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BLINDING MALNUTRITION IN CHILDREN

An all day symposium will be held on OCTOBER 5th 1979, Institute of Child Health, 30 Guilford St. London W.C.1. starting at 9 a.m. to mark the Year of the Child. Sponsored by the Royal Commonwealth Society for the Blind and the Xerophthalmia Club of the U.K. Full programme in next Bulletin. Further details from Dr. G. J. Ebrahim Institute of Child Health.

INCAP Publication I-1071

HYPOVITAMINOSIS A AND ITS EFFECT ON HEMATOPOIESIS AND IRON METABOLISM.

A REVIEW

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The existing references on the effect of hypovitaminosis A on hematopoiesis show two different lines of contrasting evidence. On one hand the occurrance of anemia and on the other of polycythemia.

Early reports of hematopoietic changes associated with vitamin A deficiency in either humans, experimental animals or both, have appeared since 1922. For example, anemia has been found by Findlay and Mackenzie (1), Wolbach, and Howe (2), Koessler *et al.* (3), Sure et al. (4), Blackfan and Wolbach (5), Frank (6), Wagner (7), the ICNND Nutrition Survey of Paraguay (8) and by O'Toole et al. (9). In contrast, elevated levels of hemoglobin and hematocrit have been observed by McLaren et al. (10, 11), Nockels and Keinholz (12), Amine et al (13), Corey and Hayes (14), and Mee and Stanley (15). All these findings have been reviewed in a recent publiction (16).

Most recent data on the subject comes from the human vitamin A deficiency study by Hodges and associates (16). In this particular experiment, vitamin A deficiency was induced by feeding diets deficient in vitamin A to eight middle-aged men who voluntarily participated. Despite a daily intake of 18-19 mg of iron in their diets, the men gradually began to manifest a mild degree of anemia. Serum iron was low and the levels of retinol in plasma correlated significantly with the concentration of hemoglobin in blood. More interestingly, when medicinal iron was given orally to these men, there was a poor and transient response in hemoglobin levels. It was only after vitamin A was given back to them that a full hematologic recovery was attained. Supporting these observations, the same report also shows two additonal lines of evidence. First, a positive correlation between serum retinol and blood hemoglobin among several countries surveyed by the ICNND. Secondly, a drop in hemoglobin levels in chronically vitamin A deficient rats, accompanied by an elevation of liver iron. These findings suggested a positive role of vitamin A on hematopoiesis and stimulated new research on the subject. Thus in 1977, Mejía *et al.* (17) performed a retrospective evaluation of the six INCAP/OIR Nutrition Surveys of Central America in order to investigate the role of vitamin A nutriture in the prevalence of anemia in rural children between 1 and 12 years of age. Positive correlations between hemoglobin and plasma retinol were found in children 5-12 years old, but not in the youngest group. Serum iron however, correlated significantly with serum retinol in all groups. The significance of this correlation became stronger when iron intake was "adequate". These findings have been confirmed by Mohanram *et al.* (18) in Indian children. Again, a positive correlation was found between serum retinol and hemoglobin levels. Furthermore, when vitamin A deficient children were treated with daily oral supplements of 8000 μg of retinyl palmitate, within 2 to 3 weeks their plasma retinol, hemoglobin, hematocrit and plasma iron became significantly elevated.Similar results have been obtained in Bangladesh by Rowshan *et al.* (19). It was found that administration of 8000 I.U. of vitamin A for two weeks to anemic children, raised their hemoglobin. More recently, a positive significant correlation has been also found between plasma retinol and serum iron by Brubacher, *et al.* (personnal communication) in a group of elderly persons in Vienna. These new observations support a positive role of vitamin A on hematopoiesis and suggest that this vitamin brings about an elevation of serum iron levels making this element more available for hemoglobin synthesis. Iron absorption however, is not altered in vitamin A deficiency. In spite of the early work of Amine *et al.* (13) in which a greater retention of Fe 59 was found in the vitamin A deficient rat that suggested an "increased" iron absorption, new experiments by Mejia *et al.* (20, 21) had shown that there is no difference in the absorption of this mineral following a single oral dose of radioactive iron given to vitamin A deficient rats. The incorporation of this isotope was however significantly

higher in liver and spleen of the deficient animals. This may had been the reason why Amine *et al.* (13) found a greater Fe^{59} retention in their vitamin A deficient animals. Mohanram (22) has also found no change in the absorption of iron in vitamin A deficient children after administration of Fe^{59}. Thus, the hematopoietic changes in hypovitaminosis A are not related to iron absorption.

What seems more likely to occur, however, is that in vitamin A deficiency, iron accumulates in storage tissues, from which it becomes mobilized directly or indirectly upon vitamin A action. Thus, iron utilization is increased. In fact, some of the early pathological findings in vitamin A deficiency had been hemosiderosis of the spleen and liver (2, 5). More recently, greater iron levels have been found in liver and spleen of vitamin A deficient animals by either chemical analysis of iron in these tissues (16, 23) or by measuring the incorporation of radioactive iron after administration of Fe^{59}. If indeed, when vitamin A increases, iron is removed from storage, this would also explain the positive correlation between serum iron and plasma retinol.

Another important aspect of the hematologic changes observed in vitamin A deficiency is the fact that anemia can be observed only in either early or in chronic hypovitaminosis A and not when the deficiency becomes severe and is associated with inanition and severe weight loss (23).

In the severely vitamin A deficient rat, there is a significant reduction in plasma and blood volumes that leads to hemoconcentration which results in an elevation of the hematologic parameters (24). Thus, there is an apparent polycythemia and the anemia can be masked. Alterations in water metabolism in vitamin A deficiency that may cause hypovolemia have been also reported by others (25-28). This phenomenon may explain the failure to observe anemia in vitamin A deficient animals by some investigators.

Considering the public health importance of this area of research, a new study is now underway in our Institute to further elucidate this problem and evaluate its implications at the population level. Preschool rural children are being examined longitudinally in terms of any changes in indictors of iron nutrition that may have occurred during the fortification of sugar with vitamin A in Guatemala. These indicators include, serum iron, total iron binding capacity, percent saturtion of transferin and serum ferritin. Plasma retinol and retinol binding protein are also included, as indicators of vitamin A nutritional status.

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HYPOVITAMINOSIS A AND ITS CONTROL

Bull. WHO, 56(4): 525-541 (1978).

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Hypovitaminosis A is considered to be the most common cause of blindness in the developing countries but it is not possible to estimate the prevalence of keratomalacia directly attributable to it. Subclinical hypovitaminosis A is not measurable at present in human subjects, but studies in animals indicate that the possibility of subclinical effects should not be ignored. The recommended procedure for identifyng the "at risk" population involves a three-part survey to evaluate dietary intake, biochemical indices, and clinical signs. This article examines all three approaches in some detail, but in the present state of knowledge, none of them gives a satisfactory estimate of vitamin A status. For community assessment, the article discusses preliminary experience with a predictive model of the number of children in a population at risk of hypovitaminosis A that is based on associations noted repeatedly between protein-energy malnutrition and certain child-rearing practices, family economics, and morbidity. Criteria have been established for deciding on the need for a programme of prevention and the types of programme most

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XEROPHTHALMIA CLUB BULLETIN 17
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IVACG ABSTRACTS and REVIEWS

VITAMIN A AND GLYCOPROTEIN SYNTHESIS

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The synthesis of a great variety of different glycoproteins is affected by vitamin A, either by deficiency or, as shown quite recently, by excess (1). Thus, GP[1] synthesis in small intestine (2), in trachea (3), in serum (4) and in cornea (5) declines in deficiency. Synthesis of the tracheal GP is restored to normal levels 48 hours after vitamin A administration. The serum GP which declines in vitamin A deficiency has been identified as α_1-macroglobulin (in the rat). It is known to be synthesized in the liver. It is a potent anti-protease, and was found to combine, for instance, with collagenase from cornea (6). Since collagenase is released from cornea in vitamin A deficiency (7), one could speculate that there may be a causal connection between the lack of collagenase inhibitor (α_1-macroglobulin) and the increased activity of corneal collagenase in severe vitamin A deficiency.

The serum GP of the human species corresponding to the α_1-macroglobulin in the rat is α_2-macroglobulin. This GP has been shown to decline in the serum of vitamin A-depleted children (8).

DeLuca and his group (1) showed that very large doses of vitamin A given to normal rats by stomach tube greatly stimulated the uptake of mannose, but not of galactose, into one particular liver GP, which was isolated and partially characterized.

Not only in vivo, but also in vitro, can one observe stimulation of GP synthesis by vitamin A: when rat corneas from normal animals were incubated in a nutrient medium for several hours, they synthesized and released a number of GP's into the medium. One of these GP's was absent in corneas from deficient rats. Recovery to normal level was achieved with 2×10^{-7}M retinol in the medium, and 60% of maximal level was attained with 2×10^{-9}M retinol within 3 hours of incubation (9). We have recently found that retinol bound to RBP[1] could stimulate GP synthesis in cornea equally well.

Obviously, then, vitamin A is somehow related to the synthesis of glycoproteins. By which mechanism can one visualize vitamin A affecting GP synthesis? A much explored reaction discovered a few years ago is the transfer of mannose from the activated form of this sugar (GDP-mannose) to protein by the intermediate formation of a mannose phosphate ester with the isoprenol dolichol. This glycophospholipid inserts the core mannoses, close to the attachment of the oligosaccharide chain to the protein (10). It is possible that other mannose moieties are added through other isoprenols such as retinol. Retinol can be chemically phosphorylated to retinyl phosphate: the RP[1] biosynthesis reaction I has not been shown to occur as yet, though DeLuca (11) found RP to exist in liver and intestine. Microsomal membranes from a variety of tissues are very efficient in catalyzing reaction II. The enzyme for this reaction was found to be localized in the rough and smooth endoplasmic reticulum of liver microsomes, but was absent in plasma membrances (12). MRP has been detected in the intact rat, both in liver and intestine (13). Even retinoic acid, when injected into vitamin A-depleted rats, stimulated MRP synthesis in vivo 1 hour after injection (14). Though the rat cannot reduce retinoic acid to retinol, it apparently can metabolize it to MRP.

(I) R + ATP ⟶ RP + ADP
(II) RP + GDP-M ⟶ MRP + GDP
(III) MRP + GP ⟶ GP-M + RP

Recently, a galactosylretinyl phosphate was isolated upon incubation of UDP-galactose with RP and a preparation of microsomes from tracheal epithelium. The GalRP[1] was thoroughly characterized (15). Though liver microsomes can catalyze the formation of MRP, they are inactive in making GalRP.

The transfer of mannose to protein (reaction III) has not yet been satisfactorily established. No exogenous protein capable of accepting mannose from MRP when added to a microsomal preparation has yet been found. There is a low level of transfer of mannose to endogenous protein (16), but recently we found a non-enzymic reaction in which mannose from MRP becomes attached to microsomal protein. We are currently attempting to distinguish between the enzymic and the non-enzymic products.

This is the present position with respect to vitamin A and GP synthesis. Clearly, enzymes exist for the synthesis of MRP and GalRP. However, the transfer of mannose and galactose to protein through these retinol intermediates has yet to be defined. Even if MRP can be shown to function as an intermediate in the synthesis of one or more specific GP's with recognizable functions, the connection would have to be made between GP synthesis and the very complex action of vitamin A on cells and tissues observed histologically. This includes the action of vitamin A on growth and on maintenance of epithelia, and how the vitamin prevents epithelial keratinization.

Footnote: (1) Abreviations: GP, Glycoprotein; R, retinol; RP, retinyl phosphate; MRP, mannosyl retinyl phosphate; GDP-M, guanosyldiphosphate mannose; GalRP, galactosyl retinyl phosphate; RBP, retinol binding protein.

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Inter-Relationships between Hormonal and/or Nutritional Status and Endemic Goiter Epidemiology. Y. Ingenbleek, Inst. de Nutr. Infant., Univ. of Dakar, Senegal, W. Africa.

Iodine deficiency is universally recognised as the primary but not the sole factor responsible for endemic goiter epidemiology. The present survey, conducted in a goitrous area in the southern region of Senegal, attempts to define associated etiological conditions. 1098 inhabitants were investigated in 3 rural villages with an overall goiter prevalence of 44.1 percent. Besides the conventional parameters of iodine status and thyroid dysfunction, plasma prealbumin (PA), retinol-binding protein (RBP) and retinol were measured. The 3 constituents of the retinol circulating complex fluctuate in a molar 1 : 1 : 1 ratio and their liver secretory rate seems highly dependent on the hormonal and nutritional status of the body. The relative drop of serum PA-RBP-retinol, as a result of modified hormonal and/or protein status, might constitute a critical factor capable of inducing goiter hypertrophy. Lower retinol concentrations are negatively correlated with increased goiter incidence. This situation apparently occurs through the mediation of impaired incorporation of mannose into nascent thyroglobulin (Tg), leading to an early blockade of the full glycoprotein production. This additional concept of goiter, founded on a defective glycosylation reaction of Tg, clarifies most unresolved data described in goitrous areas and provides a comprehensive explanation of epidemiological findings related to sex, age, geographical and social circumstances. Abstract of paper given at Internat: Cong: Nutrition, Brazil, 1978.

Nutrification of Foods with Vitamin A in Developing Countries. J. C. Bauernfeind, Roche Research Center Hoffmann-La Roche Inc. Nutley, N. J. 07110. U.S.A.

One form of blindness, xerophthanmia, occurs in infants and young children in Asia, the Middle East, Africa and Central and South America, etc., where intakes of vitamin A food sources are inadequate. It is estimated that as many as 100,000 children, around the world, may go blind annually as a result of this nutritional deficiency. In addition to ocular symptoms, other outward symptoms of vitamin A deficiency are growth depression, suspected greater susceptibility to infectious and parasitic diseases, and in many instances, death. A list of countries where vitamin A deficiency is a public health problem is given.

Tentative List of Countries and Territories where Vitamin A Deficiency is a Public Health Problem*

Afghanistan	Iran	Sao Tome and Principe
Antigua	Iraq	Senegal
Benin	Jordan	Socialist Republic of Viet Nam
Bangladesh	Kenya	Somalia
Bolivia	Lao People's Democratic Republic	South Africa
Brazil	Lebanon	Southern Rhodesia
Burma	Libyan Arab Republic	Sri Lanka
Cape Verde	Malawi	St. Kitts — Nevis & Anguilla
Chile	Malaysia	St. Lucia
Columbia	Maldives	St. Vincent
Comores	Mali	Sudan
Democratic Kampuchea	Mauritania	Syrian Arab Republic
Democratic People's Republic of Korea	Mozambique	Thailand
Dominica	Nepal	Togo
Ecuador	Nicaragua	Tonga
Egypt	Niger	Tunisia
El Salvador	Nigeria	Turkey
Ethiopia	Pakistan	Tuvalu
Fiji	Papua New Guinea	United Republic of Tanzania
Ghana	Peru	Upper Volta
Grenada	Philippines	Uganda
Haiti	Republic of Korea	Uruguay
Honduras	Rwanda	Zaire
India		Zambia
Indonesia		

* Adapted from PAG Bulletin, Vol. VI, No. 4 (1976). Prepared by WHO for guidance in world food programs. The list includes countries where existence of xerophthalmia has been reported, even if it be a small area of the country.

Through the cooperative efforts of the Agency for International Development of the U.S. State Department, WHO, UNICEF, the international blindness prevention societies, and other international and national groups, a concerted effort is being made to wipe out xerophthalmia worldwide. An International Vitamin A Consultative Group (IVACG) was formed in 1975 with representatives of the above groups for this purpose. Programs at various stages and of various types have been or are underway or are planned in India, Indonesia, Bangladesh, Pakistan, Sri Lanka, Haiti, Guatemala, Costa Rica, El Salvador, Panama, Brazil, the Philippines, etc.

A number of intervention programs have been developed to overcome the vitamin A deficiency problem, one approach being the addition of vitamin A to foods, referred to as Vitamin A nutrification of food. When seeking out a food to be nutrified, it should be one that is regularly consumed by the segment of the population to be protected against the deficiency disease. The food also has to be one which is centrally processed with an existing technology for the addition of vitamin A or one for which a technology can be developed. Obviously, the nutrified product should not have a changed appearance, or taste and the added vitamin should be physiologically available to the body. Lastly, some monitoring system should be possible to gauge the intake of the nutrified product in the concerned population.

Currently the food products which are serving or are being tried as food vehicles for added vitamin A in developing countries are wheat flour, skim milk powder, sugar (refined sucrose), tea dust, and/or leaves and seasonings (monosodium glutamate). Wheat flour exported from the USA to developing countries must contain 4000-6000 I.U. vitamin A/lb of flour. UNICEF has employed vitamins A and D nutrified milk powders for more than the past decade and WHO has had a long-standing position in favour of nutrifiction of dried skim milk.* USA exported skim milk powder contains 2200 I.U. vitamin A and 440 I.U. vitamin D/100g. Other donor countries are gradualy nutrifying it. Sugar, nutrified with vitamin A in the Central American countries, contains 50 I.U./g. Technically, tea dust and tea leaves can be nutrified to contain 200 I.U. and 50 I.U./g, respectively, and monosodium glutamate in limited trials has been nutrified to contain 15,000 I.U. of vitamin A per 2.4 g

packet intended for daily consumption of a family (2 adults and 2 children).

USA has exported vitamin A nutrified wheat flour and skim milk powder to a number of developing countries over the yers. For a time a limited amount of bread baked in India contained added vitamin A but India is putting greater emphasis on intermittent oral dosing rather than nutrification. Pakistan has shown interest in nutrification of atta, a wheat product, but has not put it into commercial practice. Some trials in nutrified bread have been made in Iran and interest continues. Nutrification of sugar has been carried on in country-wide practice in Guatemala and Costa Rica and developing in Panama. Other Central American countries are expected to follow. Tea nutrification has been under test in a limited program in Pakistan but has not gained wide momentum. Vitamin A nutrification of monosodium glutamate in the Philippines has had a successful trial test and country-wide practice is a possibility in the future if successful indications continue.

Nutritional interventions exist to minimize xerophthalmia or eradicate it entirely but a strong continuous effort is required with full governmental committment to the program in the country involved.

* The European Economic Community has at last decreed that all skim milk donated under the World Food Aid Programme shall be fortified with vitamin A.

Leaf protein and other aspects of fodder fractionation. N. W. Pirie, Cambridge Univ. Press, London, 1978, £8.00.

It has long been known that leaves contain protein, and that ruminants are equipped to subsist largely on leaves but that man's digestion limits the amount of leaves that he can eat, despite that fact that they contain dietary components that would be nutritionally good for him. It has also been known that much of the nitrogen consumed by ruminants in fresh leaves is subsequently voided in their faeces (hence the value of their manure as fertiliser). It therefore seemed reasonable to suppose that there might be advantages in extracting some of the protein from leaves, for consumption by man or other non-ruminants, before feeding the remainder to cattle. However, as this most interesting book states in its opening sentence, "The suggestion that it might often be advantageous to fractionate leafy crops was for many years received with scepticism, or even hostility". The fact that this attitude has changed, and that sufficient knowledge is now available to justify publication of a book on fractionation, is almost solely due to the perception, patience and persistance of the author, N.W. Pirie FRS.

The book introduces the subject of leaf protein with an historical survey, which gives a fascinating account of the way in which various developments in quite disparate fields, none concerned directly with the fractionation of leaves, have gradually been pulled together (largely by the author) to provide a coherent system that may well develop into a new branch of crop husbandry and food technolgy.

A long chapter gives much information about work that has been done to determine the potential of different crops for fractionation, and the yields of protein that might be obtained from them. It is clear that a good deal more work is needed before the best species are identified, partly because lack of a standard method of assay has reduced the value of much of the exploratory work that has already been done, and partly, because only a small fraction of the candidate species has yet been studied To overcome the first difficulty, a standard assay method has now been developed by Pirie as part of the IBP programme.

Chapters on the "Separation, purification, composition and fractionation" of leaf protein (LP) and the "Prevention, storage and modification" of the product, show that the technology has reached the point where it could doubtless be developed on a medium to large scale by the food and feedstuffs industries and by farmers' co-operatives. The evidence on which uptake of LP by the agricultural industry will probably be decided is contained in three well-argued chapters on "Digestibility *in vitro* and nutritive value in animals", "The value of the extracted fibre and the 'whey' " and "The role of fodder fractionation in practice".

A chapter that will doubtless interest most readers of this Bulletin is on "Human trials and experiments", from which it seems that there is growing evidence, from careful trials, that LP can be regarded as an acceptable source of protein, particularly useful in areas where milk is scarce, because it could be produced from local sources of leaves.

The value of LP as a source of β carotene and vitamin A is carefully assessed (pp 91-94), with emphasis on the importance of the source leaves being dark green — etiolated leaves such as occur in the hearts of cabbage are apparantly much less useful as providers of β carotene. Analyses of the leaves of 24 species show a range varying by a factor of 40 in their ability to provide this vital component, and a wider search might well identify species whose leaves are even richer in this component than nasturtium. There seems little doubt that LP could play an important role in this type of therapy for blinding malnutrition, but horticulturists should also perhaps direct more effort towards seeing that year-round supplies are available of leaves that are rich in β carotene, attractive to eat as vegetables, and within the price range of the poorest families.

Pirie has served humanity well in his crusade to establish LP as a product for feeding man and beast, and it is gratifying that his work has now been widely recognised. No one but him could have drawn on the 500 references that are cited and condensed the mass of available information into such a coherent and readable account of the subject. This will be the standard book on leaf protein for a very long time to come.

J. P. Hudson

Vitamin A — Responsive Panocular Xerophthalmia in a Healthy Adult. A. Sommer, Sugana Tjakrasudjatma, Edi Djunaedi, W. R. Green. Arch. Ophthal. 96 : 1630 1978. Reprint requests to Dr. Sommer USAID Jakarta, Washington, DC 20523 U.S.A.

An unusual case of classical xerophthalmia occurred in an otherwise healthy, well-nourished, 25 year old woman. She had marked conjunctival and corneal xerosis, including early stromal edema, evolving pigmentary alterations of the retinal pigment epithelium, and notable constriction of her visual fields, which paralleled the distribution of the retinal lesions. Abnormalities of the conjunctiva, cornea, and visual fields disappeared within two weeks of oral vitamin A therapy, and 1.5 months later, many of the retinal lesions cleared as well. This case supports the primacy of isolated vitamin A deficiency in the etiology of corneal xerosis and "fundus xerophthalmicus"; demonstrates that stromal edema is an important early component of corneal involvement; and localizes the funduscopic abnormalities to the retinal pigment epithelium.

This very interesting paper has beautiful colour photos, both of the cornea and of the retinal lesions, and diagrams of the visual fields which show how rapidly they return to normal on treatment. L.B.

Topical Retinoic Acid in the Treatment of Corneal Xerophthalmia. A Sommer* and N. Emran. Am. J. Opthal. 86, 615, 1978. *Box 134, Bandung, Indonesia.

Indonesia.

The only proven effective remedy for corneal xerophthalmia in humans is systemic vitamin A given as retinyl ester. In 50 children receiving a standard therapeutic regimen (hospitalisation, high protein diet, systemic vitamin A), the clinical response was delayed up to 4 days with occasional corneal deterioration meanwhile. This can be attributed to a reduction in circulating retinol-binding protein associated with protein deficiency.

Topical application of 0.1% retinoic acid in arachis oil to the cornea was tried with 8 xerophthalmic children in an attempt to bridge this critical period. Standard vitamin A therapy was utilised in conjunction. Each child was treated with retinoic acid in one eye and an oil placebo in the other. Frequency and quantity of application varied throughout the group up to a maximum of two drops 5 times daily. No significant evidence of toxicity was observed. Four of the subjects had relatively symmetrical disease in both eyes and with each of these the eye receiving retinoic acid showed earlier improvement and more rapid healing. Therefore, topical retinoic acid therapy can be proposed as a useful adjunct to standard treatment for active xerophthalmia. L.B.

Vitamin A deficiency and blindness in Indian children V. Reddy. Ind.J.Med.Res. 68 (Suppl), 26, (1978). Nat.Inst.Nutr.Hyderabad, India.

This review surveys the whole problem; the *assessment* through recording of clinical signs, the *pathogenesis* of vitamin A deficiency and influencing factors such as, low levels of vitamin A in breast milk, low dietary intake by mothers and infants and the trigger action of infections and parasitoses. The interrelationship between protein-energy malnutrition and vitamin A deficiency is described; biochemical changes in serum retinol-binding protein and in vitamin A; the relation of vitamin E and vitamin A; and the effect of deficiency on somatomedin activity and on metabolism of mucopolysaccharides, lysozomal enzymes, immune responses and haematological changes are all noted.

The next section concerns *treatment* of xerophthalmia with intramuscular injection of water-miscible preparations or oral doses with an oil solution of the vitamin. The final section concerns *prevention.* Supplementation with green leafy vegetables is advocated as a long term measure and massive oral doses of vitamin A given periodically to pre-school children is recommended as a short-term but effective measure to reduce the minor clinical signs of the deficiency. The difficulties of evaluating the impact of this programme on the incidence of blindness are set out and work now started which may help to solve this problem is briefly described.

"It is difficult to demonstrate such an impact in community studies because of various problems in identification of the severe cases. Recently a study has been undertaken by the Institute to assess the effect of the massive dose programe in Hyderabad city on the inflow of keratomalacia cases into hospitals. The study has just started and envisages effective implementation of the programme in urban slums from where a majority of the cases come. Records maintained at the pediatric and ophthalmic hospitals in the city will be examined to find out whether there is a decline in the prevalence of keratomalacia after the programme has been implemented. The results are awaited to answer the question regarding the impact of the massive dose programme on the incidence of blindness."

This interesting and most useful review has 70 references. A.P.

Regulation of retinol-binding protein metabolism in cultured rat liver cell lines. J. E. Smith, C. Borek, D. S. Goodman. Cell. 15. 865, 1978. Depts. of Med., Radiol. and Path., Columbia, Univ. Coll. of Phys. and Surg., New York, New York 10032, U.S.A.

In vivo studies in the rat have shown that the secretion of retinol-binding protein (RBP) by the liver is specifically regulated by vitamin A.

A liver cell culture system was established to investigage the regulation of RBP synthesis and secretion. On assaying several cell lines derived from rat liver and cultured in vitro, two were found which secreted RBP into the medium and retained detectable amounts within themselves. The net synthesis of RBP (cells and medium) was directly related to the number of cells per dish and the length of incubation.

A relatively large proportion (14-56%) of the RBP was retained within the cells when they were incubated in medium (NTS) free of serum and vitamin A. Addition of serum had two effects. Release of RBP from the cells into the medium, resulting in a significantly lower percentage retention, was stimulated within 24 hours, and after 2-3 days a stimulation of net RBP synthesis was apparent. Both effects were relted to the amount of serum present, which represented a source of vitamin A.

Cells incubated in NTS medium alone resembled those in the liver of the vitamin A deficient rat, being virtually devoid of retinol but containing large amounts of RBP. Addition to small amounts of retinol to these cells stimulated secretion of RBP into the medium and led to a small elevation in the net synthesis of RBP. By contrast retinol had no effect on net synthesis or the cell/medium distribution of rat serum albumin.

These results are consistent with in vivo work. L.B.

Experimental temporal bone histopathology in rats drprived of dietary retinol and maintained with supplemental retinoic acid R. A. Chole and C. A. Quick, J. Nutr. 108. 1008 (1978)

Although rarely mentioned as a symptom of vitamin A deficiency, loss of hearing has been observed in both man and animals severely deprived of vitamin A. With the sole exception of the hair cells of the inner ear all special somatic afferent receptor cells (retinol rods and cones, gustatory cells, olfactory cells) have been shown to depend on vitamin A for normal function. Reports of histopathological changes in the inner ear of vitamin A deficient animals are conflicting. Since Dowling was only able to demonstrate atrophy of the rod cells of the retina in severely deficient rats when the animals were kept alive by supplementing their diet with retinoic acid the same technique has been used to study the effect of prolonged deficiency of vitamin A on the structures of the inner ear. If these are vitamin A dependent, degeneration might be expected to occur in animals deprived of retinol but kept alive by supplementation with retinoic acid.

Weanling rats were fed a diet devoid of vitamin A but supplemented with retinoic acid and killed after 2, 4, 6, 8, 10 and 20 months. Controls were fed the same diet supplemented with vitamin A. After 8 months amorphous eosinophilic material had accumulated in the scala media of the upper turns of the cochlea. A more fibrous material accumulated at the helicotrema after 10 months. At this time there was almost total atrophy of the visual cells. But when studied under the light microscope the inner and outer hair cells as well as vestibular hair cells appeared normal.

These findings imply that some tissues of the inner ear depend upon retinol and that retinoic acid does not supply all metabolic requirements. But there seems a fundamental difference between the neuroepithelium of the inner ear and that of the eye because the former did not atrophy during 12 months of vitamin A lack. I. B

appropriate in different situations are discussed. The methods of programme evaluation must take into account the stated objectives of the programme. Authors Summary.

'A much fuller account of this valuable report should be given but, alas, the Bulletin has not the space. However, knowing how difficult it is to get the water-miscible preparation of vitamin A for intramuscular injection one further paragraph is quoted to reassure those who have only the oil preparation to give by mouth. The dosage schedule would then be:— first day, 100,000 I U vitamin A in oil orally, and, second day, repeat this dose.

"The treatment schedule recommended by WHO when xerophthalmia is diagnosed, although based on the best currently available information, is in need of substantiation. For example, the recommendation that a water-miscible preparation containing 55 mg (100,000 I.U.) of retinol palmitate be given intramuscularly (IM) is based on the assumption that diarrhoea and vomiting, which decrease absorption of the dose, frequently accompany the xerophthalmia syndrome. Children with concurrent protein-energy malnutrition and infections often do have these complications. Nevertheless, substantial amounts of a high-potency oral dose are absorbed, even when gastrointestinal upset occurs, and such an oral dose should be given, particularly if the IM preparation is not available. Moreover, confirmation is required of the assumption that the watermiscible IM preparation, which enters the blood rapidly from the injection site, is taken up by the liver, processed, and secreted bound to RBP in the form physiologically available to tissue-binding sites (holo-RBP) more rapidly than an oral dose. The oral preparations are readily obtained, and oral delivery has many inherent physiological safeguards that intramuscular delivery does not have, particularly under field conditions with auxiliary personnel as the providers." A.P.

COMMENTS ON THE LEAF PROTEIN FEEDING TRIAL CARRIED OUT IN COIMBATORE 1975—1977

Dr. George Wadsworth formerly of the London School of Hygiene and Tropical Medicine, Member of W.H.O. Committee on Nutrition.

Unlike animals, human subjects cannot be standardised exactly for investigatory purposes. This is especially so in the present trials of leaf protein, because of the relatively small number of children who could be involved (300). For the whole duration of the trial, for example, separate groups consisted of 40 children (50 in one group). Not all the individual children were exactly the same age, of the same home environment or of the same nutritional status at the start of the enquiry. Other variables, for instance genetic traits, must also have been involved. To take statistical account of these variables much larger groups would have been needed. But even so, information of great value has been obtained.

Many people have been talking about leaf protein and other unusual products as a human food for many years. But until the present investigation was made, no adequate tests have been made into the acceptability of leaf protein by village children and the effects of eating it in places where diets need to be improved. Furthermore information about the diet of the same children over a period of two years and the relation of this diet to health is unique. Much is said and much is strongly advocated about what young children should eat, but there is extremely little acceptable information about what young children actually *are* eating, anywhere in the world. The present study quite apart from its value in relation to the use of leaf protein, is also a source of precious information about children's intake of food.

Some readers of periodic reports of the Coimbatore study have apparently been worried about characterisation of the villages and the children before the start of the trials, and about the comparability of the different test groups. But these matters are not relevant to the fact that a group of 40 children consumed leaf protein regularly, practically every day for a continuous period of no less than two years. During this time no ill effects of ingestion of the product arose, the children grew at an acceptable rate and their standard of health improved. Therefore the trials proved that leaf protein is an acceptable, harmless and useful material to incorporate into the diet of young children.

About ten years ago enthusiasm was increasing for the use of leaf protein in human diets. At that time there seemed to be greater urgency in the minds of leading nutritionists about the "protein gap" and impending disastrous shortage of food throughout the world than there is at present. The truth is that no one can foretell the future and nothing seems to have changed in the way of prognostications for the future growth of the world population — only peoples' attitudes about the way of coping with the associated problems have changed. Therefore, despite some lack of enthusiasm just now, there still seems justification for exploring new sources of food. The investigation made in Coimbatore is a unique and crucial experiment in this connection.

But the experiment is not yet complete. Further enquiries are needed, especially to explore feasibility and ways in which leaf protein could be made in villages, either as a household or community cooperative activity.

All "household technological" food products must at some time have been new. Some of these products, for example "bean curd" in China, must have been introducted as new products an indefinite time ago, though now integral parts of "traditional" diets. Leaf protein, and dietary items made from it, need not be regarded as any more strange or novel than these traditional foods.

Dr. Devadas and her colleagues believe that manufacture of leaf protein must be carried out in villages if the product is to benefit the majority who are poorly nourished. This belief seems to be highly justified according to the history of "high protein foods". Whenever these have become commercial products their use has been diverted to the higher socio-economic groups. Berg (1971), for example, found that three-quarters of the Incaparina produced in Guatemala is consumed by those who are not in need of this source of protein.

At the moment, extension of the use of leaf protein depends on the elaboration of mechanical techniques for producing it. Funds would be needed and technically sound plans made to explore ways of producing leaf protein, either as a household, or communal cooperative practice, and to develop the machinery required. Coimbatore January 1978.

Comment: Leaf protein, made by simple extraction of the fresh leaf followed by heat precipitation of the protein is a rich source of β carotene, most leaves tested yielding over 1.0 mg/g dry wt. All children in the Coimbatore Study got β carotene in their food but those given the leaf protein supplement got the most and their mean serum retinol level (35.7 μ g/100ml) was higher than that of any other group being nearly double that of the unsupplemented group and slightly higher than that of the group given skim milk at the end of the two year feeding trial.

TREATMENT and PREVENTION of DEHYDRATION in DIARRHOEAL DISEASES.

A Guide for use at Primary Level. WHO Geneva 1976, Sw.Fr.6.

This admirable, practical, pocket-sized booklet gives full details of the well tested oral treatment of diarrhoea with large volumes of a dilute solution of salts plus glucose which clears up diarrhoea and mild dehydration within the day and, as one observer assures me, leaves the child hungry, alert and ready to eat. *Since diarrhoea so often precedes or accompanies xerophthalmia, particularly corneal xerophthalmia, an easy, quick-acting, home-based treatment could perhaps lower the prevalence of xerophthalmia, without any other intervention,* as well as improving the general health of the children.

The cause of death in diarrhoea is *dehydration.* Replacement of body fluid and salts is essential. The most suitable fluid recommended for oral use is:

Sodium chloride (table salt)	3.5 g.
Sodium bicarbonate (baking soda)	2.5 g.
Potassium chloride	1.5 g.
Glucose	20.0 g.

These should be dissolved in a litre (a little less than 2 pints) of boiled (cooled) water. Do NOT boil the solution. If this solution is not available take two "thumb and two finger" pinches of table salt to 2 pints (one litre) of water.[1] Glucose is unlikely to be available in homes and although the WHO guides does not suggest use of sugar there have been several reports that ordinary sugar can replace glucose. Sugar or glucose are beneficial because they increase absorption of the salts and make the fluid more palatable.

The Guide suggests that patients may be given as much fluid as they are willing to drink and should be encouraged to drink continuously for the first 4-6 hr. Infants can be given the fluid with a spoon from a cup, whose volume is roughly known so that the total volume given can be calculated from the number of cups drunk.

The Guide also gives instructions for treatment of severe dehydration at clinic or hospital using a nasogastric tube or intravenously and describes how to look for other complicating conditions such as cholera, dysentery, pneumonia, malaria, high fever, which have to be referred to the hospital.

What is important?

(1) Give back the water and salts already lost in the diarrhoea stools. This is REHYDRATION and this initial replacement should be completed within six hours.

(2) Continue to replace the losses of water and salts as long as the diarrhoea continues so that dehydration does not return, and start feeding the child his usual diet such as breast milk, or cereals and other weaning foods. Treat other infections and complications. Give drugs only when needed. This is SUSTENANCE and goes on until the diarrhoea stops with CURE.

If vitamin A deficiency and xerophthalmia with danger of blindness is a problem in your area give the patient a dose of 100,000 I.U. vitamin A in oil by mouth to protect him as soon as he starts to feed.

Starvation is harmful, especially to children and especially during an illness such as diarrhoea. Breast feeding should be continued. Do not force food on the child but when he is able to eat he should be started on the local foods such as cereals, bananas, well cooked legumes and root vegetables. Cows milk is good if he is not upset by it. It is important to follow up the child and make certain he does not slide back into malnutrition and another attack of diarrhoea.

Guide says:

The treatment of a child with diarrhoea gives an opportunity to teach the mother how dehydration may be prevented and how her child's nutrition may be improved so that another attack becomes less likely and less dangerous. The best way to teach the mother is to involve her in the treatment of her child from the start.

The child's nutrition must be improved if it is poor, and kept up if it is good by telling the mother that diarrhoea should not stop her feeding her child. She must be encouraged to continue breast feeding and not to resort to any breast-milk substitutes.

Finally, it is important to learn from the mother her beliefs about diarrhoea and feeding, and to distinguish between those that are helpful and those that are harmful. A.P.

See a splendid article by Dr. C. S. Lal, Calcutta in Feb-March 1979 WORLD HEALTH on use of glucose-salts (Chorosol).

Low intakes of food during diarrhoeal attacks as a cause of under-nutrition in Bangladeshi children, M. Mujibur Rahaman, Shankari Kar and K. M. S. Aziz, Cholera Research Laboratory, Dacca, Bangladesh.

In a prospective community based study on the relationship betwen diarrhoeal attacks and growth in rural children below 60 months age, a significant faltering in weight gain was noticed in those having multiple episodes of diarrhoea. Dietary intake was measured by actual weighing and observation during episodes of illness and again after full recovery. It was noticed that children betwen 13-36 months have a daily average intake of 450 Calories and 20 gm of protein during the healthy period compared to 150 Calories and 5 gm of protein during the period of sickness. Those betwen 37-60 months of age take an average of 600 Calories and 25 gm of protein during the healthy period compared to 200 Calories and 10 gm of protein during the period of illness. In the predominantly poor families or rural Bangladesh where the availability of food is limited, it is unlikely that food not eaten during the illness is subsequently available for consumption to allow for "catch up" growth. Abst. of paper given at Int. Cong. Nutr. Brazil 1978.

Effect of periodic deworming on nutritional status of ascaris-infested preschool children receiving supplementary food. Gupta M.C., Mithal S., Arora K. L. and Tandon B. N. Dept. of Gastroenterology, Human Nutr. and Micro-biol. All-India Inst. of Med., Ansari Nagar. New Delhi-110016 India.

The weight for age of 154 undernourished preschool children were given tetramisole every 4 months, while supplementary food was monitored for a year. 74 children were given etramisole every 4 months, while 80 controls were given placebo. The prevalence of ascaris (roundworm) infection and the severity of protein-energy malnutrition were the same in the two groups at the onset of the study. Stool-positivity rates for ascariasis came down signficantly in the experimental group during the year, but eradication of the worm was not possible owing to constant re-exposure. *Nutritional status remained unaltered in the controls but improved strikingly in the treated children 8 and 12 months after the start of the study.* Periodic deworming should form a part of the supplementary feeding programme if malnutrition is associated with ascariasis in the community. Abst. of paper given at the Int. Cong. Nutr. Brazil 1978.

[1] With free running table salt it is difficult to hold any sort of "pinch" however many fingers and thumbs you use, but 3.5 g. is one heaped teaspoonful, 2.5 g. one flat teaspoonful, 1.5 g. half a teaspoonful and 20 g. five heaped tespoonsful. A teaspoon is the smallest household spoon usually available.