THE CORNEA IN KWASHIORKOR

BY

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A thesis submitted for the Degree of

MASTER OF SURGERY

in the University of East Africa

1968

D E C L A R A T I O N

I hereby declare that the work embodied in this thesis is mine and the views expressed therein are mine.

I also hereby declare that this thesis has not been submitted for a degree in any other University.

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November, 1968.

A C K N O W L E D G E M E N T S

I wish to acknowledge the help and encouragement I received from Professor M. S. R. Hutt, M.D., F.R.C.P.,F.C. Path., Department of Pathology; Professor M. Davanger, Dr. Med., and Professor H. Leira, Dr. Med., Department of Ophthalmology, Makerere Medical School.

My sincere thanks are also due to Mr. R. C. Wellingham and Mr. J. E. Busulwa of the Medical Illustration Department, Makerere Medical School, for the photographs which they produced for me.

Mr. R. Okel, A.I.M.L.T., of Mulago Hospital kindly assisted me in the estimation of Serum Carotene and Proteins. Mr. A. L. Lalwak, A.I.S.T., of the Pathology Department processed the corneae for me.

Lastly I wish to record my gratitude to Roche Products Ltd., London, for the free gift of Crystalline beta-Carotene they donated to me.

CONTENTS

SUMMARY

The resistance of the cornea to infection is lowered in Kwashiorkor. There is more morbidity of the cornea among children who have been malnourished. Thus among 1,000 well-nourished children examined, there were only 2 (0.2%) children with corneal opacity, whereas among 200 children who were being treated for Protein-Calorie Malnutrition 4 (2%) had corneal lesions.

The lowering of resistance of the cornea to infection must be explained on the basis of the histopathological change brought about by the state of malnutrition. In the main, this change affects the corneal epithelium. Furthermore clinical observation suggests that humoral defence reaction is impaired in Kwashiorkor. The eye has poor inflammatory vascular response in the presence of a severe corneal ulcer.

The normal corneal epithelium acts as a defence barrier against bacterial infection by imperviousness

of its cells. With the exception of gonococci, diptheria bacilli, and viruses, the intact corneal epithelium is impervious to bacterial toxins ordinarily present. But in Kwashiorkor this barrier is weakened, as the corneal epithelium is thinned by atrophy, the cells are abnormal and may be keratinised. Epithelial abrasions, which commonly occur in severe Kwashiorkor, may permit the entry of bacteria, thus rendering the cornea more liable to infection.

Vitamin A deficiency is probably not the main aetiological factor in the pathogenesis of the corneal abnormality in Kwashiorkor children in Mulago. Primary Vitamin A deficiency is known to be rare in the native population in Uganda. The diet of even the poorer people contains adequate amount of the provitamin, mainly from green vegetables and fruits. Even in Kwashiorkor, the clinical manifestations of Vitamin A deficiency is rare. In this study no child with the authentic signs of Vitamin A deficiency was seen, nor did the estimations of serum carotenes indicate a severe deficiency state. Other workers in Mulago have stressed the rarity of Vitamin A

deficiency. Similar observations have been made elsewhere in Tropical Africa.

However, secondary Vitamin A deficiency occurs in Kwashiorkor, but the levels are not so low as to cause a clinical deficiency state. It has been observed that levels of Serum Vitamin A and Carotenoids must be virtually at zero or very low before its classical deficiency state.occurs.

The histopathological changes observed in the cornea of Kwashiorkor children in Mulago cannot therefore be explained on the basis of Vitamin A deficiency alone.

In the past the corneal changes in malnutrition, namely Xerosis Corneae and Keratomalacia have been attributed to Vitamin A deficiency alone. But the evidence for this is not convincing. These conditions were first described in areas where primary Vitamin A deficiency occurs, so that severe Vitamin A deficiency was a prominent feature of the state of malnutrition. In spite of the almost invariable presence of protein deficiency in all the cases, it is not clear why undue emphasis had always been made on Vitamin A.

Although the eye lesions in malnutrition have for long been attributed to Vitamin A deficiency alone, it is becoming more generally considered as a multiple deficiency syndrome.

Because of the relative unimportance of Vitamin A deficiency, it is postulated here that the primary aetiological factor in the pathogenesis of the histopathological change in the cornea in Kwashiorkor children in Mulago is protein deficiency, with Vitamin A deficiency playing a secondary role. Protein is the body-building material and in its severe deficiency state, the growth of the body is arrested generally. This postulate is further borne out by the fact that the condition of the eyes improves on dietary treatment of high protein value alone without Vitamin A supplement.

In Uganda a child is more likely to develop protein deficiency but have an adequate intake of the easily available carotenes. There must be in the population a wide spectrum of protein malnutrition ranging from subclinical to frank Kwashiorkor and Nutritional Marasmus. Consequently there must be

a large number of children whose corneae have been rendered less resistant to infection to a variable extent by a state of protein malnutrition. This would explain why in underdeveloped countries measles causes so much blindness among children.

INTRODUCTION

It is a common clinical experience in Uganda that in Protein-Calorie Malnutrition, the cornea has reduced resistance to infection. In this study 1,000 apparently well-nourished children were examined in the Paediatric Clinic and only 2 (0.2%) of them had corneal opacities. A similar examination of 200 children who were attending Malnutrition Clinic revealed 4 (2.0%) children with corneal opacities. Among 100 children with moderate to severe Kwashiorkor 6 eyes had corneal ulcers and 2 children lost vision through perforating corneal ulcers. There is thus more morbidity of the cornea among malnourished children.

A corneal ulcer in a Kwashiorkor child does not respond well to treatment and may go on to perforation. In measles perforation of the cornea often occurs. Indeed, measles is one of the commonest causes of blindness in children in Uganda.

It has been observed that in prosperous countries measles is not a danger to vision while in under-developed countries it is, and a question has been

posed whether blindness attributed to measles was specific for morbilli or "were cases of Xerophthalmia masquerading under that diagnosis", (Oomen et al., 1964).

There is evidence to suggest that blindness attributed to measles, which is a universal affection in childhood, is not a manifestation of the virulence of the infection but a reflection of the lowering of resistance to infection by a state of malnutrition. Differences in response have been noticed in well-fed European and poorly-fed African children in the same hospital at the same time (Dean, 1965). Clearly the nutrition of the host is the primary factor. Not only is measles a danger to vision but it also causes a high mortality among malnourished children (Lowenstein et al., 1963).

In South Africa it has also been noted that malnourished children, mostly cases of Kwashiorkor, seem to have poor resistance to infections (Kahn et al., 1957).

There is much evidence to show that malnourished children are more susceptible to infections.

Necropsy findings in Cape Town, Jamaica and Mulago have established that children with Kwashiorkor or Nutritional Marasmus often have acute bacterial infections. In Cape Town, Campbell (1956) found microscopic pyaemic abscesses or bronchopneumonia in the lungs of 31 out of 40 malnourished children and another 6 had evidence of renal infection. Renal lesions, many of them infective, were noted in two-thirds of a Jamaican series (Stirling, 1962). Many of the deaths of malnourished children in Cape Town were found to be due to infection of the gut and septicaemias (Smythe, 1958; Smythe and Campbell, 1959). In a survey of paediatric necropsies done over a 12-year period in Mulago, Brown (1965) found a 45% incidence of bronchopneumonia among malnourished children. More recently Phillips and Wharton (1968) carried out bacteriological studies on 75 children, 63 of whom had Kwashiorkor and 12 had Nutritional Marasmus, who were admitted to Mulago over a period of nine months. Their study revealed that half of the children had acute bacterial infections. All these findings confirm that malnourished children are not only more susceptible to infections but also have poor resistance fo infections.

Little is known about resistance to infections in malnutrition. It is believed that acquired resistance depends upon the ability to produce specific antibodies (Cannon, 1945), mainly from the gamma globulin fraction (Kabat, 1943). But there is conflicting evidence about immune-body production in malnutrition.

Some investigators believe that immune-body production is not impaired in malnutrition (Leading Article: Lancet, 1953). Gamma globulin has been shown to be normal or even raised in malnourished children (Trowell, Davies & Dean, 1954a; Anderson and Altmann, 1951). Estimations of specific group of antibodies, the isohaemagglutinins suggest that the immune-body production in malnourished children is not impaired (Kahn et al., 1957). Others have found that there is no relationship between antibody response and serum globulin levels and that in spite of malnutrition malnourished children are capable of producing antibodies (Balch, 1950; Havens et al., 1954; Pretorius and de Villiers, 1962).

But Krebs (1946) found low levels of gamma globulin

fraction in malnutrition. Wohl and his co-workers (1949) noted an appreciable impairment of anti-body production in patients with disturbed protein metabolism, associated with hypoalbuminaemia. More recently, Brown and Katz (1965) have demonstrated an impaired anti-body response to yellow fever vaccine in Kwashiorkor children in Mulago. Their study revealed that serum immunoglobulin fractions, especially gamma - 2 fraction, was depressed in Ugandan children with Kwashiorkor.

McLaren (1964) believes that Vitamin A deficiency, which often occurs in malnutrition, causes a breakdown of immunological response to infection. Indeed, Vitamin A had for long been regarded as the anti-infective factor (Eusterman and Wilbur, 1932) and its deficiency is believed to cause much blindness in some countries.

In Uganda, Primary Vitamin A Deficiency seems to be rare in the population and among malnourished children. Mitchell (1933) and Owen (1933) saw cases of Xerophthalmia in Kampala among prisoners only,

who were being fed on an inadequate diet, but they saw no other cases in Mulago Hospital although they were watching for signs of Vitamin A deficiency.

Owen concluded that the "free population practically never suffers from Xerophthalmia", and attributed this to the local diet of plantain and sweet potatoes. The only recorded case of Keratomalacia in Mulago was described in a prisoner who had liver failure (Owen and Hennessy, 1932). Trowell (1946) also stressed the relative unimportance of vitamin deficiencies in Uganda. Welbourn (1954) examined children attending Child Welfare Clinics in Buganda for signs of malnutrition over a period of two years but did not mention Xerophthalmia in her findings and stated that on the whole signs of vitamin deficiencies were very uncommon. In other parts of Uganda Xerophthalmia seems to be equally uncommon. A survey in Kigezi revealed no clinical evidence of vitamin deficiencies (Jelliffe et al., 1961). In another survey involving 543 pre-school children in Acholi, only one child with a Bitot Spot was found (Jelliffe et al., 1963). In certain parts of Teso, however, Loewenthal (1935)

reported an incidence of 30% of cases with Xerophthalmia. This high figure seems to be an isolated incidence, because subsequent records and observations in the District Hospital do not indicate that Vitamin A deficiency is a problem in Teso.

Even among Kwashiorkor children in Mulago Xerophthalmia seems to be uncommon. Thus Trowell, Davies and Dean (1954b) write: "The children with Kwashiorkor occasionally have slight Xerosis and Xerophthalmia, but Bitot spots have not been seen". In a later publication, however, Trowell & Jelliffe (1958) state that Xerophthalmia in Kwashiorkor is rare in areas in Africa if plantains are eaten. McCance (Personal Communication) who has worked in the Infantile Malnutrition Unit, Mulago, Medical Research Council, for several years never saw any sign of Vitamin A deficiency in Kwashiorkor children.

Vitamin A deficiency is rare in Uganda because it is one of the greenest countries in the world! Green vegetables especially amaranthus ("Doodo") and fruits abound and are an easily available relish for

the poor, commonly eaten with matoke, cassava, sweet potatoes or millet.

The poor resistance of the cornea to infection in Protein-Calorie Malnutrition as seen in Uganda cannot therefore be easily explained on the basis of Vitamin A deficiency alone.

The object of this study is to make an attempt to explain how the resistance of the cornea is reduced in Kwashiorkor and to show whether Vitamin A deficiency contributes to this.

THE BACKGROUND TO KWASHIORKOR

This study was confined to children suffering from one type of Protein-Calorie Malnutrition, namely Kwashiorkor. Although Kwashiorkor is basically the same disease wherever it occurs, it may differ in detail in other countries depending upon whether or not there are, for instance, certain Vitamin deficiencies, (Trowell; Davies; and Dean; 1954c; Jelliffe D.B., 1955a). In order to understand Kwashiorkor as it presents in Mulago it is necessary to define the background to the development of the disease.

Mulago Hospital, where this study was undertaken, is in Buganda, one of the regions of Uganda. Mulago is the main hospital in the country but it draws its patients mainly from Buganda.

Buganda lies at the Equator, north of Lake Victoria. It has a tropical climate with an ample rainfall which is spread almost throughout the year. The people living in this area are the Baganda, but there are immigrants from other tribes who have come

either to work in Kampala or to settle in the country. More than 50.% of the people can read and write, but superstition and taboos are still deeply rooted among the ordinary people. The general standard of living is low, the per capita income being £24.7 (Figure for 1967-68). There is social stratification among the Baganda which is partly a legacy of the past feudal system. At the apex are the chiefs, landlords and top-civil servants. This class enjoys a high standard of living. The middle class consists of the people who partly earn their living from land but have jobs or some trade, while at the base of the pyramid are the peasant cultivators, the poor uneducated class. It is the peasant cultivator with whom we are concerned in this context.

Buganda is an agricultural country, the main cash crops being cotton and coffee. The food crops grown are matoke, sweet potatoes, cassava, beans, vegetables and fruits.

The people live in family groups. Polygamous marriage is common. The average number of children

in a productive family is five to seven, but in a polygamous home there may be many more children. The size of the family may determine the general standard of living.

The ordinary peasant does not know the various food requirements. There are taboos about food. The females do not eat chicken and eggs, and the Mamba Clan do not eat mud-fish. The average meal consists of steamed matoke, sweet potatoes or cassava, eaten with a sauce of beans or green vegetables. Meat and fish are bought and eaten about once a week. The Baganda are not nomadic, so milk is usually not drunk except by people who can afford to buy it. Green vegetables and fruits are common.

The protein and Vitamin-A values of the various foods are given on the next page (M.R.C. Special Report Series No. 302).

Representative Values per 100 Gm of Edible Portion

Items	Water Content	Protein Gm.	Vitamin - A I.U.
STAPLE FOODS:			
Matoke (Plantain)	67	1.0	100
Sweet Potatoes	70	1.5	100
Cassava	60	0.7	-
Peas	10	25.0	-
Beans	10	24.0	-
VEGETABLES:			
Amaranthus	85	5.0	3000
Pumpkin Leaves	91	2.0	1000
Cabbage	93	1.5	30
Tomato	94	0.4	150-1200
FRUITS:			
Mango	83	0.5	500-2000
Orange	86	0.8	30
Banana (Sweet)	70	1.0	100
Pineapple	85	0.4	20- 200
Lemon	90	0.7	-
Pawpaw	89	0.6	1000

It will be observed from the table that the foods commonly eaten have low protein content but adequate in Vitamin A.

Babies are normally breast-fed for about one year, but should another pregnancy occur prematurely, the baby is weaned to a solid diet. There is still superstition among some peasants that in the presence of another pregnancy if the mother continues breast-feeding the baby grows thin, becomes difficult and may develop certain illnesses. In the normal circumstance, however, the baby is gradually introduced to solid food from the age of about six months until it is finally weaned in about a year's time. Unfortunately in some cases the baby is weaned to a diet which, although it provides a comparatively large supply of calories, is deficient in protein (Trowell and Muwazi, 1945). Kwashiorkor thus starts shortly after weaning.

Other factors which may contribute to the development of Kwashiorkor are Psychological and Medical (Geber and Dean, 1957; Farmer, 1960; Jelliffe and

Jelliffe, 1963). The most important psychological factor is "maternal deprivation". Often the child is sent away to stay with a relative because of another pregnancy or the child may have been abandoned because of a broken home or the child may be displaced by another sibling. Such a separation deprives the child of maternal security. The child becomes unhappy and commonly develops anorexia (Geber and Dean, 1956). Most children remain in a latent state of malnutrition indefinitely until some medical condition such as measles, malaria, diarrhoea, intestinal infestation, or some other illness precipitates the disease.

THE EYE IN KWASHIORKOR

Programme of Study

A (i) The incidence of corneal lesions of 200 children who had been on treatment for Protein-Calorie Malnutrition was compared with that of 1,000 apparently well-nourished children.

(ii) Clinical observations were made on 100 children suffering from Kwashiorkor disease in both the Outpatient Clinic and the Children's Ward. All the eyes were examined by inspection. Every cornea was stained with fluorescein and inspected with a corneal loupe. The authentic signs of Vitamin A deficiency were deliberately being looked for. It was not practicable to examine the fundi of these children; neither was dark adaptation test done.

B Estimations of Serum carotene levels were done in 20 children with Kwashiorkor. This was compared with the levels in 20 children who had no sign of malnutrition.

C Histopathological examinations were made on post-mortem corneae of 10 children dying of or with Kwashiorkor. This was compared with postmortem histology of the corneae of 5 children dying of other medical conditions.

Definition of Kwashiorkor

The clinical features of Kwashiorkor have been fully reviewed in the literature (Miklejohn and Passmore, 1951; Brock and Autret, 1952; Joint FAO/WHO Expert Committee, 1953; Trowell, Davies & Dean, 1954d; Jelliffe, 1955b; Dean, 1965). Only the salient features of this syndrome will be mentioned here.

Kwashiorkor is a state of malnutrition which is brought about by a deficiency of dietary protein in the presence of a comparatively large supply of calories. In this condition, growth is retarded as manifested by a low body weight for the corresponding age, decreased length and muscle wasting. There is dyspigmentation of hair and skin. Oedema associated

with hypo-albuminaemia and dermatosis occurs in severe cases. Gastro-intestinal disorders are common. There is an impaired secretion of digestive enzymes, leading to intestinal malabsorption. Anaemia is almost invariably present. On occasion Kwashiorkor may be associated with various types of Vitamin deficiencies. Various pathological changes have been noted. These include fatty infiltration of the liver, atrophy of the pancreatic exocrine glands, thymus and intestinal mucosa.

The biochemical changes that occur in Kwashiorkor are not fully understood. But in the main there appears to be a generalized slowing down of protein metabolism although the enzyme systems for synthesis are normal (Waterlow, 1962). As a result the serum albumen is reduced but the gamma globulins are usually normal or even increased. Many of the essential amino-acids are reduced while most of the inessential amino-acids are increased (Dean, 1965).

Carbohydrate metabolism is also affected. There

is intolerance to Lactose (Dean, 1952), so that diarrhoea frequently occurs. Hypoglycaemia which sometimes is fatal is another feature of Kwashiorkor whose cause is unknown (Kahn and Wayburne, 1961; Wayburne, 1963). There is also some electrolyte imbalance. The oedema of Kwashiorkor is associated with retention of sodium, while the frequent diarrhoea often leads to potassium depletion.

(Ai) MORBIDITY OF THE CORNEA IN PROTEIN-CALORIE MALNUTRITION

There is more morbidity of the cornea among malnourished children. This was revealed by the findings in this study.

The incidence of corneal lesions among 200 children who had been on treatment for Protein-Calorie Malnutrition and were being followed up in the "Mwana Mugimu" (Clinic for malnourished children) was compared with that of 1000 apparently well-nourished children who were attending the Paediatric Clinic for other medical conditions. Children of the same age group of 1-5 years were examined. The children were selected at random as they came into the Clinic. Similar examination method was applied in both groups. Examination was carried out in each case by observation and inspection of the cornea using a monocular loupe of x 10 magnification with focal illumination.

Among the 1000 well-nourished children only 2 had corneal opacities. But among the 200 malnourished children 4 had corneal opacities.

Applying the Chi-Square Test to assess the significance of this finding:-

	Normal Children	Malnourished Children	TOTAL
Normal	998	196	1,194
Affected	2	4	6
TOTAL	1,000	200	1,200

$$X_1^2 = 7.5376$$

$$.001 < \text{Prob.} \left[X_1^2 \geq 7.5376 \right] < .01$$

$$.1\% < p < 1\%$$

The Chi-Square test indicates that there is an association between Protein-Calorie Malnutrition and increased morbidity of the cornea.

A(ii) THE OCULAR MANIFESTATIONS OF KWASHIORKOR

It is difficult to examine the eyes of children suffering from Kwashiorkor. They are usually irritable and when confronted with a medical examiner they start crying and struggling away. Many of them appear to have photophobia. This is not in many cases due to ocular causes but it is part of the mental change of these patients.

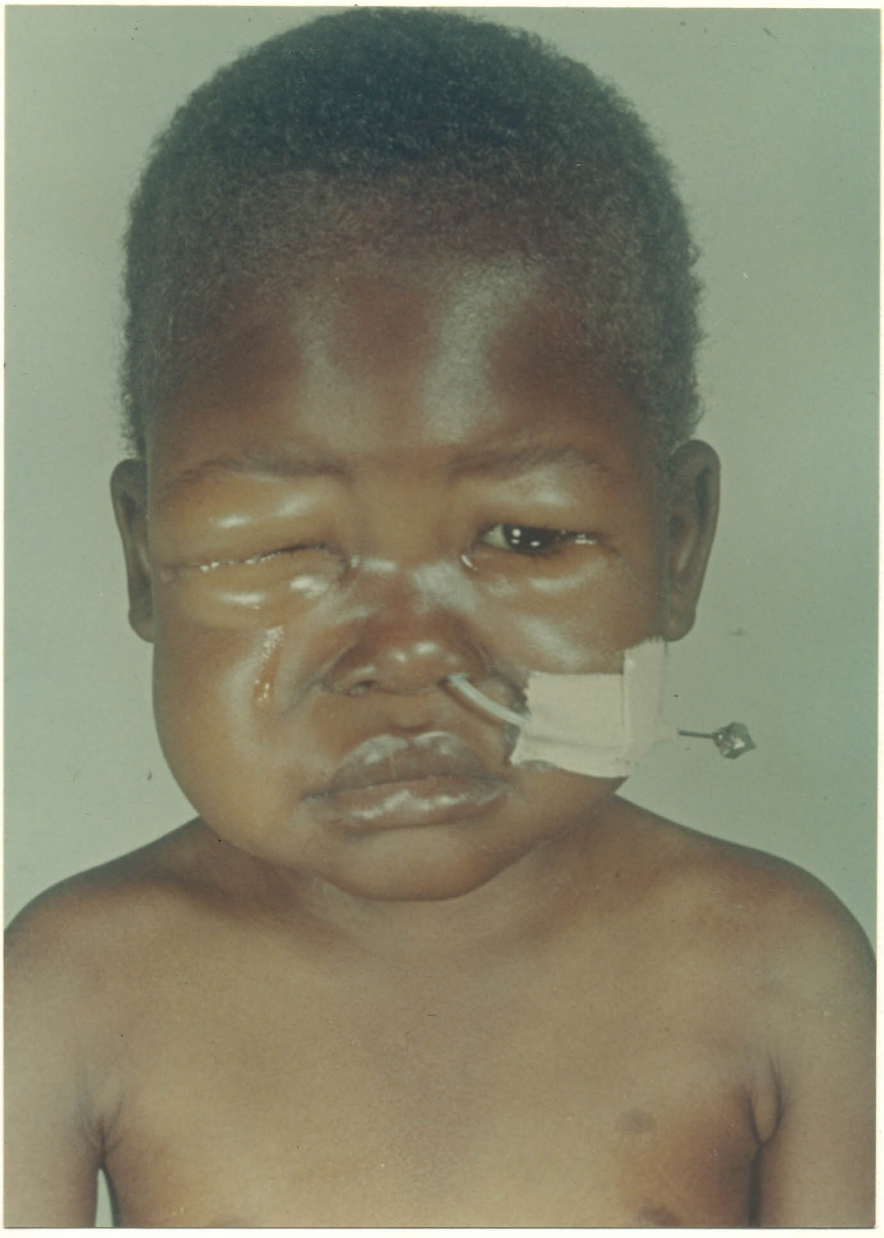
The Eyelids

In severe Kwashiorkor the moon-shaped appearance of the face is a striking feature. The eyes are puffy with oedema of the lids. The oedema may be so gross that the eyes are closed and the skin of the opposed surfaces of the lids may become excoriated. Oedema is always a sign of severe Kwashiorkor. It is associated with a low serum albumen and retention of excess water with sodium in the extracellular spaces.

The skin of the eyelids, like the skin elsewhere on the body, may show dyspigmentation due to loss of pigment. This may be patchy or diffuse. But the

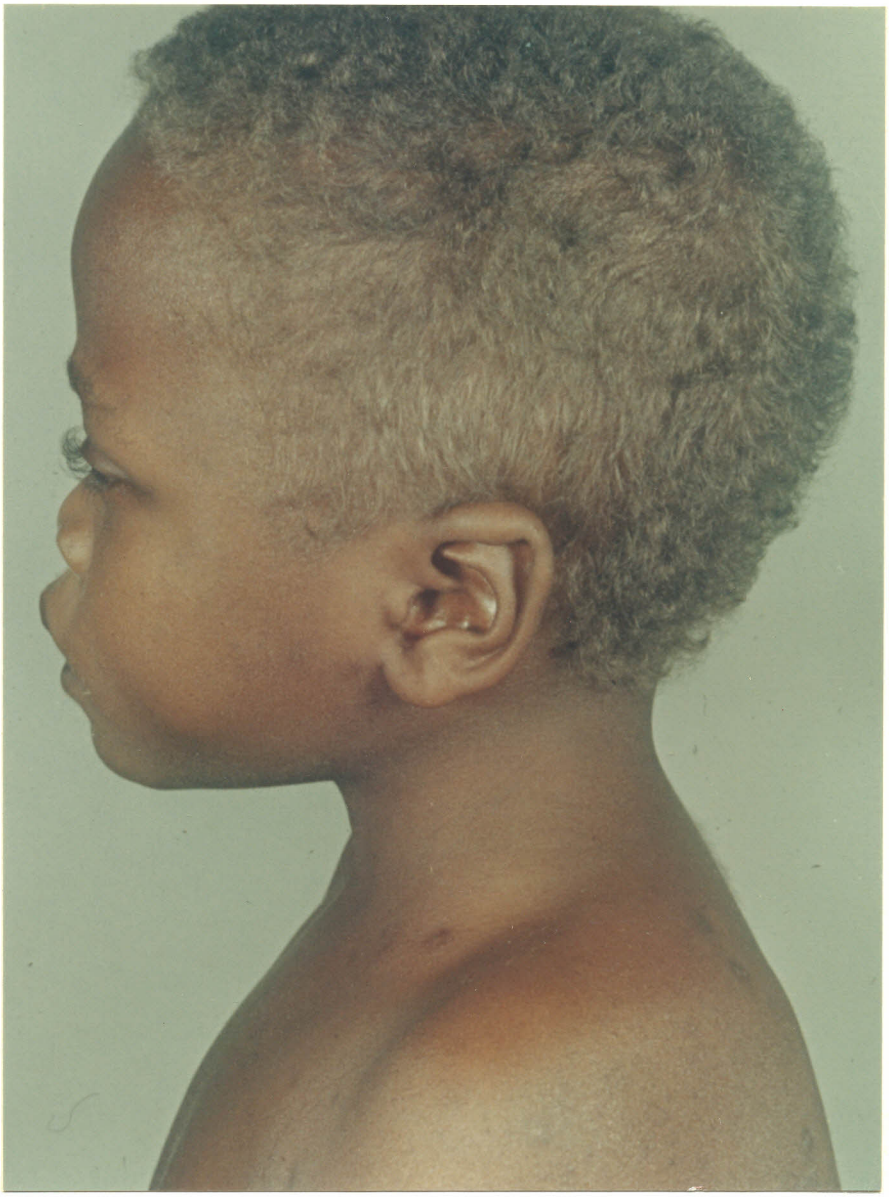
face generally seems to be spared from the "flaky-paint" dermatosis which occurs in the more severe cases. Kwashiorkor is typified by dyspigmentation of hair to brown colour. Except in albinism, congenital hypopigmentation and individuals of mixed race, the African hair is black and curly. The upper eyelashes curl upwards and the lower ones curl downwards. In Kwashiorkor the eyelashes change in texture and become thinner, rather silky and straight. The straightening gives the impression of the eyelashes having grown longer than normal. As the disease progresses, the eyelashes become easily pluckable. Some come off and the eyelashes appear sparse. If malnutrition is of long duration, dyspigmentation of hair takes place from black to brown and finally greyish-brown. These changes affect the eyebrows as well. The hair of the scalp undergoes change in texture and dyspigmentation earlier while the eyelashes and eyebrows seem to be more resistant to change, although eventually become affected too. There is correlation between the hair change and duration of the disease. (See Plates I and II)

PLATE I



Severe Kwashiorkor with oedema
of the face and hair changes

PLATE II



Moderately severe Kwashiorkor
with hair changes

The longer the duration the more is the dyspigmentation.

The cause of dyspigmentation in Kwashiorkor is not known. It has been suggested that it may be due to ariboflavinosis (Hughes, 1946). Pantothenic acid deficiency has also been suspected as a possible cause (Brock and Autret, 1952). Waterlow (1955) believes that the hair changes are associated with protein deficiency rather than with any Vitamin deficiency. Whatever the cause is, it is a constant feature of Kwashiorkor and was seen in nearly all the cases examined.

EYELID CHANGES

(No. of Patients seen 100)

Lesion	Number
Change in Texture of Eyelashes:	87
Dyspigmentation of Eyelashes:	55
Oedema of Lids:	18

The Conjunctiva

The conjunctiva appears white and the vessels seem to be reduced in number and calibre. Nearly all the children seen were anaemic. The anaemia was commonly due to ankylostomiasis and malaria. Megaloblastic anaemia and anaemia from diminished erythroid activity in the bone marrow have also been shown to occur in Kwashiorkor children in Mulago (Allan and Dean, 1965).

Most of the conjunctiva seen were of normal lustre and transparency. The bulbar conjunctiva did not appear dry as the surface was uniformly wetted by tears, nor was there thickening and wrinkling. There was no increased pigmentation of the conjunctiva, except perilimbal pigmentation which is a common feature of African eyes. No single Bitot spot was seen.

Five children had acute conjunctivitis with muco-purulent discharge but mild conjunctival hyperaemia. Three of the five children had co-existent corneal ulcers one of whom developed

perforations of the cornea. One child had conjunctivitis complicating measles. She also had corneal involvement with punctate keratitis which cleared on antibiotic treatment.

In the presence of conjunctivitis, the conjunctiva in Kwashiorkor showed a poor inflammatory vascular response. One did not see the red vascular congestion of acute conjunctivitis as in a well-nourished child.

CONJUNCTIVAL LESIONS

(No. of Patients seen: 100)

Lesion	Number
Pallor (anaemia):	91
Xerosis Conjunctiva:	-
Bitot Spots:	-
Acute Conjunctivitis:	5

The Cornea

On casual observation one might think that the cornea in a severe case of Kwashiorkor is normal but careful examination reveals that the cornea has reduced lustre. In the patients examined 34% of the cornea showed reduced lustre and transparency. There was slight haziness of the cornea. However, the smoky haze of xerophthalmia was not seen. A normal cornea is clear and transparent and has a thin pre-corneal film of tears and oily secretion which is uniformly spread over the entire cornea. When the normal cornea is exposed, it takes a few minutes before the pre-corneal film dries. But in severe Kwashiorkor the cornea shows breaking of the pre-corneal film on exposure for about 10 ~~minutes~~ seconds, with a tendency to drying more quickly. This is due to loss of surface epithelial continuity. The breaking of the pre-corneal film seemed to be aggravated by a state of dehydration. Many of the children were admitted with a history of diarrhoea and dehydration of varying degree was present. 17% of the corneae had epithelial abrasions which were more frequent in

the lower quadrant. These were small, superficial discrete abrasions. Eight eyes had corneal ulcers which were slow in responding to antibiotic treatment. Two of the patients developed perforation of the cornea.

None of the corneae showed any apparent vascularisation.

CORNEAL LESIONS

(No. of Corneae seen: 200)

Lesion	Percentage with Lesion
Reduced Lustre:	34%
Xerosis Cornea:	34%
Epithelial Abrasions:	17%
Corneal Ulcer:	3%
Perforation of Cornea:	1%

The high percentage of corneal lesions may be due to the fact that most of the children seen were those admitted with severe Kwashiorkor. It does not

represent the incidence of corneal lesions in Kwashiorkor children generally.

The occurrence of Xerosis cornea and corneal lesions seemed to be related to the level of serum protein. All the children who had xerosis cornea had serum protein of less than 4.5 Gm/100 ml. One of the children who developed a perforation of the cornea had serum protein of 2.8 Gm/100 ml. The only exception was a child who had perforation in both eyes after measles. He had a moderate level of serum protein (5.5 Gm/100 ml.). Both cases are described in more detail later.

It was not possible to do the serum protein in all the children seen. Serum Protein levels were done in 26 cases and the results are tabulated against the condition of the cornea on the next page.

Case No.	Serum Protein	Xerosis Cornea	Corneal Lesion
	4.1	+	-
	3.9	+	-
	4.0	+	Abrasion
	5.8	-	-
	4.0	+	-
	3.4	+	-
	4.1	+	-
	4.6	-	-
	4.1	+	-
	4.2	+	-
	4.1	+	-
	3.6	+	-
	3.8	+	-
	4.2	+	-
	3.2	+	Corneal Ulcer
	3.7	+	Abrasion
	4.9	-	-
	3.8	+	Abrasion
	4.7	-	-
	4.4	+	Abrasion
163905	2.8		Perforation
	5.2	-	-
128983	5.5		Perforation
	3.5	+	Abrasion
	3.4	+	Abrasion
	2.7	+	Abrasion

Case Histories of special interest

Patient No. 128983: A male child of $2\frac{1}{2}$ years of age was admitted with a history of having had measles one week previously. The mother had noted that there was something wrong with both eyes a few days before

admission. The child was admitted as a patient of Protein-Calorie Malnutrition.

The general clinical signs were apathy, retarded growth, muscle wasting, dyspigmentation of skin and sparse silky hair with hypochromotrichia. The child was anaemic - Hb 7.3 Gm; Total Serum Protein was 5.5 Gm.

Examination of the eyes revealed perforation of the right cornea, mainly involving the lower quadrant, with prolapse of the iris and lens. The eye had only mild injection. The left eye had a corneal ulcer. The corneal stroma beneath the ulcer appeared so thin that perforation was imminent. It did perforate the following day in spite of pressure bandage. Intensive local and systemic antibiotics were administered, but both eyes developed panophthalmitis after a few days.

This is a typical case of perforation of the eyes in a child with Protein-Calorie Malnutrition complicated by measles.

Case No. 163905: A male baby of one year was admitted with severe Kwashiorkor - (See Plates III and IV).

General clinical signs consisted of retarded growth, oedema of the legs and face, "flaky-paint" dermatosis, dyspigmentation of hair and severe anaemia.

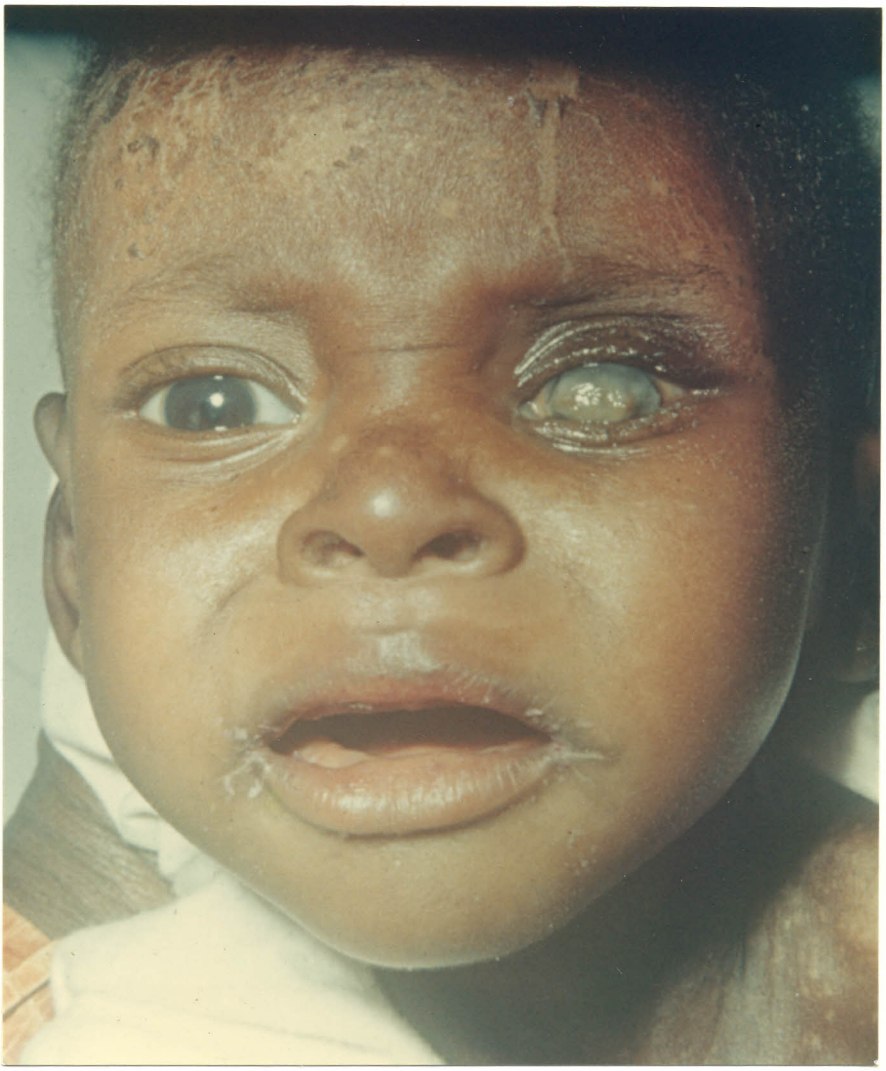
The eyes had oedema of the lids more marked in the left lids. The right cornea was hazy but did not show any stain with fluorescein. The left eye, however, had a severe corneal ulcer, with purulent discharge, but mild conjunctival and ciliary injection.

The child had severe anaemia - Hb 5.4 Gm; Total serum proteins was 2.8 Gm; Serum carotene was 30 micrograms. Eye swab revealed mixed organisms.

In spite of treatment, the cornea perforated after three days.

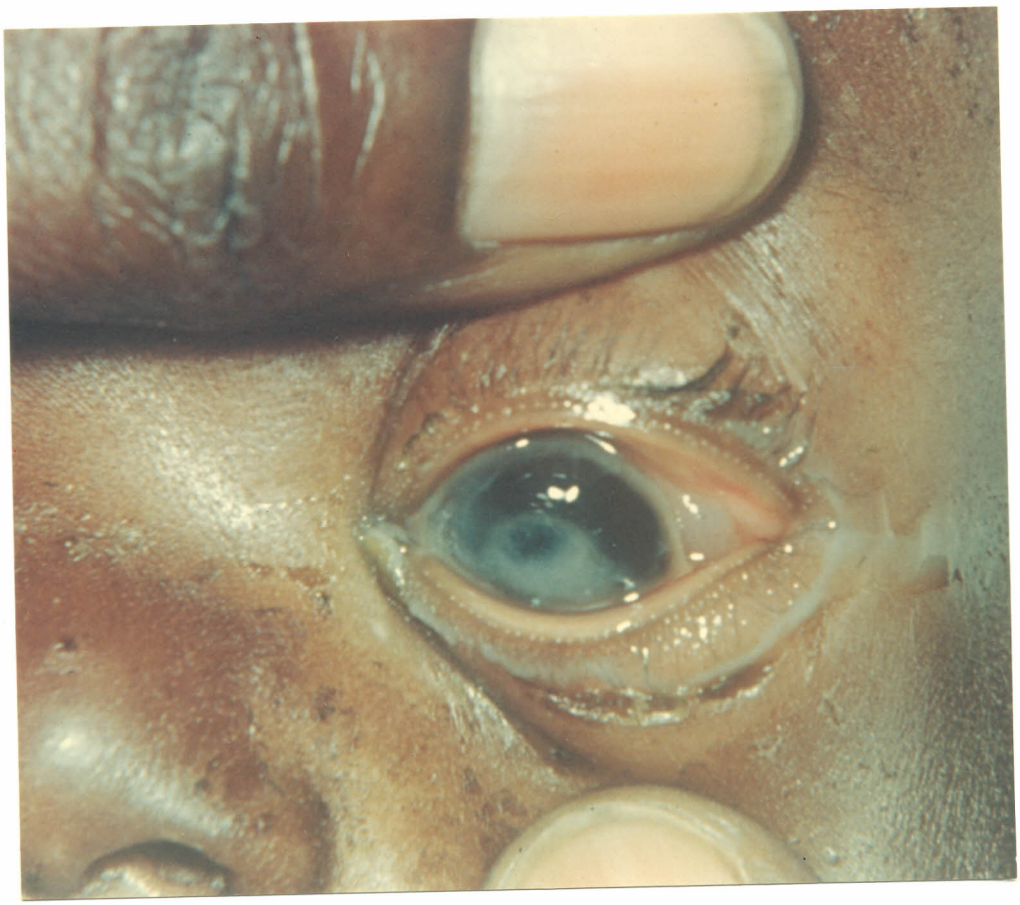
After about one week the right cornea also

P L A T E III



Patient No. 163905: Perforation of left Cornea.
Note the "flaky-paint" dermatosis of the forehead.

P L A T E IV



Patient No. 163905:
Perforated Cornea

developed a corneal ulcer. Again there was only mild ciliary injection. Culture of a swab from the eye revealed Ps. Pyocyanea (Lab. No. 1834/68) which were resistant to Streptomycin and Tetracycline and sensitive to Chloramphenicol. Unfortunately the mother absconded with the child from the hospital.

Here is a case of corneal ulcer in severe Kwashiorkor not responding to treatment. The poor vascular response in the presence of a severe inflammation was noticeable. This case also illustrates the role of infection in perforation of the cornea in malnourished children.

The Dietary Treatment of Kwashiorkor in Mulago:

There is no uniform acceptable diet in the treatment of Kwashiorkor. There are variations from place to place, the differences being related to the associated dietary deficiencies and a desire to achieve a locally applicable regimen (Wharton B.A., et al., 1968).

All cases of severe Kwashiorkor are admitted

and put on dietary treatment of high protein value. The regimen at Mulago is to provide in a digestible form a milk mixture, rich in protein and calories and suitable for a sick and anorexic child. The current Kwashiorkor milk is Casilan-dried skimmed milk - sucrose (CaDSu), the composition of which is as follows:

Ingredients of Dry Mixture		Nutritional Value of 100 Gm of reconstituted diet	
Casilan	33	Protein	4.0 Gm
Dried Skimmed Milk	30	Fat	6.1 Gm
Sucrose	30	Carbohydrate	4.6 Gm
Cotton Seed Oil	60	Calories	90
Potassium Chloride	2.7	Potassium	4.7 Meq.
Magnesium Hydroxide	0.3	Magnesium	1.3 Meq.
Sodium Chloride	none	Sodium	0.9 Meq.

The Kwashiorkor milk is given during the first week and from the second week or when the child is able to take feeds by mouth, the calorie intake is increased by introducing local foods, namely, sweet

banana, cooked plantain (matoke), sweet potatoes and groundnuts. No Vitamin A supplement is given at Mulago Hospital.

The children usually improve in a few weeks. The weight begins to increase from the second week, the serum protein rises at the rate of 1-2 gm per week and the demeanour improves (Staff 1967).

By the third week the condition of the eye also improves. Normal lustre of the cornea is restored and corneal abrasions are not demonstrable. It should be noted here that the condition of the cornea improves without additional Vitamin A therapy.

C O M M E N T

None of these children had Xerophthalmia. Xerophthalmia is a combination of xerosis conjunctiva with xerosis cornea. Xerosis conjunctiva is described as a dry, thickened and wrinkled conjunctiva, with increased pigmentation and on occasion with Bitot spots in the interpalpebral fissure (McLaren, 1962). None of these signs alone indicates Vitamin A deficiency, but the presence of them all (Paton & McLaren, 1960). In these children there was not a single case of Xerosis conjunctiva.

Xerosis cornea by itself does not constitute Xerophthalmia.

There is therefore no authentic clinical sign of Vitamin A deficiency in these children. Xerosis cornea is not necessarily a sign of Vitamin A deficiency. Oomen (1958) believes that corneal lesions in malnutrition are not due to exactly the same aetiology as Xerophthalmia, thus suggesting that there may at times be a different pathogenesis

for the condition.

Clinical Vitamin A deficiency does not seem to be an invariable feature of Kwashiorkor. Williams (1935) noted the absence of Vitamin A deficiency in Kwashiorkor in Accra, Gold Coast (Ghana). In Durban, South Africa, Scragg and Rubidge (1960) examined 1,565 children with Kwashiorkor but they described only corneal lesions and did not mention other signs associated with Vitamin A deficiency.

On the other hand, in India, where lack of Vitamin A and Protein are the most frequent cause of nutritional deficiency (Chandra et al., 1960), Kwashiorkor is associated with signs of hypovitaminosis-A. Venkatachalam and Gopalan (1960) reported 32% of children with Kwashiorkor in Hyderabab and 36% at Coonoor, India, of having signs of Vitamin A deficiency. Pereira (1966) reported 136 children with Vitamin A deficiency among 175 Kwashiorkor children. In Jordan Xerophthalmia occurs in Protein-Calorie Malnutrition (McLaren et al., 1965). In

Indonesia, Oomen (1954) noted Keratomalacia and Xerophthalmia in 29 out of 44 Kwashiorkor children.

There would therefore appear to be a regional variation in the occurrence of Vitamin A deficiency in Kwashiorkor. This variation appears to be related to the adequacy of Vitamin A in the local diet.

ASSESSMENT OF VITAMIN "A" STATUS IN KWASHIORKOR

There is as yet no accurate and reliable laboratory method of estimating the level of Vitamin "A" in Serum. The current spectrophotometric methods have inherent difficulties which render the estimations unreliable (Caster & Mickelson, 1955).

Moreover, the estimations of serum Vitamin "A" have been shown to bear an unreliable relationship to the nutritional status of either an individual or groups of individuals (Caster & Mickelson, 1955). Certain physiological factors influence the level of Vitamin "A" in the plasma. A rise in body temperature or acute infections cause a fall in the level of Vitamin "A" in the plasma (Clausen S. W. et al., 1938; Aron et al., 1946). Gastro-intestinal disturbances which impair the absorption of fats may be associated with a low level of serum Vitamin A (Ralli et. al., 1941). In experiments with human beings, it has been observed that changes in the level of Vitamin A occur only after the deficiency state has become prominent, whereas the serum carotene

level decreases rapidly in the early part of Vitamin A depletion (Hume & Krebs, 1949). It has also been shown that if the level of serum carotene is high, falsely low values of Vitamin A may be obtained. (McLaren et al., 1965). In any case the level of serum Vitamin A seems to be a characteristic of an individual rather than a reflection of Vitamin A intake (Caster & Mickelson, 1955; Rodger F. C. et al., 1964).

Determination of serum carotene levels on the other hand seems to be a better indicator of Vitamin A status in human beings (Caster & Mickelson, 1955; Kuming & Politzer, 1967).

In this study, therefore, serum carotene levels were estimated as a measure of Vitamin A status in children with Kwashiorkor. The method used was that of Kimble (1939 - See Appendix). Estimations in 20 Kwashiorkor children were compared with estimations in an equal number of children without any sign of malnutrition. The data obtained were as follows:

Serum Carotene in Normal Nourished Children

Age in Years	Sex	Serum Protein Gram per 100 ml.	Serum Carotene microgram per 100 ml.
3	F	6.3	50
6	F	7.2	45
3½	M	6.7	60
4	M	6.7	95
1½	M	6.1	50
3	M	7.3	160
3	F	7.5	95
1½	M	7.6	115
5	M	7.6	160
3	F	7.2	110
3	M	6.5	45
3	F	7.4	120
4	F	8.1	140
2	M	6.7	50
2½	F	6.9	75
1½	F	6.5	55
1	F	7.6	60
3	F	7.4	80
2	M	6.7	50
2½	M	7.6	65

	Serum Protein:-	Serum Carotene:-
Range:	6.1-8.1 Gm.	45-160 microgram
Mean:	7.1 Gm.	84 microgram
Standard Error:	0.12	8.58

Serum Carotene in Kwashiorkor Children

Age in Years	Sex	Serum Protein Gram per 100 ml.	Serum Carotene micro-gram per 100 ml.
2	M	5.0	35
1	M	3.4	45
1	M	2.8	30
1	F	4.3	30
1	M	3.7	20
8	F	3.6	20
2	M	3.8	30
2	F	3.5	40
1	M	4.5	45
1	F	4.6	35
2½	F	3.4	30
2	F	2.6	30
2½	M	4.4	25
1	M	3.5	30
1½	F	3.4	40
2	M	3.0	35
2	F	4.5	40
1½	F	3.5	35
2½	M	3.4	25
2	M	4.5	40

	Serum Protein	Serum Carotene
RANGE:	2.6-5 Gm.	20-45 microgram
MEAN:	3.8 Gm.	33 microgram
STANDARD ERROR:	0.15	1.64

The serum carotene levels in Kwashiorkor children were lower than those of normal children. The carotene levels for normal children ranged from 45-160 micrograms, with an average of 84 micrograms. In Kwashiorkor children, the levels varied from 20-45 micrograms, with an average of 33 micrograms. Although the children in the control group were a little older (average age $2\frac{3}{4}$ years) than the Kwashiorkor children (average age $1\frac{3}{4}$ years), the serum carotene levels would not differ significantly because of age. McLaren (1965) found age difference in serum carotene levels in much older children (average age $7\frac{3}{4}$ years).

Earlier in Mulago, Trowell and his co-workers (1954) found an average of 23 micrograms in Kwashiorkor children as compared with an average of 107 micrograms in the normal control group. The figures for Mulago are a little higher than those reported for Bantu children in South Africa (Kuming and Politzer, 1967).

These findings reflect a low level of serum Vitamin A in Kwashiorkor children. But the levels are not so low as to suggest a clinical deficiency

state. The levels in children who develop clinical Vitamin A deficiency are reported to be lower than these. Rodger and his colleagues (1964) noted that in children who developed xerophthalmia the individual serum carotene levels were markedly reduced, sometimes being practically at zero. McLaren and his co-workers (1965) also found very low serum carotene levels of not more than 12 micrograms (mean value) in children who had eye lesions. Kuming and Politzer (1967) gave a similar average figure of 12 micrograms in children with eye lesions in Kwashiorkor.

The reduced level of Vitamin A and carotene in Kwashiorkor is believed to be due to impaired absorption of Vitamin A, hypoproteinaemia and fatty infiltration of the liver, (McLaren, 1958; Moore, 1960; Scrimshaw, 1958; Arroyave et al., 1963).

However, there is evidence to show that although the liver undergoes fatty infiltration, it is not depleted of Vitamin A. Treatment of Kwashiorkor children with protein, without Vitamin A supplement,

causes a significant rise, in one week or two of Serum Vitamin A, which must have been released from the liver. (Arroyave et al., 1961 - 1963).

There is also conflicting evidence as to whether or not the absorption of Vitamin A is impaired in protein malnutrition. Some workers believe that the absorption of Vitamin A is impaired (McLaren, 1958; Arroyave et al., 1959; Moore, 1960). On the other hand Vinodini and his co-workers (1965) found that there was adequate absorption of Vitamin A when it was administered simultaneously with fat. They concluded that the high incidence of signs of Vitamin A deficiency in Protein Malnutrition may be explained on the basis of dietary inadequacy of Vitamin A, the factor of faulty absorption not being involved.

It is indisputable, however, that the low level of Serum Vitamin A in Protein Malnutrition is, at least, due to the reduced plasma protein carriers (Arroyave et al., 1963; Friend et al., 1961.)

The ratio of the mean serum protein and serum carotene in normal nourished children is 7.1 : 84 = 1 : 12. The ratio of the mean serum protein and serum carotene in the Kwashiorkor group is 3.8 : 33 = 1 : 9. Although one cannot put undue statistical significance to such biological variants, these two ratios, which are about the same, suggest that a fall in serum protein would cause a corresponding reduction in serum carotene and that therefore the low serum carotene in Kwashiorkor children is due in the main to their low serum protein (Arroyave et al., 1963; Friend et al., 1961).

In the presence of adequate dietary intake of Vitamin A and carotene, the secondary Vitamin A deficiency which occurs in Kwashiorkor does not seem to cause a clinical deficiency state. Moreover, in Kwashiorkor the growth of the body is arrested generally, so that the requirement for Vitamin A is correspondingly reduced (Moore, 1960).

THE HISTOPATHOLOGY OF THE CORNEA IN KWASHIORKOR

The literature on the histopathology of the cornea in Protein-Calorie Malnutrition is scanty. McLaren (1959, 1963a) described corneal changes in a rat which he had fed on a diet of cassava. Kuming and Politzer (1967) seem to be the first in reporting the histopathology of the human cornea in Kwashiorkor. They described post-mortem findings of the corneae of three children who had died of Kwashiorkor. This study makes a further contribution to their findings.

Post-mortem histological examinations were made on the corneae of 10 children who died of or with severe Kwashiorkor. Similar examinations were made on the corneae of 5 children who died of other causes as a control. The corneae were removed a few hours after death.

Processing of the Cornea

After removal from the body the cornea was fixed in 10% Formal Saline. It was then processed through the Automatic Tissue Processor (Histokinette).

Dehydration, clearing and infiltration of tissue was effected by automatic changing through the reagents over a 24-hour period as follows:

Dehydration	
Rectified Spirit:	30 minutes
" " :	30 "
" " :	1 hour
" " :	2 hours
Absolute Alcohol:	1 hour
" " :	2 hours
" " :	3 hours
Clearing	
Absolute Alcohol/Xylene:	30 minutes
Xylene:	1 hour
" :	2 hours
Infiltration	
Molten Wax at 56°C	4 hours
" " " "	6½ hours

The tissue was then embedded in a pan of fresh molten wax at 56° C and the wax allowed to cool to block in a sink of cold water.

Sections of tissue were cut at 5 microns on a rotary Microtome and mounted on clean slides over warm water at 50° C. They were then allowed to dry in an oven at 55° C for 30 minutes.

The staining methods used were Haematoxylin and Eosin, Mallory's Phosphotungstic acid-haematoxylin (P.T.A.H.) and Alcian blue.

Haematoxylin and Eosin Technique

1. Take Sections to water (deparaffinise in Xylol-absolute alcohol rectified spirit).

2. Stain with Harris Haematoxylin for 10 minutes.

3. Rinse in water to remove excess stain for 30 seconds.

4. Differentiate in 1% Hydrochloric acid in alcohol for 30 seconds.

5. Wash in running tap water for 5 minutes.

6. Counterstain with 1% aqueous eosin for 2 minutes.

7. Rinse quickly in water.

8. Dehydrate, clear in Xylol and mount in D.P.X.

By this technique the nuclei are stained blue while other tissues are stained shades of pink.

Phosphotungstic Acid-haematoxylin (P.T.A.H.) Technique

1. Take sections to water.
2. Place in 0.25% aqueous potassium permanganate for 5 minutes.
3. Wash in running water for 2 minutes
4. Rinse in distilled water.
5. Place in 5% Oxalic acid until sections are bleached for 10 minutes.
6. Wash in running water for 5 minutes.
7. Rinse in distilled water.
8. Stain in P.T.A.H. solution for 12-24 hours.
9. Dehydrate rapidly, clear in Xylene and mount in D.P.X.

This method applied to the cornea stains the nuclei blue while other tissue elements are stained red.

Alcian Blue Technique

1. Take sections to water.
2. Stain in 0.3% Alcian blue in 3% acetic acid for 20 minutes.
3. Rinse in distilled water.
4. Stain with 1% Neutral red for 30 seconds.
5. Rinse in water.
6. Dehydrate rapidly, clear in Xylene and mount in D.P.X.

The nuclei stain red, and other tissue elements including acid mucopolysaccharides and keratin stain blue.

The Normal Cornea

The normal cornea is made up of epithelium, Bowman's membrane, Substantia Propria, Descemet's membrane and the endothelium. The epithelium consists of five layers of cells, representing about 10-20% of the corneal thickness. The basal cells are columnar. The remainder of the cells are polyhedral while the superficial cells are flattened. Few leucocytes may

be seen in between the basal cells. All the cells are arranged in regular layers (See Plate V). Bowman's membrane is a structureless thin layer which separates the epithelium from the stroma. The Substantia Propria constitutes about 80-90% of the corneal thickness and is made up of laminae of bundles of collagen fibrils, running parallel with the surface. In between the fibre bundles are the nuclei of the corneal corpuscles. Deep to the stroma is Descemet's membrane. The endothelium, the deepest layer, is a single layer of flattened cells.

The normal cornea is avascular.

The epithelial cells go through a normal, regular maturation by simultaneous change in the nucleus and cytoplasm. The nuclei of the basal cells are large and oval. But as the cells approach the surface the nuclei become smaller until the cells and the nuclei are flattened at the surface. The normal cells do not become koratinised.

As the superficial cells desquamate, the epithelial cells are continuously being replaced by

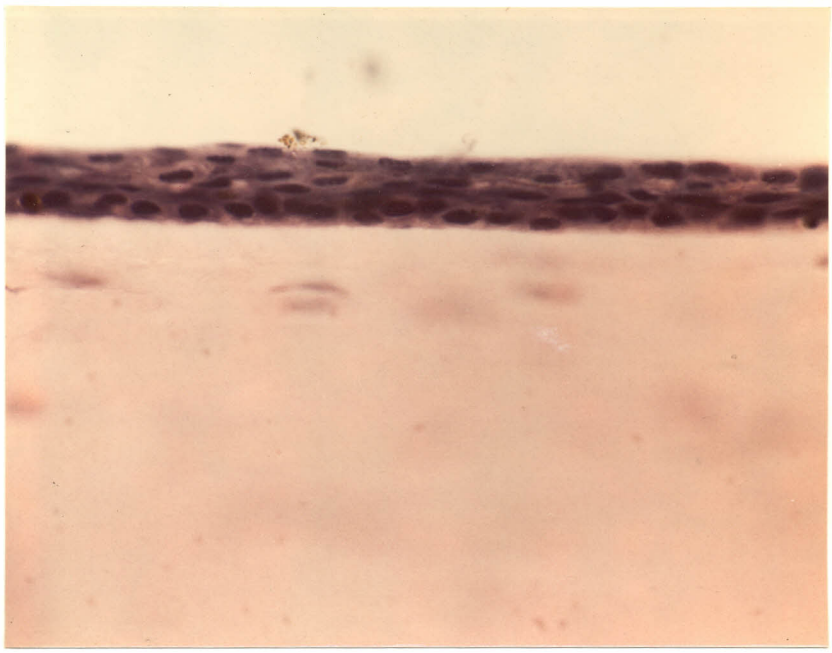
mitotic division of the basal cells. In injury of the epithelium, when a large area is denuded, replacement may take place from the adjacent conjunctival cells (Mann I., 1944).

The Cornea in Kwashiorkor

The main change observed in the corneae of the ten Kwashiorkor cases was that of atrophy of the corneal epithelium (See Plates VI, VII, and VIII; and Table on Page 58,59). The epithelium was reduced in some cases to only two cell layers. The extent of the atrophy seemed to correspond with the duration of the illness and the level of serum protein. The longer the duration of the illness and the lower the serum protein the more was the atrophy. The atrophy of the epithelium may be due to an arrest of mitosis of the basal cells.

The epithelium showed loss of regular maturation. Large vesicular nuclei could be seen near the corneal surface and there was loss of normal layering. In some sections there was keratinisation.

P L A T E V

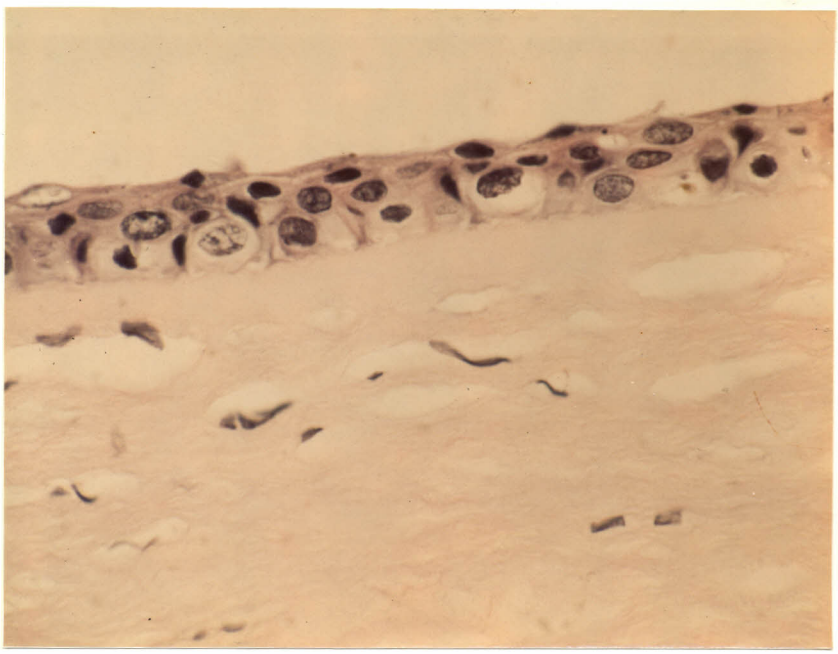


Normal Corneal Epithelium,
Bowman's membrane and part
of Substantia Propria.

P L A T E VI

Atrophy of Corneal Epithelium
Bowman's membrane destroyed
by vascularisation

P L A T E VII



Vacuolation of the basal cells.
Note large vesicular nuclei
near the surface.

P L A T E VIII

Atrophy of Corneal Epithelium.
Note oedema of Substantia
Propria.

The basal cells in most cases were abnormal, unlike those described by McLaren (1962). There was vacuolation of the basal cells. McLaren (1959) had earlier noted a similar abnormality of the basal cells in the corneae of rats with severe protein deficiency and said that they were unlike the appearance seen in Vitamin A deficiency. Vacuolation of the epithelial cells may indicate a breakdown in the normal metabolism of the cell, allowing the entry of excess fluid into the cell.

Bowman's membrane was destroyed in three corneae. One of them was destroyed in places by an ulcer and another partly by vascularisation.

The stroma had a variable amount of oedema as shown by more separation of the fibre bundles. This was unlike the appearance seen in the five normal sections.

Descemet's membrane and the endothelium appeared normal.

There was no cellular infiltration of the cornea, except in one cornea which had an ulcer. The three cases reported by Kuming and Politzer (1967) had severe corneal ulcers which accounted for the inflammatory cellular infiltration. McLaren (1962) also mentions cellular infiltration of the stroma as a sign of Xerosis cornea. This phenomenon was not observed in these autopsies, except in one which had a previous corneal ulcer. It does not seem to be a constant feature, but is probably an inflammatory vascular response.

POST-MORTEM HISTOPATHOLOGY OF CORNEA IN KWASHIORKO

AGE	SEX	SEVERITY OF KWASHIORKOR	DURATION	CAUSE OF DEATH	SERUM PROTEIN	CORNEAL EPITHELIUM	CORNEAL STROMA
2 yrs K1	M	severe	Few months	Kwashiorkor	-	Atrophy of epithelium. Irregular cell layers. Vacuolation of basal cells.	Bowman destroyed in some places. Cellular infiltration due to ulcer. Oedema of stroma.
3½ yrs K 2	F	severe	1 Year	D & V	4.1/gm	Atrophy. Irregular cell layers. Keratinized.	Oedema of stroma
3 yrs K 3	F	severe	1 Year	Kwashiorkor	3.3/gm	Marked atrophy (2 cell layers). Irregular cell layers. Vacuolation of basal cells. Keratinized.	Bowman destroyed Oedema of stroma
2 yrs K 4	M	severe	1 Year	Kwashiorkor	-	Marked atrophy (2 cell layers). Irregular cell layers. Vacuolation of basal cells. Keratinized.	Bowman destroyed and vascularized. Oedema of stroma.
1½ yrs K 5	M	severe	6 months	Pneumonia Ruptured oesophagus	4.6/gm	Atrophy	Oedema of stroma

1½ years K 6	M	severe	Few months	Kwashiorkor	3.4/gm	Atrophy (2-3 cell layers). Irregular cell layers.	Oedema of stroma.
2½ Years K 7	F	severe	6 months	Kwashiorkor	3.6/gm	Atrophy (2-3 cell layers)	Oedema of stroma.
1½ Years K 8	M	severe	6 months	Kwashiorkor	3.0/gm	Atrophy	Oedema of stroma.
2 Years K 9	F	severe	Few months	Generalized infection.	4.6/gm	Atrophy (3 cell layers. Vacuolation of basal cells. Keratinized.	Oedema of stroma
1½ Years K 10	M	severe	6 months	Kwashiorkor	4.2/gm	Atrophy	Oedema of stroma

D I S C U S S I O N

In spite of its exposure, constant presence of potential pathogenic bacteria and its avascularity, it is remarkable that the normal cornea resists bacterial infection. The conjunctival sac has always some bacterial flora. Although most of the organisms normally present are non-pathogenic, some of them are morphologically identical with pathogenic organisms, (Gibson, 1951; Smith, 1954; Duke-Elder, 1965). Kuming and Politzer (1967) did a survey of 30 Bantu children and found that most of the eyes had flora of potential pathogens. The same organisms which flourish in the conjunctival sac are found on the corneal epithelium as well (Duke-Elder, 1965).

The intact corneal epithelium is the vanguard of the defence mechanism of the cornea against infection. The normal corneal epithelium acts as a defence barrier against bacterial infection by imperviousness of its cells. With the exception of gonococci, diphtheria bacilli, and viruses, the intact corneal epithelium is impervious to bacterial toxins ordinarily present

(Duke-Elder, 1965).

In addition, the relatively low surface temperature of the cornea, due to its exposure, constant evaporation of the precorneal film of fluid and lack of blood supply, does not allow easy propagation of bacteria. Except during sleep, the constant blinking enables the tears to wash away from the sensitive cornea, irritating particles, deleterious agents and their products. The same blinking mechanism maintains the precorneal film and thus avoids drying of the corneal surface which would otherwise lead to abrasions of the epithelium.

Furthermore, the tear fluid contains an antibacterial enzyme, namely, lysozyme. The bacteriocidal activity of lysozyme depends upon its property of dissolving the mucopolysaccharidic coats of certain bacteria.

The Lowering of Resistance of the Cornea in Kwashiorkor

The resistance of the cornea to infection is lowered in Protein-Calorie Malnutrition. There is more morbidity of the cornea among children who have been malnourished. Thus among 1,000 well-nourished children examined there were only 2 children with corneal opacity, whereas among 200 children who were being treated for malnutrition 4 (2%) had corneal opacities.

The lowering of resistance of the cornea to infection must be explained on the basis of the histopathological change brought about by a state of malnutrition. In the main this change affects the corneal epithelium. Furthermore clinical observation suggests that humoral defence reaction is impaired in Protein-Calorie Malnutrition. The eye has poor inflammatory vascular response in the presence of a severe corneal ulcer.

In Kwashiorkor the corneal epithelium becomes thinned by atrophy, the cells are abnormal and they may be keratinized. Corneal epithelial abrasions

frequently occur. Thus in the 100 patients examined 17% had epithelial abrasions. Abraison of the epithelium renders the cornea liable to infection. The disease process may then spread rapidly to perforation as Bowman and Descemet's membranes are permeable to toxins and the substantia propria, because of its avascularity, is slow to mobilize defence reactions.

The condition of Keratomalacia or so-called Discrete Colliquative Keratopathy is probably not just a spontaneous necrosis of the cornea, but is almost certainly the perforation of an abnormal cornea brought about by a rapidly advancing infection in the face of impaired defence mechanisms. McLaren (1963b) observed in experimental animals that a break in the corneal epithelium may permit the entry of infection which may lead to keratomalacia. In one of the cases cited in the text organisms were isolated from the corneal ulcers which subsequently perforated.

The Vitamin A Hypothesis

Systematic knowledge on clinical Vitamin A deficiency seems to date from about the middle of the 19th

century. Reports of ocular signs were given by several clinicians among whom were Bitot (1863), Simon Snell (1876), and Von Graefe (1883). Simon Snell (1876) treated children who were suffering from night blindness associated with Bitot spots with cod-liver oil and iron. In Denmark, Bloch (1924) described children with Vitamin A deficiency, some of whom developed perforation of the cornea associated with infection. Although he attributed the ocular signs to Vitamin A deficiency, it is obvious from his descriptions and photographs that many of his patients were suffering from protein-calorie malnutrition. It should be noted that his patients improved on treatment with milk and cod-liver oil. Biswas (1941) described Vitamin A deficiency in children in Bengal who developed malnutrition from a diet which was deficient in protein. He writes, "an insufficient supply of milk to children is one of the commonest causes of this deficiency," and that "insufficiency or absence of breast feeding" was another cause. There could be no better setting for protein-calorie malnutrition!

There is a spate of reports in the literature on clinical Vitamin A deficiency. But it is difficult to explain why Vitamin A deficiency was supposed to be the prime cause of the ocular signs in malnutrition.

Experiments of Vitamin A deficiency in human beings do not seem to lend support to the Vitamin A hypothesis.

Booher and his co-workers (1939) did an experiment on 5 adults who were fed on food deficient in Vitamin A. They noted impairment of dark adaptation after 16 days but they did not see keratinization of epithelial structures of the eye after 124 days. Similarly Wald and his co-workers (1942) reported only impairment of dark-adaptation in the volunteers who were fed on a diet deficient in Vitamin A. Neither did Brener and Roberts (1943) note any eye signs apart from poor dark adaptation in adults after $7\frac{1}{2}$ months on a diet without Vitamin A. They concluded that either the demand for the organism was not great enough to cause sufficient depletion of the hepatic stores in $7\frac{1}{2}$ months or the alleged signs of Vitamin A deficiency were not solely a result of uncomplicated Vitamin A deficiency.

Perhaps the most comprehensive investigation on the effects of Vitamin A deficiency in the human was the "Sheffield Experiment" which was carried out during the second World War (Hume and Krebs, - 1949). Great care was taken to exclude more than traces of Vitamin A and provitamins from the diet on which volunteers were fed. After 18 months, apart from deterioration of dark adaptation, clinical examinations revealed no significant differences of the appearance of the cornea and conjunctiva between the deprived and non-deprived group or in the same person before and after deprivation of Vitamin A.

It may be argued that these experiements were carried out on adults who are subject to no special physiological demand on Vitamin A such as is imposed by rapid growth in children.

Vitamin A deficiency is probably not the main aetiological factor in the pathogenesis of the corneal abnormality in Kwashiorkor children in Uganda. Estimations of serum carotenoids do not indicate a severe Vitamin A deficiency state. Primary Vitamin A deficiency is rare in the native population in

Uganda. Vitamin A deficiency is also rare among malnourished children in and around Mulago (Mitchell, 1933; Trowell, 1946-1958; Welbourn, 1954; Jelliffe et al., 1961; Jelliffe et al., 1963). Among the 100 Kwashiorkor children examined in this study there was none with the authentic signs of Vitamin A deficiency. McCance (Personal Communication) who has worked in the Infantile Malnutrition Unit, Mulago - Medical Research Council - for several years never saw any sign of Vitamin A deficiency in Kwashiorkor children.

Similar observations have been made elsewhere in Tropical Africa. Williams (1935) noted the absence of Vitamin A deficiency in Kwashiorkor in Accra, Gold Coast (Ghana). Jelliffe (1955c) also stressed the rarity of Vitamin A deficiency in West Africa.

Although the level of Serum Vitamin A is low in Kwashiorkor children in Mulago, as reflected by low serum carotene levels, it does not seem to be so low as to cause a clinical deficiency state. The low level of Vitamin A in Kwashiorkor is due to protein deficiency (Scrimshaw, 1958; Arroyave, 1963).

Protein deficiency leads to impairment of Vitamin A transport because of the reduced plasma protein carriers. Also in Kwashiorkor the child is either anorexic or so ill that the dietary intake is reduced and the associated diarrhoea reduces the absorption of food. The levels of serum Vitamin A and Carotenoids must probably be virtually at zero or very low before its classical deficiency state occurs, (Rodger et al., 1964; Yap-Kie-Tiong, 1956; McLaren, 1962; McLaren et al., 1965).

The histological changes observed in the cornea of Kwashiorkor children in Mulago cannot be explained on the basis of Vitamin A deficiency alone. Vitamin A deficiency is assumed to cause hyperplastic keratinized epithelium (McLaren, 1962). Yet experimentally protein deficiency may cause keratinization (McLaren, 1963c). It has been suggested that keratinization may be a repair process of the basal cells, stimulated by atrophy of the epithelium (Wolbach and Howe, 1925).

It is improbable that atrophy of the corneal epithelium is a result of Vitamin A deficiency. Friedenwald and his co-workers (1945) found that mitotic

activity of the corneal epithelium in experimental animals was impaired in Vitamin A deficiency but they concluded that the inhibition of mitosis could not be attribu ed to a failure in the growth of individual cells. Blackfan and Wolbach (1933) stated that atrophy of the epithelium was a specific effect of Vitamin A deficiency. But it is clear from the cases they described that they were dealing with Protein-Calorie Malnutrition. Atrophy of the epithelium seems to be a sepecific feature of Kwashiorkor (Trowell, Davies & Dean, 1954e). But it is more probable that a deficiency of protein is the principal factor in the epithelial atrophy since protein is the body-building material. Severe protein-calorie deficiency arrests growth of the body generally.

The Protein Deficiency Hypothesis

Although the eye lesions in malnutrition have for long been attributed to Vitamin A deficiency, it is becoming more generally considered as a multiple deficiency syndrome (Bagchi et al., 1959; Oomen, 1958; Kuming & Politzer, 1967; Yap-Kie-Tiong, 1956; Venkataswamy, 1967). Besides lack of Vitamin A,

protein deficiency plays an important role in the pathogenesis of keratomalacia (Yap-Kie-Tiong, 1956). Vinodini and Srikantia (1965) found that protein deficiency was invariably present in children with hypovitaminosis A. McLaren and his co-workers (1965) noted that Xerophthalmia is almost always associated with protein malnutrition in Jordan. Oomen (1958) believes that "keratomalacia is not due to exactly the same aetiology as is Xerophthalmia".

There seems to be a regional variation in the involvement of the eye in Kwashiorkor. This seems to depend upon whether or not there is lack of dietary Vitamin A. In areas where there is both lack of Vitamin A and protein in the diet, Kwashiorkor is associated with signs of hypovitaminosis A (Chandra et al., 1960; Venkatachalam and Gopalan, 1960; Pereira, 1966). On the other hand in areas where there is adequate dietary intake of Vitamin A, Kwashiorkor is not associated with signs of Vitamin A deficiency (William, 1935; Scragg and Rubidge, 1960).

Because of the relative unimportance of Vitamin A deficiency in Uganda, it is postulated here that the

primary aetiological factor in the pathogenesis of the corneal histological changes in Kwashiorkor children in Mulago is protein deficiency, with Vitamin A deficiency playing a secondary role. Protein is the body-building material and in its severe deficiency state the growth of the body is arrested generally. This is further borne out by the fact that the condition of the eyes improves on dietary treatment of high protein value alone, without Vitamin A supplement.

In Uganda, a child is more likely to develop protein deficiency but have an adequate intake of the easily available carotenoids. There must be in the population a wide spectrum of the state of malnutrition ranging from the subclinical to frank Kwashiorkor and nutritional marasmus. The consequent change reduces the corneal resistance to infection. This also explains why in underdeveloped countries measles causes so much blindness among children.

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A P P E N D I X

Determination of Carotenes in Serum (Kimble, 1939)

(Extract from Practical Clinical Biochemistry, by H. Varley, Fourth Edition, Page 608 - Heinemann):

Technique: Pipette 3 ml. of serum or plasma into a stoppered 25 ml. measuring cylinder and add 3 ml. of absolute ethanol, slowly drop by drop with shaking, in order to obtain a finely divided precipitate of protein. Add 6 ml. of the light petroleum and shake vigorously for ten minutes. Pour the emulsion thus produced into a centrifuge tube, cork, and spin at a low speed for about one minute. Pipette off as much as possible of the light petroleum layer, taking care not to remove any of the watery layer with it.

Determination of the Carotenes

Place the light petroleum extract in the colorimeter cup and read directly, using a violet filter, or transmission at 440 millimicrons. Use light petroleum as blank or to set the instrument. Prepare a standard curve from a stock solution containing 50 mg. β-carotene per 100 ml. of light petroleum, diluted

1 in 50 to give a standard solution for use containing 1 mg. per 100 ml. Use this to set up a series of standards as follows:

Micrograms carotenes per 100 ml. serum:	0	50	100	200	400	600
Ml. of standard solution (1 mg. per 100 ml.):	0	0.25	0.50	1.0	2.0	3.0
Ml. light petroleum:	10	9.75	9.50	9.0	8.0	7.0

The concentration of carotenes in micrograms per 100 ml. of serum is read directly from this curve. The fact that 2 ml. of light petroleum contain the carotenes from 1 ml. serum has been taken into account.