly been focused on protein-energy malnutrition (PEM) and eye diseases other than xerophthalmia, and the signs of vitamin A deficiency are usually not recognized or recorded. Measles is widespread but its association with eye disease and possibly with vitamin A deficiency has been, with a few exceptions, neglected. Certain regions within countries have been identified as probably having a higher endemicity of vitamin A deficiency than others. An increasing awareness of the problem is apparent and where vitamin A deficiency has been identified, further assessment and control measures are being undertaken or planned.

5.3.1 Benin

Endemic areas have been identified in Atakora and Borgou provinces, where xerophthalmia associated with measles is the most common cause of blindness in preschool-age children. Night blindness is recognized by a local name and is especially common in the dry season. Surveillance, capsule distribution and health education measures are being planned.
5.3.2 Ethiopia

The Ethiopian Nutrition Institute, with the assistance of WHO, has conducted a countrywide preliminary assessment by collecting data for 1978–80 on background information and the reporting of xerophthalmia, measles and PEM in health centres and hospitals. Xerophthalmia was rarely recorded; measles was prevalent but only occasionally was reported to affect the eyes. Four ecozones were identified as areas of possible high risk. Nutritional surveillance (undertaken since 1975) has not included vitamin A status or xerophthalmia. It is planned to incorporate these and to carry out further assessment.

5.3.3 Kenya

Independently of the WHO/USAID-sponsored investigations mentioned above (section 5.3), an extensive study of the interrelationships of xerophthalmia and measles has been carried out (58).

5.3.4 Malawi

Previous investigations have suggested that there are about 5000 cases of corneal blindness in young children at any one time. Measles and vitamin A deficiency are recorded as the major causes. The highest endemicity appears to be in the Lower Shire. Night blindness is not generally recognized and there are no local names. Surveillance of xerophthalmia is proceeding in 12 out of 24 districts by trained ophthalmic medical assistants. There is limited distribution of fortified dried skim milk and capsules.

5.3.5 Mali

A preliminary assessment has been made with the assistance of WHO. Local vitamin A sources are limited and xerophthalmia is not generally recognized. Night blindness is endemic in the three regions of the country, especially in the dry season, and local names occur. Corneal scarring, attributed to measles, is common. There is sporadic capsule distribution. Surveillance does not at present include vitamin A status.
5.3.6 *Somalia*

With WHO assistance, a limited survey was carried out in Mogadishu and surrounding villages. There was little evidence of vitamin A deficiency as such, but there were a number of cases of corneal scarring that were attributed to measles.

5.3.7 *Sudan*

A limited assessment, with WHO assistance, was carried out in Khartoum and Gezira provinces and showed little evidence of vitamin A deficiency, although the latter area was highly endemic some 20 years ago. The situation in other provinces, where the nutritional status is poorer, is not known.

5.3.8 *United Republic of Cameroon*

A limited assessment by a USAID consultant ophthalmologist and nutritionist failed to produce any evidence of vitamin A deficiency in the country. Special emphasis was placed on the northern areas since preliminary visits to other regions of the country indicated that there was adequate vitamin A in the diet.

5.3.9 *Upper Volta*

Endemic areas are recognized in the Sahel zone and the zones of the north and centre of the country. Occasional cases of keratomalacia are recorded in hospitals, the ocular complications of measles are well recognized, and night blindness is common (especially in the dry season) and has local names. Local sources of vitamin A are scarce; UNICEF capsules are distributed sporadically.

5.3.10 *Zambia*

A high incidence of childhood blindness has for some time been recognized in Luapula province and has been attributed to a combination of measles, vitamin A deficiency and the use of local medicines. A preliminary assessment throughout the country, in 1980, revealed a high incidence of measles and PEM but a general lack of recognition of vitamin A deficiency. However, in one hospital alone in Luapula province, several hundred cases of keratomalacia, frequently associated with measles, are recorded annually. Capsule distribution is planned for 1981.
5.4 Latin America and the Caribbean

5.4.1 Brazil

In recent years there has been considerable interest in the problem of vitamin A deficiency, especially in the north-east of the country (81, 82). Autopsy liver vitamin A values have been shown to be very low in a significant proportion of the preschool-age children studied (83, 84).

5.4.2 Guatemala

Dietary intake and retinol concentrations in serum, breast milk, and liver have been monitored in the evaluation of the sugar fortification intervention (see section 7.2.2.1).

5.4.3 Haiti

A nationwide prevalence survey (72) revealed few active lesions. Corneal scars, which are considered to be related to a previous vitamin A deficiency, had a prevalence of 8.1/1000 in the north, indicating a problem of public health magnitude by the above-mentioned criteria, but only 1.2/1000 in the south. Capsule distribution, nutrition education, and surveillance have been instituted since the prevalence survey.

6. TREATMENT AND PROPHYLAXIS SCHEDULES

6.1 Treatment

The recommended treatment schedule, given overleaf, applies to all patients above the age of 1 year, with all stages of xerophthalmia. The schedule is designed not only to treat active vitamin A deficiency but also to increase the liver reserves.
Treatment schedule for xerophthalmia

Immediately on diagnosis: 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU) orally, or 55 mg retinol palmitate (100 000 IU) by intramuscular injection

The following day: 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU) orally

Prior to discharge, or if clinical deterioration occurs, or 2–4 weeks later: 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU) orally

Recommended preparations of vitamin A

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil-based solution of retinol palmitate or acetate, as capsules or liquid (with or without added vitamin E)</td>
<td>Oral</td>
<td>110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU)</td>
</tr>
<tr>
<td>Water-miscible retinol palmitate</td>
<td>Intramuscular</td>
<td>55 mg (100 000 IU)</td>
</tr>
</tbody>
</table>

Explanatory notes on the recommended treatment

(1) The intramuscular route, using a water-miscible preparation, is preferred when there is repeated vomiting or severe diarrhoea.
(2) Oil-based solutions of vitamin A should never be injected intramuscularly because the vitamin is liberated extremely slowly, if at all, from the injection site.
(3) The ocular condition may appear to worsen temporarily, even with adequate treatment, as the keratinized epithelium is sloughed off. A true failure of response to treatment should suggest a need to revise the diagnosis, provided that the dosage of vitamin A was adequate, an intramuscular injection of an oil-based solution had not been given, and there was no gross interference with RBP (retinol-binding protein) synthesis as may occur in kwashiorkor.
(4) Malnourished children with an eye condition suspected of being due to an infection which fails to respond to appropriate antibiotic therapy, or with measles, should receive appropriate treatment with vitamin A and other nutrients.
(5) The frequently differing degree of involvement of the two eyes often permits useful vision to be preserved in at least one eye.
(6) Underlying conditions such as PEM and other nutritional disorders, diarrhoea, dehydration and electrolyte imbalance, infections and parasitic infestations, and other conditions must be treated appropriately.
(7) All cases of PEM without obvious eye lesions, on admission, should be given vitamin A in a prophylactic oral dose of 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU); because of low reserves of this vitamin, xerophthalmia may be precipitated when growth is stimulated during recovery.

(8) Infants below 12 months of age should be given half the above-mentioned dosage.

6.2 Prophylaxis

Infants (under 12 months of age). 55 mg retinol palmitate or 33 mg retinol acetate (100 000 IU) as liquid or capsule at 6-monthly intervals. If the standard 200 000 IU capsule is used, it should be cut, the first two drops discarded and the remainder of the contents administered.

Older children. 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU) as standard capsule or as liquid, at 4–6-monthly intervals.

Pregnant women. Vitamin A, in doses above 10 000 IU/day, should not be given at any time during pregnancy. During the first trimester, teratogenic effects may result, according to strong animal (and suggestive human) evidence (85). In the second and third trimesters, there is the possibility of excessive transfer of vitamin A to the fetus.

Women who are considered to be vitamin A deficient may safely be given small frequent doses throughout pregnancy, not exceeding 10 000 IU daily. This is in accord with the IVACG guidelines on the safe use of vitamin A (85).

Women at and after delivery. A single oral dose at delivery has been shown (86) to be effective in significantly raising the vitamin A concentration in breast milk for 1 month or even longer; 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU) as capsule or liquid should be given at the time of delivery or once during the next four weeks.

Lactating women. Vitamin A in doses above 10 000 IU/day should not be administered prophylactically after the month following delivery. This is because a further conception may take place at any time during lactation and a large dose of vitamin A may damage the conceptus. Supplementation with high doses of vitamin A to the lactating mother at delivery or within four weeks of delivery (maternal channelled supplementation) will raise the level in breast milk for at least one month (86).
7. CONTROL OF VITAMIN A DEFICIENCY AND XEROPHTHALMIA

7.1 Introduction

Inadequate vitamin A status can vary from a marginal condition of inadequate body reserves of vitamin A without clinical signs, through the presence of early and reversible clinical signs, such as night blindness (XN) and conjunctival changes (X1A, X1B), to a severely depleted state mainly characterized by advanced corneal changes (X2, X3A, and X3B) with a high probability of blindness. A prevention programme can therefore be directed towards improving the vitamin A status of a population or controlling blindness that is causally related to vitamin A deficiency.

The objective selected at a given time in a given country will clearly depend on many factors, such as the severity of the problem, the availability of personnel, and technological and financial resources. The objective must be clearly defined because the methods used, the nature of the data collected, and the strategy employed will all depend on the goals that are set. Quantification of the objective is equally important; that is, collection of prevalence data prior to instituting a programme and definition of the minimal acceptable reduction in prevalence which is to be achieved by the programme.

If the objective selected is the prevention of xerophthalmia, the prevalence criteria (see Table 6) should ideally first have been satisfied for the area concerned. It is recognized that for various reasons this procedure has not always been, and will not always be, followed. It must be pointed out that in these circumstances it will be difficult to evaluate the effectiveness of the measures undertaken. These same criteria should be used, possibly in modified form (see section 4.6), in the evaluation of the programme.

If the objective is more broadly based (i.e., to improve the vitamin A status of target groups), the following must be taken into account: dietary intake, plasma and autopsy liver concentrations of vitamin A, night blindness and Bitot's spot (see sections 4.1, 4.2 and 4.3).

Several different strategies exist for controlling vitamin A deficiency and xerophthalmia; specific technical interventions, such as capsule distribution and fortification of widely consumed foodstuffs, and promotional activities, such as nutrition education through schools and communication media, encouraging the cultivation and use of
vitamin A and carotene-rich foods, and improving nutritional aspects of primary health care. In all such strategies, the training of personnel for their respective roles and the education of policy-makers are essential components.

There is no doubt that the ideal method for ensuring a population’s adequate intake of vitamin A is to make use of the locally available foods. It is nevertheless recognized that, where a vitamin A deficiency exists, such foods, even when frequently available, may not be utilized by the vulnerable groups and in some areas may be in short supply, especially at certain times of the year. When a problem of public health magnitude is identified, it is clearly inappropriate to rely solely on long-term promotional measures. In these circumstances it is necessary to adopt a short-term approach.

The most effective intervention results are obtained by a multi-strategy approach, combining both short-term and long-term programmes which usually reinforce each other. For example, the periodic dosing system (see below) provides an opportunity for direct contact with parents for nutrition education.

7.2 Vitamin A interventions

7.2.1 Periodic dosing

About 30–50% of a 200 000 IU dose of vitamin A (110 mg retinol palmitate or 66 mg retinol acetate) is stored by the body, and the protective period for a growing child has been calculated to be about 180 days. On this basis, periodic dosing programmes have been instituted in several countries where a problem of vitamin A deficiency of public health magnitude has been identified. Young children, usually between the ages of 1 and 5 years, have received an oral dose of 110 mg retinol palmitate or 66 mg retinol acetate (200 000 IU) vitamin A in oil at 3–6 monthly intervals. Besides the programmes discussed below, capsule distribution has also been undertaken on a limited scale in other countries, including El Salvador and parts of Brazil and Thailand.

A number of basic principles should be observed in any periodic dosing programme.

(1) The optimum is to aim at the widest, administratively feasible coverage of a population which is at greatest risk, and to do so at minimum cost and with maximum participation at the community level.
(2) Distribution systems should be designed and implemented with emphasis on primary level conditions, existing infrastructures and ongoing health activities, with the involvement of local leadership.

(3) Priority should be given to identified areas of highest prevalence of vitamin A deficiency.

(4) Education in health and nutrition should be an integral part of the periodic dosing programme.

(5) Plans for monitoring and for the evaluation of effectiveness should be built into the delivery system from the outset.

Three models of delivery system are suggested: medical, universal, and targeted. The medical (or therapeutic) system is appropriate as an initial measure in any endemic area, and provides vitamin A prophylactically (as part of their treatment) to all preschool-age children who are ill and come to hospitals, clinics and health centres, especially for those with diarrhoea, measles, marasmus and kwashiorkor.

In the universal (or prophylactic) system, all preschool-age children within a designated area receive a periodic dose of vitamin A at established intervals from field workers who are in some way related to the health network. This system is used in India, Bangladesh and Indonesia.

The targeted (prophylactic) system operates among young children who are identified as being especially at risk. The workers involved may be similar to those in the universal system but function in more highly structured circumstances and require more intensive training and supervision. The Haitian programme is an example of the targeted distribution system.

7.2.1.1 *India.* The National Vitamin A Prophylaxis Programme for the Prevention of Blindness in Children was initiated in 1970 after pilot studies at the National Institute of Nutrition in Hyderabad. Children aged 1–5 years receive at 6-monthly intervals 110 mg of retinol palmitate (200 000 IU) in 2 ml (one small teaspoonful) of a flavoured concentrate in arachis oil, which is supplied in 100-ml bottles.

The programme is planned and directed by the Directorate-General of Health Services. The maternal and child health and family welfare organization is responsible for the administration of the programme. At state level, the state nutrition officer is responsible for all logistics and for submitting accurate reports to the centre. The district health
and family planning officer is charged with transmitting vitamin A supplies to the field. In rural areas, the programme is implemented through the primary health centre and its subcentres under the supervision of medical officers of the primary health centre. The auxiliary nurse midwife (ANM) is responsible for administering the concentrate to children in the area covered by her. In the areas not so covered, lady health visitors (LHV) or family planning health assistants (FPHA) distribute the vitamin A concentrate.

The programme, which initially covered 1.6 million children in 7 states, has now been extended to all the states in the country. During 1979–80, about 25 million children living in rural areas were targeted to be covered by the programme.

An interim evaluation of the programme was carried out in the states of Karnataka and Kerala. The coverage was between 75% and 90% of the expected number of children. There was about 75% reduction in the prevalence of conjunctival signs of vitamin A deficiency in children who had received two doses of the vitamin. More recently an evaluation of the programme in 8 states has been carried out (87), using a method based on observed age trends of eye signs of vitamin A deficiency (88). In areas of high prevalence where this method was regarded as applicable, the programme was considered to have been effective in reducing vitamin A deficiency.

It has not hitherto proved possible to demonstrate an effect of periodic vitamin A dosing on the prevalence of the corneal lesions. A programme with this objective is being undertaken in Hyderabad city.

7.2.1.2 Bangladesh. The Bangladesh Blindness Prevention Programme was inaugurated in 1973 as a result of a WHO assessment and with substantial support from UNICEF. The programme's components include:
— periodic distribution of vitamin A capsules (200 000 IU) to preschool-age children;
— nutrition education aided by appropriate material (flip-books, posters, films and slides);
— supply of vitamin A capsules (200 000 IU) and injections (100 000 IU in water-miscible preparations) to hospitals and health centres for therapeutic administration to ill preschool-age children;
— training of health, medical and nutrition personnel in the detection, treatment and prevention of xerophthalmia.

The programme is a part of the Directorate of Health Services in
the Ministry of Health and functions through the rural health system; its operations are supervised by physicians in charge of the *thana* (part of an administrative subdivision) health complex at the *thana* level and through the infrastructure to the village level. The capsule distribution is carried out by between 12,000 and 14,000 multipurpose health workers, called family welfare workers (FWWs), who make house-to-house rounds every 6 weeks and distribute capsules on rounds every 6 months. In the past 8 years, 12 rounds of distributions have reached an estimated average of 62–65% of the target population.

There have been continuing assessments of the programme for coverage, efficiency, change in the disease rates, parents' knowledge regarding the purpose of the dose, etc. It is planned that a national joint prevalence survey will be carried out in 1981–82 to determine the current magnitude and distribution of the problem, the coverage of capsule distribution, characteristics of the children not receiving the capsules, dietary patterns, and other relevant information which will provide essential data for decisions concerning future intervention, directions and activities.

7.2.1.3 *Indonesia.* The distribution of capsules of 200,000 IU vitamin A at 6-monthly intervals to preschool-age children in 20 sub-districts was initially planned and directed by a Vitamin A Committee established by the Ministry of Health in 1972 for a pilot demonstration project. Evaluation of this project in its first 2 years of operations, while it showed a decrease in the early ocular signs of xerophthalmia, raised questions of an epidemiological nature. A comprehensive 3-year research programme was subsequently carried out and some of the findings are described in this report.

Intervention, planning and programme operations were initiated as the research findings emerged. The major components include massive-dose capsule distribution, nutrition education, training of health personnel, and exploration into the potential of fortification of monosodium glutamate (MSG) with vitamin A. This vitamin A programme is under the leadership and responsibility of the Nutrition Directorate of Community Health in the Ministry of Health.

Currently the distribution of capsules is carried out through four types of community outreach programmes:

1. The Special Vitamin A Distribution Programme is a vertical programme. Single-purpose volunteers distribute capsules twice a
year to children aged 1–6 years, under the supervision of the district health centre (Puskesmas).

(2) Usaha Perbaikan Gizi Keluarga (UPGK), which means family nutrition improvement effort, is a programme which includes weighing of children, distribution of oral rehydration salts (ORS) and iron tablets, nutrition education, and help with home and village gardens. Vitamin A capsules are distributed twice a year.

(3) A Nutrition Intervention Pilot Project (NIPP) has broadly-based nutrition activities, including distribution of first-aid packages to selected primary health workers in several districts in four provinces. These packages include vitamin A capsules for distribution every six months.

(4) The BKKBN, a family planning programme, is expanding to include a “nutrition package”, one of the components of which is the distribution of vitamin capsules.

These four distribution systems are carried out in separate geographical areas and attempts are under way to test them for efficiency and results, although the variety of modes of distribution presents problems for monitoring and supervision. To date, there has been no distribution of vitamin A in low-income urban areas although this is in the planning stage.

A surveillance system is being established in selected sentinel health centres, for which the first 100 health workers have been trained for recognition and recording of ocular disease signs. A strategy for the nutrition education component of the vitamin A programme has been designed and is being implemented with planned development and testing of educational materials at the village level. A national media campaign on this subject is also being organized.

A major research project is planned in a region of Indonesia which is already known to have a high prevalence of xerophthalmia in order to assess the impact of capsule distribution, food fortification and integrated health/nutrition/family planning programmes on blinding malnutrition. Additionally, the study will determine the level of reduction of blindness and whether it is proportionate to the degree of coverage of the programme.

7.2.1.4 Haiti. Following the national xerophthalmia survey in 1974–75, a capsule distribution programme was instituted to reach sick and malnourished children and lactating women. The vitamin A programme is directed from the Nutrition Bureau of the Ministry of Health and Population and functions through the rural health infra-
structure. Preschool-age children and lactating mothers, seen in the health centres (and through their outreach programmes), are given capsules at not more than 4–6-month intervals. Children enrolled in malnutrition centres are given doses every 4 months. The flow of capsules is through the health districts, where their distribution is supervised and reported. An evaluation after 2 years provided valuable information leading to modification of operations and reporting and indicated a reduction in the problem. However, the very low prevalence of corneal scars made interpretation of the results difficult. There has been a steady increase in the number of children contacted by the programme, but the most significant sign of progress has been the inclusion of vitamin distribution activities as a recognized function of health auxiliaries and centre personnel, as well as the intensive training of community and district-level health workers and nutrition workers.

7.2.1.5 Sri Lanka. Capsule distribution is proceeding in the 2 districts where the National Nutrition Pre-school Survey in 1975–76 revealed a problem, and in 4 others with marginal deficiency. It is planned that this should continue until all malnourished children at risk of xerophthalmia could receive regularly a fortified food supplement providing 366 μg retinol palmitate (665 IU) daily.

7.2.1.6 Philippines. In 12 barangays of Cebu province, the effects of three alternative strategies were monitored (89) for nearly 2 years. Two urban and 2 rural barangays received one of the following interventions: distribution of vitamin A capsules (200 000 IU) every 6 months; fortification of monosodium glutamate (MSG); or activities in health education, horticulture, and disease prevention. MSG fortification resulted in the greatest reduction in clinical signs and also gave the largest rise in serum vitamin A values.

7.2.1.7 Evaluation of periodic dosing. The comments that follow, which are based on the reports of investigators who have evaluated the vitamin A capsule periodic-dosing programmes, highlight the difficulties and defects encountered and are aimed at overcoming them in the future.

Dosage techniques. Both capsule and concentrate were found to be easy to administer and store under field conditions and had a long shelf-life. Problems of soiling of the health workers’ hands occurred if the capsule had to be cut to administer part of the contents to
infants. Scissors should be provided to cut the protruding end of the capsule when necessary. Capsules are not always administered personally by the health workers, and difficulties were encountered with swallowing. The concentrate used in India was rejected by some children and some mothers objected when the same spoon, without washing, was used for multiple dosing. In most programmes, children with diarrhoea and those judged to be ill were not dosed in order to avoid allegations that illness or death was caused by the vitamin A administered.

Dosage flow from source to consumer. In most countries except India (where locally produced liquid preparations are available), the procedure for procuring capsules is for the government to provide its own capsules or formally to request a specific supply from UNICEF or other agencies. Depletion of stocks may occur owing to insufficient notice being given by the management for processing requests and to administrative delays by both the government and donor agencies. Delay may also occur at the port of entry and during shipment within the country.

Irregularity of supplies has been one of the major obstacles in all the countries concerned. Inaccuracies in record-keeping cause further problems. Supplies often arrive at the periphery only a short time before the expiry date.

Delivery systems. Different approaches have been adopted in attempts to promote effective coverage of those at greatest risk, to ensure against repeated dosage at intervals less than that prescribed, and to make use of existing personnel and infrastructure. Distribution through clinics is less demanding of personnel, effort and time required, but distribution in homes reaches a wider group.

Data collection. Training in registration, recording and reporting has been carried out intensively but there are gaps in the system. For example, the rate of loss of family health cards is often high, the reasons why a child did not receive vitamin A are frequently not recorded, successive doses are received regularly only at the level of the field worker, poor maintenance of records is often a major weakness, and transmission of information is irregular. Consolidation of data at the centre is usually not made unless a special review is undertaken.

Supervision. This was very often limited and sporadic, mainly because of the large number of programmes to be supervised.

Training. Training of staff, both administrative and operational, has been undertaken on a multi-tier basis. Executives have been
trained at the national level, and supervisors for each district at the regional or state training centres. Functionaries/distributors and auxiliary personnel or field workers have been trained or reoriented in short courses at the local level. These personnel have frequently engaged in measures to inform the community with the use of supportive materials provided from the centre. Much of this effort has lacked impact owing to positions often remaining unfilled and to poor functional competence in those responsible.

*Evaluation.* In practice, evaluation is only rarely an integral aspect of programme design but is carried out as an isolated activity at specific times. In several programmes, the efficacy of the programme in achieving coverage has been evaluated and in general a progressive fall in coverage has been recorded through successive cycles till it reaches a plateau.

The efficacy of a programme in achieving reduction of xerophthal-mia has been evaluated in several areas and its efficacy in reducing the prevalence of conjunctival signs has been demonstrated. Reduction in the prevalence of the much less frequent corneal lesions has not yet been demonstrated anywhere, although evaluation of at least one programme is under way (see section 7.2.1.1) and the need for other studies is recognized (section 8.2.5).

The efficiency of a programme in relation to workload and to the health workers' knowledge and that of the community served has been evaluated in several areas. These enquiries have revealed a considerable lack of efficiency in these respects, which is attributable to a variety of causes.

*Economic analysis.* The cost factor can be calculated for the materials, personnel and personnel training, programme support (transport, reporting, equipment and so forth), and for monitoring and evaluation.

Estimates of the cost of distributing a periodic dose have varied considerably, not so much because of the differences in the delivery systems, but because of the selection of items included in the cost estimates. For example, some estimates only include actual cash outlays for materials and services not already covered in current expenditure. An auxiliary health worker who is paid to make rounds of house visits once a month is not paid extra to give vitamin A capsules to children every 4 or 6 months during these visits.

Since cost is one of the major determinants in decisions concerning delivery system options, it is recommended that a standard budget schedule should be developed. This will serve as a guideline for
estimates, providing realistic figures, with a clear indication of the costs that require additional funding and those that have been reckoned in other ways (e.g., manpower hours, transport, travel, and other costs that are financed in integrated activities).

All-inclusive figures for the cost of a programme are always difficult, and may be impossible, to obtain if they are incorporated in governmental accounts. The figures for the pilot project in Indonesia for 1972–75 (Table 9) give some indication and work out at Rp 80.5 or US $0.19 per capsule administered at that time.

Table 9. Project operational costs in Indonesia, 1972–75, borne by the Government and by UNICEF

<table>
<thead>
<tr>
<th>Items</th>
<th>Central administration</th>
<th>Provincial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government of Indonesia:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incentives</td>
<td>4 395</td>
<td>20 598</td>
<td>24 993</td>
</tr>
<tr>
<td>Supplies</td>
<td>6 747</td>
<td>1 855</td>
<td>8 602</td>
</tr>
<tr>
<td>Equipment</td>
<td>642</td>
<td>602</td>
<td>1 244</td>
</tr>
<tr>
<td>Handling</td>
<td>843</td>
<td>2 277</td>
<td>3 120</td>
</tr>
<tr>
<td>Travel</td>
<td>2 048</td>
<td>2 222</td>
<td>4 270</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3 373</td>
<td>2 212</td>
<td>5 585</td>
</tr>
<tr>
<td>Total</td>
<td>17 406</td>
<td>29 766</td>
<td>47 172</td>
</tr>
<tr>
<td>UNICEF:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 bicycles for field workers</td>
<td></td>
<td>2 000</td>
<td></td>
</tr>
<tr>
<td>Purchase and shipment of capsules</td>
<td></td>
<td>5 134</td>
<td></td>
</tr>
<tr>
<td>UNICEF total</td>
<td></td>
<td>7 134</td>
<td></td>
</tr>
<tr>
<td>Grand total</td>
<td></td>
<td>54 305</td>
<td></td>
</tr>
</tbody>
</table>

7.2.2 Fortification

Fortification of foods with various nutrients has been practised extensively for a long time and the general principles, together with their application to the fortification of foodstuffs with vitamin A, were discussed in the previous report (*J*). A number of products, such as dairy products (including dried skim milk) and margarine, are customarily fortified with vitamin A and plans for the fortification of others, such as tea and salt, are under consideration.

At the present time, a sugar fortification programme in Central America has reached an advanced stage of implementation and evaluation in Guatemala. The fortification of monosodium glutamate (MSG) is being field-tested in the Philippines and is under consideration in Indonesia. Attention here will be focused on these three
programmes; and on the fortification of dried skim milk for use in food aid programmes.

7.2.2.1 *Sugar fortification in Central America.* This programme has been described in detail (90). Nutrition surveys, conducted in the 1960s in Central American countries, revealed a very inadequate intake of vitamin A-containing foods and serum retinol levels below 0.7 μmol/l (20 μg/dl) in a high proportion of rural children aged 0–9 years. In 1969, the Institute of Nutrition of Central America and Panama (INCAP) embarked on a research programme leading to a process for the fortification of a suitable dietary vehicle with vitamin A and the eventual implementation of national programmes in the Central American region.

White sugar (centrifuged washed (plantation white) or refined sugar) satisfied the necessary criteria on the basis of (1) little variation in day-to-day per capita consumption, (2) organoleptic characteristics and acceptability, (3) consumption by essentially the whole population, (4) the economic aspects, and (5) centralized production in a few technically well-equipped and administered factories. Brown sugar (*panela*) is also consumed but it was shown to be consumed at a much lower level than white sugar.

Laboratory and industrial-scale tests resulted in the development of a satisfactory and chemically stable premix by mixing 250-CWS (cold water soluble) water-dispersible retinol palmitate (Hoffman-La Roche) with sugar and a small amount of peanut oil by a process yielding a premix containing the equivalent of 15 mg retinol per gram (50 000 IU/g). The system used regulates the amount of premix added to the sugar and requires neither special equipment nor special personnel. A level of fortification equivalent to 15 μg of retinol (50 IU) per gram of sugar was chosen. An average teaspoonful of sugar (thus fortified) consumed per day provides an intake equivalent to about 120 μg retinol (400 IU). At this level of fortification there is no danger of excessive consumption of vitamin A.

This approach to the control of vitamin A deficiency in the population was strongly promoted among government and unofficial health-related agencies in Central America and, as a result, four countries—Costa Rica, Guatemala, Honduras, and Panama—passed laws to the effect that all sugar for home consumption should be fortified with vitamin A.

An evaluation programme was instituted in Guatemala immediately before the initiation of fortification at national level in 1975. The
first phase consisted of a survey of the vitamin A nutritional status and food consumption. Four follow-up surveys, of 2 months' duration, were carried out between April 1976 and November 1977 in 12 rural communities (with populations between 750 and 2000 inhabitants) representative of the rural areas of the country. Within each community, 30 families were randomly selected for study. The changes outlined below were attributed to the national programme of 2 years' duration. There was a computed extended average consumption of fortified sugar contributing 10 μg of retinol (33 IU) per gram consumed, because only two-thirds of the sugar was fortified.

Dietary aspects. The vitamin A intake from natural sources remained essentially unchanged but the consumption of fortified sugar significantly increased the overall intake (P < 0.001). By the end of the evaluation, the average intake of sugar by preschool-age children was 36 g per day, which was calculated to provide 360 μg of retinol

Fig. 1. Decrease in the percent of children with “deficient” serum retinol levels (80)

SURVEY PERIOD

1Figures in parentheses = total number of cases.

Inc: 79 19
(1200 IU) and is approximately the estimated average recommended daily intake (by INCAP) for children aged 1–9 years.

Biochemical estimations. The serum retinol value for rural preschool-age children (below 71 months old) was selected as the main indicator for evaluation. The results, presented in Fig. 1, showed a significant \( P < 0.001 \) decrease in the percentage of children with values less than 0.35 \( \mu \text{mol/l} \) (10 \( \mu \text{g/dl} \)) by the third survey which was thereafter maintained. The values for all the children obtained in 3 surveys between 1975 and 1977 are presented as distribution curves in Fig. 2. There is a highly significant \( P < 0.001 \) difference between the first and last curves, with a shift to the right and a change towards a normal distribution. Longitudinal data were obtained for a number of the children studied and the results (Table 10) show significant increases in mean serum retinol values.

To estimate breast-milk retinol, samples were analysed from 1375 women at various stages of lactation. The results (Table 11) show significant decreases in the percentage with retinol values less than 1.05 \( \mu \text{mol/l} \) (30 \( \mu \text{g/dl} \)) over the period of fortification at all but one of the stages of lactation.
Table 10. Blood serum retinol levels in preschool-age children in Guatemala, 1975–77

<table>
<thead>
<tr>
<th>Survey period</th>
<th>No. of cases</th>
<th>No. (and %) of cases by levels of serum retinol</th>
<th>&lt;0.35 μmol/l (&lt;=10 μg/dl)</th>
<th>0.35–0.7 μmol/l (10–20 μg/dl)</th>
<th>0.7–1.05 μmol/l (20–30 μg/dl)</th>
<th>&gt;1.05 μmol/l (&gt;30 μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct–Nov 1975</td>
<td>543</td>
<td>18 (3.3)º</td>
<td>100 (18.2)</td>
<td>189 (34.4)</td>
<td>242 (44.1)</td>
<td></td>
</tr>
<tr>
<td>Apr–May 1976</td>
<td>585</td>
<td>6 (1.0)</td>
<td>77 (13.1)</td>
<td>205 (26.6)</td>
<td>296 (50.4)</td>
<td></td>
</tr>
<tr>
<td>Oct–Nov 1976</td>
<td>644</td>
<td>2 (0.3)</td>
<td>31 (4.8)</td>
<td>165 (25.6)</td>
<td>447 (69.0)</td>
<td></td>
</tr>
<tr>
<td>Apr–May 1977</td>
<td>676</td>
<td>6 (0.9)</td>
<td>69 (10.2)</td>
<td>189 (28.0)</td>
<td>410 (60.9)</td>
<td></td>
</tr>
<tr>
<td>Oct–Nov 1977</td>
<td>721</td>
<td>2 (0.3)</td>
<td>64 (9.9)</td>
<td>260 (36.1)</td>
<td>386 (54.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Figures in parenthesis are percentages of cases.

Table 11. Decrease in the percentage of breast-milk samples with retinol values of less than 1.05 μmol/l (30 μg/dl) by period of lactation, Guatemala, 1975–1977

<table>
<thead>
<tr>
<th>Survey period</th>
<th>Lactation period (months)</th>
<th>&lt;2</th>
<th>2–4</th>
<th>5–6</th>
<th>7–8</th>
<th>9–10</th>
<th>≥11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 303)</td>
<td>(n = 216)</td>
<td>(n = 196)</td>
<td>(n = 195)</td>
<td>(n = 194)</td>
<td>(n = 217)</td>
<td></td>
</tr>
<tr>
<td>Oct–Nov 1975</td>
<td>24.1</td>
<td>40.9</td>
<td>63.2</td>
<td>40.0</td>
<td>48.1</td>
<td>38.8</td>
<td></td>
</tr>
<tr>
<td>Apr–May 1976</td>
<td>22.2</td>
<td>27.1</td>
<td>47.4</td>
<td>30.0</td>
<td>43.4</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>Oct–Nov 1976</td>
<td>11.1</td>
<td>13.1</td>
<td>29.7</td>
<td>30.6</td>
<td>17.6</td>
<td>31.0</td>
<td></td>
</tr>
<tr>
<td>Apr–May 1977</td>
<td>6.3</td>
<td>13.1</td>
<td>16.7</td>
<td>12.3</td>
<td>7.0</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>Oct–Nov 1977</td>
<td>11.6</td>
<td>18.2</td>
<td>22.8</td>
<td>33.4</td>
<td>13.8</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>

χ² 9.88  <0.05  <0.025  <0.001  N.S.  <0.001  <0.005

Table 12. Cost (in US $) of sugar fortification in Guatemala, 1975–77

<table>
<thead>
<tr>
<th>Cost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol palmate</td>
<td>395,452</td>
</tr>
<tr>
<td>Manufacturing of premix</td>
<td>42,000</td>
</tr>
<tr>
<td>Transportation of premix</td>
<td>3,500</td>
</tr>
<tr>
<td>Monitoring:</td>
<td></td>
</tr>
<tr>
<td>Inspector (part-time)</td>
<td>750</td>
</tr>
<tr>
<td>Chemical analysis</td>
<td>500</td>
</tr>
<tr>
<td>Inspector’s visits (transport)</td>
<td>1,200</td>
</tr>
<tr>
<td>Total</td>
<td>443,352</td>
</tr>
</tbody>
</table>

To estimate liver retinol, liver samples were collected throughout the period of evaluation from the coroners’ autopsies in Guatemala City on essentially all accidental deaths of both sexes and all ages. As shown in Fig. 3, the percentage of livers with less than 0.7 μmol/l (20 μg/dl) decreased significantly (P < 0.001) over the period of fortification. There was no tendency for the percentage of values above 300 μg/g to increase after July–September 1976.
Cost analysis. The cost per year over the 2-year evaluation period is shown in Table 12. As will be seen, almost 90% of the total was the cost of the vitamin A product. This amount, together with the cost of manufacturing the premix, was borne by the National Association of Sugar Manufacturers of Guatemala. The cost per pound of sugar fortified was US $0.0013 (US $0.0029 per kg). The cost per inhabitant of the country in 1976 was computed to be US $0.07.1

These results provide convincing evidence of the efficiency and efficacy of the vitamin A sugar fortification programme in Guatemala at the national level. Nevertheless, it is evident that unpredictable difficulties may arise unless there is full government commitment to long-term financial support. In 1979 there was resistance to sugar fortification in Central America in the sugar industry owing to economic constraints as a result of the halving of the price of sugar and tripling of the price of the vitamin A product. Panama has interrupted its programme while Guatemala and Honduras are continuing, but on a reduced scale.

1 If it is assumed that the prime target population must be children aged 1–5 years in the low- and medium-income strata, then the cost per “person protected” worked out at US $20.02 for those with a serum vitamin A of less than 0.35 μmol/l (10 μg/dl) and US $3.66 for those with values over 0.7 μmol/l (20 μg/dl).
7.2.2.2 MSG fortification in the Philippines. Monosodium glutamate (MSG) is the best known and most widely used flavour enhancer at the present time. The annual worldwide production is approximately 200 000 tonnes; it is used in the cooking of oriental dishes not only in Asia but also in many other countries. Studies in the Philippines have led to a pilot fortification programme using commercially available MSG.

A 3-year study in the early 1970s demonstrated the presence of a widespread vitamin A deficiency problem in the island of Cebu (73). In an evaluation of three strategies (MSG fortification, capsule distribution, and horticulture/public health intervention), the first one was found to be the most effective (89).

In further studies (91) of possible vehicles, MSG was found to be the most suitable, satisfying all the necessary criteria as a vehicle for vitamin A fortification on a population basis. MSG is produced by two Philippines-based companies, although about 98% comes from one of them. Families were found to consume two 2.4-g packets of MSG daily on average. They cost about US $0.01 per package. No family consumed more than 3 packets per day. Most is used in Cebuano soup dishes on the island.

For the evaluation of alternative strategies a process of MSG fortification was devised. Dry retinol palmitate type 250-SD (Hoffman-La Roche) (in a concentration of 250 000 IU/g) was added to MSG with particle size of 100 mesh. Silicon dioxide was added as a flow-enhancing agent. The fortification level was 15 000 IU per sachet of 2.4 g MSG. Retention rates averaged 76% after 6 months of storage at 36°C, with loss rates averaging 3% per month for the first six months of storage. A number of problems were encountered and the production method was changed for the subsequent pilot fortification project in two provinces, as described below.

A pilot fortification project is proceeding at the present time in Nueva Vizcaya (an island province in northern Luzon) and in Marinduque (an island province south of Luzon), with Cebu as the control province. Fortified MSG is being distributed throughout the province through the normal commercial channels and evaluation will take place one year after the commencement of distribution. In this programme, the usual crystalline form of MSG was used in order to avoid changing the appearance of the original product to which the public had become accustomed. A beadlet form of the vitamin A fortificant, type 325-L (in a concentration of 325 000 IU/g), which was closer to the particle size of MSG, solved the problems of "flying off" and
caking and maintained the white colour of the product. As the 325-L type cost more, the original 2.4-g MSG cachet was reduced to 2.0 g to maintain the retail cost at 15 centavos per sachet.

Operational difficulties have included continuing objections by the manufacturer that the addition of an extraneous substance might in various ways create a business hazard. Professional and academic groups have also questioned the safety of MSG and adverse publicity may affect the national fortification programme.

7.2.2.3 Fortification in Indonesia. Three food products—wheat flour, refined sugar, and MSG—are being studied as potential vehicles for fortification with vitamin A. Exploratory studies in 1979 indicated that the annual cost per child would be US $0.47 for wheat flour, $1.83 for sugar, and $0.06 for MSG compared with $0.22 for capsule distribution. Because of the vitamin A fortification, the price of wheat flour, refined sugar and MSG would be increased by 1.9%, 2.9% and 1.5% respectively. Wheat flour and refined sugar belong to the nine basic commodities which are subsidized by the Government. Any change in price would have a wide impact on the people and the Government. MSG is freely marketed and its fortification would involve relatively little price change. Technological problems, consumer acceptability, and other aspects of MSG fortification are being pursued.

7.2.2.4 Fortification of dried skim milk for food-aid programmes. As health adviser to the World Food Programme (WFP), WHO gave warning of the potential dangers inherent in supplying non-fortified dried skim milk (DSM) for use in supplementary feeding programmes in countries where both vitamin A and protein-energy deficiencies were problems of public health magnitude. With the expansion of WFP operations, particularly in the early 1970s, it became clear that this programme was in need of larger quantities of vitamin A enriched DSM than was available from the donations then being received. The solution to this predictably threatening situation was to persuade some DSM-donating countries to contribute enriched DSM which would be supplied to countries that needed it.

In 1976 WHO was requested by the World Food Programme to submit a special study of the subject; this was done and WHO's contribution included a simple field test and a comparatively simple laboratory method to detect the presence of the recommended vitamin A enrichment (97, 98). These tests were specially for the benefit
of countries that needed to verify such DSM enrichment, even if their laboratory facilities were limited.

As a result, the policy adopted by not only the World Food Programme but also several bilateral programmes (and the European Economic Community) is that DSM, which is distributed through supplementary feeding projects in countries where xerophthalmia is a public health problem, must be enriched with vitamin A even if the problem affects only part of the country in question.

In addition, a very special effort is being made by industry to develop increasingly stable vitamin A preparations for DSM enrichment. Microcapsules allowing 9 months storage (instead of 6 months, which was the best in 1980) are being worked on and it appears likely that a capsule with a one-year shelf-life (at 35°C) will soon be within reach.

7.2.3 Educational programmes

In countries where vitamin A deficiency and xerophthalmia present a serious problem and where periodic-dose or fortification programmes have been instituted, various educational measures have also been adopted over a considerable period of time. It is understandable that the limited resources available should have been largely devoted to the implementation of short-term measures to combat the problem, but it has also been realized that the ultimate answer lies in the promotion of an adequate intake of vitamin A from locally available foodstuffs, together with the control of those factors that impair its utilization. Examples of the educational measures being pursued in a number of countries are described below.

7.2.3.1 Philippines. Education on nutrition and health, including that related to vitamin A, in the Philippines uses both the interpersonal approach and the mass media in a variety of combinations depending on the needs of the situation. The measures range from the adoption of various types of printed media to the application of modern audio-visual technology, and from small group orientations to multi-media organized study systems beamed to specific professions throughout the country. Resource limitations continue to keep the quantity and quality of production of these communication materials at a modest level.

For policy-makers the medium used is print. Among the agencies, the National Nutrition Council (NNC) and the Nutrition Center of
the Philippines (NCP) publish newsletters (containing information on developments in the Philippine Nutrition Programme, including news about the vitamin A supplementation project) which are distributed to national and local leaders. The NCP has also produced one-sheet information leaflets for similar distribution. One of these is devoted to vitamin A, outlining the nature of the problem and providing guidelines on the production, preparation and consumption of food sources of vitamin A.

A citywide survey among physicians in the Manila Health Department revealed a considerable lack of knowledge and the absence of resource material on vitamin A deficiency and other nutritional problems. Subsequently the NCP conducted a seminar-workshop on these subjects and published some literature in support.

The main resources of the long-term educational thrust of the Philippine Nutrition Programme are the 300 000 teachers throughout the country. Educational materials distributed include a comprehensive manual on nutrition, weight charts and guidelines for their use, and pamphlets for a Teacher-Child-Parent (TCP) communications system.

The Barangay Nutrition Scholars are selected residents who have been trained to deliver basic nutrition and health services; they are the closest manpower link to the family in the Philippine Nutrition Programme. One of their most important resources is the Nutri-bus, a communications project using mobile vans equipped with videotape recorded (VTR) playback facilities and manned by trained communicators. The Nutri-bus travels to a number of villages periodically to conduct VTR shows and to distribute publications as well as seeds, seedlings and food supplements (e.g., in the specially packaged Nutri-pack). At the household level, the primary medium of communication is through the Barangay Nutrition Scholars. Posters to hang on house walls and comic books, utilizing the wide popularity of heroes in Philippine folklore, have proved especially successful.

A nutrition surveillance system in the country has recently been instituted and some evaluation instruments have been developed. Financial and technical support has been received from international agencies and private industry as well as from the government.

7.2.3.2 Bangladesh. A survey carried out in 1979 revealed that only 32% of mothers knew why vitamin A was being given to their children. A flip-book has been developed that explains the relationship between low vitamin A intake and night blindness and blindness,
stresses the importance of increased consumption of the cheap and abundantly available green leafy vegetables, particularly by children, and explains the importance of breast-feeding, weaning foods, and feeding during illness. Each of the Family Welfare Workers (FWW), who are responsible for distribution of vitamin A capsules, and their supervising personnel will receive a copy of the flip-book. Coloured pictorial leaflets and a new chapter on preventable blindness have been incorporated in the latest edition of the FWW manual. Blindness prevention posters have been distributed to health centres, primary schools and voluntary organizations. A 16-minute film on vitamin A has been produced locally for mass use throughout the country by the 210 cinema halls and the 61 mobile units of the Ministry of Information and Health. Radio, television and newspapers are being utilized to create public awareness of nutritional blindness and the means for its prevention.

7.2.3.3 Indonesia. Since the inception of the vitamin A programme, the importance of behaviour change with regard to feeding practices for very young children has been recognized. Steps have been taken to include in the manuals for personnel who distribute the vitamin capsules some information for mothers, to develop and test training materials on the subject, and to incorporate in the manuals for health workers and family-planning workers pertinent material about the prevention of xerophthalmia. However, as a result of the findings of the 3-year comprehensive epidemiological research project it has been possible to refine the messages and to target more precisely the areas of highest prevalence for more culture-specific behaviour-change approaches.

There is close collaboration between the Directorates of Health, Education and Nutrition of the Ministry of Health in the planning and implementation of the nutrition education component of the vitamin A programme. An overall strategy design has been developed, involving participation of the agricultural, health and religious sectors and other groups, such as women’s organizations and voluntary agencies. The currently used materials, such as poster, a flip-book and visual aids, will be reviewed in the light of recent information and new material, especially designed for use at village level, will be developed. A film and other mass-media measures for disseminating this information are being prepared. Capsule distribution in urban slums will commence in a few selected cities, simultaneously with application of an information campaign strategy.
7.2.3.4 India. It is not possible to enumerate the many educational measures that are being undertaken to combat the problem of vitamin A deficiency and xerophthalmia in such a large and diverse country as India. However, mention may be made of the literature and other educational materials that have been produced for nationwide distribution by the National Institute of Nutrition, Hyderabad, and the Voluntary Agency for Health Planning, New Delhi. Besides its activities in the treatment and rehabilitation of children with established xerophthalmia (92), the Nutrition Rehabilitation Centre at the Government Erskine Hospital in Madurai carries on an educational programme whose published results demonstrate the educational value of participation of the mother in buying, cooking and sharing the food given to her child.

7.2.3.5 Thailand. Nutrition education, including a vitamin A component, has been carried out through the community nutrition programmes. Discussion groups, posters, T-shirts, games, tape cassettes and flip-charts have been used to promote proper infant feeding practices and increased intake and production of locally available vitamin A-rich food sources.

7.2.3.6 Haiti. From the outset, nutrition education has been an integral part of the vitamin A capsule distribution programme. Emphasis has been placed on the training of health personnel at all levels in the knowledge of the causes of vitamin A deficiency and concerning preventive measures, treatment of xerophthalmia, and messages to communicate in regard to eating habits. Besides frequent lectures by the director of the vitamin A programme in the medical and nursing schools, seminars have been held each year in the health districts for the supervisory and health personnel who are involved in capsule distribution. For several years a weekly radio talk on nutrition education has been broadcast in Port-au-Prince by the nutritionist of the vitamin A programme. A cassette (for radio use) with an introductory Haitian song about vitamin A has been produced and plans have recently been completed for regular radio broadcast time in four other major cities. With the support of the Ministry of Health and Population, information about measures for treatment and prevention have been incorporated into all the major instructional materials disseminated to the rural health sector, and advantage has been taken to bring this message to most of the conferences of health personnel.
A flip-book has been produced, with illustrations by a Haitian artist, which has served as a model for other countries. A film is being planned.

7.2.4 Primary health care

At the International Conference on Primary Health Care, held in Alma-Ata in 1978, one of the recommendations stated that "... single-purpose programmes should be integrated into primary health care activities as quickly and smoothly as possible" (93). Primary health care forms an integral part of both a country's health system, of which it is the nucleus, and the overall social and economic development of the community. It is likely to be most effective if it employs means that are understood and accepted by the community and are applied by community health workers at a cost the community and the country can afford.

The health sector has been involved for many years in both short-term (vitamin A supplementation) and long-term (nutrition education) measures to combat blindness resulting from vitamin A deficiency. As mentioned elsewhere, these efforts have been redoubled in a number of countries in the past decade as a result of the greater awareness of the problem. It has to be recognized, however, that two-thirds of the world's population do not have adequate health care, and many millions have no access whatsoever to any form of health care.

The periodic-dose programmes for vitamin A that are in operation are clearly single-purpose programmes. The available evidence suggests that, although coverage has been incomplete, there has been a considerable reduction in the prevalence of night blindness and conjunctival changes among the population covered, and there is some evidence to indicate that the prevalence of nutritional blindness has been reduced. However, the utilization of workers in specific unipurpose programmes for vitamin distribution on an emergency basis has at least two serious disadvantages. There is a tendency for those who are least accessible, and therefore most at risk, not to be covered, and other measures to control the precipitating factors may not be in operation at the same time.

The primary health care system, which is being adopted in many developing countries, has several advantages over single-purpose programmes. Primary health care is a community-centred system in which the community takes a leading part in identifying problems and in developing and implementing measures for their control. The im-
portance of community participation for the success of a health pro-
gramme is recognized (94).

7.2.5 Nutritional rehabilitation programmes

A unique contribution to the rehabilitation of children with xeroph-
thalmia has been made by the Nutrition Rehabilitation Centre attached
to the Government Erskine Hospital, Madurai, in south India (92).
An analysis of the records of 296 children, treated there between
January 1971 and April 1974 and followed up for periods ranging
from 2 months to 3 years, showed that this form of management (96)
was at least as effective as that provided by the more expensive, and
usually unobtainable, treatment in hospital.

7.2.6 Horticulture and related production activities

Throughout those parts of the world where vitamin A deficiency
and xerophthalmia constitute a public health problem, vegetable
(rather than animal) products are the main available source of dietary
vitamin A (i.e., carotene). The richest sources of carotene are red
palm oil (used for cooking in only a few areas), certain vegetables
-especially dark green leafy vegetables and carrots), and some fruits.
Some staple foodstuffs such as yellow corn (maize) provide some
carotene. However, as noted previously (section 2.6), there is at
present considerable doubt concerning the reliability of the customary
figures in food composition tables for the provitamin A content of
many foodstuffs and there is urgent need for the re-evaluation of the
sources that have traditionally been relied upon for promotional
activities.

Increased consumption of many of the carotene-rich foods will
also ensure the increased consumption of other essential nutrients.
For example, 100 g of Amaranthus leaves provide 3.6 g of protein
and useful amounts of ascorbic acid, iron and other nutrients. Many
horticultural crops are, however, available only seasonally and this
may influence the occurrence of vitamin A deficiency.

In most developing countries there are few trained horticulturists
and knowledge is limited concerning the best varieties of fruits and
vegetables for a particular area, the optimum means of production
under local conditions, and pest and disease control. In addition there
are problems of transport, marketing, storage and preservation.
Horticulturists may tend to encourage the production of vegetables and fruits that give high yields or realize good market prices and ignore the nutritive values of the produce. Many of the dark green leafy vegetables that are eaten traditionally in tropical countries have a much higher carotene content than the pale green leafy vegetables such as cabbage. The bio-availability of carotene is greater from young than from old leaves. Certain tropical fruits, notably mango and papaya, provide useful amounts of carotene whereas citrus fruits and non-tropical fruits in general contain very little. Institutions such as the Asian Vegetable Research and Development Center (AVRDC) are working towards the solution of some of these problems.

Horticultural and allied activities (such as in home, school and community gardens) should clearly be coordinated with the aspects of nutrition education programmes that are directed at the promotion of the consumption of locally available and cheap provitamin-rich sources, especially by young children. The reasons why these foodstuffs are not consumed at all, or not in significant amounts, even in areas where they are abundant, are being looked into and more research on this aspect of the problem is needed. The reasons probably vary in different circumstances. Indigenous green leafy vegetables may sometimes be regarded as “weeds”, acceptable as food only in periods of scarcity, or as being inferior to the imported varieties (95).

The Nutritional Blindness Prevention Project (35) in Indonesia has obtained some preliminary data on this problem. Table 13 shows the widespread and frequent consumption of green leafy vegetables by all groups. This suggests that the nutrition education programme should stress the importance of an increase in the amount (rather than the frequency of consumption) of green leafy vegetables, especially by children over 2 years old; for younger children, breast-feeding and the intake of fruits such as mango and papaya are important. Tables 14 and 15 give the explanations offered by parents or guardians

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Total No.</th>
<th>% Distribution by frequency of consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;=1/day</td>
</tr>
<tr>
<td>X1B</td>
<td>358</td>
<td>79.1</td>
</tr>
<tr>
<td>MC</td>
<td>340</td>
<td>81.5</td>
</tr>
<tr>
<td>N</td>
<td>34 576</td>
<td>81.9</td>
</tr>
</tbody>
</table>

* Based on data from the Nutritional Blindness Prevention Project, Indonesia (35).
* X1B = Bilir's spot; MC = matched controls; N = normal
* Family data for each child in the study; some families are therefore included more than once.
Table 14. Reasons why some children (in a random sample) never eat green leafy vegetables in an Indonesian study\(^{a,b}\)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of children(^c)</th>
<th>% distribution by reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not bought</td>
<td>Not available</td>
</tr>
<tr>
<td>0</td>
<td>773</td>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
<td>274</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>2.6</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>1.9</td>
</tr>
</tbody>
</table>

\(^{a}\) Based on data from the Nutritional Blindness Prevention Project, Indonesia (35).
\(^{b}\) The random sample included normal and X1B subjects, and matched controls.
\(^{c}\) Children who never consume green leafy vegetables.
\(^{d}\) Vast majority of those under 2 years were not yet weaned.

Table 15. Reasons why some affected children (X1B) never eat green leafy vegetables in an Indonesian study\(^b\)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of children(^b)</th>
<th>% distribution by reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not bought</td>
<td>Not available</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>0.0</td>
</tr>
</tbody>
</table>

\(^{b}\) Based on data from the Nutritional Blindness Prevention Project, Indonesia (35).
\(^{c}\) Children who never consume green leafy vegetables.

why children never eat green leafy vegetables. The rates for normal and abnormal (X1B) subjects are similar. These results suggest that instructions to mothers on how to prepare green leafy vegetables for their young children, with a stress on the importance for the young child's health, might increase consumption in this age group.

7.3 Disaster relief

It is estimated that there are more than 12 million refugees in danger of starvation and disease, of whom half are children under the age of 15 years. In addition, there are many others who are victims of environmental or manmade disasters in their own countries. Young children are especially vulnerable in a disaster situation and, besides their susceptibility to infections and protein-energy malnutri-
tion, they are particularly prone to develop xerophthalmia if their previous intake of vitamin A was low.

Several relatively simple measures need to be taken to prevent the development of this complication. The most readily implemented single measure is the distribution of vitamin A capsules to all young children. In the early stages of a disaster it is unlikely that this can be done other than on an ad hoc basis but the programme should be put into action at the earliest opportunity. Field personnel should be trained in the recognition of the eye signs of vitamin A deficiency, including night blindness. Adequate vitamin A should be provided in food relief. Most preparations of skim milk, which is usually one of the basic foods supplied after a disaster, are now fortified with vitamin A. The meeting recommends that all such supplies should be fortified. Mothers should be encouraged to breast-feed their infants; the growing (and use) of local green leafy vegetables should also be encouraged.

In order to implement these measures at the field level, it is vital that the many international, bilateral, governmental and private agencies involved in disaster relief operations should be aware of the existence and nature of the problem of vitamin A deficiency.

8. RESEARCH

8.1 Recent contributions

In the previous report (I), attention was drawn to the fact that research on vitamin A had largely been concentrated on the fundamental aspects of metabolism and function. Human studies had been mainly confined to the severe, blinding effects of vitamin A deficiency and there was need for epidemiological investigations of the prevalence and severity of vitamin A deficiency and xerophthalmia in many parts of the world and for evaluation of the effectiveness of the control programmes that were being undertaken. Since that time, there has been a gratifying intensification of activity in various areas of applied research which is partly due to the impact of the previous report (I).

Unquestionably the most significant advances, in recent years, in our understanding of the nature and occurrence of human vitamin A deficiency and xerophthalmia have been contributed by the various studies carried out by the Nutritional Blindness Prevention Project in Indonesia. This work has provided a more sure foundation for the

55
identification, treatment and control of vitamin A deficiency and xerophthalmia not only in that country but also in other areas where the problem occurs. The results of this research have been referred to throughout this report and their references have been cited (35, 36, 48, 56, 57, 61–63, 76).

8.2 Priorities for future research

In 1980 a WHO task force reported on a programme of research on the control of vitamin A deficiency and xerophthalmia (unpublished document NUT/80.1). The need to integrate control programmes into primary health care and into the newly developing action-oriented research and development programme in nutrition and the programme of blindness prevention of WHO was stressed. The recommendations that were made at that time, together with those made at the present meeting, form the basis for the recommendations that follow. The areas of research are listed in the order of priority granted to them by the task force; within each area the items with the most important research needs are marked with an asterisk (*).

8.2.1 Increasing vitamin A and provitamin A intake

Vitamin A status depends primarily on vitamin A intake but is influenced by a variety of secondary factors. Increasing the intake of vitamin A by whatever means is essential if vitamin A deficiency and xerophthalmia are to be controlled.

8.2.1.1 Increasing the vitamin A and provitamin A content of the diet. This is considered the most natural and permanent approach to increased vitamin A intake. Research is needed to determine:

— Vitamin A requirements in young children, pregnant and lactating women and women taking oral contraceptives.

— Provitamin A carotenoid content of major food sources in various regions.*

— Biological activity and availability of provitamin carotenoids from plant sources and the influence of dietary lipids on the efficiency of their utilization.*

— Safety of natural sources of carotenoids—with special reference to possible toxic or pharmacological factors they may contain.

— Factors limiting the intake of vegetables by young children despite their availability.*
— Methods for encouraging the consumption of green leafy vegetables by young children when they are available.*
— Ways to increase availability of sources of vitamin A.

8.2.1.2 Periodic dosing. Because vitamin A is stored in the body, periodic doses of the vitamin will tend to maintain adequate nutriture. This approach is directed towards the most vulnerable groups of the population and is to be used in special circumstances. Research is needed to determine:
— Optimal preparations.
— Optimal frequency/dose relationships.*
— Side-effects, toxicity in young children and in pregnant and lactating women.
— Alternative strategies for effective distribution (e.g., integration into primary health care systems).*

8.2.1.3 Fortification. This is a measure which is directed to the population at large and which can be implemented within a relatively short period of time with minimal dependence on active participation of the recipients. Research is needed to:
— Improve the technology for fortification through various vehicles.
— Improve techniques for monitoring the efficiency of the system for delivery of the nutrient.
— Study the compatibility of nutrients in cases of multiple fortification of a single vehicle.

8.2.2 Epidemiological assessment

The design of intervention strategies requires assessment of the nature, magnitude and distribution of the problem. The assessment should include information on the infrastructure and the resources that are potentially available for implementation of programmes. These data are essential for selection of appropriate interventions and for subsequent evaluation of their efficiency and impact on the problem. Research is needed in the following areas:

(a) Clinical diagnosis
— The methodology to assess night blindness, particularly in young children.*
— The nonocular effects of vitamin A deficiency in man.
— Identification of other noninvasive early indicators of vitamin A deficiency in young children.

(b) Vitamin A status
— Improved methodology for determining retinol in serum and liver.*
— The relationship between serum retinol and clinical signs.*
— Range of plasma retinol values in healthy subjects, especially young children.
— Development of methods for assessing the total body stores of vitamin A in human subjects.*

(c) Dietary factors
— Methods for assessing the availability and use of green leafy vegetables to feed young children.*
— Identification of potential vehicles for fortification.*

(d) Interrelationships of vitamin A deficiency, malnutrition and meases.

8.2.3 Determining the impact of a programme
A surveillance system is needed for determining the impact of the programme. Research is required to determine the usefulness for this purpose of:
— specially standardized clinical reporting centres;
— periodic limited cross-sectional prevalence surveys;
— alternative approaches to cost-effectiveness;
— operational research to determine the efficiency of an intervention.*

8.2.4 Controlling the factors that impair vitamin A absorption and utilization
There is considerable evidence that various secondary factors adversely affect the absorption and utilization of vitamin A. There is need, however, to quantify these effects, particularly under conditions of marginal or low intake. Research is needed on the following:
(a) Factors that impair absorption

— Intestinal infections, i.e., giardiasis, ascariasis, “gastroenteritis”;
— Other infections (systemic);
— Protein-energy malnutrition.

(b) Factors that affect utilization

— Systemic infections and febrile illnesses, i.e., measles, chickenpox, etc.;
— Protein-energy malnutrition.

8.2.5 Controlling the ocular factors contributing to xerophthalmia

There is need to identify the ocular factors that may contribute to corneal ulceration and “melting” and to determine their significance and potential for controlling, for example, bacterial flora and measles and other viral infections.
REFERENCES


Annex 1

LIST OF PARTICIPANTS

Dr G. Arroyave,
Division of Biology and Human Nutrition,
INCAP,
Guatemala City, Guatemala

Dr J.C. Bauernfeind,
Department of Clinical Nutrition,
Hoffmann-La Roche,
Nutley, NJ, USA

Dr K. H. Brown,
Instituto de Investigación Nutricional,
Miraflores, Lima, Peru

Dr S. Dhammimitta,
Faculty of Medicine,
Ramathibodi Hospital,
Bangkok, Thailand

Dr Edi Djunacdi,
Ciudad Eye Hospital,
Bandung, Indonesia

Dr J. E. Dutra de Oliveira,
Dean, Medical School,
Universidade de São Paulo,
Faculdade de Medicina de Ribeirao Preto,
São Paulo, Brazil

Dr D. Susanto,
Nutrition Research and Development Center,
Bogor, Indonesia

Dr R. F. Florentino,
Nutrition Centre of the Philippines,
Makati, Metro Manila, Philippines

Dr H. Flores,
Federal University of Pernambuco,
CIDADE UNIVERSITARIA,
Recife, Brazil

Dr J. Glover,
Department of Biochemistry,
University of Liverpool,
Liverpool, England

Dr J. Gmünder,
F. Hoffmann-La Roche & Co. Ltd.,
Basle, Switzerland

65
Dr I. M. M. Setyadi Harjadi,
Agricultural University of Bogor,
Bogor, Indonesia

Dr G. Hussaini,
Nutrition Research and Development Center,
Bogor, Indonesia

Dr M. A. Hussain,
Department of Nutrition,
University of Ibadan,
Ibadan, Nigeria

Professor M. S. Jalil,
Blindness Prevention Programme,
Department of Health Services,
Dacca, Bangladesh

Dr Sri Kartijati,
Department of Public Health,
School of Medicine,
University of Airlangga,
Surabaya, Indonesia

Dr D. Karyadi,
Nutrition Research and Development Center,
Bogor, Indonesia

Dr C. Kupfer,
Director, National Eye Institute,
National Institute of Health,
Bethesda, MD, USA

Dr J. A. Kusin,
Koninklijk Instituut voor de Tropen,
Amsterdam, Netherlands

Dr M. C. Latham,
Professor of International Nutrition,
Graduate School of Nutrition,
Cornell University,
Ithaca, NY, USA

Dr Loedin (Vice-Chairman),
Ministry of Health,
Jakarta, Indonesia

Professor S. Mandel,
Biometrics Unit,
University of Otago,
Dunedin, New Zealand

Dr D. S. McLaren (Rapporteur),
University of Edinburgh,
Department of Physiology,
University Medical School,
Edinburgh, Scotland
Dr H. Muhilal,  
Nutrition Research and Development Centre,  
Bogor, Indonesia  

Dr J. A. Olson,  
Department of Biophysics and Biochemistry,  
Iowa State University,  
Ames, IA, USA  

Dr R. Pararajasegaram,  
Regional Chairman, Southern Asia  
International Agency for the Prevention of Blindness,  
Colombo, Sri Lanka  

Dr H. S. R. Parlindungan Sinaga,  
Jan Swammerdam Institute,  
Amsterdam, Netherlands  

Mr F. Pepping,  
Department of Human Nutrition,  
Agricultural University,  
Wageningen, Netherlands  

Dr A. Piric,  
Nuffield Laboratory of Ophthalmology,  
Oxford, England  

Dr M. Mujibur Rahaman*  
Deputy Director,  
International Center for Diarrhoeal Disease Research,  
Dacca, Bangladesh  

Dr S. K. Reddy,  
Vepery, Madras, India  

Dr V. Reddy,  
National Institute of Nutrition,  
Jamal Osmania,  
Hyderabad, India  

Dr K. L. Simpson,  
Professor, Department of Food Science and Technology,  
University of Rhode Island,  
Kingston, RI, USA  

Dr R. Soebekti (Chairman),  
Ministry of Health,  
Department of International Affairs,  
Jakarta, Indonesia  

Dr M. Solon,  
Nutrition Centre of the Philippines,  
Makati, Metro Manila, Philippines  

* Unable to attend
Dr. A. Sommer,
International Center for Epidemiologic and Preventive Ophthalmology,
Wilmer Institute,
Baltimore, MD, USA

Dr. I. Tarwotjo,
Chief of Division of Nutrition,
Ministry of Health,
Jakarta, Indonesia

Dr. H. R. Taylor,
International Center for Epidemiologic and Preventive Ophthalmology,
John Hopkins Hospital,
Baltimore, MD, USA

Dr. Tin Tin Oo,
Department of Medical Research,
Rangoon, Burma

Dr. S. Tourjeau,
Bureau de Nutrition,
Port-au-Prince, Haiti

Dr. B. Underwood,
Department of Nutrition and Food Science,
Massachusetts Institute of Technology,
Cambridge, MA, USA

Dr. Aree Valyasevi,
Professor of Pediatrics,
Faculty of Medicine,
Ramathibodi Hospital,
Bangkok, Thailand

Representatives of other organizations:

United Nations Children's Fund

Mr. N. Batt,
UNICEF Country Representative,
Bangladesh

Dr. L. Teply,
Senior Nutritionist,
UNICEF,
New York, NY, USA

Food and Agriculture Organization of the United Nations

Dr. R. U. Qureshi,
Nutrition Adviser,
FAO,
Bangkok, Thailand

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US Agency for International Development
Dr J. McKigney,
Nutrition Adviser,
Office of Nutrition,
Technical Assistance Bureau,
Department of State,
Agency for International Development,
Washington, DC, USA

Helen Keller International Inc.
Ms S. F. Leone,
Programme Officer,
Blindness Prevention,
Helen Keller International, USA
Ms Carol Measham,
HKI Field Representative,
Dacca, Bangladesh
Dr S. Pettiss,
Helen Keller International,
New York, NY, USA
Dr R. Tilden,
Direktorat Gizi,
Jakarta, Indonesia

International Vitamin A Consultative Group
Dr C. O. Chichester,
The Nutrition Foundation,
New York, NY, USA

Secretariat:
Dr E. M. DeMaeyer (Secretary),
Senior Medical Officer,
Nutrition Research,
World Health Organization,
Geneva, Switzerland

Observers:
Ms J. E. Andersen,
Consultant to the Nutrition Center of the Philippines,
USA
Ms M. Hotasavit,
Chairman of the Eye Bank of Indonesia,
Jakarta, Indonesia

69
Dr Abdul Majid Molla,
International Centre for Diarrhoeal Disease Research,
Dacca, Bangladesh

Dr S. Pudjiadi,
Department of Child Health,
Medical School,
University of Indonesia,
Jakarta, Indonesia

Ms E. Reyes,
Nutrition Center of the Philippines,
Makati, Metro Manila, Philippines

Dr J. Sullanti Saroso,
Adviser to Minister of Health of Republic of Indonesia,
Jakarta, Indonesia

Dr Soedarsono,
Chairman, Foundation Against Blindness,
Jakarta, Indonesia

Dr N. Studzinski,
Public Health Adviser,
U. S. Embassy,
Jakarta, Indonesia