The Development of Concepts of Malnutrition[1]

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The idea that edematous malnutrition was caused by hypoalbuminemia, and that this was directly attributable to a low protein diet, was present in the 19th century. After the conceptual framework was laid by Starling, of the effects of the plasma protein's oncotic pressure being responsible for fluid distribution between the interstitial and vascular compartments, the idea that a low protein diet caused edema was quickly established on this theoretical background.

There followed a series of experiments initiated by Denton (1,2), which were quickly translated to man (3,4), although, even at this early stage, there were other causes of experimental nutritional edema reported (5) and the sodium intake in the diet was regarded as a major factor determining the appearance of edema (6). There followed a series of experiments using plasmapheresis, which were interpreted as confirming the thesis of protein deficiency causing edema (7–11). However, there were noted anomalies in the relation of clinical edema in both nephrotic syndrome (12) and nutritional edema (13–17).

The problems raised by these early experiments on the pathophysiology of nutritional edema and the inadequacy of current physiological explanations were raised in the classical reviews of McCance (18) and Keys (19). Keys gave adult volunteers cabbage, potatoes and salty soups to emulate the diet of prisoners of war; they developed edematous malnutrition, but their plasma oncotic pressure was not particularly low. He cited numerous studies from the literature to support the finding of nonconcordance between plasma proteins and edema. After World War II McCance (18) studied German POWs returning from the Russian front with edematous malnutrition; their edema was unrelated to their protein status. The controversy remains unresolved. Nevertheless, the firm theoretical hypothesis given by Starling has been repeated in every textbook of physiology written in the past century (20) and is known by every medical student as the "cause of edema" in both malnutrition and nephrotic syndrome.

In children, around the turn of the century, most work was done in Germany, where the condition in children was known as *Mehlnahrschaden,* or flour dystrophy (21), because it was recognized in poor children weaned to a diet of cereal flour. As in adults there was controversy over the cause, but protein deficiency was most commonly cited on the basis of low plasma protein concentrations. In the Spanish literature, kwashiorkor was described in 1908, where it was known as *Sindrome Policarencial Infantil,* with reports in many local journals from most of Latin America (22); as the name implies, the Spanish ascribed the condition to multiple coexistent deficiencies, a view that agrees with modern ideas of the pathophysiology of kwashiorkor. By 1913 Guillon described kwashiorkor in the French literature, where it was called *Bouffissure d'Annam,* or Swelling [disease] of Vietnam. The French reports are of particular interest as the accompanying photographs show the typical features of kwashiorkor, and also show that the disease occurred in older children (23). There were occasional reports in English from both the temperate regions (24,25) and the tropics (26). However, it was only following Williams's (27) reports in widely read English journals, that the disease in children acquired its present name, *Kwashiorkor,* and became widely recognized. There followed a controversy in which several influential authors maintained that kwashiorkor was in fact a form of pellagra, so that reports of kwashiorkor from this period may refer to the condition as "infantile pellagra."

Williams (27) ascribed kwashiorkor to weaning to a maize-based diet and showed that they responded to a high protein diet of milk and "marmite." Perhaps one of Waterlow's early observations is germane here, given that he described a toxic effect of maize bran in an early study (28). Of special interest are the studies of Youmanns et al. (13,14), who investigated families of American subsistence farmers who got "epidemic" nutritional edema seasonally, and yet their plasma proteins were normal. The importance of these studies is that the diet of the families was maize based, the same staple that Williams's patients (27) in the Gold Coast (Ghana) were taking. In a remarkable wartime study, Petrides (29) induced kwashiorkor in several children by feeding them the diets of the poor of Athens; he found that they did not respond to egg white but did to egg yolk. This supports the view that the deficiency was corrected by some other component of egg yolk apart from the protein.

Many leading scientists worked on malnutrition during World War II. This was mainly because of the need to be prepared for the specter of famine in Europe and to manage concentration camp survivors. Following the war, interest in malnutrition was intense, given that many had personal experience of starvation or had friends who had been in concentration camps; the scale of the problem was overwhelming and there was a realization that the basic physiology of the responses to starvation was relatively unexplored. Those who went to the tropics reported that malnutrition, as recently experienced in Europe, was common throughout the world; however, in most poor communities it mainly affected chil-

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dren. These reports, coupled with a new attitude toward the colonized territories, awakened interest in examining the problem of malnutrition globally. Waterlow's report (30) and other reports were instrumental in the American and Colonial governments setting up research units to study malnutrition in many parts of the developing world: Jamaica, Uganda, South Africa, Peru, Thailand, Lebanon, Egypt, India, The Gambia, Guatemala, Indonesia and the Congo. In Jamaica, Waterlow concentrated on both the liver pathology and protein metabolism in the firm belief that protein deficiency was the underlying cause of kwashiorkor and energy deficiency the cause of marasmus (31–38).

In Jamaica, one set of experiments, in particular, were critical in laying the foundation for the "free-radical" hypothesis of kwashiorkor and allowing the interpretation of the low levels of glutathione that were later found. Waterlow (31) was trying to measure oxidative phosphorylation in the livers of children with kwashiorkor. However, he found that he had to make his measurements very rapidly after the biopsy was taken because the rate of oxidative phosphorylation quickly declined after the specimen was taken from the child. Fine homogenization significantly hastened the rate of deterioration, a phenomenon that Waterlow termed "Aging." Incubation of the biopsy for 15 min at 37°C or 180 min at 0°C resulted in an 82% loss of activity. If even a portion of this inhibition of the capacity for energy production had occurred in vivo it would have been lethal. During recovery of the child from kwashiorkor, aging of the biopsy specimens caused a much smaller reduction in oxidative phosphorylation, long before there was a change in the liver fat content, indicating that this was a characteristic of the kwashiorkor liver itself that reversed during successful treatment. Biopsies from children who had $<$15% of liver wet weight as fat retained 67% of phosphorylation activity; those with 15 to 30% fat retained 41%; and those with over 30% retained only 20% of the activity of oxidative phosphorylation after aging. Control specimens from rats maintained their activity under these circumstances for many hours without deterioration and did not show the "aging" phenomenon of the malnourished child's liver.

Waterlow went on to show that mixing the kwashiorkor hepatic homogenate with rat liver mitochondria caused poisoning of the rat mitochondria and that this property was particularly associated with the lipid fraction of the kwashiorkor liver. Addition of various chemicals had little effect on the aging process, although some protection was afforded by albumin. When Waterlow obtained these results there was no knowledge of the importance of single-electron reactions in causing damage within the body, the problems of iron decompartmentalization or the mechanisms of action of many hepatotoxins, such as carbon tetrachloride. Interest in free radicals was confined to those dealing with radiation injury. The in vivo role of antioxidants and their nutritional requirement was unknown and deficiency thought to be very rare, if it occurred at all. It was later when pioneers such as Professor Trevor Slater showed that these hepatotoxins acted through a free-radical mechanism that the way was open to reinterpret fully the experimental results of Waterlow.

Now, with the advance of free-radical biology we can go back to Waterlow's unique experiment, which could not be repeated nowadays because of changes in the ethical climate. When the biopsies were taken from the body and exposed to ambient oxygen they started to peroxidize, or "age." This process would be accelerated by decompartmentalization, particularly of any liver iron stores, and is the probable reason that Waterlow found that the degree of homogenization of the liver specimen was important. Peroxidation is retarded by antioxidants. Indeed, several assays have since been developed in recent years that measure "total antioxidant" power, by adding a radical generator to a biological specimen and measuring the delay before the specimen starts to peroxidize or produces radicals that can be trapped. This is, in effect, exactly the experiment performed by Waterlow on specimens of liver from children with kwashiorkor, in which he measured the aging of the liver. He exposed them to oxidative stress and measured the rate at which they lost function: the more rapidly they lost function, the lower the levels of hepatic antioxidants must have been and the more vulnerable the liver to oxidative stress/free-radical damage. That the fat became peroxidized, and thus itself toxic, was elegantly shown by Waterlow's observation that it was this fraction, in particular, that poisoned respiring rat liver mitochondria.

Indeed, these early experiments by Waterlow remain the only direct evidence that the fatty liver of kwashiorkor is related to a deficiency of hepatic antioxidant capacity and that relatively minor stress, such as being exposed to atmospheric oxygen concentrations, can cause a devastating loss of function. These data provide very strong support for the free-radical hypothesis of fatty liver and kwashiorkor.

The first serious attack on the protein-deficiency hypothesis came from Gopalan (39), who examined the diets of village children in India. He could find no antecedent dietary difference between those that developed marasmus and those that developed kwashiorkor. Unfortunately, this work was not formally reported in a peer-reviewed journal, which has led many to disregard these data.

The study of Picou, who examined the rate of protein turnover in severely malnourished patients, had surprisingly found a much higher rate of protein synthesis in the malnourished than that in the recovered children. This result was thought to have been obtained because, although the children Picou studied were still "anthropometrically malnourished," they were in fact in the early phase of catch-up growth, where a high rate of protein synthesis would be expected. Therefore in the early 1970s we wanted to repeat these studies, but this time to keep children in a stable condition immediately after admission for a few hours to make the measurements of the dynamics of protein turnover while they were still "metabolically malnourished." For this we gave them a diet designed to emulate the low protein content of the diet that they were presumed to have been taking while they became malnourished, and they were monitored very closely with a physician sitting at the bedside. We were surprised to see a marked clinical improvement in the children on this diet. Cautiously, we extended the period and found that the children improved remarkably, with a lowered mortality, fed a diet supplying less protein than was then presumed to cause kwashiorkor. During this time they lost all their edema without any change in their serum albumin level (40), and the rate of loss of edema was entirely independent of the protein content of the diet (41). The early argument that kwashiorkor was the result of protein deficiency because of the response to diets rich in protein was then judged to be fallacious. Is a headache the result of aspirin deficiency because it is cured by aspirin? This comment was made facetiously during a symposium on malnutrition in Jamaica, to show the faulty logic when the question in posed in a positive way. However, posed in a negative form, the same argument has impeccable logic; if a headache gets better without aspirin then it was not the result of aspirin deficiency! The demonstration that kwashiorkor could be cured with a diet lower in protein than the diets taken by poor children in Jamaica showed that some other cause had to be found for kwashiorkor apart from protein deficiency. These findings in

children are the same as those of Keys (19), McCance (18) and Youmans (13,14) in adults and removed the necessity for a separate pathogenesis to be postulated for the same clinical features in the different age groups.

In retrospect, given the degree of hepatic derangement of these patients and the known effect of high protein diets on patients with other liver diseases, it is surprising that high protein diets persisted for so long in the management of kwashiorkor. In adults, at the end of the war, the POWs were initially treated with protein hydrolysates, again on the assumption that they had protein deficiency; however, they had a very high mortality (42). In addition protein injury had been described in nephrotic syndrome patients treated with high protein diets (43). It is unfortunate that this experience was not applied to the disease in childhood. There are several abnormal amino acid metabolites excreted in kwashiorkor (44–47); such metabolites are similar to those found in inborn errors of metabolism and come from an acquired loss of the enzymes of the catabolic pathways (36,48). To give such a patient a high protein diet, before the enzymatic machinery has recovered, is against the lessons learned from treating inborn errors of metabolism. More recently, Collins (49) treated adults with kwashiorkor in the Somalian famine of 1992–1993 with the standard high protein diets available; when he switched to a low protein diet, similar to that used in children (50), the mortality rate fell to one quarter, the rate of loss of edema improved dramatically and the patients quickly regained their appetites. These results show how knowledge has come full circle, from the adults of World War II to Jamaican children and back to adults in tropical famine.

Protein deficiency

Once protein deficiency had been relieved of the liability of causing kwashiorkor, the way was open to explore the real effects of human protein deficiency. All animal species, given a low protein diet, reproducibly and predictably fail to grow normally; and, with time, become nutritional dwarfs. Indeed, early supplementation experiments with children showed that provision of extra milk leads to increased growth (51–53). In retrospect, there are many examples where the average height of children and adults in populations subsisting on low protein staple diets is lower than that of those with a higher protein staple food (54). One of the major drawbacks to the protein-deficiency hypothesis of kwashiorkor is that these infants are not usually stunted in height, whereas those with marasmus usually are stunted. An extension of the concept, that protein deficiency in man and animal causes stunting, to other nutrients whose deficiency primarily causes stunting or weight loss, has allowed the development of a new concept of the types of response to a nutrient deficiency (55,56). A rational classification of the nutrients into those that cause specific clinical signs (type I) and those that cause growth failure (type II) then allows us to appreciate how anthropometrically normal or even obese people can, for example, be iron or thiamine deficient, whereas deficiency of other nutrients such as protein, sulfur, phosphorus, zinc or potassium leads to stunting and wasting. The inadequate convalescence and lack of catch-up of children that after an episode of acute illness, such as diarrhea or pneumonia, can be ascribed to failure to provide this specific portfolio of type II nutrients: the poor growth is usually ascribed to the infection alone, although children on a normal diet quickly regain what they have lost, whereas children on a poor diet become stunted even where they do not have frequent infection (57).

We have recently described 209 children with kwashiorkor who are being breast fed, some exclusively, in African refugee camps; the mothers were not themselves anthropometrically malnourished (M.H.N. Golden and Y. Grellety, unpublished data, 1998). In this group the amount of edema and mortality was the same in both the breast-fed and the weaned children, and the breast-fed children grew slightly more slowly than did the weaned children. The concentration of protein and the other type II nutrients are stoutly defended in breast milk; furthermore, maternal deficiency of these nutrients would express itself in maternal weight loss. This again suggests that kwashiorkor is not the result of a deficiency of protein or any other type II nutrient. These data, and the lack of stunting in many of these patients, suggest that deficiencies that cause kwashiorkor belong to the type I category of nutrients.

Oxidant stress

Srikantia (58) had reported that children with kwashiorkor had high levels of circulating ferritin using a bioassay. When immunoassays became available we confirmed this observation in Jamaica (59). We also confirmed an original and critical observation by Waterlow (30), that the liver of children that died contained excess iron. We now understand that iron is a potent free-radical catalyst undergoing one-electron oxidation–reduction reactions. Waterlow found little iron from the liver biopsies and stated "it is difficult to understand why iron should be present in the liver in fatal cases, and absent in babies of the same age-group, who were clinically similar, but did not die." Waterlow suggested that "iron which can be seen microscopically in liver tissue taken at autopsy has been unmasked by reactions occurring after death." It is a pity that the state of knowledge at that time was insufficient for the appreciation that Fenton chemistry could occur in vivo. Nevertheless, again this is a critical and original observation reported by Waterlow in 1948 (30), that can be reinterpreted 50 y later as being of great importance to the concepts of the deranged pathophysiology of kwashiorkor. We measured iron overload by measuring the excretion of iron after the administration of desferrioxamine (60). The levels of transferrin in kwashiorkor are very low (60) and we calculated that most of the children would have free iron available for free-radical cycling. Iron overload has since been confirmed in South Africa (61) and free iron in the plasma directly demonstrated (62).

Golden and Ramdath (63) showed that there is a very low level of glutathione specifically in kwashiorkor. Glutathione is a potent cellular reductant controlling the oxoreductive potential of the cell and is a free-radical scavenger. It is also a critical cofactor of enzymes that dispose of the products of free-radical injury and, by maintaining cellular sulfhydryls in a reduced state, enables cellular function. Indeed, tissue glutathione levels had been used as a measure of the degree of the imbalance between free-radical generation and their disposal (oxidative stress) (64).

Golden and Ramdath (63) also showed that the low glutathione was not a function of edema, per se, by finding normal values in children with nephrotic syndrome and congestive heart failure. We then investigated the enzymes responsible for maintaining glutathione in the reduced state, hexose-monophosphate shunt [glucose-6-phosphate dehydrogenase (G6PD); 6-phospho-gluconate dehydrogenase (6PGD)] and glutathione reductase, and found them to be much more active in all forms of malnutrition than in control children (65). In response to an oxidative stress there is increased activity of G6PD and 6PGD to provide additional NADPH for glutathione reduction. When this supply is adequate, NADPH levels are maintained; when the rate of oxidation of glutathione

exceeds the capacity to supply reducing equivalents, the NADPH level can fall despite the increased rate of its supply. We found that NADPH levels were normal in marasmus but reduced in kwashiorkor with a corresponding rise in $NADP^+$. These results confirm that there is an oxidative stress in kwashiorkor; such results could not be produced by protein deficiency. The oxidized form of glutathione, GSSG, is toxic to cells because it reacts with protein sulfhydryls; for this reason, if the maximum rate of GSSG reduction is less than its rate of production, GSSG is actively exported from the cell. It is for this reason that the glutathione level inside the cell decreases and can be used as an index of oxidative stress. During treatment it takes about 2 wk before the NADPH and GSH levels return to normal values.

Whether such oxidative stress causes all the clinical features of kwashiorkor is uncertain. When normal red cells are incubated with enzyme inhibitors (BCNU), so that the level of glutathione is reduced to the levels seen in kwashiorkor, there is an increase in the membrane leak to electrolytes such that the cellular sodium concentration rises, the potassium concentration falls and the sodium pump is stimulated (66). These are precisely the abnormalities seen in edematous malnutrition (67,68). There is also a very close relationship between the amount of liver damage, as measured by γ-glutamyltransferase levels, and the level of glutathione (M. H. Golden and D. Ramdath, unpublished data, 1989), as well as the plasma ferritin concentration. There is also a relationship between the red cell glutathione and the amount of liver fat measured by ultrasound (T. Doherty, D. Ramdath and M. H. Golden, unpublished data, 1990). The appearance and evolution of the skin lesions of kwashiorkor exactly mirror those of sunburn, an unequivocal radical-generated injury, with an initial increase in pigmentation and then direct dermal damage. The skin lesions do resemble those of pellagra; indeed, kwashiorkor and pellagra were confused in early descriptions. Our findings help to explain this because of similar mechanisms; however, in pellagra the niacin deficiency leads to a lack of reducing equivalents for oxidized glutathione resulting from a low concentration of NADPH, whereas in kwashiorkor the total NADP(H) levels are normal (65) and the oxidative stress comes from elsewhere.

Mortality

The mortality rate in hospitals, from severe malnutrition, has not changed in about 40 y at between about 20 and 40% (69), despite the fact that under refugee camp conditions mortality rates of 5 to 10% are achieved (70). Why should this be?

It is unclear how oxidative stress causes edema. That it can is shown by the edema of newborn infants with vitamin E deficiency (71), birds with selenium deficiency, and the edema of pure radical injury such as exposure to ionizing radiation. Subcutaneously injected dye dissipates rapidly (72), as if the interstitial hyaluronate and glycoseaminoglycans were disrupted and interstitial water was in a free state. Such damage to the interstitium, with loss of the normal negative charge, if generalized, would explain our findings of effacement of the podocytes onto the glomerular basement membrane (73) and invasion of normally resistant cells, such as hepatocytes, with herpes simplex virus in kwashiorkor (74). Recently, we have observed in a therapeutic feeding center experiencing a cholera outbreak that the attack rate in children and adults with kwashiorkor is about 1%, whereas for those with marasmus the attack rate was 25% (M. H. Golden and Y. Grellety, unpublished data, 1997). Disruption of complex carbohydrates would also explain this observation.

The oxidative stress comes mainly from infection, from ingested aflatoxin and bacterial endotoxins and from small bowel overgrowth. Diseases such as measles are harbingers of kwashiorkor in susceptible populations. In kwashiorkor, in comparison to marasmus, there seems to be a specific increase in the levels of leukotrienes (75), a product that one would not expect if glutathione was limiting, given that glutathione is a precursor. Furthermore, we have estimated the endogenous production of nitric oxide, from arginine, by measuring the excretion of nitrate in malnourished children on a nitrate-free diet. High levels of nitrate are produced in kwashiorkor and are similar to those seen in other syndromes that resemble aspects of kwashiorkor metabolically, such as toxic shock syndrome, multiorgan failure and adult respiratory-distress syndrome. Like these other diseases, kwashiorkor is an acute disease; the history is usually of only a few days and frequently presents with hypovolemia, which is attributed to uncontrolled vasodilatation. The second reason for the high mortality rate from kwashiorkor in most hospitals is that these children are diagnosed as being "dehydrated" on the basis of their hypovolemia and perhaps a history of frequent small mucoid stools, which the mother reports as diarrhea. It is a contradiction in terms to say that a person can be overhydrated (edematous) and underhydrated simultaneously. These edematous patients, who have both a high extracellular and high intracellular sodium content (cf. Lot's wife, who was also a pillar of salt) are often rehydrated intravenously or with ORS (90 mM/L Na). They die from heart failure (76), which is easily misdiagnosed as pneumonia in these children.

In kwashiorkor, because of the cell membrane leak, the intracellular potassium is reduced and the sodium is increased. If this defect is corrected precipitously, then there is the danger of the induced $Na^+ + K^+ +$ ATPase exporting sodium from the intracellular compartment faster than the kidney can excrete the excess, particularly if the interstitial defect is also corrected and fluid shifts from the interstitial to the intravascular space. Acute volume overload, hypokalemia and death can result from this disequilibrium syndrome (77).

Until we know much more about the details of the disordered physiology and how it should be safely corrected, it would be unwise to administer large doses of antioxidants to these patients. A toxin-free, low-protein, low-sodium, high-potassium diet with adequate amounts of phosphate and magnesium and which contains the known type 1 nutrients in "replacement" amounts is prudent. There should be adequate easily absorbed carbohydrate, to prevent hypoglycemia and limited fat at this stage. Nevertheless, using such diets and treating the inevitable infections blindly, the mortality is still usually between 5 and 10%. This is a tragedy, because the patients that recover are absolutely normal without any known long-term sequelae.

Refugees and famine relief

Much of the "academic" work reported above had very little effect on humanitarian organizations organizing relief to the many thousands of patients who had malnutrition secondary to complex emergencies and disasters. This is quite unlike the situation during the war, where there was close collaboration between the relief and academic communities. The WHO manual that was published in the early 1980s was a rewrite of the PAHO manual that had been written in Jamaica in 1974 and was based largely on the experience at that time. This informed the international community to some extent, but

was seen to be "academic" and the provisions of this manual could not be adapted to treating patients en masse or without highly trained nursing staff. It was not really adopted in resource-poor settings. The humanitarian movement largely used the methods that were developed empirically during the Biafran war of independence in Nigeria. It was at that time that Médecins sans Frontières (MSF) was formed, that the International Committee of the Red Cross (ICRC) took on a nutrition department and that the Oxford Committee for Famine Relief (Oxfam) expanded and formed an effective nutrition department. It was these three organizations and their advisors who developed the methods; their academic links were largely through the personal contacts of those in the Oxfam head office. Such was the state up until the 1990s. The diet that UNICEF was advocating for treatment of severe malnutrition even as recently as 1996 was "K-mix 2," the diet that had been developed during the Biafran war 20 y earlier. In late 1991, International Dietary Energy Consultative Group convened a meeting to "update" the manual on treatment of severe malnutrition, which was written over the next year. In 1993 a Groupe d Etudes et de Recherche sur la Malnutrition meeting was organized by Daniel Lemonier for the Francophone countries on malnutrition. At that meeting, I gave a copy of the draft manual to several representatives of the humanitarian movement organizing famine relief in Africa. This was followed by a series of meetings that culminated in Yvonne Grellety, Andre Briend and Michael Golden forming a Scientific Committee for Action International contre le Faim (International Action Against Hunger). The committee translated the provisions of the manual into a simplified format and protocols that could be applied en masse in famine situations and also worked with a company in France (Nutriset) to develop a commercial preparation of the F100 diet given in the draft manual. Later Andre Briend resigned from the committee to work closely with Nutriset to refine this and other refugee foods that had been advocated by the committee.

Meanwhile, the draft manual was offered to, and accepted by, the World Health Organization. WHO then gave the manual to its other divisions and advisors, who prepared derivative guidelines (e.g., Integrated Management of Childhood Illness guidelines) and formally tested the provisions of the manual in Internation Diarrhaeal Diseases Research Center-Bangladesh and published their results. This showed that by use of the provisions in the "new" guidelines, the mortality rate in a research center can be halved (78).

The mortality rate in the centers that were using the protocols that were derived from the draft manual have been about 10% since 1994 (79). Since that time we have been working with UNICEF and have introduced National Protocols into Burundi and more recently Angola and Honduras. In Burundi in 1999, about 40,000 severely malnourished patients were treated with the protocols, with an overall mortality of 4% and a child mortality of 7%. Analysis shows that this is significantly less than would be expected according to the prognostic formulas developed by Prudhon et al. (79). The WHO finally published the manual in late 1999. With the delay, there is already sufficient knowledge and experience warranting substantial changes being made to this document.

Conclusion

It seems that the translation of findings in research units and academic centers into practical guidelines that are used at field level depends on chance meetings between those academics who are still active in research on severe malnutrition and humanitarian workers. All academics are being urged to publish their important findings in "high impact" journals such as Nature and Science. Such journals are not read by most practicing clinicians, let alone the people in the field who are actually treating severely malnourished patients. Those who are organizing treatment in the head offices of humanitarian organizations do not attend "academic" meetings and academics do not attend humanitarian conferences.

History shows that it can take many years for the results of research in these orphan diseases to have any impact on treatment practices and that the international organizations are neither timely nor effective in dissemination of the necessary knowledge or skills.

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