Keywords
Malnutrition · Metabolism · Policy making

Abstract

**Background:** This analysis sets out an overview of an IUNS presentation of a European clinician’s assessment of the challenges of coping with immediate critical clinical problems and how to use metabolic and a mechanistic understanding of disease when developing nutritional policies.

**Summary:** Critically ill malnourished children prove very sensitive to both mineral and general nutritional overload, but after careful metabolic control they can cope with a high-quality, energy-rich diet provided their initial lactase deficiency and intestinal atrophy are taken into account. Detailed intestinal perfusion studies also showed that gastroenteritis can be combated by multiple frequent glucose/saline feeds, which has saved millions of lives. However, persisting pancreatic islet cell damage may explain our findings of pandemic rates of adult diabetes in Asia, the Middle East and Mexico and perhaps elsewhere including Africa and Latin America. These handicaps together with the magnitude of epigenetic changes emphasized the importance of a whole life course approach to nutritional policy making. Whole body calorimetric analyses of energy requirements allowed a complete revision of estimates for world food needs and detailed clinical experience showed the value of redefining stunting and wasting in childhood and the value of BMI for classifying appropriate adult weights, underweight and obesity. Lithium tracer studies of dietary salt sources should also dictate priorities in population salt-reduction strategies. Metabolic and clinical studies combined with meticulous measures of population dietary intakes now suggest the need for far more radical steps to lower the dietary goals for both free sugars and total dietary fat unencumbered by flawed cohort studies that neglect not only dietary errors but also the intrinsic inter-individual differences in metabolic responses to most nutrients. **Key Messages:** Detailed clinical and metabolic analyses of physiological responses combined with rigorous dietary and preferably biomarker of mechanistic pathways should underpin a new approach not only to clinical care but also to the development of more radical nutritional policies.

Introduction

The challenge of nutrition is unknown to most doctors who regard it as a peripheral interest that can be readily met by calling on the services of dietitians for those with intestinal disease and malabsorption, or for those with diabetes or for frail elderly patients. I certain-
ly had no nutrition teaching whatsoever and at that stage we had not learned of the major impact of folate on the propensity to developing neural tube defects. It is only very recently that I have remarked on my journey into nutrition [1], but here I consider the crucial role of nutritional science in answering many of the challenges in public policy making, particularly for lower-income countries.

**Treating Protein Energy Malnutrition**

My introduction to nutrition came when I started work in Jamaica where there were many severely malnourished children with a high death rate at that time. I soon learned how critical it is to feed these children frequently with modest amounts of high-quality food and not pile the food in – a feature I readily understood having heard of the experiences of several survivors of the Belsen and Auschwitz concentration camps when working as a house physician in London.

Dietary control in the first few days was critical since providing too much sodium could precipitate cardiac failure and sudden death and one obviously also needed to assess whether there was a coexisting infection associated with the drastically impaired immune function.

**Growth Rates and Appetite Control**

Once equilibration had occurred after a few days, then it was possible to refeed children with much higher energy and protein intakes to stimulate remarkable rates of weight gain as set out by my colleague Ann Ashworth [2]. These analyses helped Ann to develop for the World Health Organization (WHO) suitable feeding systems for malnourished children on a global basis, since we knew that many centers in Africa and Asia were finding it extremely difficult to get malnourished children to grow and regain their appropriate size [3]. This then was an example of meticulous metabolic work founding the principles for coping on a large scale with childhood malnutrition both in clinics and within the community. Children on reaching their appropriate weight for height immediately reduced their intake overnight demonstrating the remarkable appetite control mechanisms.

**The Cause of Diarrhoea and Sensitivity to Excess Food in Malnourished Children**

One of the obvious features of malnourished children is their loose stools and the frequent coexistence of gastroenteritis but was the cause excessive intestinal motility, malabsorption, or some other defect? New approaches to assessing objectively intestinal absorption with two lumens and later three lumen tubes were being introduced [4, 5], so this system was further developed with the construction of a 5 lumen tube (Fig. 1) to study intestinal motility and the rates of disaccharide digestion and carbohydrate absorption rates at the same time. The motility studies were added, as it was unclear whether the intestine was so active that it did not give time for the luminal contents to be digested and absorbed, thereby inducing diarrhoea.

It soon became apparent that excess motility was not the intrinsic problem, but the lumen of the malnourished gut was narrow and inflexible and transit was accelerated if the glucose input to the intestine (or if the carbohydrate load provided in a meal) was too great. This then explained the inability of these very malnourished children to tolerate rapid early refeeding. Indeed the rate of transit on both malnourished and recovered children rose in proportion to the unabsorbed sugar, so the overall transit rates down the narrower lumen were faster in the malnourished state. Lactase concentrations in the mucosa (measured by a separate enzymatic technique) related directly to the rates of digestion of lactase in the small intestine and increased as the child recovered. Sucrase activity and in vivo sucrose hydrolysis were also somewhat depressed when malnourished but they improved during recovery [6] (Fig. 1a in [1]). However, there was no evidence of increased permeability of the intestine in the malnourished – assessed by calculating the sodium drag effect in relation to water transfer and the osmotic pressure in the lumen [7]. There was also no evidence of excess water secretion into the gut with high sodium content indicative of plasma leakage.

**Stimulating the Use of Sugar/Saline Treatment for Childhood Diarrhoea as Well as Cholera**

Then when assessing by similar techniques the intestinal response of gastroenteritis in children, who were often also moderately malnourished, it became clear that they were secreting electrolytes and water into their intestine but providing glucose could combat this if sodium was also included in the fluid infused into the gut (Fig. 2)
This reinforced Ingelfinger’s emphasis on the conjoint need for both sodium and glucose to facilitate absorption. John Banwell told me that my studies on malnutrition and gastroenteritis, together with those of Torres-Pinedo [9] in Puerto Rico (whom I visited during my studies), had justified him and his colleagues in Dhaka, Bangladesh to advocate the use of glucose/saline for children in the community with gastroenteritis as well as for their patients with cholera [10]. This has already saved 93% of deaths in clinical settings and probably many further millions in the community [11].

**Assessing Nutritional State**

**Biomarkers – Is Measuring Serum Albumin Useful?**

In the mid-1960s, there was a real debate about the distinctions between marasmus and kwashiorkor but also about which markers could be used to identify incipient problems in children. Serum albumin levels were being used as one of the indicators. This was the era when we were just learning from Cahill’s elegant work in Boston about the metabolic and organ responses to starvation in terms of fuel use and changing organ amino acid balances [12]. So the question was how sensitive to controlled reductions in protein intake were the circulating levels of albumin? We could have undertaken a series of standard feeding tests, but the impression already gained was that the fall in blood albumin levels was delayed for some reason despite relatively poor nutritional conditions. By then undertaking a detailed tracer study with I\(^{131}\) albumin and using an accepted model of albumin that included an extravascular albumin mass, we were able to calculate albumin synthesis and breakdown rates. It rapidly became apparent that when protein intake is reduced, there is an immediate fall in albumin synthesis and a transfer of albumin from the extravascular space into the blood stream with a slowing of albumin catabolism after the initial fall in albumin synthesis [13]. These adaptive processes preserve plasma albumin, so measuring albumin levels is a late indication of the relatively prolonged inadequacy of protein intake. Furthermore, under conditions of starvation the inflow of muscle and other peripheral sources of amino acids helped to keep albumin levels up. This implied that a child could become very deprived of nutrients before plasma albumin levels fell and this response was analogous to the adaptive mechanisms already apparent in general protein metabolism [14].
Anthropometric Measures and the Highlighting of Childhood Stunting as the Major Public Health Problem

Once back in London, I was asked by the UK Ministry of Overseas Development to respond to the challenge from political leaders in the Caribbean island of Montserrat. They claimed that the UK government’s support was inadequate and food-deprived children were unable to benefit at school, thereby accounting for their poor school performance. So with a new PhD student, Bike Aksu, we examined and measured both preschool and school children throughout the island and calculated by hand each night their weights and heights in relation to the new WHO growth standards just set out by Derrick Jelliffe and based on data of US children’s growth monitoring standards [15]. We immediately found that a high proportion of children were simply short for their age with far fewer below their expected weight for height. Yet this deficit in weight for age then classified them as malnourished. This seemed of immense significance, as these very active children were not deprived of energy, even though their growth had been slowed presumably by intercurrent infections and the prevailing nutritional conditions. The Montserrat Governor then allowed us to fly first to Barbados to inspect their renowned school feeding system and then to Jamaica to see Derrick Jelliffe at the Pan American Health Association’s Caribbean Food and Nutrition Institute. He agreed totally with our analyses as did John Waterlow back in London. Waterlow then published the new approach to distinguishing between wasting and stunting, the data from our work being used to illustrate the point [16, 17]. This approach then became the WHO standard approach that has served us so well. However, it again illustrated how a clinical metabolic perspective allowed a new approach to be developed in public health.

Adult Anthropometry – the Development of Normal and Obesity Criteria and Indices of Adult Undernutrition

In 1971, I had proposed to the Department of Health that we assess why the seemingly new phenomenon of general obesity seemed to be afflicting particularly middle-aged women in the United Kingdom. Waterlow was therefore asked by the Department of Health and MRC to chair an expert group with myself as the secretary. Digging into the archives I discovered the Metropolitan Life Insurance Tables and simplified the definitions of normal or acceptable weight by finding that by using the old Quetelet expression of weight/height$^2$, then roughly the same values emerged for minimum mortality for both men and women whatever their so-called frame size and height [18]. We then highlighted obesity as a major potential public health problem with John Garrow, a member of our team, rounding the figures to normal or “acceptable” body mass indices (BMIs) of 20–<25 BMI, which then meant obesity occurred with weights 120% above normal, that is BMIs of 30+.

A decade later in Guatemala during a discussion of a US feeding program in the Americas and Africa for what was termed “chronic energy deficiency” on challenging the meaning of the term, it was possible quickly to calculate that many of the supplemented mothers were already obese. We therefore devised a new complex chronic energy deficiency definition [19], based originally on both the health impact and laboring capacity of adults with lower BMIs. However, given the often unpublished data we had originally accumulated showing the progressive morbidity and probably greater mortality the lower the BMIs Anna Ferro-Luzzi and I simplified the definition during a visit to Ethiopia, so

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**Fig. 2.** The importance of providing glucose as well as electrolytes to change the net water transfer across the small intestine of children with protein-energy malnutrition (PEM) and those with the additional problem of acute gastroenteritis. These data are compared with the effects in children fully recovered from both malnutrition and gastroenteritis. In each child, the impact was tested with isotonic electrolytes (shown on the left in each group of children) and then with glucose (on the right of each category of children). Reproduced from [8].
that we again had simple BMI cutoff analogous to the definitions of overweight and obesity [20]. WHO and international authorities have now all accepted these anthropometric definitions of both underweight and overweight.

**Individual and Population Energy Needs and Assessing Food Inadequacy**

Just as the reassessment of a nation’s rates of childhood malnutrition depended on gaining an understanding of malnutrition in a Jamaican metabolic ward, the same concept of detailed metabolic analyses underlay our first efforts at estimating the food needs of the world. I was invited to attend the new 1981 FAO/WHO/UNU meeting on protein and energy requirements. But I refused on the grounds that I had no real field experience of national food supplies. However, after persisting requests I agreed to attend for the first few days only to find myself as Chair of the energy group, which was meant to collect and analyze food intake data from across the world. Yet in Cambridge, we were now running the MRC Dunn Clinical Nutation Centre and exploring the basis for energy balance. We were very critical of the supposed accuracy of food intake techniques, so we routinely used biomarkers of intake and were meticulously weighting our food for days and even weeks on end. It then became clear from work undertaken with our PhD student, the late Sheila Bingham, that food intake data were very inaccurate whether assessed by 24-h recall or food frequency questionnaires [21, 22]. Then with Prakash Shetty, also a PHD student, we realized that the data on so-called energy adaptation based on food intake data in what was then called the Third World were bogus [23] if one considered parallel analyses of resting or basal metabolic rates and even crude estimates of minimal physical activity. These estimates and a new approach to energy balance were based on insights gleaned from building and using whole body calorimeters in Cambridge, UK. This showed that the adult body was metabolically, finely controlled with a 24-h reproducibility of about 0.7% if physical activity was standardized. Physical activity levels (PALs) could also be expressed simply as a ratio of total expenditure to the basal metabolic rate (BMR). So food needs were predictable and our semi-starvation studies (primarily relating to attempts to understand obesity) showed the limits of energy adaptation. This led us to consider how to generate equations for the BMR of men and women – essentially relating to their fat-free mass that we knew declined with age. So in the FAO/WHO/UNU meeting in Rome, we changed the whole basis for estimating global food needs calculating these not on purported food intake data but by predicting the intrinsic energy needs of a population with a specified age structure, stature, appropriate BMI, and minimum physical activity. This immediately seemed to raise the world’s food needs by 30%, so we had to delay the final recalculation of global food needs and the needs of individual countries [24] to ensure we had a new collation of data with estimates of BMRs in different circumstances [25]. This and our work on BMIs [26] and the re-evaluation of physical activities globally, expressed as PALs, [27] transformed FAO’s approaches to estimating the number of hungry people in the world. This scheme persists to this day [28] and depends on setting an appropriate mean BMI for a community and their designated PALs.

**Salt Sources: From Cooking and Metabolic Studies to Policy Priorities**

Colleagues at the London School of Hygiene and Tropical Medicine in the early 1970s highlighted new analyses of death rates across the globe showing that strokes were a major cause of death in poorer countries. Already excess salt had been invoked as a major cause of increasing blood pressures with age, so this raised the question of the sources of dietary salt and the need to distinguish salt in purchased food as distinct from the “discretionary” salt used in cooking and at the table. We therefore assessed the potential value of lithium as a tracer for sodium. Cooking experiments showed that lithium tracked sodium well into foods during cooking but with a substantial loss in the discarded cooking water [29]. In metabolic studies, the lithium also tracked sodium in sweat, urine, and feces [30], so by measuring 24 h urine outputs in a small town in East Anglia, UK, we were able to show that 85% of the sodium was derived from salt in purchased foods [31]. So public policies had to be changed to focus on driving the salt content of food down by progressive reformulation and not just by advising individuals on their cooking skills. This strategy has now been shown to work [32] with accompanying falls in blood pressure. With WHO in the Eastern Mediterranean Region, we have also successfully promoted food reformulation starting with the salt content of bread in many countries, for example, Kuwait, Iran, Bahrain, and Oman [33]. We also found tenfold differences in the salt content.
of the standard Arab flat bread purchased in over 10 country capitals in the region. This shows just how variable the salt content of seemingly standard foods can be. It had been shown in Portugal decades earlier that reducing the salt added by the main bakery of one village reduced the average blood pressure of the villagers [34] and Chinese data have shown a 74% reduction in stroke mortality within 5–7 years of reducing both canteen salt and fat intakes, and advising these dietary changes at home with better hypertension control of >100,000 steel workers [35]. Nevertheless, in countries with less food processing as in the Mediterranean, for example, Italy [36], or in lower-income countries such as Indonesia [37] or Guatemala [38] much more salt is under discretionary use in the home (Table 1). This emphasizes the importance of using scientific approaches to identify the major industrially driven sources of salt use before choosing public health policies. In the Middle East, we found that salt production mainly supplied the chemical industries but even with salt iodination costs, the profits were greatest from the salt sold to the food manufacturers and retailers.

### Deriving the Dietary Fibe and 400 g/day Vegetable and Fruit Goals

During the evolution of the first set of agreed dietary goals integrated for the prevention of both childhood malnutrition and adult chronic diseases [39], we were confronted with estimating an appropriate dietary fiber goal and ensuring this was not just derived from bran or other cereal fiber extract. So we generated fiber values from our Cambridge analyses [40] of fecal weight responses to acetone-extracted fiber, produced for us on an industrial scale by Unilever. These data combined with meticulous Italian household EURATOM analyses in the 1960s allowed Anna Ferro-Luzzi to recalculate the magnitude of adult vegetable and fruit intakes at a time when the beneficial Mediterranean diet was routinely eaten. So again meticulous metabolic/balance studies were combined with carefully validated representative dietary analyses to produce dietary goals rather than using cohort analyses with all their errors and their neglect of large inter-individual responses to standard dietary changes.

### Combatting Diabetes and Obesity: The Importance of a Lifelong Approach to Dietary Change and the Need for More Rigorous Prevention Policies Than Those Promulgated in Affluent Societies

Our studies in Jamaica showed that malnourished children had an exceptionally poor insulin response to glucose tests, but to our surprise, this did not recover very much even after months of rehabilitation (Fig. 1b in [1]). Now we know that this defect in insulin secretion persists into adult life [41] and is also seen in survivors of early fetal deprivation during the Dutch famine [42]. This then may link to our finding that there is much greater sensitivity to later adult diabetes in some countries, for example, Mexico [43] and other Latin American societies, many Asian countries [44], and those in the Middle East [45] and Africa. Their diabetes rates are in excess of what one can show in equivalently overweight Australasian, Western European or non-Hispanic US Caucasian populations. So it is tempting to conclude that these other populations, exposed for centuries to long-standing malnutrition in childhood, have an intrinsically lower pancreatic capacity for insulin secretion. Whether or not this is true, the data emphasize the importance of considering health across the lifespan, a concept we introduced 2 decades ago [46, 47]. Logically public health policies also

### Table 1. Some examples of the use of the lithium gold standard technique for quantifying salt sources. These analyses totally change salt-reduction policies for lowering salt intakes, as it depends on the degree of food manufacturing in the country

| Salt sources                  | UK  | Italy (Vallo) | Guatemala | Benin | Indonesia |
|------------------------------|-----|---------------|-----------|-------|-----------|
| Discretionary: home cooking + table use, % | 15  | 40            | 77        | 52    | 51        |
| Total purchased foods, %     | 85  | 60            | 23        | 48    | 49        |
| Total intake salt, g/day     | 9.0 | 11.3          | 5.2       | 9.0   | 5.8       |

The values for the % sources of salt are valid even with incomplete urine collections, but the accurate measurement of individuals’ total intake requires complete 24 h urine collections over several days. References: UK [31], Italy [36], Guatemala and Benin [38] and Indonesia [37].
need to be far more interventionist than the current rather feeble efforts promulgated in the United States, or in Europe.

Dental Caries, Sugar, and Total Fat Goals

The need for this more rigorous view is amplified by our recent reanalyses of the meticulous Japanese studies during the Second World War on the causal role of sugar in the development of dental caries [48]. Different students each monitored the rates of dental erosion tooth by tooth over many years. The late Aubrey Sheiham and I then found that exceptionally low sugar intakes are needed to avoid the development of caries. This is true even with the full fluoridation of drinking water, the use of fluoridated toothpaste, and intensive dental hygiene over many years. Caries is a nutritionally neglected subject despite being a lifelong affliction with huge public health costs. So it now seems clear to us that sugar intakes – on a population average intake basis – should be less than 2–3% of energy intake. These reports were cited by WHO when generating their final analysis of the importance of reducing national sugar intakes, so that no individuals had more than 5% for maximum benefit [49]. These meticulous studies match the other metabolic studies [50] and carefully analyzed epidemiological studies of weighed food intakes in relation to the BMIs of nearly a third of a million people throughout Brazil on different diets [51], suggesting that in our affluent and profoundly inactive world, fat intakes should ideally be about 20% or less.

The dietary goals set out here are or were far from the prevailing thinking, but in public health terms – especially for the poorer countries of the world – it is of exceptional economic as well as of social and health importance to be more rigorous. This also then implies the need for a radical rethink of agricultural and food policies. These lower dietary goals then would also be far more consistent with the need for a sustainable food system in a rapidly warming world afflicted by climate change.

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