

## Nutritional update: relevance to maternal and child health in East Africa.

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### Abstract

In this review of recent advances in nutrition, we shall follow the 'life cycle' with special attention to maternal and foetal nutrition, linear growth, and nutritional assessment. We also consider nutrition, infection and micronutrients, and recent concepts of the pathophysiology and management of protein energy malnutrition PEM.

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### Foetal programming

Pregnant mothers may be less conscious of periconceptual health than in regions where pregnancy is 'planned, but they are aware of the importance of nutrition. Folate deficiency, in women homozygous for a common mutation in the gene for methyl-tetrahydrofolate reductase, leads to an increased risk of neural tube defect in the foetus. Adverse pregnancy outcomes associated with other genetic polymorphisms (affecting folate) may become apparent<sup>1</sup>.

Nutritional and hormonal factors in pregnancy influence, not only immediate foetal outcome, but also morbidity and mortality in later life. Analysis of the health of cohorts of British adults, born at different birth weights and sizes, indicate an association between underweight and low weight for height at birth and later adult disease. Specifically, intra-uterine growth retardation IUGR is linked with a greater risk of cardiovascular disease, hypertension, and diabetes mellitus in later life<sup>2</sup>. The process whereby a foetal insult provokes late effects is known as foetal programming.

Detrimental foetal programming may be implicated in the rising incidence in Africa of the 'diseases of affluence', commonly attributed to the urban transition towards a high fat diet, which echoes Western dietary and health trends in the early 20<sup>th</sup> century. The survival of Gambian adults known to have been born in the 'hungry' season was significantly shorter than those born in post harvest season, therefore less prone to low birth weight<sup>3</sup>. Differences in survival, were not due to childhood death, but became apparent in early adulthood.

### Metabolic adaptation in pregnancy

Women in developing countries gain less weight in pregnancy than women in industrialised countries (6 to 9kg, compared with 11 to 13 kg). Gambian women who were lean before pregnancy appeared to exhibit metabolic adaptation, tending to conserve energy during the early months<sup>4</sup>. The effectiveness of such adaptation is explained by the comparatively slow growth rate of the human foetus. Failure of protective adaptation leads to IUGR and low foetal birth weight FBW. It is further suggested that the ratio of FBW to total pregnancy weight gain may be a useful index of pregnancy stress (see below). By contrast, African American women with high rates of pregnancy weight gain are more likely than whites to retain weight post delivery<sup>5</sup>. Rates of weight gain within 7 to 11 kg, are now recommended<sup>6</sup>.

Low birth weight is more commonly due to IUGR rather than to pre-term delivery, and, in rural communities, is highly seasonal. A combination of arduous work and relatively low energy intakes in the pre-harvest season results in a significantly higher rate of LBW at this time. Classical studies in the Gambia<sup>7</sup> showed that

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nutritional supplementation of women, pregnant in the 'hungry season', was more cost beneficial in terms of enhanced FBW and neonatal survival, than 'general' supplementation. The authors suggest targeting nutritional supplementation to groups with 'stress', evidenced by low pregnancy weight gain and a high ratio of foetal to total pregnancy weight gain (i.e. >40% c.f. 25% in well nourished women).

### **Micronutrient nutrition in pregnancy**

Micronutrient status may vary independently of overall nutritional status, and in unexpected ways. For example even when vitamin intake shows seasonal variation, biochemical estimates of vitamin status do not always follow suit. In the case of vitamin A, intakes of beta-carotene peak during the mango season, but regular release from hepatic stores of retinyl esters results in a relatively constant plasma concentration of retinol. By contrast, although water soluble riboflavine intake shows little seasonal variation, plasma riboflavine activity is higher during the hungry season, due to mobilisation of riboflavine during weight loss<sup>8</sup>.

Factors influencing iron status in pregnancy include the demands of the foetus, temporary changes in blood volume and body mass, alterations in absorptive capability, and on the bioavailability of iron in a largely vegetarian diet. The total requirement for pregnancy approximates 1000mg of iron, of which around 50% will be 'restored' during physiological recovery in the puerperium. Iron supplementation is recommended, even in the absence of haematological evidence of deficiency. Bothwell<sup>9</sup> advises 60mg elemental iron daily for six months with a higher dose for those presenting late for antenatal care. The choice of regimen is dictated by the magnitude of intended effect; and weekly treatment may reduce the prevalence of anaemia. Bearde<sup>10</sup>. Bothwell (op cit) is less optimistic, warning that large programmes may fail to replicate the benefits claimed in smaller (localised) trials, due to the multi-factorial nature of pregnancy anaemia, and problematic compliance. Holistic strategies to improve the nutritional health of women, should address not only present and past nutrition e.g. in childhood and adolescence, but also general empowerment in many aspects of female behaviour<sup>11</sup>.

### **Choice of infant feeding method for the HIV positive mother**

It is impossible to move on without referring to the present controversy concerning breast-feeding in the time of HIV. UNICEF<sup>12</sup> has advised that where a woman is HIV positive and 'replacement feeding' (previously known as breast milk substitute!) is 'acceptable, affordable, sustainable, and safe, she should be counselled not to breast feed.' Further provisos include knowledge of her status and ability to purchase BMS, because UNICEF cannot undertake to provide formula. Should agencies and governments work towards provision of free formula for the poor HIV positive mother? In an authoritative review, Coutsooudis et al.<sup>13</sup> weigh the risks of vertical transmission in the breast-fed against those of death (from diarrhoeal disease) in the formula fed baby. Careful lactation management reduces the risk of breast disease, which is known to increase mother to child transmission MTCT. Mixed feeding, which via mucosal damage to the infant gut, also increases this risk, is best avoided. If we accept 1) that exclusive BF for the first 6 months carries a lower risk of viral transmission than the cited 5% risk due to mixed BF, and 2) that the risk of death in the first 2 months, independent of HIV status, is likely to be much (six-fold) higher in the formula fed, then there is little advantage in providing free formula to the most vulnerable. Furthermore, Humphrey & Iliff<sup>14</sup> argue that, in countries with a moderately high infant mortality rate, safe suckling practices may prove preferable to avoidance of breast-feeding. Clearly, policy in this matter should be decided locally, after community consultation, and carefully audited.

### **Determination of linear growth and weight gain in childhood**

Weight gain is valued by health professionals and parents alike. The parent held under-five's weight chart facilitated age estimation and, thereby, the use of weight as a public health indicator. This may have contributed to reluctance to undertake the technically more demanding length/height measurement and, indirectly, to the sparsity of national data on wasting<sup>15</sup>. Protein energy malnutrition has been conveniently graded, in primary care and public health, in terms of prevalence & severity of underweight for age, whereas clinicians found the velocity of convalescent weight gain a simple measure of catch up growth. Stunting was known to be common and regarded as an inevitable sequel of a period of negative energy balance. Put more strongly, lack of awareness of the different factors responsible for linear and weight growth, led us to regard stunting merely as an obstacle to interpretation of weight data!

It is now clear that control of linear growth is subject to different influences from those affecting weight

gain. Energy intake has little influence on linear growth, whereas protein, or more precisely, certain amino-acids, have a direct effect. Golden and Golden<sup>16</sup> have defined (as 'type 2') those nutrients whose deficit results in stunting without biochemical evidence of deficiency. Nutrients influencing linear growth are active at the growth plate of long bones, affecting the proliferation and hypertrophy of chondrocytes, also controlled by the (local) action of growth hormone GH and insulin like growth factor (IGF-1)<sup>17, 18</sup>.

The main nutritional influences on linear growth are certain essential amino-acids, (specifically lysine) and micronutrients, specifically zinc, copper, molybdenum and possibly vitamin A<sup>19</sup>. Catch up in linear growth by stunted children may follow repletion of specific nutrient deficits (by dietary supplementation), but uncertainty about their action is due to 'confounding' in both animal and human studies. For example it is difficult to ascertain the effect of deficient protein intake, when overall energy intake from a low protein diet tends to be low. In practice, nutrient deficiencies are usually multiple, and it is no surprise that adequate growth by children in a three country growth study, was explained by the general 'quality' of the diet rather than adequacy of supply of individual nutrients<sup>20</sup>.

Faltering or cessation of weight gain during infection was commonly attributed to negative nitrogen and energy balance. Inhibition of linear growth during infection, however, may be due to the direct action of the acute phase response (APR) at the bony growth plate. The complex interaction of cytokines, including tumour necrosis factor (TNF)  $\alpha$ , interferon  $\gamma$ , and interleukin-1, slows the velocity of bone growth<sup>21</sup>. The inhibiting effect of HIV infection on the linear growth of infants<sup>22</sup> may be mediated by similar mechanisms. The effects of infection on intracellular metabolism are reviewed below.

The different causation of linear and ponderal growth may also explain the observation in previously stunted children that catch up weight gain precedes and is more evident than catch up in linear growth<sup>23</sup>. Catch up in linear growth may follow immediately upon repletion, may manifest in a prolonged adolescent growth spurt, or may fail entirely<sup>17</sup>. Complete catch-up i.e. achieving the genetic potential for final adult height may require a permanent change in environment, or even cross generational catch-up<sup>24</sup>.

### **Assessment of nutritional status in children**

The term 'protein energy malnutrition' PEM is applied to a spectrum of conditions, ranging from severe wasting with or without oedema to nutritional stunting with a normal weight for height. It is evident that PEM is usually accompanied, and often exacerbated by micronutrient deficiency. Simple anthropometric observations of body size, particularly of weight for height, are logical indicators of the state of energy stores at times of nutritional stress. They have proved their worth as predictors of mortality. However, despite the detrimental effect of micronutrient deficiency on linear growth, it is not advisable to regard anthropometry as an index of micronutrient status.

### **Operational value of nutritional indicators**

Anthropometric measurements are valid nutrition indicators in so far as they represent the actual 'state of the (nutritional) system'<sup>25</sup>. The system's ability to survive periods of stress clearly depends on the magnitude of (protein-) energy stores. Weight loss (and, for an influential minority, excessive weight gain) causes concern, and yet weight alone gives insufficient information. The importance of height in interpreting weight data is obvious, even when we know the age (of a child). Consequently, indices relating body weight and height are preferred, although the choice of indicator varies with the situation. For example, Body Mass Index (weight/height, BMI) is now the preferred indicator of the risk of obesity<sup>26,27</sup>, and of chronic energy deficiency (CED) in adults<sup>28</sup>.

When childhood PEM is the main concern, the weight for height ratio is preferred. Prudhon et al<sup>29</sup> recommend that the weight for height index is expressed as a percentage of the reference median rather than as the z score. The better statistical prediction of risk given by this simpler indicator may be explained by the narrow age range of subjects in the authors' study. It must be stated that auxologists recommend the z score because of marked differences in the reference distributions of weight and height in children<sup>30</sup> (c.v. for weight and height of 2 year old boys are respectively 8% & 4%, and both increase with age).

Grading of degree of underweight for height (wasting) is particularly useful in emergencies or in hospital practice, where acutely malnourished children are over-represented. On the other hand, in situations of long-standing under-nutrition, it is common to find severely underweight and stunted babies, who are NOT wasted (Medecins sans Frontieres Malawi personal communication). In such situations and for longer term follow up, weight or height for age are preferable indicators<sup>30</sup> (not forgetting that age is recorded in the road to health chart). Length / height measurement is extremely

useful at all levels of child health; an using, in the absence of high technology equipment, and simple length and height measuring boards constructed from local materials, are preferable to (fragile) imported equipment, which may difficult to assemble<sup>31</sup>.

### **Comparative analysis of growth and nutrition**

Notwithstanding arguments in favour of a local growth standard, the NCHS data were a convenient international reference<sup>32</sup>. These North American data have now been replaced by the 2000 NHANES standards ([www.cdc.gov/growthcharts/](http://www.cdc.gov/growthcharts/)), which are not recommended for international reference, because they represent growth patterns of infants on mixed feeding. A new set of international growth standards waits the completion of a seven country study of exclusively breast-fed infants<sup>33,34</sup>. Nevertheless, data on BMI based on six country studies (one in Africa) are already available for comparative studies of obesity, which appears to be increasing in global prevalence<sup>26</sup>. The tools for estimating BMI are relatively simple; and the index is less dependent on age than weight for height. However its optimal use requires some mathematical training and it will probably be most useful in tertiary centres. The time is ripe for a study of BMI in healthy East African children.

### **Nutritional indicators in adults**

BMI is a useful index both of obesity and of chronic energy deficiency CED in adults. In the absence of an accepted international reference, data from affluent communities are used as predictors of risk. Based on a normal range of BMI of 18.5 to 25, three grades of obesity are defined by respective ranges of BMI 25 –30, 30 to 40 and >40. Grading of CED is less straightforward. Whereas BMI<16 is generally associated with functional deficit, it is clear that many people in DCs function adequately with BMI below 18.5. When 'intermediate' levels of BMI, ranging from <18.5 to >16.0 are accompanied by consistently low energy expenditure, they are termed grade 1 or 2 CED<sup>28</sup>. Ferro Luzzi et al<sup>35</sup> confirmed that low BMI plus year round low physical activity level (PAL<1.4, where PAL is the ratio of total to basal energy expenditure) is associated with a reduction in work capacity. The proportion of a community defined as unfit by the combined criteria is smaller than when BMI is used alone. Sequential surveys

have shown an association between CED and economic variability<sup>36</sup>. Further operational research e.g. combining BMI with biochemical indices used in sports physiology may elucidate this area. Certainly more information is needed to facilitate the development of guidelines e.g. for food supplementation.

### **Oedema and childhood PEM**

Despite the relatively rarity of oedematous malnutrition (around 1%) in community surveys, the health seeking behaviour of anxious parents, aware of its high mortality, results in its high prevalence in hospitals. Admission rates vary with season or with epidemics e.g. measles (now mercifully rare). Paediatricians have sought long and hard to elucidate the cause of oedematous malnutrition.

Golden and Ramdath<sup>37</sup> succinctly summarise the aetiologies which had been postulated during the last half century viz:- protein deficiency, niacin deficiency, dysadaptation to a protein deficient diet, hormonal dysadaptation to unbalanced protein energy deficiency, aflatoxin intoxication. Golden's group advanced the most recent hypothesis viz:- that oedema in the malnourished child is explained by an imbalance between the generation of reactive oxygen species (commonly termed free radicals) FR and their safe disposal<sup>37</sup>.

In reviewing the evidence for their hypothesis Waterlow<sup>38</sup>, welcoming new understanding of the processes involved in the causation of oedematous malnutrition, cautioned that concomitant protein deficiency remains a problem for public health and nutrition policy makers. Recent studies have further elucidated and underpinned the links between the FR and earlier hypotheses.

### **Present understanding of the pathophysiology of oedema in PEM**

Golden's unifying theory indicates that the characteristic features of kwashiorkor are explained by severe perturbation of intracellular metabolism, commonly triggered by infection, in an organism already affected by protein energy malnutrition. In a state of health, the stable state of cells throughout the body, is maintained by the reduction-oxidation (redox) action of glutathione (GSH), supported by anti-oxidant micronutrients,.

GSH maintains many substances in a reduced state, either directly or via linked enzyme systems; it is active in detoxication of foreign substances, including drugs, and is active, together with  $\omega$ -3 and  $\omega$ -6 polyunsaturated fatty acids (PUFA) in the synthesis of leukotrienes. GSH is formed from glutamate, cysteine, and glycine. Cysteine, itself capable of conversion from methionine, provides the sulphhydryl group<sup>39</sup>. GSH is consumed during the redox

reaction, especially when one of the possible pathways fails due to selenium deficiency<sup>37</sup>. Low concentrations found in oxidative stress are thought to be due to excessive consumption of SGH rather than failure of synthesis. Nevertheless cysteine supplementation results in a rise in the level of erythrocyte SGH in malnourished children<sup>40</sup>.

Infection, common in children, and exacerbated by contamination risks associated with poverty, is the most common immediate cause of this metabolic disruption. Furthermore, PEM per se has an adverse effect on both the innate and adaptive response to infection<sup>41</sup>. The acute phase response (APR) is attenuated, due to inability to synthesise the inflammatory cytokines IL-1, IL-6, TNF alpha, possibly exacerbated by failure of supply of certain essential aminoacids (EAA). CD4 T helper cells are few in PEM, resulting in a lower CD4/CD8 ratio. Furthermore complement components C3, C5, and factor B are reduced, opsonisation is reduced and phagocytosis is diminished<sup>42</sup>.

Notwithstanding the enfeebling effects of PEM, infection provokes a cellular defence which generates FR. These, as well as contributing to bacterial killing, cause oxidative stress to the organism. Effectiveness of the body's protective antioxidant response depends not only on the effective redox action of GSH, but also the complex action of associated metallo-enzymes, containing copper zinc, manganese and selenium. Thiamine and riboflavine are also involved in the enzyme systems. At the same time Vitamin E acts as a FR scavenger for lipids, while zinc and glutathione are FR scavengers in the aqueous domain. The role of iron is problematic, since its multivalent capability permits it to act as a FR. An essential nutrient, it is safest when protein bound.

The failure of defences against oxidative stress in the malnourished child results in leaky membranes, leading to sodium retention and loss of intracellular potassium. Golden also speculates that the skin changes of kwashiorkor are due to oxidative damage, and tends to minimise the role of hypoalbuminaemia in the causation of oedema. Waterlow<sup>38</sup> maintains that 'hypalbuminaemia is the number one cause (of oedema) and potassium deficiency the number two!'. Despite differences of emphasis these eminent scientists agree that protein, energy and micronutrient deficiencies, and infection are causally implicated. They also emphasise the importance of phased and

meticulous, clinical management (see below)

### **Modulation of the adverse effects of inflammation**

A prolonged or excessive inflammatory response can be harmful e.g. the hepatic granulomata associated with schistosomiasis, the auto-antibody responses in rheumatic fever etc. An unbalanced immune response can result in the toxic action of oxidants, and the detrimental action of cytokines such as nuclear factor kappa B. Certain harmful immune responses may be modulated by administration of particular nutrients. For example fats rich in the long chain n-3 PUFA (*Eicosapentanoic acid 20:5 n3*) slow tissue response to certain cytokines, thus reducing (chronic) inflammation. A new science of immunonutrition concerns the therapeutic modulation of immunological activity by 'administration of nutrients or food items fed in amount above those normally encountered in the diet'<sup>43</sup>. Further examples include the administration of certain aminoacids involved in glutathione synthesis, or known to improve T cell function.

### **Micronutrients, infection and the genome**

We have emphasised the importance of micronutrients, both trace minerals and vitamins, in the protection of the (malnourished) organism against oxidant damage. Micronutrient, specifically selenium deficiency affects the virulence of viruses (infecting mice). A normally benign strain of Cox-Sackie B virus becomes virulent in selenium deficient mice and this virulence persists after passage through non deficient individuals. Beck<sup>44</sup> postulates that alteration in the viral genome is mediated by increased oxidative stress. It seems likely that deficiency of other 'antioxidant' micronutrients might have similar consequences, possibly explaining 'geographical' differences in HIV epidemiology.

### **Mortality and management of PEM**

he persistence, over nearly half a century, of high mortality in PEM gives cause for concern. Irrespective of those socioeconomic and public health factors (including HIV) which determine its overall community prevalence, and of the hidden contribution of PEM to death from other causes, children continue to die in hospital and nutrition rehabilitation units during treatment for recognised PEM. Case fatality remains above 20%, (ranging from 20% in marasmus to 30% in marasmic kwashiorkor) although 'good practice' is associated with significant lower case fatality. Schofield and Ashworth<sup>45</sup> list common omissions and faulty practices, and the benefit of simple measures e.g. routine use of broad spectrum antibiotics, and mineral supplements. They emphasise caution with re-feeding, and extreme care to avoid over-hydration. While expressing

concern about the negative effects of poverty of resources, they do not address the vexed question of staff shortage. Manary and Brewster<sup>47</sup> report the persistence of high mortality (25% c.f.30% with 'standard' care), despite improved staffing (nurse:patient ratio 1:3), broad-spectrum antibiotics, avoidance of IV fluids, and phased feeding. Comparing 'intensive' and 'standard' care, these authors note the paucity of predictive signs of severe, often lethal, metabolic disturbance. Death occurs early, 37% of deaths within 48 hours of admission, leading to predict little effect on high case fatality until improved laboratory support and intensive care become available.

### **Principles of management**

We may argue whether children should be treated in dedicated units or hospitals, where (in the past), they risked death from hospital acquired measles, or discharge without (parents) understanding the nutritional basis of the illness. Survival depends on correct initial assessment, recognition and appropriate treatment of complications accompanied by holistic rehabilitation. For all of these, training and teamwork are essential. Since weight for height deficit is a better predictor of acute risk than weight for age<sup>29,38</sup>, height (length) should be measured and weight for height used as a nutritional index. Despite the tropical paediatrician's skill in managing dehydration and anaemia in general paediatrics, s/he must face the fact that, in the child with severe PEM, such complications require particularly diligent supervision, because of the child's greater vulnerability to circulatory overload.

In addition to phased feeding and mineral supplementation Golden ( personal communication) recommends management according to protocol by specifically trained staff. He emphasises the importance of simple observations e.g. attention to the history so that e.g. a clinical impression of dehydration is supported by a history of recent fluid loss or carer's observation of change in appearance of the child's eyes. He regards the 'staring eye' as a particularly useful sign of dehydration, explained by retraction of eyelids due to sympathetic over-activity. The risks of over-treatment of dehydration, and particularly risks associated with intravenous rehydration, are grave. Fluid loss should be corrected via the oral or nasogastric route, using low sodium fluids rather than the WHO/UNICEF

sachets, which, even when correctly reconstituted, provide an excess of sodium (60 mmol/litre)<sup>38</sup>. The recommended commercial OR formula 'Resomal'<sup>47</sup>, (which provides 45mmol Na/litre), may be approximated by diluting 'standard' ORS and adding glucose and minerals.

The detailed instructions on clinical management given in the draft protocol for management of severe PEM, due to replace the 1999 WHO document<sup>48</sup> (Golden personal communication) will undoubtedly prove useful. Nevertheless, existing staff: patient ratios cannot give the necessary detailed supervision. Commercial formulae are not widely available and food supplies (e.g. by short term international programmes) may be intermittent or incomplete, preventing preparation of therapeutic diets of recommended nutrient density or proportions (Walford & Duggan personal communication). Where there is no nutritionist capable of devising safe alternatives, there is a risk of dangerous misuse of ingredients. Finally, where local case fatality is high, sensitive interval audit provides an opportunity to identify and correct poor practice or to support advocacy for improved supply e.g. of antibiotics or micronutrient supplements. Such operational research should be given greater recognition in the academic training of paediatricians.

### **Arguments for and against iron therapy in childhood**

Iron is a necessary nutrient but may also be hazardous. Low transferrin concentration in PEM leads to the circulation, with detrimental effect, of de-compartmentalised iron<sup>49</sup>. Nevertheless children with PEM are commonly iron deficient and require repletion during re-feeding; the draft management protocol (Golden op cit) advises adding iron to the phase 2 (convalescent) diet.

The dangers of iron treatment to children at risk from malaria have also been reported in the past. In a randomised controlled trial of iron administration to children with varying degrees of iron deficiency and at risk of malaria, iron supplementation was found to reduce the prevalence of anaemia and iron deficiency without substantially increasing the risk of malaria<sup>50</sup>. When iron supplementation was combined with malaria prophylaxis; the enhancement of haemoglobin concentration was marginal, although malaria infection was reduced.

### **Main messages and conclusions**

Epidemiological study of the links between foetal and adult well-being is relevant and it is time for more local research. So too, there is need for more local information on targeted nutrition intervention in pregnancy. The vexed question of choice of infant feeding method in the age

of HIV is more easily faced by an informed mother, who is aware of her status. We should pay more attention to the distinct determinants of linear growth, and to the additional information provided by inclusion of height in nutritional assessment. Micronutrient nutrition appears to be an active area of research and we should expect to hear more about micronutrients and the genome. Finally, PEM remains with us, accompanied by persistently high case fatality. The latter will only fall if respect for physiological vulnerability in PEM leads to more cautious and precise management by trained (nursing) staff. Operational research in this area is urgently needed.

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