Undernutrition and Mental Development

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Introduction

Childhood malnutrition is currently diagnosed by comparing children’s anthropometric measurements to the median of international references (NCHS [1]) for their age and sex, and expressing the results in standard deviation scores (SDs) [2]. Moderate underweight is weight $<-2$ SDs, moderate stunting is height $<-2$ SDs, moderate wasting is weight-for-height $<-2$ SDs and severe is $<-3$ SDs. All these conditions are usually termed protein energy malnutrition (PEM), however this term is misleading because it is well recognised that various micronutrient deficiencies are usually also present [3]. Therefore, in this paper we will refer to undernutrition rather than PEM.

There are several causes of undernutrition including inadequate dietary intake, due to lack of sufficient and/or suitable quality of food, frequent infections, particularly diarrhoea, also contribute.

Prevalence of Undernutrition

UNICEF [4] estimates that 31% of children under 5 years in developing countries are moderately underweight, 38% are moderately stunted and 11% moderately wasted. In least developed countries, 40% of children are underweight and 47% are stunted. The prevalence of undernutrition has declined in most countries over the last two decades; however, because the numbers of young children have increased, the actual number of undernourished children has also increased. Contrary to general trends, many countries in Sub-Saharan Africa are showing an increase in the prevalence of childhood undernutrition.
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[5]. Low birth weight (LBW) occurs in 18% of births in developing countries compared with 6% in developed countries [4]. A higher proportion of LBW babies in developing than in developed countries are small-for-gestational-age (SGA) and factors associated with poverty including maternal undernutrition and infections are thought to contribute to the excess numbers [6].

If childhood undernutrition affects children’s development, the enormous numbers of children involved have grave implications not only for the individuals but also for the national development of many developing countries.

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For at least four decades, researchers have studied the effects of undernutrition on children’s mental development. It would be expected that, by now, all the questions would be answered. Unfortunately this is not the case, because as we have learned more, it has become clear that child development is extremely complex [7]. Development is affected by a large number of factors, including genetics, the child’s individual characteristics, the proximal environment (e.g. the quality of the relationship with family members and the amount of stimulation in the home), the distal environment (e.g. the culture, area of residence and socio-economic status) as well as the child’s health and nutrition. Moreover, these influences operate throughout childhood. Their effect depends on the presence of previous, concurrent and future influences as well the child’s stage of development.

Most undernourished children are exposed to poverty and associated factors such as low parental education, poor housing and unstimulating environments. These influences may independently detrimentally affect children’s development. In the past, researchers have focused attention on separating the effects of poor socio-economic environments from that of undernutrition. Although this approach has had some success, it is now recognised that undernutrition may not always have direct effects on development but may interact with other influences. Researchers are now more aware of the importance of taking into account the socio-economic context of undernutrition rather than controlling for it. Examples of interactions between nutrition and the environment are LBW babies in Brazil had poor levels of development if they lived in homes where the stimulation was poor but normal birth weight babies were not affected [8]. Nutritional supplementation in Guatemala benefited cognition in children from poor homes but not those from better homes [9]. The coexistence of micronutrient deficiencies, hunger and infections with undernutrition and their possible effect on children’s development has not received as much attention. However, stunted Jamaican children’s cognition was affected by short-term food deprivation whereas adequately nourished children were not affected [10] and parasitic infection is more likely to affect undernourished children’s cognition than adequately nourished ones [11].
In 1994, a technical group meeting of the International Dietary Energy Consultative Group reviewed the state of knowledge on the relationship between undernutrition and mental development [12]. In this review, we will build on the reports from that workshop adding more recent research findings. We will examine the role of severity and duration of undernutrition and the children’s stage of development and possible mechanisms.

**Mechanism**

There are several possible ways in which undernutrition could affect cognition [13]. One possible mechanism is that undernourished children ‘functionally isolate’ themselves from the environment and explore less, are more apathetic and have reduced activity levels. They thus acquire fewer skills. In response to their children’s altered behaviour, the caretakers become less stimulating towards them, exacerbating their poor development. Another hypothesis is that undernourished children are treated as younger children because of their small size, and this contributes to their poor development. A third possible mechanism is through direct and irreversible changes to the brain.

Animal studies have shown that there are many changes to the brain structure and function in rats, which have been severely malnourished prenatally or in the early postnatal period. It is now recognised that the period of mitotic activity is extended with refeeding and many of the changes are reversible [13]. However, several alterations to brain structure are thought to be irreversible including, for example, a reduction in myelin, an increase in neuronal mitochondria, a reduction in cortical dendrites in neural spines, and a reduced ratio of granule to Purkinje cell in the cerebellum. There is also some indication of altered neurotransmitter metabolism with reduced adaptive ability to stress.

There is limited evidence of changes to brain function in children. Severely malnourished children have been shown to have abnormal auditory evoked potentials, which remain abnormal after recovery from the acute stage [14].

A recent study [15] found that stunted children had altered hypothalamic-pituitary-adrenocortical activity with raised cortisol levels, heart rates and increased urinary epinephrine. It is possible that altered stress response may contribute to poor cognitive function.

**Severe Clinical Undernutrition and Mental Development**

Early investigators focused on the development of children who had been hospitalised for kwashiorkor, marasmus or marasmic-kwashiorkor (using the older method of classifying undernutrition [16]) in the first 3 years of life.
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These studies were recently reviewed in depth [17]. In general, the findings showed that during the acute stage, the children’s developmental levels were much poorer than those of adequately nourished children who were in hospital with other diseases. The children also showed altered behaviour with reduced activity and exploration and increased apathy. On recovery, the undernourished children’s behaviour improved but they did not decrease their developmental deficit relative to the controls and remained with poor levels of development for some time following recovery.

Many investigators have compared children at school age, who were severely undernourished in early childhood, with children who were not undernourished and matched for socio-economic background or with siblings. Previously undernourished children generally had poorer fine and gross motor function, and levels of school achievement and cognitive function, they also had more behaviour problems. They made poor relations with peers and teachers, had poor attention spans and were less happy and more inhibited.

The quality of the children’s environment following an episode of severe undernutrition determines to a large extent their developmental progress. Where children have been adopted into more affluent environments, marked improvements in cognitive development occurred [18, 19]. In addition, a small Jamaican study showed that a simple intervention programme of psychosocial stimulation produced benefits to severely undernourished children’s development which were sustained up to adolescence [20].

Discussion of Studies of Severe Clinical Undernutrition

The evidence for a concurrent short-term effect of severe clinical undernutrition on children’s development is clear but because of the possibility of poor socio-economic conditions confounding the findings, a long-term effect is not unequivocally established. However, considering the consistency of the findings and the results from studies of nutritional supplementation discussed below, it is almost certain that where children return to unsupportive environments they will continue to show deficits at least through later childhood. There is extremely little data from adults. On the other hand, in supportive environments, vast improvements occur.

Contribution of Severity and Duration

The relative importance of severity and duration of undernutrition is not well established.

Wasting is considered an index of severity but can change rapidly, whereas stunting takes longer to develop and improve and is considered a marker of duration. A few studies have examined associations between anthropometric
measurements and the presence of oedema in the acute stage, and cognition in later childhood. Findings indicate that height-for-age or weight-for-age is a better predictor of later cognitive ability than wasting or the presence of oedema [17].

Similarly, in studies of moderately undernourished school-aged children, stunting is more frequently associated with poor cognitive development, school achievement and school enrolment than wasting [21]. Stunting usually occurs in the first 3 years of life [22], and it is now clear that children are able to improve in height after the first 2 years if the environment is favourable but not if they continue living in poor environments [23–25]. Children who are stunted at school age are therefore likely to have been exposed to poor nutrition since early childhood.

These findings suggest that moderate undernutrition of long-term duration may be more important than transient severe undernutrition. However, in many of the studies of moderate undernutrition linking stunting and wasting to performance, wasting was not as frequent or as severe as stunting (when expressed in standard scores), making it more difficult to demonstrate a relationship.

A recent longitudinal study of children who were stunted at 2 years in the Philippines [26] found that children who remained stunted in later childhood (persistent stunting) had poorer cognition than children who recovered from stunting. However when severity of stunting, at 2 years of age, was considered concurrently in multivariate analyses, persistence of stunting was no longer significant and only severity at two remained significant. It is likely that both duration and severity play a role.

The stage of development probably also modifies the effect. For the rest of this paper we will discuss the evidence for moderate undernutrition affecting development and whether the stage of development modifies the effect.

Effect of Moderate Undernutrition and Timing on Mental Development

Several cross-sectional studies have found associations between stunting and poor development in infants and between stunting and poor cognitive development, school achievement, school enrolment and drop out in school aged children. However, cross-sectional studies are little help in establishing causal relationships and will not be discussed further. Longitudinal observational studies provide useful information but there is always the possibility that variables associated with poverty may confound the findings. The most valid way of addressing questions of causality and timing is by determining the effect of supplementing children at different stages of development who are either highly likely to become malnourished or already undernourished. Only few studies have attempted to do this, however, looking across all longitudinal
observational and supplementation studies provides some answers and these will be discussed in the following section, classified by the stage of child development.

**Prenatal Period**

**Observational Studies**: A meta-analysis of studies of LBW babies established that they usually have poorer cognitive development than normal birth weight babies [27]. However, almost all of the studies were from developed countries where most of the LBW babies would have been premature [6]. There is less information available on the development of SGA babies. Recent reviews of studies of SGA babies’ development [8, 28, 29] concluded that after the first year of life, children usually show small deficits in cognition throughout childhood with an increase in minimal neurological dysfunction and behaviour differences. The children were reported to be less active, vocal, responsive, happy and co-operative in the first 2 years but at school age they were described as more fidgety, anxious and less happy and have poor attention span. The findings from late adolescence and adulthood were too few and inconsistent to interpret with confidence.

Unfortunately, only two long- or medium-term studies came from developing countries [30, 31], where SGA is extremely prevalent. One study in Guatemala showed cognitive deficits in the SGA children in early childhood but they were no longer present in adolescence [31]. In the other study in India [30], three groups of children aged 10–12 years were compared in their performance on a battery of cognitive tests. The groups were children with normal growth in the first 5 years (C), those with LBW followed by poor growth (LBW), and those with poor growth beginning between 6 and 12 months and continued to 5 years (UN). Group C had significantly higher scores in all cognitive tests than the other two groups. The LBW group’s scores were lower than group UN in all but one test (scores in that test were the same) although the individual differences did not reach significant levels. It may be that childhood undernutrition tends to overwhelm the smaller effect of SGA.

**Supplementation Studies**: Two early studies of supplementation to pregnant women, in developed countries [32, 33], showed no benefits to their children’s development, but the mothers were probably not undernourished initially.

In an unusual randomised controlled trial of supplementation of preterm babies in the UK [34], infants were given preterm (enriched) or term formula, controlling for breast-feeding. The group receiving term formula showed marked deficits in IQ at 7–8 years of age, compared with those receiving preterm formula. The deficits were greater in boys. The finding was remarkable because the diets were given for only a median of 4 weeks after delivery and
suggests that early development is particularly sensitive to nutritional deficits. But the relevance of the findings to undernourished children in developing countries is questionable.

In another randomised controlled trial in Taiwan [35], supplementation was given throughout pregnancy and the mothers alone were supplemented during lactation. Their children had better motor but not mental development at 8 months of age than the placebo group. They were followed up at 5 years of age [36], when no benefit was detected in their performance on an IQ test. This study is unique in focusing on the total gestation period in a high-risk population and having a placebo group. Unfortunately, no details of the follow-up were reported.

**Early Childhood and Prenatal Period Combined**

*Supplementation Studies:* In an early supplementation study in Bogota [37], three groups of children received supplementation over different age ranges. One group was not supplemented (A), one group was supplemented from 6 to 36 months of age (B), one was supplemented from the last trimester of pregnancy to 6 months of age (C) and a fourth group was supplemented over the whole period (D). At 36 months of age, there was no significant difference in the children’s development between groups B and C, but B was better than A. In contrast, C was not different from A and significantly worse than D, indicating no benefit lasting to 36 months from supplementation stopping at 6 months of age. There were two other study groups which received supplementation from the last trimester through to 36 months with stimulation from birth or stimulation alone. At 36 months, each treatment had concurrent benefits on cognitive and motor development. A brief report of a follow-up at 5–8 years of age [38] showed benefits from supplementation to reading readiness and retention in school grade, although loss from the study was considerable.

In two other studies, supplementation also began in the last trimester of pregnancy and continued throughout early childhood or longer [9, 39]. In both studies, children showed concurrent benefits. In Guatemala [9], children supplemented from pregnancy through to at least 24 months of age showed sustained but small benefits in a wide range of cognitive and achievement tests at adolescence. In a group who were supplemented after 24 months of age, benefits were found in only two tests; numeracy and general knowledge. Although fewer children received supplementation at the older than younger age, so the statistical power to show differences was reduced, there was no tendency for improvement in the other tests. Also, it is not clear how long supplementation continued. In Mexico [40], small benefits to the IQ scores of boys but not girls were reported in adolescence.
**Discussion of Studies in Prenatal and Early Childhood Period**

The studies of SGA babies are observational and thus less rigorous than supplementation studies. Many studies lacked comprehensive control for the possible confounding effects of poor social backgrounds and there was often a large and biased loss of subjects from follow-up. However, the findings were reasonably consistent that deficits are found in early childhood and usually sustained to middle childhood. There is some indication that the long-term effects of SGA vary in different populations. There is a particular need for more studies of SGA children in developing countries.

The findings from supplementing throughout pregnancy [35] indicate that prenatal nutrition has short-term but not long-term [36] benefits on children’s development. Supplementation from the last trimester through the first 6 months [38] also failed to have sustained benefits. The latter study does not allow us to examine the first few months of life with rigour because most of the placebo group would have been breast fed and therefore likely to be adequately nourished for at least the first 3 months. There are remarkably few studies of the effects of supplementing pregnant women on children’s development in developing countries and we should be cautious when extrapolating, from two studies showing no sustained benefit, to other populations.

All the supplementation studies including late pregnancy and the first 2–3 years showed concurrent benefits from supplementation, affecting motor development first, and those studies with middle [38] or long-term follow-up [9, 40] found some benefits. It is not possible to know whether the antenatal period contributed to these gains and the studies had many design problems. For example, in Mexico, the samples were very small and not randomised to treatment.

**Early Childhood Period Alone**

*Observational Studies:* Several longitudinal studies have shown significant correlations between children’s early height deficits and later development. Height at 3 years in Guatemala predicted performance on tests of numeracy, literacy, general knowledge and grade placement at adolescence [41]. Height between 18 and 30 months of age predicted cognition scores at 5 years in Kenya [42] and height at 12 months predicted school achievement between 9 and 11 years in Jamaica [43].

In the Philippines [26], taking into account social background, severity of stunting at 2 years of age had a significant effect on cognition at 11 years of age. However, severity of stunting was related to age of onset of stunting and children who were stunted by 6 months of age had the most severe stunting at 2 years. No analyses were reported of birth weight but in another report of the study [23], LBW was strongly related to early and severe stunting.
Therefore, intrauterine growth retardation may have explained some of the cognitive deficit attributed to severity of stunting at two. In a second Jamaican study [44], stunted children were enrolled between 9 and 24 months of age, then followed up to 11–12 years of age when they were given an IQ test. The relationship between IQ at follow-up and the children’s anthropometry on enrolment and at 3–4 years, 7–8 years, and at the test at 11–12 years was examined. Controlling for birth weight and social background, only height-for-age on enrolment and head circumference on enrolment and 2 years later were significantly related to IQ. Neither later measures of height and head circumference nor any measures of weight-for-height were significantly correlated with IQ. These findings suggest that the first 2 years of life are the most vulnerable to undernutrition and effects are sustained at least through to adolescence. However, as in most of these studies, undernutrition was most severe at the younger age, thus age and severity were confounding.

Supplementation Studies: There are only few studies of supplementation beginning when the children were already undernourished. In a Jamaican study, stunted children aged 9–24 months on enrolment showed concurrent cognitive benefits from 2 years of supplementation [45]. Small global benefits to cognition were apparent at 7 years but were no longer detected at 12 years of age [25]. It is interesting that children receiving stimulation in the same study had sustained benefits.

In an Indonesian study [46], undernourished children aged 6–60 months were supplemented for only 3 months. Children younger than 20 months showed concurrent benefits to motor but not mental development, whereas older children showed no benefit [Pollitt, pers. commun.]. At follow-up, around 9 years of age [47], 63% of the sample were located and no differences between supplemented and unsupplemented were detected in tests of arithmetic, vocabulary, emotionality, simple and choice reaction time, recall and working memory. However, the subsample of children who were under 18 months during supplementation showed benefits on the working memory test.

In a Colombian study [48], undernourished children aged between 4 and 66 months showed concurrent benefits from supplementation to their development, assessed on the Griffiths test, but details by age distribution were not reported. There was no long-term follow-up. Also in Colombia [49], children who entered a programme of education and supplementation at 42 months had better cognitive function at follow-up than those who entered older. But the age of entry was confounded by the duration of the intervention. Furthermore, it is impossible to separate education from supplementation. Supplementation alone was given to one group beginning at 42 months and was reported to have no cognitive benefit, but the details were only sketchily reported so are not possible to evaluate.

Adoption Studies: Two studies showed that undernourished children adopted at a young age recovered more on follow-up than later adopted children. Korean children adopted before 2 years of age caught up to American
norms for achievement and IQ but those adopted at an older age did not [18, 50]. However, the effect of nutrition did not differ with age among those adopted between 2 and 5 years.

Moderately undernourished Romanian children adopted in the first 6 months of life showed complete catch up in IQ by 4 years of age compared with adequately nourished English children adopted at the same age [51]. In contrast, children adopted between 6 and 24 months improved but did not catch up. However, in children adopted before 6 months, there was a significant 10 IQ points difference between those with weight-for-age below and above −2 SDs on adoption. In contrast, weight was unrelated to later cognition in children adopted later, although current head circumference was related.

These results are difficult to interpret because age at adoption is confounded by the time to recover between adoption and follow-up. In addition, most of the children spent their early years before adoption in extremely poor institutions. It may be that psychosocial deprivation overwhelmed all else.

Discussion of Findings from Early Childhood Alone

All studies of supplementation alone of children younger than 5 years who were already undernourished have shown concurrent benefits except one in which children were the oldest (42 months) at the beginning [49]. The long-term follow-up studies suggest that the effect of supplement is more sustainable the earlier it begins. Three studies reported some long-term benefits. In Bogota, one group began supplementation at 6 months and showed some benefit at pre-school testing [38], in Indonesia [46], a benefit was found in one test of working memory in children supplemented before but not after 18 months of age. In Guatemala [9], children supplemented after 24 months showed benefits in two tests from a battery of tests, much less than found in children supplemented from pregnancy. Two studies which began in children aged 9–24 months [25] and 42 months [49] showed no long-term benefits. There is therefore only limited and inconsistent evidence of a long-term benefit to cognition from a period of supplementation begun after 18 months.

School Age

We were unable to locate studies at this age except for school feeding ones. These have been reviewed elsewhere and few have had rigorous designs. A recent Jamaican study [52] showed that two semesters of providing breakfast at school improved arithmetic scores of children in grades 2 and 3 (mean age

10
8 years) but not grades 4 and 5. However, the mechanism could be through changing attitudes to school and better attendance.

**Summary of Findings from All Stages of Development**

*Short-Term Effects*

In undernourished populations, supplementation has a concurrent and at least short-term effect on children’s development when given in pregnancy or any age during the first 3.5 years of life [9, 35, 37, 39, 45, 46]. Between 3.5 and 5 years the findings are few and inconsistent [48, 49]. Evidence from older children is inadequate to draw conclusions but school achievement can benefit from school feeding.

*Long-Term Effects*

1. Premature babies may be especially sensitive to nutrition in the first few weeks and effects sustained up to 8 years [34].
2. The effect of supplementation in pregnancy alone or pregnancy and the first 6 months may disappear with time [36, 37]. But it is unclear what the long-term effects are of SGA births.
3. Supplementation beginning in the last trimester of pregnancy and continued for 3 years at least, has small benefits, which are sustained for some time [9, 38, 40].
4. Supplementation alone beginning between 6 and 18 months has small sustained benefits [38, 47], but beginning older than this no sustained benefits [25, 49] or very limited sustained effects are found [9].
5. We could find no studies of older children.
6. Large and sustained improvements can take place in undernourished children with continuous supplementation combined with environmental enrichment as found in adopted children [19] which are probably greater the younger the child [18, 51].

It is obvious from the above summary that the evidence is too weak to allow us to make firm conclusions about the effects of timing of undernutrition. But the impression is that poor nutrition lasting for the first 2–3 years of life is likely to have a long-term detrimental effect on children’s development. Supplementation throughout the first 2 years is likely to have sustained benefits. However, supplementation restricted to pregnancy plus or minus the first 6 months, or beginning after 18–24 months is less likely to have sustained benefits.

Although vastly improved environments will facilitate recovery, they are not usually available. Combined stimulation and nutrition programmes appear to offer the most promising treatment for undernourished children.
References


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Discussion

Dr. Uauy: Now that we are in the micronutrient era, how much of this earlier work can be interpreted as truly reflecting protein-energy malnutrition, or is it really combined PEM and micronutrient deficiency? Might that not induce some noise into the system, because we were mainly intervening with protein energy at that time? It was an era when growth was the outcome measure more than chemical indices or micronutrient status.

Dr. Grantham-MacGregor: I think that’s an interesting point. I haven’t gone through all the supplements in detail to see how many contained micronutrients, but I will do now.

Dr. Uauy: But what is your own opinion? The micronutrient people say forget about protein energy!

Dr. Grantham-MacGregor: I wouldn’t agree with that. I certainly still feel that energy is very important, and maybe protein. I’m not saying that micronutrients aren’t important, but when you see these children who are so undernourished, to say that all they need is iron or zinc is, I think, really questionable.

Dr. Fernstrom: When you discussed the Taiwan study, the message I got was that supplementation throughout all three trimesters of pregnancy was unnecessary. That struck me as very curious, when you reflect on how nutrients may have such a direct impact on the developing nervous system, folic acid for example. Why should there be no positive benefit of supplementation in all three trimesters?

Dr. Grantham-MacGregor: It seems that the fetus is vulnerable to certain specific deficiencies, for example iodine deficiency. Folic acid is another good example. But for most nutrients the placental supply seems to protect the fetus from deficiency and there is little to suggest that additional supplementation is of much benefit.

Dr. Rosenberg: On the matter of the first trimester supplementation, I think we need a great deal more information about the interaction between nutritional quality and later outcome. With folic acid, for example, the only way you can have an impact on nervous system development is to achieve better folate nutrition before pregnancy. Studies on supplementation during the first trimester are usually begun after the diagnosis of pregnancy, which of course is after the neural tube has closed. So that’s another uncertainty that we have to resolve.

Dr. Grantham-MacGregor: The other point about that Taiwan long-term follow-up [1] is that it was only presented in abstract form, which is really not adequate. Also, once people find there is no effect, they hide the data; they say ‘no effect’ and you don’t hear any more about those data. That’s a shame, because those are the important samples that need to be followed up. Thus in the Cali follow up [2] they don’t mention...
the group that only had supplementation because they were dismissed as unimportant. People are frightened of negative findings.

Dr. Faintuch: I’m in the adult field and would like to ask a question regarding adults. Do you know what happens to the adult brain if you withhold food for long periods? Will it cause damage? This question arose recently in São Paulo, where there was a large group of people on hunger strike, who remained for nearly 2 months without any food at all. We were asked whether there would be any long-term consequences and I really didn’t know what to answer.

Dr. Grantham-MacGregor: Well, there was a famous study in 1950 by Keys and Brozek [3] where they investigated volunteers on starvation diets and did a series of cognitive tests. Unfortunately there is a practice effect in all cognitive tests, and people tend to improve, which acts as a confounder. But there was a tremendous change in affect in these people, which seemed to recover on follow-up.

Dr. Kaye: I study anorexia nervosa, which is a kind of natural experiment. We study people when they’re underweight and again after full recovery, with normal body weight, normal menses, and so on. We’ve been measuring different chemicals in the cerebrospinal fluid as a reflection of what’s going on in the brain. There is a host of changes in various neuropeptide systems when people are underweight. But for the most part, those systems normalize with recovery. A few don’t – maybe they just reflect the underlying traits that are associated with anorexia nervosa – but most do, even after years of starvation.

Dr. Crozier-Willi: You told us about what happens when undernourished children are given supplements of protein energy, and more recently I’ve become aware of some work looking at rats which were given extra choline, over and above the usual amount required for normal nutrition. In the rats given the supplement there were very clear changes in physiological function and behavior [4, 5]. I wonder if you have any comments about the possibility of improving brain function in the normal child?

Dr. Grantham-MacGregor: I think it may be possible, but I’m not having anything to do with it!

Dr. Haschke: The data you showed are always a mixture of environmental, socioeconomic, nutritional and other factors. Are there any good data on the development of children who had intrauterine growth retardation, and who were then brought up in a favorable environment? These children have had a period of malnutrition at a very critical time for brain development before birth. Can they catch up, or is there a permanent deficit?

Dr. Grantham-MacGregor: All those studies that I showed were done in developed countries, so even under those favorable circumstances there does seem to be a small residual deficit.

Dr. Haschke: Even in developed countries, those studies are not really controlled for the social environment.

Dr. Grantham-MacGregor: No, you’re right.

Dr. Uauy: There are data from developed countries on children with clinical conditions that happen in families of good socioeconomic status, such as pyloric stenosis. In those cases, the deficits seem to be almost fully reversible.

Dr. Grantham-MacGregor: But some of them don’t catch up. Anyway, I’m not sure that this is quite the same situation, because those children have chronic illnesses. And their parents behave differently.

Dr. Uauy: Those illnesses are curable. When you treat pyloric stenosis the child becomes normal. When you give enzyme replacement, growth resumes. So it is important to bear in mind that in the right socioeconomic environment there is the potential for full catch up, as you also showed with the adopted children.
Dr. Grantham-MacGregor: I’m not questioning that they can catch up if you have vast social improvement, but the point about pyloric stenosis study is that it involved a very short period of undernutrition, and some of the children weren’t even that undernourished.

Dr. Holm: What are the main reasons for SGA low birthweight in your studies? Is it caused by malnutrition, or infection, or because the mother is at work during pregnancy, or other factors? I think these variables may be interrelated. Is factor analysis employed in examining these data? That would show which of the variables are really interrelated, which are independent.

Dr. Grantham-MacGregor: The studies that I’m talking about involving pregnancy are mostly old studies. I don’t know of any really recent ones. I don’t believe that factor analysis was used, though of course we use it now.

Dr. Bhargava: I would like to supplement the information which has been given us with some Indian data. I am a neonatologist and I have done long-term follow-up studies on low birthweight infants, some of whom are now nearly 30 years old. In India, there are four major causes of low birthweight: teenage pregnancies, a short interval (less than 2 years) between pregnancies, inadequate height and weight of the mother, and finally infection. Early marriages, before 19 years, and short birth intervals are very common factors associated with low birthweight.

We have several supplementary nutrition programs for mothers and infants, and also for schoolchildren. I am sure that some of you will be aware of one of the largest existing supplementary programs, known as the ‘Integrated Child Development Service’, a national program that was initiated in 1977. We have information on about 20 years of data, and many of these studies, controlled and uncontrolled, have shown that supplementation does indeed help achieve better weight gain. Data are now emerging that cognitive development is also improved.

In our country, we have a 30% low birthweight rate, the majority being IUGR. Our prematurity rate is about 10–14%, which is also high. In our long-term studies we have clearly established that premature babies, once they are past the initial period, do very well. They seem to catch up in terms of physical growth and intellectual achievement. With the IUGR babies we can identify two different groups: in one, all the measurements (weight, length, head circumference) are less than the third centile; in the other, only the weight is less than the third centile, while brain growth seems satisfactory. In this latter group, catch up occurs at around 8–10 years. We do not see catch up in growth or functional status between zero and 3 years, as we do in the premature infants. Worst of all are those IUGR babies who are small in all dimensions. These never seem to catch up, even up to 14 years of age. One of the findings that has disturbed us particularly is in relation to cognitive development in those children: when we did a longitudinal study between age 2 years and 8–10 years, we found that the gap had not narrowed, but had actually widened with respect to the controls, who came from the same background. We are in the process of repeating this study.

I want to ask a couple of questions about your presentation. You said that intervention during the first 18 months is likely to be most useful. If so, then our ICDS program is suboptimal because it starts in preschool children. It is very difficult for us to get to the children in the age group you described, because most deliveries are still done at home and the children tend not to be brought to health centers. Also our health centers do not give supplements. Do you have any ideas about how we can get to the children of this young age? Secondly, you said that you also showed improvement on intervention. Was the intervention only in terms of nutrient supplements, or did you also have a stimulation program?

Dr. Grantham-MacGregor: To be honest, I think that the large-scale program you have in India is actually feeding the wrong age population, but whether that’s the best
that can be done in the circumstances I don’t know. I would have thought that to try
and reach out to the under-2s was more important than feeding the 3-and-over group.
I also think that if you start with children who are already undernourished, you have to
include stimulation as well as food, because the data suggest that you’re not going to
get adequate catch up with food alone. Studies in this field need longitudinal follow-up.
A lot of published studies have only cross-sectional data at a few time points, like the
Taiwan follow-up, and who’s to know that later on things aren’t going to get better,
because that’s the nature of child development?

There are only two studies I know of from developing countries on SGA babies.
One was the Guatemalan study where they went back and looked specifically at the
SGA babies. No effect of SGA was found in that study [6]. The other was an Indian
study by Agarwal [7] who looked at schoolchildren and divided them into SGA with
good nutrition, SGA malnourished, and normal birthweight malnourished. There was
no difference between SGA children who later became malnourished and children who
were not SGA but who became malnourished, though there was a trend for the SGA
infants who had postnatal malnutrition to be slightly worse.

Dr. Ritz: Quite a lot of the data you showed related to factors that affect IQ around
a mean of 80. Shouldn’t we expect mean IQ to be 100? Or is IQ not the proper tool for
these analyses?

Dr. Grantham-MacGregor: That’s a hot potato because these tests are usually not
culturally standardized and so we should really be presenting the data as standard
scores rather than absolute scores. However, the ‘normal’ population I was dealing
with is so deprived in some countries that I think a value of 80 is not extraordinary.
There is no proper tool for these countries, though there is a tendency now to go for
specific cognitive functions rather than IQ.

Dr. Uauy: Should we be redefining ‘normal’ on the basis of the appropriate reference
population?

Dr. Grantham-MacGregor: Well, obviously we should, but it would slow down a
great deal of research to standardize a test for a particular population. I think we
shouldn’t be looking at the actual scores but rather at the relative difference between
the controls in that population and the experimental group.

Dr. Fernstrom: On the basis of your long experience do you think that any nutri-
tional supplementation program benefits cognitive development or IQ or performance?
I’m not overwhelmed by the benefit of any treatment on cognitive function.

Dr. Grantham-MacGregor: Well, I think the data are reasonably consistent, that if
you supplement a child who would normally be malnourished through the first 2 years
of life, there will be a sustained benefit—not enormous but sustained.

Dr. Fernstrom: That’s a hypothesis or do the data support that?

Dr. Grantham-MacGregor: All the data available support that, but the data are far
from perfect.

Dr. Kaye: What happens when these malnourished children become adults? Is it a
vicious cycle that perpetuates itself?

Dr. Grantham-MacGregor: I think it is undoubtedly a vicious cycle that perpetuates
itself. Malnourished children become malnourished adults, become poorly educated
adults, have children early, have many children, have children who are likely to be
malnourished, and so on. That’s well established. However, having said that, there are
really no data on the cognitive function of adults.

Dr. Kaye: Does this affect reproductive rates? Is it reduced at all?

Dr. Grantham-MacGregor: The famine studies showed that fertility declined during
the famine, but I don’t know whether early childhood undernutrition affects long-term
fertility. I don’t think it does.
Dr. Freeman: As you talked about the cycle of poverty and malnutrition going on from one generation to another, I was wondering if there are many different points at which you can enter that cycle. If you have enormous poverty, there is more likely to be malnutrition and undereducation, which is going to affect the nutrition of the children, and their education and stimulation as they grow up. How do you know that nutrition is the point at which you enter that cycle?

Dr. Grantham-MacGregor: It would be very surprising if nutrition alone could solve the problems of underdevelopment. If I was asked to put my money somewhere, I would put it on education first, and feeding young babies.

References