

VITAMIN A STATUS IN CHILDREN
WITH PROTEIN-ENERGY MALNUTRITION
AND
MEASLES AT KENYATTA NATIONAL HOSPITAL

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A DISSERTATION PRESENTED IN PART FULFILMENT FOR THE
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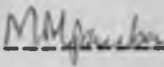
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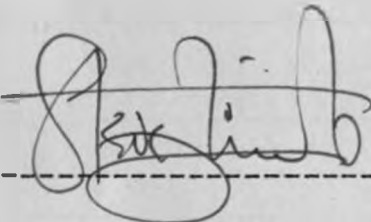
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ABBREVIATIONS

ICNND	-	United States Interdepartmental Committee on Nutrition for National Defense.
		Later renamed: Interdepartmental Committee on Nutrition for National Development.
IDH	-	Infectious Diseases Hospital.
PDU	-	Paediatric Demonstration Unit.
PEM	-	Protein - Energy Malnutrition.
POW	-	Paediatric Observation Ward.
RBP	-	Retinol - binding Protein.

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SUMMARY

Serum levels of retinol, retinol-binding protein and prealbumin were measured in 50 children with protein-energy malnutrition, 17 well-nourished children suffering from measles and 33 children with protein-energy malnutrition suffering from measles. These were compared with 37 controls.

Protein-energy malnutrition and measles were found to depress retinol and prealbumin levels. There was no significant difference in mean retinol levels among the study groups. Protein-energy malnutrition with measles combined were found to have a more depressing effect on serum prealbumin level than protein-energy malnutrition alone. Measles on its own did not have a marked lowering effect on prealbumin. Only the combination of measles with protein-energy malnutrition were found to have a depressing effect on serum retinol-binding protein level.

Immunisation against measles and supplementation of vitamin A in the management of children with protein-energy malnutrition and measles will prevent xerophthalmia and therefore blindness.

INTRODUCTION

Protein-energy malnutrition is a commonly encountered deficiency state in the developing countries. Associated with it are deficiencies of other nutrients. Hypovitaminosis A in association with PEM has been reported in many areas of the world, mainly in the developing countries, while hypovitaminosis A as a cause of blindness has also been widely recognized similarly in the developing countries (1 - 19).

The rate of xerophthalmia complicating PEM ranges from 1 - 2% in Lebanon and Uganda to 75% in Indonesia (2,7,14,16,17). These high rates were found in hospital cases. The differences may partly be explained on the basis of vitamin A content of the staple foods. Outside the rice-dependent areas the usual rates are below 5-10% but within rice dependent areas rates are as high as 20-40% (7).

Children with PEM and xerophthalmia have an associated higher mortality rate than children with severe PEM without eye lesions (1,16,19). Studies have shown that these children have significantly lower plasma vitamin A levels than those who survived. Infections and general malnutrition may have contributed to the higher mortality rate (1,16,17)

In East Africa xerophthalmia has been noted mainly during famine (10,20,21) and in prisoners (22, 23). Though PEM is one of the main public health problems in Kenya (21,22) xerophthalmia has not been recognised as an important accompanying feature. Maletnlema in Tanzania mentions vitamin A deficiency leading to blindness as an important form of malnutrition in addition to PEM, iron deficiency anaemia, and iodine and fluorine deficiency (24).

Jansen et al in a review of literature summarised that though vitamin A deficiency occurs throughout Kenya it does not appear to be a major public health problem (23).

Hypovitaminosis A in PEM may be a primary dietary insufficiency or may be the direct result of protein deficiency (1,17).

In the majority of the population in the developing world food sources of preformed vitamin A are scarce and expensive and consequently are not consumed in sufficient amounts (1,8,20). Provitamins are much more readily available but these have to be converted to the vitamin in the intestinal wall; this function is likely to be impaired in the malnourished child. Furthermore carotene is poorly absorbed by individuals on a low fat diet (1,8,14,17). These factors may lead to low levels

Protein deficiency directly causes low levels of Vitamin A due to a defect in its transport mechanism. Retinol circulates bound to a specific transport protein retinol-binding protein. This complex then binds with another protein prealbumin (2,3,16,27). In PEM both RBP and prealbumin levels are low due to reduced hepatic production (2,3,4,5,27) leading to a low circulating level of vitamin A. Treatment of PEM with protein and calories alone without vitamin A supplements has been shown to give a rise in all three components that is RBP, prealbumin and retinol (2,3,4,5).

Infections too have an effect on vitamin A status. They tend to lower concentrations of serum retinol, RBP and prealbumin (27,33). Measles has been noted to have a particularly striking effect in lowering plasma retinol, RBP and albumin values to 50%, 70% and 89% respectively of those in previously uninfected control children (6,27,29,30,34). Clinical manifestations of vitamin A deficiency are frequently precipitated by the onset of intercurrent illness in children with PEM often leading to blindness. The infections commonly incriminated are measles, chicken-pox, small-pox, diarrhoea, whooping cough, intestinal worms and respiratory infections (1,17,18,27,29,30,31,32,35). Infections also often lead to PEM.

Vitamin A deficiency has been associated with a wide variety of infections in experimental animals. This may be due to the depressed non-specific immunity that is, reduced mucus production and phagocytosis with breakdown in epithelia, as well as depressed humoral and cell-mediated immunity (27).

Infections may lower vitamin A by:

- i. increased demand in tissue metabolism (27),
- ii. increased heavy losses in urine, and
- iii. reduced efficiency of retinol absorption, transport and utilisation (17, 27).

Measles precipitates xerophthalmia due to the following reasons: it is associated with a protein-losing enteropathy (17, 37, 38) thus causing protein deficiency which compromises vitamin A transport; complications of measles such as diarrhoea, bronchopneumonia and sepsis increase protein breakdown, contributing to protein loss; loss of appetite and difficulty in feeding by the severely ill-child reduce protein intake; and additionally measles keratitis has been associated with an increased vitamin A demand for repair. Secondary infection by herpes simplex

virus may be a local factor contributing to ulceration (34). Protein deficiency directly has a role in corneal ulceration (15,34), the more malnourished the subject is the more severe are the corneal lesions.

Lack of local data on vitamin A status in relation to PEM and measles infection prompted this study. It is hoped that the results of the study will lead to better management of severely malnourished children, particularly in those suffering measles in preventing blindness associated with vitamin A deficiency.

OBJECTIVE

To determine the effect of PEM, measles and the combination of PEM and measles on serum vitamin A levels.

MATERIALS AND METHODS

This study was carried out from November 1983 to July 1984, the year 1984 was noted to be a particularly dry one.

Subjects included in the study were children whose ages ranged from six months to sixty months. The patients and controls were matched for age.

All children in the study were allocated into nutritional classes according to the Wellcome Trust Classification of infantile malnutrition based on the presence or absence of oedema and body weight deficit (46). These classes were normals; kwashiorkor; marasmus; marasmic-kwashiorkor and underweight children. Kwashiorkor, marasmus, marasmic-kwashiorkor and underweight children were identified as children with PEM.

Definitions

- Normal or expected weight for age was taken as the 50th percentile of the Boston standard.
- Kwashiorkor applied to those children whose weight was 60-80% of the expected weight for age, these children also had oedema associated with hypoalbumineamia, skin and hair changes and mental dullness.
- Underweight applied to those children whose weight was 60-80% of the expected weight for age without oedema.
- Marasmus applied to those children whose weight was below 60% of the expected weight for age without oedema.

- Marasmic-kwashiorkor applied to the children whose weight was below 60% of the expected weight for age with oedema.

The subjects were then grouped into four groups depending on whether they had measles or not, that is,

- i. children with PEM and free from measles,
- ii. children with PEM suffering measles,
- iii. children of normal nutrition suffering measles, and
- iv. controls. These were children of normal nutrition that is, their weight was above 80% of the expected weight for age, they were infection free and were matched for age.

Study Area

Children with PEM were selected from the Paediatric Observation Ward (POW), the Paediatric Demonstration Unit (PDU), and the Paediatric Filter Clinic. Majority of the patients with measles were taken from the paediatric block of the Infectious Diseases Hospital (IDH), the rest were selected from POW before transfer to IDH. Patients included in the study were those whose stay in the ward was less than one week. Children who presented with PEM within six weeks of measles infection were included in the group of children with PEM suffering measles.

Controls were selected from the healthy infants attending the maternal and child health clinic in the PDU, patients with minor or corrected surgical problems in the paediatric surgical ward and clinic, and children being followed up for problems like asthma or febrile convulsions in the general paediatric clinic.

An informed consent was obtained from the parent or accompanying guardian. A proforma shown in Appendix I was filled for each child.

Each child was weighed, examined then allocated their group as above. Presence of Xerophthalmia was recorded. The diagnosis of measles was made on clinical findings.

The following were the models of weighing machines used depending on the machine found in the unit and the age or size of the child;

1. W + T Avery Ltd. Unicef.
Weighs from 0-4.0kg
2. Toledo Scale, Model Sentinel.
Weighs from 0-9.00kg.
3. Seca - Made in Germany.
(Balancing Pan) weighs from 0-15kg.

4. Seca - Made in Germany (Standing Model).

Weighs from 0-150kg.

Weight was taken to the accuracy of 0.1 of a kilogram.

From each child 5cc. of venous blood was taken by venepuncture under sterile condition. The specimen was kept in a universal bottle which was wrapped in aluminium foil to prevent breakdown of vitamin A by light. The specimens were transferred within an hour of collection to the Medical Research Nutrition Laboratory where the serum was separated and stored at -20°C . In all stages of handling the specimens, precaution was taken against exposure to light. At the time of analysis after thawing, each specimen was divided into two aliquots. One was used for estimation of retinol and β -carotene, the other was transferred to the Clinical Research Centre for estimation of total RBP and prealbumin.

Laboratory Analysis

Neeld and Pearson method was used to determine serum retinol (47).

Retinol was extracted from a mixture of serum (1.0ml) and alkaline ethanol (2ml) with light petroleum b.p. at $40-60^{\circ}\text{C}$. The absorbance of the extract was measured at 450nm using a Vitatron Reaction Rate Photometer. After the removal of

the solvent, the lipid residue was dissolved in chloroform (0.1ml), trifluoroacetic acid (1.0ml) was then added and absorbance was measured at 620nm exactly 30 seconds after addition of the acid. The concentration of retinol was then calculated after making a correction for the absorbance contributed by carotenes at 620nm.

RBP and prealbumin serum levels were measured by radial immunodiffusion in agar using commercially prepared plates (Behringwerke AG). The agar plates were coated with their respective antisera. The diameter of the precipitate was measured 48 hours after addition of test-sera and left at room temperature. The concentration of RBP or prealbumin was read from graphs plotted using standards of known concentrations of RBP and prealbumin.

Methods of statistical analysis

For retinol levels analysis was based on transformed data. The square root transformation was used to reduce the skewness and for variance stabilisation.

Student t-test was used for the difference of means for comparison between the groups.

For RBP and prealbumin serum levels a conditional χ^2 test was used in analysis of data. Analysis of variance

was carried out to test for variation between the different groups.

RESULTS.

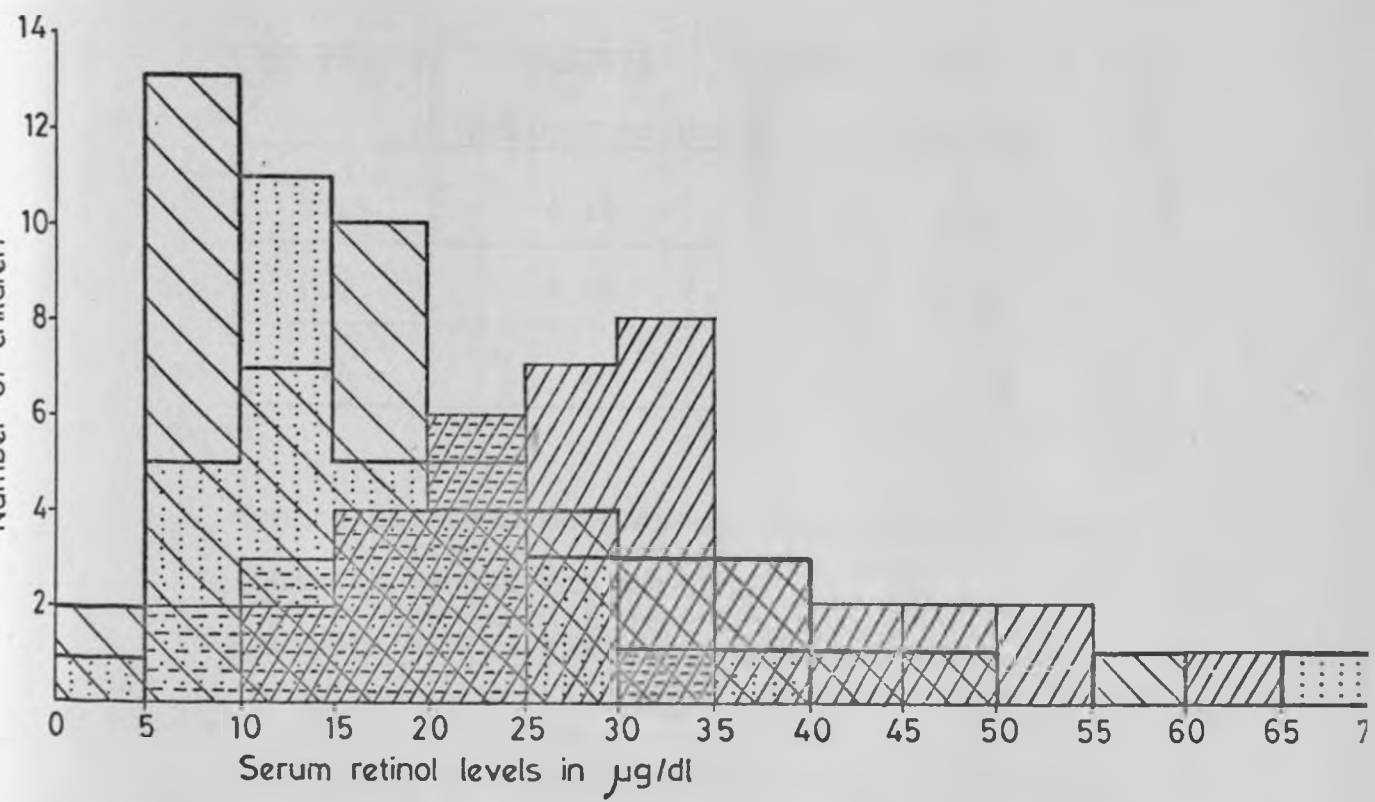
A total of 134 children were included in the study. There were 50 children with PEM, 33 children with PEM suffering measles and 17 well-nourished children suffering measles. 37 were controls.

There were 68 other children not included in the analysis because of apparently high retinol levels. These children came from the three study groups, their sera had been in storage for three months and over. These apparent high levels of retinol were found with stored sera in a study by Parkinson and Gal (50). RBP and prealbumin means for these children were analysed and showed no significant difference with those in the study.





82.3% of well-nourished children contracted measles before the age of 24 months and for those with PEM the percentage was 81.8%.

Fig. 1 shows the distribution of the subjects in the four groups in relationship to their serum retinol levels. Table 1 shows the mean values of serum retinol given as the square-root of the mean and the S.D. Mean retinol levels were lower than in controls in measles, PEM and in the

FIG. 1 A HISTOGRAM TO SHOW DISTRIBUTION OF CHILDREN IN RELATIONSHIP TO THEIR SERUM RETINOL LEVELS



KEY

 Controls	 Measles well nourished	 Measles with PEM	 PEM
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combination of PEM and measles.

Table I:

Mean serum retinol levels in study groups and controls

	CONTROLS	MEASLES WELL-NOURISHED	PEM	PEM WITH MEASLES
\bar{X}	5.25	4.18	4.16	4.01
S.D.	1.6	0.88	1.41	1.23
n	37	16	47	32

Controls versus measles well-nourished $p < 0.05$

Controls versus PEM $p < 0.01$

Controls versus PEM with measles $p < 0.01$

The three study groups were all significantly different from the controls but were not significantly different from each other, $p > .10$.

Table 2 shows the distribution of subjects according to the cut-off points for serum retinol levels recommended by ICNND. Approximately 50% of the controls fell within the marginal zone and below similar to the study groups.

Table 2:

Distribution of subjects according to their serum retinol levels (ICNND classification)

Serum retinol level ($\mu\text{g}/\text{dl}$)	Controls (37)	Measles well-nourished (16)	PEM (49)	Measles with PEM (32)	Total (134)
< 10	0 (6.3)	2 (2.8)	15 (8.4)	6 (5.5)	23
10-20	7 (13.0)	7 (5.6)	17 (17.2)	16 (11.2)	47
21-60	29 (17.1)	7 (7.4)	17 (22.8)	9 (14.8)	62
> 60	1 (0.6)	0 (0.2)	0 (0.7)	1 (0.5)	2
Total	37	16	49	32	134

Conditional χ^2 test was used $p < 0.001$

Figures in brackets represent values expected after variance stabilisation.

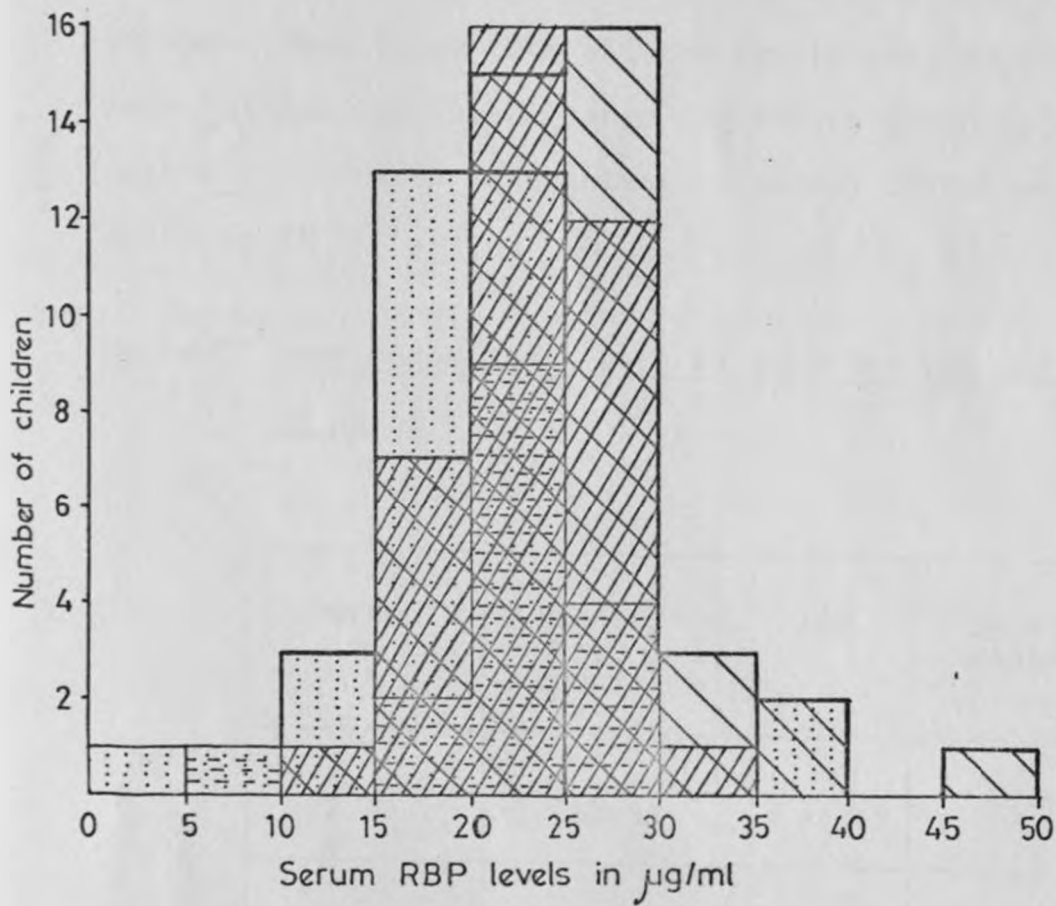
Interpretation of serum retinol levels (modified *)

10 $\mu\text{g}/\text{dl}$	- deficient
10-20 $\mu\text{g}/\text{dl}$	- low
20-60 $\mu\text{g}/\text{dl}$	- normal
60 $\mu\text{g}/\text{dl}$	- high

* For the method used normal levels ranged from 20-60 $\mu\text{g}/\text{dl}$. See Appendix II for the ICNND recommended interpretation of plasma retinol levels.

Clinical manifestation of xerophthalmia occurs when serum retinol levels are less than 10 $\mu\text{g}/\text{dl}$ by the WHO criteria.

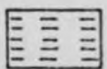
FIG. 2 HISTOGRAM TO SHOW DISTRIBUTION OF CHILDREN IN RELATIONSHIP TO THEIR SERUM RBP LEVELS



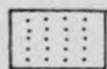
KEY



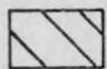
Controls



Measles well
nourished



Measles with
PEM



PEM

Figure 2 shows the distribution of the subjects in relationship to their serum RBP levels.

Table 3 shows the mean serum RBP levels. PEM had a higher mean RBP level than controls, probably due to the wider scatter of the values as is shown in Figure 2. PEM with measles had a significantly lower mean than the other groups. Mean values for all the groups were very low. They were outside the normal range for RBP as given by the International Vitamin A Consultative Group (IVACG) which is 35-45 $\mu\text{g}/\text{dl}$ (27).

Table 3 Mean serum RBP levels in study groups and controls in $\mu\text{g}/\text{ml}$

	CONTROLS	MEASLES WELL NOURISHED	PEM	PEM WITH MEASLES
\bar{X}	22.48	22.55	24.42	19.04
S.D.	4.49	2.89	7.45	6.29
n	37	15	45	33

Conditional χ^2 test was used in analysis of RBP data. The four groups were significantly different from one another $p < 0.01$.

The study groups were also significantly different from one another $p < 0.01$.

An analysis of variance was carried out to test for variation between the different groups.

Table 4 shows the mean serum levels of prealbumin in the four groups. The mean prealbumin level for well nourished children with measles was not significantly different from that of controls, while the other two study groups had significantly lower means than the control group. Children with PEM suffering measles had the lowest mean. The normal range for serum prealbumin level is 150-250 μ g/ml.

Table 4 Mean serum levels of prealbumin in the study groups and controls in μ g/dl.

	CONTROLS	MEASLES WELL NOURISHED	PEM	PEM WITH MEASLES
\bar{X}	187.28	177.96	161.23	125.42
S.D.	33.63	41.29	44.33	39.17
n	37	15	46	33

Conditional X^2 test and an analysis of variance were carried out for the four groups giving a $p < 0.001$.

Using student's t-test:-

Control versus PEM $p < 0.01$

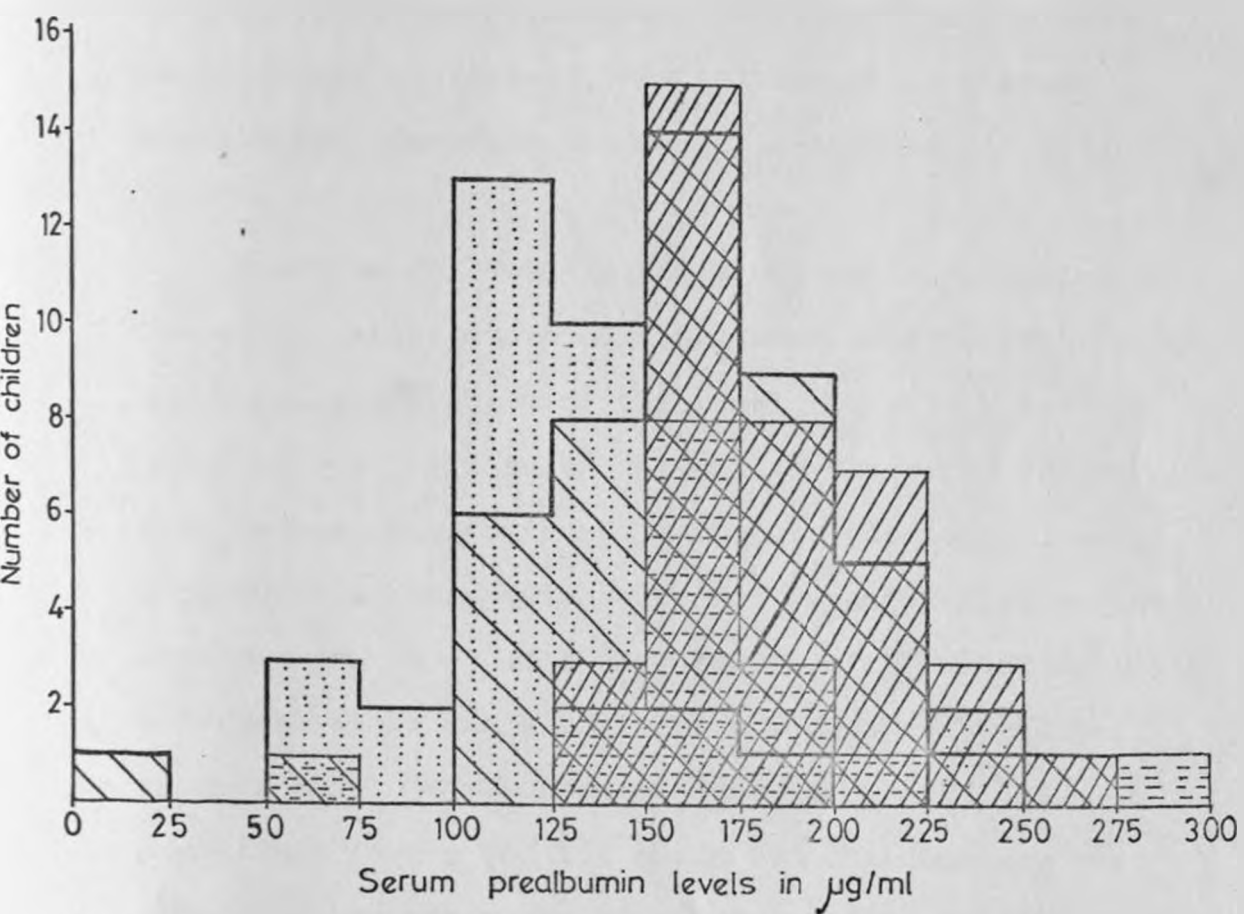
Control versus PEM with measles $p < 0.001$.

Control versus measles well nourished $p > .10$

Measles well-nourished versus measles with
PEM $p < 0.01$.

Measles with PEM versus PEM $p < 0.01$.

FIG. 3 HISTOGRAM TO SHOW DISTRIBUTION OF CHILDREN IN RELATIONSHIP TO T
PREALBUMIN LEVELS



KEY



Controls



Measles well nourished



Measles with PEM



PEM

Figure 3 shows the distribution of children in relationship to their serum prealbumin levels.

There was no significant difference in the mean serum levels of retinol, RBP or prealbumin between kwashiorkor, marasmic and marasmic-kwashiorkor children.

3 of the children in the study had keratomalacia. One was an eight month old baby with kwashiorkor who had a corneal perforation of the right eye with a scar in the opposite eye. His serum retinol levels were undetectable (the method used could not detect levels below $3\mu\text{g}/\text{dl}$). The other two were twins aged forty months with marasmic-kwashiorkor. One had a perforation of the left eye with a corneal ulcer and xerosis of the opposite eye, her serum retinol levels were undetectable. RBP and prealbumin levels for the above two children were not available because their sera was insufficient for these estimations. The other twin had corneal ulcerations of both eyes. Her serum retinol level was $8.4\mu\text{g}/\text{dl}$, RBP was $20.4\mu\text{g}/\text{ml}$ and prealbumin was $152.8\mu\text{g}/\text{ml}$. These three children had suffered measles within the previous eight weeks.

The children were given parenteral vitamin A in addition to protein and calorie supplements. The first patient succumbed to infection and died. Of the other two one had a conjunctival flap for the perforated eye which did not take, but epithelialisation had started with improved nutrition. The second one developed a corneal opacity of the left eye, the right eye showed signs of healing.

Since carotenes are not stored in the body, serum levels reflect recent intake and do not represent the true vitamin A status (7). For this reason serum carotene levels were not analysed.

DISCUSSION

From this study it has been shown that retinol and prealbumin are significantly lowered by PEM and measles. RBP was shown to be lowest in PEM compared with measles and controls, although all groups had mean serum RBP levels below normal.

There was no significant difference in the mean serum retinol levels between well-nourished children with measles, children with PEM suffering measles and children suffering PEM only, but all the three groups had lower mean serum levels than controls.

Inua et al⁽⁶⁾ found that measles had a greater lowering effect on serum retinol than malnutrition while malnutrition had a greater depressing effect on albumin concentration than measles. In this study measles and PEM lowered retinol to a similar level and the combination of measles and PEM did not lower retinol any further. PEM was shown to have a greater depressing effect on serum prealbumin level than measles while measles and PEM combined lowered prealbumin levels even further. Mean prealbumin level in controls was 187.28µg/dl, in measles well-nourished - 177.96µg/dl, PEM 161.23µg/dl while PEM with measles was 125.42µg/dl.

Some of the children in the control group which was regarded as a healthy population had serum retinol levels

in the marginal zone. This may be explained by the fact that the main sources of vitamin A are provitamins (1,8, 14,17). In a nutritional survey carried out in a number of Kenyan communities, the main source of vitamin A was found to be fruit and vegetables, the other contributing foods are animal sources and cereals (26). Intake will most likely vary from season to season depending on the availability of fruit and vegetables. These healthy children with marginal levels of retinol are therefore also at risk of developing xerophthalmia when they contract measles; measles has been shown in this study to have a lowering effect on the serum retinol level.

Measles is still an important health problem in the under five age group in the tropics and is associated with a high morbidity and mortality (6,21,30,33,36,39,48). Corneal scars and complete blindness are among the complications noted (29,36,40,45). In this study approximately 80% of the children contracted measles below the age of twenty-four months, this is comparable to a study by O'Donovan done in the same setting (48).

The age at which the children contract measles may also be important in the causation of vitamin A deficiency. This is the transition period from the toddler's diet to the adult diet with a smaller contribution from breast-milk. Breast-milk is an important source of vitamin A and has been noted to have a protective effect against

xerophthalmia (1, 17). By twelve months of age, breast-feeding is on the decline therefore vitamin A intake from this source is markedly reduced.

CONCLUSIONS

1. Retinol is depressed by PEM and by infection with measles.
2. RBP is significantly lowered in the combination of PEM and measles.
3. Prealbumin is depressed by PEM and is further depressed by the combination of PEM and measles.

RECOMMENDATIONS

1. Vitamin A should be supplemented in the management of children with PEM and those suffering measles since these two conditions have been shown to significantly lower vitamin A serum levels.
2. Immunisation against measles will also significantly play a part in prevention of xerophthalmia.

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APPENDIX ISTUDY ON VITAMIN A STATUS IN CHILDREN SEEN IN KENYATTA
NATIONAL HOSPITAL

1. Name: -----
 Age: -----
 Sex: -----
 I.P. NO: -----
2. Residence: -----
 Weight: -----
 Oedema: Present: -----
 Absent: -----
 Nutritional Classification: -----
3. Diagnosis: -----
 Complications: -----
4. Diet:
 Breastfeeding: -----
 Weaning diet (specify): -----
 Adult (specify): -----
 Staple: -----

5. Serum Levels:Vitamin A ($\mu\text{g}/\text{dl}$): -----Carotene ($\mu\text{g}/\text{dl}$): -----

Prealbumin (mg%): -----

RBP (mg%): -----

*Eye Examination:

Conjunctival xerosis: -----

Bitot's spot with conjunctival xerosis: -----

Corneal xerosis: -----

Corneal ulceration with xerosis: ,-----

Keratomalacia: -----

Xerophthalmia fundus: -----

Corneal scars: -----

* NB - Thorough eye examination was not done in every subject. Xerophthalmia was only noted after confirmation by an ophthalmologist, it was not possible for all patients to be seen by an ophthalmologist.

APPENDIX II

ICNND recommended interpretation of plasma retinol levels: (27)

<u>Level</u>	<u>µg of vitamin A/100 ml</u>
high	over 50
normal	20 - 50
low	10 - 20
deficient	below 10