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CHILDHOOD MALNUTRITION IN DEVELOPING NATIONS: Looking Back and Looking Forward

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CONTENTS

BACKGROUND

The Emergence of Kwashiorkor

Cicely Williams' first two papers on kwashiorkor, which appeared in the mid-1930s (47, 48), produced an important change in the nutritional thinking of the time. However, because she was a pediatrician and not a nutritionist, Williams did not realize the full significance of her observations. She did not

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say so explicitly, but her description of kwashiorkor developing in children weaned from the breast onto starchy paps and their cure by milk clearly pointed to the causal role of protein deficiency. The foundations of our understanding of protein metabolism had been laid, but there was controversy about how much protein humans need. Followers of Voit estimated that individuals needed 120 g per day, whereas those of Chittenden felt that 30 g per day was sufficient. Both McCollum and McCarrison had stressed in a general way the importance of the quality of dietary protein for human health. McCarrison in India compared the physique of wheat-eating Sikhs and Pathans with that of rice eaters in Bengal and Madras (20). Neither of them, however, seems to have visualized that there could be a deficiency disease caused by inadequate amount or quality of dietary protein. This was the era when the imagination of nutritionists was captured by vitamins and their roles as coenzymes, and a complete marriage between nutrition and biochemistry seemed only a matter of time.

Cicely Williams had, of course, her forerunners. European pediatricians were familiar with "flour-feeding injury" and with edema developing in children with prolonged diarrhea. From the tropics had come descriptions of what appeared to be multiple deficiency states (39), but most of these accounts were published in local or specialized journals and remained outside the mainstream of medical science. Moreover, the medical services, at least those of the colonial powers, seem to have paid little attention to diseases of children. The attention of public health physicians was naturally concentrated on the ravages of infectious diseases, and the immensely high mortality rates of children seem by and large to have been accepted as unavoidable. Williams was the first pediatrician appointed to the Colonial Medical Service, and it is fortunate that she approached what she saw without preconceived ideas about nutrition.

World War II for a time held up further work on kwashiorkor, so that when I was thrust on the scene in 1945 this nutritional disease of children was a relatively unexplored field, and it was an exciting experience to be presented with such a challenge.

MY OWN INVOLVEMENT

I qualified in medicine in 1942, and as the war drew to an end I was doing military operational research under the direction of BS Platt. He had been adviser on nutrition to the Colonial Office and had been involved in the Hot Springs Conference. He said to me that the most important postwar problem would be nutrition. I had been trained as a physiologist and knew nothing about nutrition, but this seemed to me to make sense, and I was glad to be sent in May 1945 to the West Indies to find out why so many children were dying.

The Colonial Office, which was responsible for those territories, was concerned about their nutritional situation; they had always imported food, and many of the ships had been torpedoed. I worked in the hospitals and country parts in Guyana, Trinidad, and Jamaica and investigated as best I could children with gross edema and massive hepatomegaly, who usually died. With fear and trembling I took biopsy samples of the liver, using a wide-bore veterinary needle, and found the samples to be stuffed with fat. Nutritional liver injury was a fashionable topic at the time as a result of experimental work in the US and elsewhere on choline and methionine deficiency, and I was so much impressed by the extent of the fatty change (up to 50% of the wet weight) that I called it "fatty liver disease" (34). Only when I got back to Britain and had access to libraries did I realize that my patients were probably identical to those described by Williams 10 years before as kwashiorkor.

A few years passed; the University of the West Indies, with its Faculty of Medicine, became operational in 1950. After three years working on my own there, the British Medical Research Council decided that my research was worth encouraging and established the Tropical Metabolism Research Unit (TMRU) within the university. The Unit now belongs to the university and has been operating for nearly 40 years.

Whereas Williams, after her release from POW camp, went on to concentrate on public health, I was imprisoned in my own medical training and continued to regard kwashiorkor simply as a disease; I accepted the challenge to reduce the mortality in hospital, but nearly 20 years were to pass before I gave much thought to its prevention in the community.

Worldwide Research

At this time (the late 1940s and early 1950s), pediatricians all over the world were becoming aware of the problem of childhood malnutrition. Among the first in the field were Gomez and his group in Mexico, Meneghello & Monckeberg in Chile, Hansen in Cape Town, Bhattachariyya in Calcutta, and McLaren in Lebanon. Trowell and his colleagues in Uganda published their classical book on kwashiorkor in 1954 (31). Some Western countries, realizing that more was needed than could be done in the overcrowded hospitals of developing nations, set up special institutes or units to study childhood malnutrition. My small group in Jamaica was established as a Unit in 1954, and a parallel unit for research on infantile malnutrition was set up in Uganda in the same year. The Rockefeller Foundation supported an institute in Thailand under the direction of Olson; Scrimshaw opened a metabolic unit at the Institute of Nutrition of Central America and Panama to supplement their studies, which had hitherto focused mainly on populations; in Zaire the group under Vis, supported by Belgian funds, became active and has remained so ever since; and in India Gopalan began clinical studies on nutritional edema in the Nutri-

tion Institute—I believe the first in the world—founded by Sir Robert McCarrison. Thus for some 25 years in-depth investigation of severe malnutrition had a high priority worldwide. I mention this because what I have to say in the next section is based on the work of my unit in Jamaica, and I would not like to give the impression that we were ignorant or unappreciative of the research done elsewhere.

Names and Causes

As more and more centers worked on kwashiorkor, it became essential to establish some uniformity of diagnostic criteria so that valid geographical comparisons could be made. Brock & Autret, in their report on kwashiorkor in Africa (5), considered that reddish discoloration of the normally black hair was an essential sign of the disease. Others placed more importance on skin changes; as I have said, I emphasized the fatty liver. Sometimes one change was present without the others: how to make the diagnosis? In 1969 a meeting was held in Jamaica, which resulted in agreement: that the only characteristics necessary for diagnosis of kwashiorkor were weight loss and edema (45).

There was, however, another problem. It had long been accepted that kwashiorkor and marasmus represented the two ends of a spectrum, with cases in between that exhibited intermediate characteristics. Why argue about names that do no more than describe a clinical syndrome, particularly since "kwashiorkor" was only one of some 70 dialect names that had been used in different places? Could we not use causal names, since marasmus was clearly a result of total deficiency of food—semi-starvation or lack of energy—and most workers believed that kwashiorkor was caused by protein deficiency? So the term "protein-energy malnutrition" was born to cover the whole spectrum of childhood malnutrition, other than conditions caused by specific micronutrient deficiencies, as of vitamin A, iodine, or iron. Indeed, in 1968 McCance & Widdowson organized a symposium in Cambridge, UK, with the title "Calorie Deficiencies and Protein Deficiencies".

This simple dichotomy did not last long. The report of the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) on protein requirements, published in 1973, put the requirements of infants and young children at such a low level that virtually no diet could fail to meet them. At the same time surveys of food intake showed that without exception the protein intakes of young children were adequate by the standards that then prevailed, while their intakes of energy were uniformly low. Thus all they needed was more food of the same kind. Moreover, Gopalan, at the Cambridge meeting, claimed that in a study in India there was no qualitative or quantitative difference between the diets of children who subsequently developed kwashiorkor or marasmus (11). This view put the coup de grace to the efforts of the UN to fill the "protein gap" by the production of high-protein

feeds based on oil-seed residues, bacterial protein grown on petroleum products, etc (21).

At the same time, emphasis shifted from cure to prevention, and few of the metabolic wards that flourished in the 1960s now continue in operation. Moreover, in most parts of the world full-blown kwashiorkor is not as common as it was, with the exception of Africa, where prevalence rates and mortality in hospital remain unacceptably high. Because the specific clinical features of kwashiorkor are not seen in the less severe cases, it might be thought that there is no scope for further discussion about diagnosis and causes. I hope to show that this view is incorrect and that it is appropriate to retain the name protein-energy malnutrition (PEM).

It has been said that medicine is indivisible, and it is gradually becoming apparent that much of the research on severe PEM that was done a generation ago is also relevant to the problems of sick patients in industrialized countries. I have tried elsewhere to summarize the literature on PEM in more detail (40). In the sections that follow I have chosen some aspects of the work in Jamaica that seem most interesting and with which I have been closely involved. Much has had to be omitted, particularly more recent research on trace elements and free radicals that is shedding new light on the mechanisms of cell damage under the combined onslaught of infection and malnutrition.

EXAMPLES OF RESEARCH OF CONTINUING RELEVANCE

Body Composition

It is customary to relate variables such as the basal metabolic rate (BMR) to the lean body mass (LBM). However, this association will be misleading if the LBM is diluted by excess water and by a relative excess of collagen. It was found on analysis of cadavers of children dying of PEM that collagen was well preserved—the tissues shrink inside their collagen scaffolding. What we need is a measure not of LBM but of active cell mass, for which the best candidate is whole-body potassium. It is a disadvantage of this approach that the child may also have a specific depletion of potassium, resulting from diarrhea, but when the depletion has been made good these measurements, which unfortunately require a whole-body counter, show that there is indeed a massive reduction in active cell mass. Thus in a series of cases the ratio of initial to recovered value was 0.59 for cell mass measured by potassium and 0.77 for body weight, so that the weight loss greatly underestimates the real deficit (42).

The active cell mass is not only reduced in amount, but its distribution is altered. The brain is to a large extent preserved, accounting for twice as large

a proportion of body weight in the malnourished compared with the normal child, while the bulk of the loss falls on muscle and skin. This distortion of pattern explains the behavior of the BMR. Because the BMR is determined mainly by the metabolically active tissues such as viscera and brain, when the proportion of these tissues is increased the BMR per kilogram should be high, as was pointed out many years ago by Talbot (30) in his classical studies of marasmus. However, in PEM we sometimes find a low rather than a high BMR per kilogram, which must indicate that vital processes are at a low ebb indeed and that the child is near death. If treatment is successful, metabolic rate rapidly rises to levels some 20% above normal, long before the tissue deficits are restored (22). The same applies to protein turnover (see below). These points illustrate the difficulty of finding a suitable basis of reference for measurements made on the whole body, not only of BMR and of protein turnover, but of other characteristics such as cardiac output or renal function. As Garrow has pointed out, it is impossible to compare a malnourished child with one who is the same age, the same weight, and the same height. Which basis will be the most illuminating depends on the biological context.

If muscle is preferentially reduced, muscle mass as measured by creatinine excretion might be a good index of the degree of depletion. This idea led to the development by Viteri and his colleagues of the creatinine-height index to give an estimation of the extent of malnutrition, which could then be used to examine the degree of impairment of gastrointestinal function. One problem here is that the relation between urinary creatinine and muscle mass, usually taken as 50 mg/kg, depends on the creatine content of muscle, which may be altered in malnutrition. ^{15}N creatine was synthesized, and muscle mass calculated from the creatine content of muscle biopsies (24). Measured in this way, muscle mass, expressed as a percent of that expected in a normal child of the same height, increased from 49% in the malnourished to 92% in the recovered child. The size of the creatine pool was reduced by about 25% in the malnourished muscle. Because the fractional turnover rate of creatine was unchanged at 2%, as would be expected from a nonenzymatic reaction, the creatinine-height index based on the conventional factor would somewhat underestimate the extent of depletion.

The hypothesis that kwashiorkor is the result of dietary protein deficiency led to the following question: Can the effect of this deficiency be measured by any specific change in the tissues? With protein, unlike some of the trace elements, there is no reduction in concentration except by dilution with fat in the liver.

One way around this difficulty was suggested by the finding that the DNA content of the haploid cell is constant, so that in rat liver, for example, the total amount of DNA is independent of the diet. When protein intake is reduced, the cytoplasm shrinks around the nucleus. In fact, a reduction was

found in the ratio N/DNA in both liver and muscle of malnourished children. Therefore it is appropriate to speak of a cell as depleted of protein, although the concentration of protein is not decreased. Even this measure does not give the full extent of depletion. When children with PEM are treated, there is, at least in muscle, hyperplasia as well as hypertrophy. In the studies on creatine and muscle mass referred to above, there was a 20% increase in total muscle DNA between the recovered and malnourished states.

The Cause of Edema

Kwashiorkor is distinguished from other forms of malnutrition by the presence of edema. As soon as biochemical measurements began to be made, it was found that plasma albumin concentrations were very low and the lower the level, the higher the mortality. The obvious theory then was that hypoalbuminemia causes edema and is in turn caused by dietary deficiency of protein. I believe that this theory is in its essentials still correct. There is plenty of experimental evidence that a deficient amino acid supply leads to a reduction in the rate of albumin synthesis: The best example in humans is the study of James & Hay (15), who found a 60% reduction in albumin synthesis in children after only 10 days on a low-protein intake. Moreover, edema in kwashiorkor is statistically associated with fatty liver. The cause of the vast fatty infiltration (up to 50% of the wet weight) that inspired the name "fatty liver disease" is probably inadequate synthesis of the apolipoprotein that transports fat out of the liver. It is reasonable that the same cause should affect the synthesis of both these liver-produced proteins.

Infection may depress the synthesis of plasma albumin. It has long been recognized that kwashiorkor is often precipitated by an acute illness such as measles that stimulates production of "acute phase" proteins by the liver. If one can judge from the peak levels of these proteins following an infection, synthesis of them will require some five to six times the amounts of amino acids normally used for the synthesis of albumin and thus constitute a large drain on the amino acid supply. There is also evidence for an enhanced loss of protein into the gut through the damaged mucosa. There are, therefore, plenty of reasons why hypoalbuminemia should occur in kwashiorkor. What remains to be explained is why it is much less marked in marasmus. There is evidence that the reduction in albumin synthesis is less when the energy intake is also restricted. In rats at a fixed low protein intake Lunn et al (18) found an inverse relationship between plasma albumin and energy intake. The hypothesis here is that low energy intakes, with concomitant increases in cortisol and decreases in insulin, lead to liberation of amino acids from muscle, which then become available for the liver. As Trowell succinctly put it, "The marasmic lives on its own meat". The endocrine changes predicted by the hypothesis have indeed been found in children in the field: In The Gambia, where ma-

rasmus was the most common form of malnutrition, insulin levels were low and cortisol levels high compared with children in Uganda, where kwashiorkor was more prevalent. The conclusion then is that hypoalbuminemia results from a diet that is relatively low in protein in relation to energy.

The critics of the protein-deficiency theory believe that hypoalbuminemia is irrelevant. They point out that there is not a precise correlation between albumin concentration and degree of edema; a child may lose edema without any change in albumin level (9). This observation is not surprising considering the number of factors that enter into the Starling equation describing the flow of fluids across the capillary wall; for example, the permeability may be increased by infections.

Other mechanisms may also be operating in addition to hypoalbuminemia. One of these is potassium deficiency, which promotes retention of salt and water. Hansen in Cape Town was the first to emphasize the importance of potassium deficiency, which he demonstrated by balance studies (13). These were followed by measurements in Jamaica of whole-body potassium by $^{40}K^{+}$ counting, which showed that the great majority of children were to some extent deficient in potassium (1). Recognition of this deficiency, together with the routine administration of potassium, has probably been a significant factor in the reduction of mortality.

On the other hand, in Zaire, where kwashiorkor occurs in older children and edema is accompanied by gross wasting, no evidence of potassium deficiency was found either by balances or by measurements in muscle biopsies (32). It is these regional differences that make the condition so interesting.

To summarize, although hypoalbuminemia is not the only cause of edema, I think it is a very important one. The final link in the chain, the question of whether the diets of children who develop kwashiorkor are actually deficient in protein, is considered below.

Protein Turnover

In the early 1960s the persistently high mortality led to the hypothesis that if kwashiorkor is caused by protein deficiency, perhaps the machinery for protein synthesis, which itself is composed of proteins, is run down; this could lead to an irreversible state. To test this idea it was necessary to measure whole-body protein synthesis in vivo. Sprinson & Rittenberg were the first to tackle this problem in humans by measuring the rate of excretion of ^{15}N in the urine after a single dose of ^{15}N glycine. This and the papers that followed led nowhere; the studies were performed on adults with various endocrine disorders in whom there was probably no change in protein turnover; the mathematics were inelegant and in some cases incorrect, so that for many years the subject dropped out of view. We reasoned that if by continuous infusion of the label we could produce an isotopic steady state, the rate of ^{15}N excretion in the urine

would become constant, and it would then be a simple matter to calculate the parameters of protein turnover.

The results obtained by this method partially confirmed our hypothesis. Initially, when the children were malnourished, protein synthesis was low: During the following period of rapid growth it rose to levels well above normal and on full recovery fell again (10). Thus it behaved like the metabolic rate: Two processes essential for life—oxygen turnover and nitrogen turnover—are operating at a low level, and this reduction is particularly impressive when it is recalled that one would expect the rates per kilogram to be high because of the change in the pattern of body tissues.

In these studies on protein turnover, we were venturing into uncharted territory. I have always believed that it is important to conduct animal experiments in parallel with studies on humans. In the rat it was possible to use ^{14}C-labeled amino acids and to determine synthesis rates in individual tissues, on which there was very little information available at that time, and none by the method of constant infusion of an amino acid. Moreover, the extent of internal recycling—i.e. the reuse for synthesis of amino acids liberated by protein breakdown—was not fully appreciated. We used lysine as the tracer because its amount could be determined by treatment with lysine decarboxylase and by measuring the CO_2 produced in the Cartesian diver microrespirometer (43, 44). Column chromatography in those days was not sensitive enough for application to a few microliters of rat plasma. Radioactivity was measured in a helium gas-flow counter, an instrument that is now a museum piece. In adults it was permissible to measure whole-body protein turnover with infusions of ^{14}C-lysine, but because of the low dosages, the samples had a radioactivity of about 2 cpm, against a background of 1 cpm, so that it was necessary to count them for 24 h (35).

A further development of the work with labeled nitrogen was a series of studies of urea kinetics, which have shown very clearly that "salvage" of urea through hydrolysis in the colon is increased whenever the supply of amino acids is low or the demand for them is high (14).

It seemed probable that another way of economizing amino acids might be an increase in the extent of their reuse. We attempted to study this by injecting rats with uniformly labeled arginine. Because the guanidino carbon cannot be reused, measurement of the rate of decay of label in the 6-carbon atom after treatment of the protein hydrolysate with arginase gives an index of the true half-life; the rate of decay in the 1-carbon, liberated by arginine decarboxylase, gives the apparent half-life, and from the difference between the two the rate of reuse could be calculated. Some evidence was indeed obtained of increased reuse in animals on a low-protein diet (28).

Studies were also conducted of hepatic enzymes. We confirmed Schimke's finding that in the malnourished state the urea cycle enzymes are reduced, but

we also obtained evidence of an increase in activity of the amino acyl-tRNA synthetases (29). This would represent a switch of the amino acid flux from catabolic to anabolic pathways.

These animal experiments were not strictly relevant to the problems of children with kwashiorkor, but they shed some light on the mechanisms of adaptation to low protein intakes, which seemed to us the central problem of protein malnutrition. The policy of the Medical Research Council at that time allowed us to pursue this curiosity-driven research, and indeed the stochastic approach to the measurement of whole-body protein turnover has been taken up by many other groups.

Some Problems of Treatment

Although some of the research that I have described explored other areas, my basic challenge was the high mortality associated with PEM. In the 1960s some 20% of children admitted with severe PEM died. A fair number of deaths occurred between 3 and 10 days after admission, when dehydration, electrolyte disturbances, and acute infections had been overcome and the children should in theory be able to tolerate large amounts of food. However, if the cellular machinery is indeed impaired, one could imagine that generous amounts of energy and protein could overload it. The studies on protein turnover gave some evidence of this; Whitehead's work in Uganda demonstrated abnormal amino acid metabolites in the urine (7); our work on liver enzymes has already been referred to. If urea formation is reduced the ammonia produced by amino acid oxidation could well be toxic. Therefore it was decided, contrary to the current recommendation of high-protein feeding, that only maintenance amounts of energy and protein should be given until the child's appetite was restored and he or she was ready for full nutritional rehabilitation. We believe that many deaths were prevented in this way, although it is impossible to prove it. With this measure and with better control of infection, mortality was reduced to a very low level.

Another improvement, which concerns the phase of rehabilitation, was equally simple. During rapid growth the need for extra protein is relatively greater than the need for extra energy, so that diets high in protein had been prescribed. In practice, however, it is much more difficult to increase the energy density of feeds than to increase their protein concentration by giving large amounts of dried skimmed milk. The problem can be overcome by adding vegetable oil, to provide an energy intake of 150–200 kcal/kg. Analysis of our past records showed that energy intake had been a limiting factor in the rate of recovery. When this was put right, growth rates of 15–20 g/kg were achieved (2). The physical, psychological, and economic importance of reducing the length of the child's stay in hospital is evident.

These developments are a few examples of the way in which research on

the processes of severe malnutrition has contributed to a better outcome for PEM patients and also to medical science in general. Cicely Williams used to say that this kind of research was a pointless waste of time and money. Perhaps she was right. Certainly the severe and fatal cases of PEM are the tip of the iceberg; there are many more moderately than severely malnourished children in the community, and perhaps all resources should be devoted to preventing them from slipping into a severe and sometimes irreversible state. Nevertheless, primary health care, on which prevention depends, will lose its credibility if the lives of seriously ill children cannot be saved. In spite of the knowledge that we have gained, mortality rates in hospitals of developing nations remain unacceptably high, and the challenge now is to disseminate that knowledge.

PROBLEMS OF PUBLIC HEALTH

The Significance of Stunting

In less severe PEM there are none of the characteristic signs of kwashiorkor. The best measure of nutritional state that we have is growth, both in weight and in height; my contribution was the very obvious one of distinguishing between a deficit in weight for height and a deficit in height for age. These represent two clearly different biological processes. The descriptions "wasting" and "stunting" were introduced to indicate a degree of thinness or shortness beyond the limits of normal variation, and from a statistical point of view it seemed reasonable to designate the dividing line as 2 SD below the reference median. In 1977, when this classification was introduced (41), the US National Center for Health Statistics had the only available reference data on the growth of presumably healthy children that covered a large enough sample and had been analyzed in sufficient detail. Therefore the database was adopted as an international reference, at least for the time being.

Surveys then showed enormously high prevalences of stunting in some populations of children, particularly in Asia. Does it really make sense to claim that 50% or more of children in Nepal or Bangladesh are malnourished simply because they are short?

This is one of the most important questions facing nutritional science today. To answer it, or to approach an answer, it is necessary to examine objectively the natural history of stunting, its concomitants, and its consequences. First, it is agreed that the genetic potential for growth in young children is similar in different ethnic groups. Any racial differences are small compared with those imposed by the environment. Second, the stunting begins very early and is often detectable by the age of three months, long before there is any wasting (37). It is therefore quite wrong to regard stunting as "chronic" malnutrition, as is often done.

Typically, the slowing continues until the age of about three years, at which time the normal growth rate is restored, so that the child grows along a track parallel to but below that of the reference. A deficit of perhaps 10–20 cm is maintained, but the gain in height between five years and adulthood is completely normal (65–68 cm) (19, 25). Thus there seems to be a sensitive period up to the ages of 3–5 years, after which whatever mechanism is suppressing growth ceases to operate. Usually there is no catch-up from the early growth deficit, because the child remains in the same unfavorable environment. However, in children whose situation has improved by adoption into a well-off family or by emigration to a developed country, a large degree of catch-up has been observed, showing that stunting is not irreversible. In some countries there are well-marked seasonal differences in the rate of growth in height, which is another sign of reversibility. Interestingly, in children recuperating from malnutrition and growing very rapidly, catch-up in height seems not to begin until the weight deficit has been more or less restored (33).

Systematic research into the causes of stunting is only just beginning. During the prewar slump, when farmers in the UK could not sell their milk, free distribution of milk to schoolchildren produced a small increase in height with a remarkable but unmeasurable increase in well-being and liveliness (17). Similar results have been recorded in intervention trials in India and New Guinea. Recent American studies [Nutrition Collaborative Research Support Program (CRIS)] in Kenya, Mexico, and Egypt have all revealed a relationship between linear growth and the quality of children's diets without identifying the specific nutrient involved. Possible candidates are sulphur amino acids, which could limit the production of chondroitin sulphate in cartilage, and minerals such as calcium (the intake of which is often marginal), phosphorus, and zinc.

Obviously, endocrine factors must also be considered. Karlberg (16) has proposed that normal growth can be divided into three phases: fetal, childhood, and pubertal. The childhood phase normally begins to take over from the fetal phase at about six months, under the influence of growth hormone (GH). Studies in Pakistan suggested that in children becoming stunted there was a delay in the time of transition. However, this hypothesis has not yet been confirmed by measurements of GH; moreover, the defect may lie in the receptors rather than in the hormone itself, since it has long been recognized that GH levels are high rather than low in PEM. The circulatory concentrations of the insulin-like growth factors (IGF I and II) are indeed low, both in established cases (27) and in moderate malnutrition, as judged by body weight, but no systematic investigations have been conducted in relation to the deficit in linear growth. Moreover, serum concentrations give no indication of IGF production and activity at local sites.

The development of biochemical markers of bone turnover gives promise

for future progress in understanding the mechanism of stunting, because it might then be possible to make measurements over a much shorter time-scale than is needed to establish differences in the rate of growth in length. It has been shown that the excretion of collagen "crosslinks" is much reduced in severe PEM (4), and low serum osteocalcin levels have been reported in stunted children in Dakar, compared with normal children in Paris (Ndiaye et al, unpublished data). Here we are looking forward: the stage seems to be set for a systematic attack on the causation of stunting.

It may be argued, not unreasonably, that it does not much matter for a child to be physically small. Indeed, it has been regarded as an adaptation. However, Grantham-McGregor in Jamaica has shown conclusively that the impairment of mental development that is found in previously malnourished children is specifically associated with retardation in linear growth and not with acute malnutrition, however severe (12). Of course this does not mean that the prevention or reversal of stunting by nutritional means, if it proved possible, would necessarily have an effect on mental development since the impairment must result from a multiplicity of factors associated with poverty and deprivation, not least a lack of psychological and social stimulation. Nevertheless, Grantham-McGregor's words emphasize the importance of the problem: We cannot regard stunting simply as a harmless biological adaptation; on the contrary, it is a marker of a seriously handicapping environment. If "malnourished" is defined operationally as a state that can be improved by nutritional means, I think we have to include these stunted children among the malnourished, while recognizing that poor nutrition is only one aspect of their deprived environment.

From the point of view of practical nutrition programs, whereas wasting is rightly regarded as an effect of acute malnutrition, and weight for height is used to screen children at risk and to assess the short-term effectiveness of interventions, the reduction of stunting requires a long-term policy on a broader front (49). Insofar as this policy relates to nutrition, the aim must be to improve the quality as well as the quantity of the diets of infants and young children.

Energy and Protein Requirements of Children

It is essential for our understanding of the origins of PEM and of measures for preventing it that we know the mean and the range of the energy and protein requirements of infants and young children. This subject has always very much interested me, but more as a committee member (8) and as a user than as an original research worker. It now seems probable that traditional energy estimates are somewhat too high. The conventional figures are based on the observed intakes of children who were fed mainly by bottle. The alternative approach is the factorial method, which uses the BMR as its starting point, but the problem of how to estimate expenditure on physical activity. There now

seems reason to hope that this difficulty will be overcome by the use of the doubly labeled water method. The figures collected by Prentice and others (23) indicate an average requirement for total energy expenditure and growth throughout infancy and early childhood of about 85 kcal/kg per day from the age of six months to five years. This is probably a realistic figure, although it does not take into account the need for catch-up growth after infection. It represents a reduction of ~ 10% over the age range of one to four years compared with previous figures, which, although small, is important.

The protein problem is more difficult to resolve. It is compounded by uncertainty about the efficiency with which protein is used for maintenance and growth. The conventional figure is 70%, but we do not understand why the body should be so inefficient, and we question whether adaptive mechanisms could improve the use. Children recovering from malnutrition seem to use protein more efficiently than healthy children (6). Moreover, growth is not a regular process, and because protein is only minimally stored, the daily intake must allow for a kind of mini-catch-up from the days on which no growth occurred.

An approach that seems to make sense is based on the protein/energy (P/E) ratio of the food (protein calories as a percent of total calories) rather than on absolute amounts of protein (38). First, one must assume that energy requirements are met. Then, if breast milk with a P/E of 7.2 is taken as the gold standard for a breast-fed baby, one can calculate from the partition between maintenance and growth the safe P/E needed by an older child, say at one year, who is growing more slowly than the breast-fed infant. This comes to about 5.2. A correction must then be applied for the estimated biological value of the food protein.

Figure 1 is illuminating because it shows not just the mean but the range of P/E ratios in the diets of two populations of children. In Uganda, where kwashiorkor was common, the ratio fell below the critical level of about 5 in some 10% of children. When one says that kwashiorkor is common, this is in relative terms. It still represents only a fraction of the distribution of children in a community, and probably the prevalence never exceeds 5% except in times of famine. This figure therefore shows that some children's diets, even if only a minority, are deficient in protein. It thus provides the final link of the chain in the classical theory that kwashiorkor is caused by protein deficiency. There is a good deal of rather anecdotal evidence to support the conclusions drawn from the figure. Kwashiorkor is well recognized in regions where the staple is rice, which is low in protein (6%), as in southern India; or maize, which has poor protein quality, as in Mexico, Central America, or Southern Africa; or plantains or starchy roots, which have a low and poor protein content, as in Central Africa). PEM is rare and usually takes the form of marasmus in regions where the staple is wheat or millet, as in north India, the Middle East, or the Sahel.

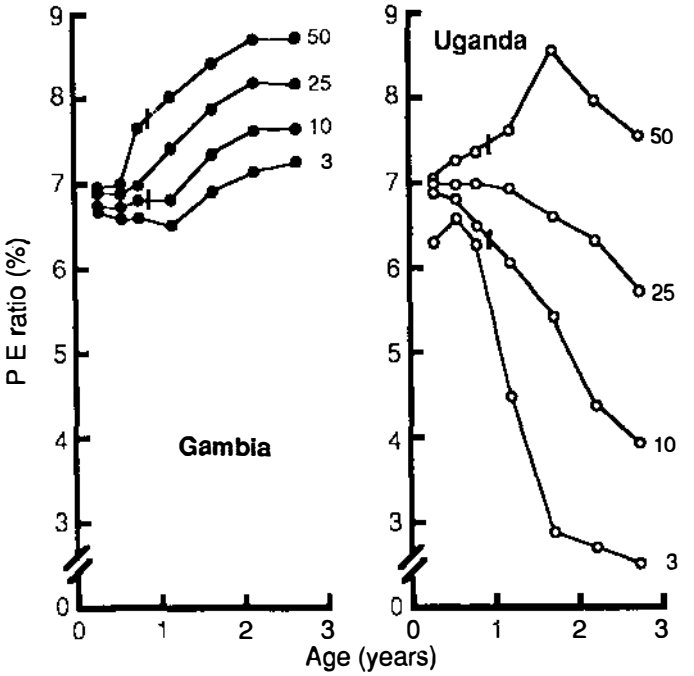

Figure 1 Centiles of the P/E ratio of diets, corrected to the quality of cow's milk, of children in Uganda and The Gambia. Reproduced with permission from Ref. 46.

I suggest furthermore that Gopalan's observation (referred to earlier) that no quantitative or qualitative difference exists between the diets of children who developed kwashiorkor or marasmus can be explained in terms of individual variability. On intakes that are marginal in both energy and protein, those children with a relatively high energy requirement will become marasmic, whereas those with a high protein requirement will present with kwashiorkor.

The Contribution of Infection to Growth Failure

The publication of Scrimshaw's monograph on nutrition and infection (26) was an important event because it emphasized that there are other factors besides food that may cause children to fail to grow, particularly diarrheal disease. The idea began to circulate that clean water and sanitation might be more important than food and that perhaps nutritionists could pass their problems to the sanitary engineers. Unfortunately, quantitative analysis does not support such a policy.

I was interested in the question of whether infection contributes to growth failure because of the protective effect of breast-feeding and the dilemma of when to wean infants onto other foods. Breast-feeding alone is not likely to be adequate beyond the age of six months, so that thereafter the children have to be given some supplementary food, with concomitant risk of infection (36). The question then arose: What is the contribution of infection to the growth failure that commonly becomes apparent in the latter part of the first year and throughout the second year and which is diagnosed as malnutrition?

The literature suggests that every day ill with diarrhea will produce a weight deficit of 20–40 g. If the percentage of days ill is known we can readily calculate the extra requirement for catch-up during the days that the child is not ill. For example, a child who is infected for 30 days out of 100 needs to make good these deficits in the remaining 70 days. From knowledge of the protein and energy costs of growth, it can then be calculated that catch-up within 100 days from this impact of infection would require an increase in energy intake of about 7% and an increase in protein intake of about 15%. Obviously such calculations can provide only a rough guide, but they indicate that even with a high prevalence of infection, the extra needs for catch-up are not large, and a diet that cannot meet them must indeed be marginal.

The same considerations apply to linear growth, although because growth is so slow it is not possible to approach the problem in the same way. Longer-term studies are needed, and a good example is that of Black et al (1984) in Bangladesh (3), where diarrheal disease is prevalent. They showed by multiple regression that over 5 years, diarrhea could account for an overall reduction of 2 cm in height growth, compared with a total deficit of 10 cm. In light of these and similar figures, it seems likely that infection only plays a subsidiary role in the development of stunting. Nutritionists therefore cannot pass the buck to sanitary engineers.

CONCLUSION

With careful application of our current knowledge of PEM and with minimal laboratory investigations, it is possible to prevent the majority of deaths from severe PEM. Although these deaths may be relatively few compared with the all-cause mortality rates of malnourished children, if they are preventable they cannot be ignored. There is an urgent need for better dissemination of the knowledge that has been gained, and it is encouraging that organizations concerned with refugees such as the Médecins Sans Frontières are becoming interested. There remains a residuum of cases, particularly of the marasmic kwashiorkor type, that seem to be resistant to treatment. It is a challenge to understand the nature of the breakdown at the cellular level: Is it free radical damage to cell membranes, the failure of key enzyme systems, or a lack of

energy to fuel essential processes? These seem to be some of the possible causal factors.

There is no doubt, however, that future action must focus on prevention of PEM in the community. One view holds that because the basic causes of this disorder are poverty and deprivation, steps must be taken in the social, economic, and political spheres; further research is unnecessary when the problem is the result of worldwide economic maladjustment and depression. It seems to me that the role of technicians such as myself is to indicate the size of the problem and the most fruitful aspects to which our limited resources should be directed. I have chosen three interrelated subjects that have interested me: (*a*) counting the malnourished, (*b*) energy and protein requirements, and (*c*) interactions of malnutrition with infection. If the points of view put forward here are correct, I can but hope that the information will be used by planners and will contribute in a small way to relieving the lot of children in developing countries. We cannot risk the wastage of human capital that results from the failure to apply scientific knowledge.

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