REVIEW

The influence of dietary status on the cognitive performance of children

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The rapid rate of growth of the brain during the last third of gestation and the early postnatal stage makes it vulnerable to an inadequate diet, although brain development continues into adulthood and micronutrient status can influence functioning beyond infancy. Certain dietary deficiencies during the first 2 years of life, for example iodine and iron, create problems that are not reversed by a later adequate diet. It is important that the intake of micronutrients varies greatly between individuals as they are essential for metabolism in general and in particular cell division and hence growth. In developing countries, there is consistent evidence that the adequacy of diet has lasting implications for cognitive development. In particular, attention has been directed to protein–calorie malnutrition and more specifically the intake of iron, iodine and vitamin A, a deficiency of which damages eyesight. In industrialized countries variations in diet are less influential, although a few well-designed studies have reported that multivitamin and mineral supplementations influence anti-social behaviour and intelligence. In the short term, there is increasing evidence that the missing of breakfast has negative consequences late in the morning. A working hypothesis is that meals of a low rather than high glycaemic load are beneficial.

Keywords:
Brain development / Breakfast / Cognitive development / Malnutrition / Micronutrients

1 Introduction

When considering behavioural and cognitive development there appears to be a ready predisposition in the population of industrialized countries to see diet as both the cause of problems and a major means of solving them. As an example in the United Kingdom 32% of boys under 10 years of age took vitamin and mineral supplements while the comparable figures in girls were 23% when under 7 years, and 16% between 7 and 14 years of age [1]. It seems in the general population there is a widespread concern that dietary deficiencies occur.

It is superficially easy to argue that diet may play a critical role in brain development and hence intellectual functioning. The brain, in a similar way to the rest of the body, is constructed from protein, fat, carbohydrate, vitamins and minerals all of which are supplied by the diet. As the brain develops more quickly than the rest of the body it is obvious to consider whether a dietary deficiency at a critical stage of development may result in lasting changes in brain structure and hence functioning. In addition, the brain is the most metabolically active organ in the body yet it has very limited stores of energy [2], so it relies on the diet for a continuous supply of glucose. Similarly, the minute-to-minute functioning of the brain requires an adequate supply of micronutrients that act as co-enzymes, or form structural parts of the enzymes required for optimal metabolic activity.

Thus, the diet is responsible both for the building blocks from which the brain is constructed and fuel on which it runs. However, all such an analysis demonstrates is that the diet has the potential to influence intellectual functioning: the important question is how often, if at all, is the diet deficient to the extent that a problem develops? To what extent should we be intervening in developing countries? Is the concern often demonstrated by parents in industrialized countries well founded, or rather misplaced with the risk that more obvious psychological or medical solutions are ignored?

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Given the range of essential nutrients, and the various stages at which they may be influential, the pressure of space ensures that all that can be presently offered is an overview. However, where ever possible review articles have been quoted to allow specific topics to be further explored. Initially, the potential impact of diet during brain development is considered and then the short-term influence of vitamin/mineral status and the provision of energy are discussed. As the topic is covered elsewhere in this issue, polyunsaturated fatty acids (PUFA) are not considered other than when they relate directly to other matters.

2 Nutritional influences on brain development

2.1 Critical and sensitive periods

Particularly when considering cognitive development sensitive and critical stages of development are sometimes distinguished during which a particular type of environmental stimulation facilitates development. A critical period is a relatively short stage, with a relatively precise onset and end, during which the body is vulnerable to an influence such as an aspect of nutrition. Good examples, discussed below, are the permanent adverse influences of a lack of iodine or iron during the early stages of brain development. During a critical period, there is a greater sensitivity to an environmental stimulus: however, if the stimulus is not experienced it will prove difficult, or even impossible, for a particular aspect of functioning to be expressed in later life. Thus, if malnutrition inhibits metabolic processes at a particular age then potentially there may be a lasting effect on cognition.

In contrast, a sensitive period is seen as offering a broader window during which the brain is sensitive to a particular type of stimulation: for example language is acquired more readily during the first 10 years of life [3]. Although particular aspects of functioning are readily acquired during a sensitive period, a skill can still be acquired at a later age although not with the same facility and not to the same level of proficiency.

In reality, the supposed differences between sensitive and critical stages of development are often subtle and the views taken vary from worker to worker and between disciplines. Some see children becoming stuck at a particular stage of development if they lack stimulation during a critical window of opportunity. At the other extreme, some believe that there are only sensitive periods and a lack of stimulation does not produce difficulties that cannot be later overcome, albeit with more effort. At least with nutrition there is good evidence of critical developmental stages. As the brain develops rapidly during pregnancy, inadequate nutrition may limit development of important aspects of the brain's architecture. The argument is that as the mother's diet provides the building blocks from which the brain is made, if during a period of rapid brain growth some aspect of nutrition is inadequate then permanent structural damage occurs.

The extent to which much of brain development occurs at an earlier stage than the rest of the body can be illustrated by the fact that the brain weight of the newborn is about 10% of body weight, while in the adult it is only 2%. By the age of 1 year, the child will be about 15% of the final body weight but the brain will be already about 70% of that of a young adult. By 2 years of age the brain will be about 77% of its final weight while the body is about 20% of the adult level [4]. It is clear that the very rapid growth rate of the human brain in the last third of pregnancy, and the first 2 years of life, inevitably places great demands on the diet to provide the basis for healthy growth. In fact, the brain is susceptible to nutritional influences from the earliest stages of pregnancy. Brain development begins with the forming and closure of the neural tube that in turn develops from the neural plate, a process that is complete from 21 to 28 days after conception.

Although there is very rapid growth in the early months of life it has become clear that later stages are also important, raising the possibility that nutritional status at these times may be influential. Based on the examination of head circumference, cortical thickness, degree of neuronal branching and the EEG profile, peaks of brain growth have been found around 7, 12 and 15 years of age [5]. You can speculate that at these times of rapid change there are great demands placed on the diet to provide the nutrition required for brain development although it is more difficult to demonstrate a nutritional influence over a prolonged period and it is likely to interact with the psychological and social environment.

2.2 Protein/calorie malnutrition

Studies of children suffering with protein/calorie malnutrition have tended to conclude that both short- and long-term cognitive and behavioural problems result from gross malnutrition. When protein and energy supplementation began before 2 years of age, the period during which the brain is rapidly growing, it has been found consistently to be beneficial. In contrast, when grossly malnourished children were given supplements beginning after 2 years of age there was little or no long-term influence [6]. Malnutrition in the first year of life has a lasting effect on both behaviour and cognition. Both motor control and language develop more slowly and both intelligence scores and school performance are poorer. However, protein–energy malnutrition in addition to these global deficits is responsible for more specific damage to the hippocampus and cortex [7].

It is impossible in such studies to establish the relative roles of energy, protein and the micronutrients that are certain to be deficient. Given the gross nature of these types of nutritional deficiency it is not surprising that the consequent problems of cognition tend to be of a global rather than specific nature. As an example 60% of children who

were malnourished in the first year of life, but not later, had problems of attention in later life, something true of only 15% of well-fed controls [8]. Early malnutrition was also associated with a higher incidence of aggressive behaviour when the children were observed when aged 9–15 years [9].

2.3 Diet and brain development in industrialized countries

Although it is accepted that in developing countries malnutrition can adversely influence brain development, is it reasonable to expect similar phenomena in industrialized countries? In world terms, the nutrition of those in industrialized countries can be viewed as adequate if not good, with obesity a greater concern than starvation. Is there evidence that minor differences in diet can have a long-term influence on brain development? Although the details are uncertain there are suggestions that even in western countries subtle differences in nutrition can be influential.

Alan Lucas was responsible for a unique project that to date, in an industrialized country, is the only long-term randomized double-blind trial of the impact of diet on cognitive development. The study took advantage of the fact that babies born premature are placed in an incubator and fed initially by nasogastric tube [10]. For a median of 4 wk, premature infants were randomly allocated to a traditional cows-milk-based formula or one that provided 17.6% *per* more energy and was enriched with 27.5% more protein, higher levels of sodium, calcium, phosphorus, copper, zinc, vitamins D, E and K in addition to a range of water-soluble vitamins, carnitine and taurine.

By 18 months, the consumption of the enriched formula was associated with more advanced social and psycho-motor development. When tested again at 8 years of age boys, but not the girls, had significantly higher intelligence scores [11]. At 16 years of age, structural magnetic resonance imaging was used to study brain structure [12]. In the boys who had received the enriched formula in infancy, although the overall size of the brain was similar, the volume of the caudate nucleus was larger and verbal intelligence was greater than if the standard formula had been consumed.

Such findings can be viewed as good evidence that differences in diet for a short period during a key development stage can have long-term consequences for both brain structure and cognition. It should, however, be recalled that the Lucas study used preterm infants whose brains were at an earlier stage of development than term babies and hence may have been more sensitive to nutrition during a critical phase. It cannot be assumed that similar findings would be observed in older children. In addition, the study provides little indication of the optimal diet, even for preterm infants. The enriched formula was little more than a best guess and involved changes in many aspects of nutrition, any or all of which may be influential. It is unclear which of the nutrients were important and in what dose. It would be optimistic to assume that the optimal formula had been created in the first of this type of study. As the formula used predated an interest in PUFA, they were not part of the supplement. The potential roles of PUFA are discussed elsewhere in this issue. However, the positive response to the enriched formula gives the message that when looking for evidence of dietary influences we should be considering more than fatty acids. It is tempting to speculate that if PUFAs had been added to the enriched formula they may have further added to the positive outcome.

2.4 Specific nutrients

Apart from the adverse effect of a grossly inadequate diet more specific effects have been proposed. After reviewing the influence of nutrition on brain development Georgieff [7] concluded that some nutrients are more influential than others including protein, energy, certain fats, iron, zinc, copper, iodine, selenium, vitamin A, choline and folate. Some of the most influential examples are therefore considered.

2.4.1 Iodine

Iodine is a clear example of a nutrient that, if deficient during a critical period of brain development, has long-term adverse consequences. In fact, Delange [13] described iodine deficiency as ''the world's greatest single cause of preventable brain damage and mental retardation''. A meta-analysis found that iodine deficiency results at a population level in a loss of 13 IQ points [14]. It is inevitable that such a deficiency has serious implications for the schooling of the individual and the economic development of the country. In 1990, nearly 30% of the world's population were said to be at risk of iodine deficiency, a problem that can be addressed by the iodization of salt [13]. Three levels of iodine deficiency have been distinguished based on daily intake: mild (50–99 μg/day); moderate (20–49 μg/day); severe (<20 μg/day). It is suggested that in most European countries there is some mild-to-moderate iodine deficiency [15]. A review concluded that although ''most women in Europe are iodine deficient during pregnancy, less than 50% receive supplementation with iodine'' and that in ''most European countries, pregnant women and women planning a pregnancy should receive an iodine-containing supplement (approximately 150 μg/d)'' [16]. Zimmermann [17] commented that the long-term implications of a mild iodine deficiency during pregnancy are unclear as they have not been examined.

A role in the synthesis of thyroid hormones is the only confirmed function played by iodine, an important role as thyroid hormones influence the metabolism of all cells and play a particularly important role in the growth of most organs, including the brain. When considering iodine status pregnant mothers and their offspring are particularly important because of the risk of brain damage. Even with

mild iodine deficiency the levels of Thyroid Stimulating Hormone increase (an indication of iodine deficiency), particularly in the newborn. There is, however, little evidence that cognitive functioning is adversely affected although there is an isolated report that when Italian children in an area of mild iodine deficiency (urinary iodine excretion 64 μg I/day) were compared with controls (142 μg I/day), reaction times were slower in the group who lacked iodine [18]. Cross-sectional studies of mothers with a mild-to-moderate deficiency have repeatedly reported that the intellectual functioning and motor skills of the offspring were impaired, although it is difficult to exclude the impact of confounding factors [19]. In such groups there have been no controlled intervention studies that have examined the influence of the supplementation of the mother on the child's cognitive outcome.

A severe deficiency during the critical period of brain development that occurs during the end of the first trimester and the early part of the second trimester of gestation is associated with a mild-to-severe impairment of both physical and mental growth. During this critical period of development, a deficiency of iodine and/or thyroid hormone will result in irreversible brain damage. Cretinism is defined by severe, irreversible alterations in brain development resulting in mental retardation and neurological signs including deaf mutism and motor rigidity [13]. As many as 15% of those with severe iodine deficiency will develop cretinism although even in those who are apparently normal severe iodine deficiency has been found to be associated with a loss of 10–15 IQ points [20].

In humans, thyroid hormone is found in the coelomic fluid from the sixth week of gestation: as this is a long time before it is produced by the foetus it must be of maternal origin, illustrating the importance of the iodine content of the mother's diet. The number of receptors in the brain, and the amount of thyroid hormones bound to them, increase 500-fold between 10 and 18 wk of pregnancy. As this occurs before the foetus is able to produce iodine-dependent hormones, the importance of maternal nutrition is again indicated [21].

Although the evidence behind such claims is less substantial, it has been suggested that even later in life a reduction in circulating thyroxine may result in impaired mental functioning. For example, in rural Albania the iodine supplementation of 10 to 12 year-old children, who were moderately iodine-deficient, resulted in improved information processing, fine motor skills, and visual problem solving [22]. A review concluded that the iodine supplementation of moderately iodine-deficient school children ''improves cognitive and motor function'' [17].

2.4.2 Iron

The World Health Organization Database on Anaemia estimates that globally about 25% of the world's population has anaemia although it afflicts 47.4% of preschool children. In younger children, the rates were greater in Africa (67.6%) and South-East Asia (65.5%). Globally, anaemia was found to occur in 25.4% of school-age children. Although it is a greater problem in developing countries, it is also well established in industrialized countries that iron deficiency occurs commonly. For example, a British survey found 3% of boys and 8% of girls, aged 4–6 years, had blood haemoglobin levels below 11.0 g/dL, the World Health Organization definition of anaemia. Similarly, in American children 8% of those between 9 and 30 months were anaemic, while another 7% were iron deficit [23]. These findings raise concerns as iron deficiency is known to adversely influence cognition. In a range of case–control studies, where infants with iron-deficiency anaemia were contrasted with those with adequate levels of iron, the mental development scores were significantly lower [24]. Iron-deficiency anaemia is associated with the child being unhappy, more wary and staying closer to the mother. A causal role for the influence of iron status in industrialized countries was illustrated by an examination of an English sample of 18-month-old inner-city children [25]. Those who received iron supplements for 2 months in a double-blind trial had an increased rate of weight gain and achieved more than the expected psychomotor development.

The influence of iron deficiency has been reviewed on several occasions leading to very similar conclusions [26–29]. The timing of iron deficiency is critical: Beard [29] concluded that if it occurred during the first 6 or 12 months of life the adverse effects were likely to persist, even if iron intake subsequently achieved recommended levels. A study in Florida is a rare example of a long-term follow up of early iron deficiency [30]. In a population-based sample haemoglobin levels in infancy were related to learning difficulties, and the need for special education, at 10 years of age. The likelihood of mild or moderate learning difficulties at age 10 increased with a history of anaemia in infancy, something true irrespective of a range of potentially confounding variables.

In contrast although iron deficiency has adverse effects in older children, resulting in problems of sustaining attention and lower affect, it can be reversed by a subsequently adequate supply [28].

At least some of the underlying mechanisms that are associated with an early iron deficiency are beginning to be understood. They include decreased myelination, changes in dopamine metabolism in the striatum and alterations in the energy metabolism of the hippocampus, an area of the brain important for memory [31]. For example, a study compared the offspring of pregnant rats that ate a diet that either did or did not contain sufficient iron, although after birth a diet sufficient in iron was consumed by the pups. In later life there was less myelination of subcortical white matter and the fimbria of the hippocampus in rats that were iron deficient before birth [32].

2.4.3 Zinc

It has been estimated that 20% of the world population are zinc deficient [33], a worrying statistic as in non-human animals a deficiency of zinc during lactation, or while in the womb, results in cognitive impairment that is not reversed by a subsequently adequate intake [34]. Zinc deficiency slows growth as it is involved in the activity of over 200 enzymes, in particular those associated with the synthesis of RNA and DNA. More specifically zinc is found in high levels in the brain where it plays both structural and functional roles [34]. At a physiological level there is increasing evidence that zinc is involved in the development of NMDA receptors, sites at which glutamate acts as a neurotransmitter, particularly in the hippocampus [35]. A meta-analysis of a series of studies involving in total 9000 mothers and their offspring [36] suggested that there may be a problem in humans. Supplementation with zinc resulted in a 14% reduction in preterm births although the number of low birth weights was not reduced. Importantly, the studies came from both developing and industrialized countries although the reduction in preterm births occurred mainly in women with low income. This review did not, however, find other benefits when various indices of the outcome of pregnancy were examined, although the reduction in the number of preterm births suggested the potential for longer-term consequences for cognitive development although these were not examined.

In fact, although the literature is limited, in humans in a similar manner to animals there are suggestions that the influence of zinc is greater at an early stage. It has been proposed in particular that preterm infants benefit from zinc supplementation [37]. When a Canadian sample of low birth-weight babies consumed a formula with or without added zinc, quicker growth and better motor development was associated with the consumption of additional zinc [38]. Yet there is some evidence that zinc supplementation has an influence on older children. Again in Canada, when zinc was given for a year to boys aged 5–7 years there was no influence on attention span, although a small group with initially low levels of zinc in their hair grew at a faster rate [39]. The first report that zinc supplementation could improve cognitive functioning beyond infancy was based on Chinese children aged 6–9 years [40]. However, an important finding was that a combination of zinc with other micronutrients had a greater influence on growth rate than when zinc was administered by itself. A meta-analysis of the study of the physical growth of children up to 13 years of age found that zinc supplementation had a significant yet small influence [41], again raising the possibility that there may be an as yet largely unconsidered influence on cognitive development.

There are isolated suggestions that zinc status may be associated with problem behaviour. In an American sample elevated levels of copper and lower levels of zinc in the blood were both associated with a history of aggression [42]. In animals the consumption of a zinc-deficient diet during gestation resulted in a more aggressive adult [43]. In addition various cross-sectional studies have found a lower zinc status in children who had Attention Deficit Hyperactivity Disorder [44] and low serum zinc levels have been found to be related to ratings of inattention [45]. It is, however, unclear whether differences in diet predated the behavioural problem or whether changes in behaviour resulted in changes in what was eaten. There is a need for intervention trials to establish causality although zinc sulphate has been reported to reduce symptoms either by itself [46] or as an adjunct to methylphenidate [47].

In summary, although it is agreed that zinc plays essential developmental roles both before and after birth, its role in the brain is poorly understood. However, irrespective of the underlying mechanism a review concluded that although there was no clear consensus, there was some evidence that zinc deficiency decreased cognitive and motor functioning. In particular, research was needed that considered the impact of zinc deficiency at different developmental stages and that the interaction with other micronutrient deficiencies needed to be examined [48].

2.4.4 Folic acid

A summary of the area concluded that folate is of fundamental importance for brain development, effects that probably reflect an influence on nucleotide synthesis, DNA integrity and transcription [49]. It is generally accepted that the taking of a folic acid supplement around the time of conception will decrease the incidence of neural tube defects [50]. As folate is involved in cell division its presence reduces the chances of disorders such as spina bifida. However, as it is a minority of women who take folic acid supplements, since 1998 in both Canada and the United States food has been fortified with folic acid. Although the incidence of neural tube defects fell after fortification, the question arose as to whether the fortified diet produced sufficient folate to prevent all neural tube defects. Relevant to this issue, it was found that after fortification the use of folic acid supplements no longer decreased the incidence of such defects, suggesting that the American diet now provides sufficient of the vitamin [51].

Although the data are more limited, there are suggestions that an adequate supply of folate is also important for growth at later stages, as supplementation during pregnancy was reported to decrease the incidence of premature birth [52]. Gross [53] found that infants born to mothers with severe folate deficiency during pregnancy showed abnormal or delayed development. Folic acid supplementation has been found to increase birth weight and developmental status [54]. In contrast, Tamura [55] found that the neuropsychological development of 5-year-old children was not associated with the folate status of the mother in the second half of pregnancy. They suggested that the most likely

explanation of the discrepancy with other findings was that their classification of low-folate status relied on biochemical measures rather than clinical signs such as megablastic anaemia.

2.4.5 Vitamin B_{12}

Folate and vitamin B_{12} are metabolically associated, so that a deficiency of one may influence the functioning of the other. If the mother is well supplied with vitamin B_{12} the infant is born with a supply sufficient for several months [56]. Although the evidence mainly relies on case studies, vitamin B_{12} deficiency results in infants who are apathetic, irritable and generally fail to thrive, although they respond quickly to supplementation [57]. Biologically, the deficiency ''may involve delayed myelination or demyelination of nerves; alteration in the *S*-adenosylmethionine:*S*-adenosylhomocysteine ratio; imbalance of neurotrophic and neurotoxic cytokines; and/or accumulation of lactate in brain cells'' [57].

As an example a breast-fed child of a vegetarian mother displayed ''neurological deterioration that commenced between 3 and 6 months of age, and progressed to a comatose premoribund state by the age of 9 months'' [58]. The infant had megaloblastic anaemia and a severe vitamin B_{12} deficiency. Although a problem with case studies is that there may be a deficiency of other micronutrients, the rapid response to supplementation suggests that in this instance a lack of vitamin B_{12} was the mechanism.

It appears that vitamin B_{12} deficiency during infancy has lasting consequences. When children were examined who up to the age of 6 had a marginal vitamin B_{12} status associated with eating a vegen diet, measures of fluid intelligence were still poorer in adolescence although subsequently they had eaten an omnivorous or vegetarian diet [59].

In most cases, a low vitamin B_{12} status in childhood reflects either a maternal dietary deficiency that often reflects a strict vegen diet, or alternatively a problem of absorption. Although adults tend to have more than a years reserve of vitamin B_{12} the newborn has only a limited supply. For example, there is a report of a 14-month boy with severe dietary vitamin B_{12} deficiency that resulted from the vegan diet of the mother. Magnetic resonance imaging showed severe atropy of the frontal and fronto-parietal lobes that responded, over 6 wk, to vitamin B_{12} supplementation [60]. Although imaging had demonstrated a positive response to supplementation in terms of gross changes in brain structure, when cognitive development was assessed at the age of 2 it remained seriously retarded. An obvious question, that has not been systematically addressed, is to consider the impact on the development of the child of a low maternal vitamin B_{12} status during either pregnancy or lactation [61].

Black [56] considered two mechanisms by which folate and vitamin B_{12} deficiency could influence the brain: by disrupting myelination or influencing the inflammatory process. She stressed the need to establish the relationship between the timing of a deficiency and an outcome such as cognitive or social development. One important role of vitamin B_{12} in the nervous system is in the fatty acid metabolism required for the maintenance of the myelin sheath that surrounds the axon. A long-term deficiency can result in irreversible brain damage. As an illustration a 14-month-old child presented with megaloblastic anaemia due to the low intake of vitamin B_{12} of the vegetarian mother [62]. A brain scan revealed ''severe brain atrophy with signs of retarded myelination; the frontal and temporal lobes being most severely affected''. The child responded well to supplementation both in terms of clinical symptoms and brain imaging. Given that myelination influences the speed of nerve impulses it is reasonable to expect that a lack of myelination will have consequences for cognitive development.

2.4.6 Vitamin D

Exposure to sunlight, resulting in the production of Vitamin D_3 (cholecalciferol) by the skin, is the major source of this micronutrient. Although it is found in a few foods such as oily fish, milk and some fortified cereals, for most people ultra-violet light acting on the skin results in the greatest source of vitamin D_3. Although traditionally attention has focused on the role played by vitamin D in calcium regulation and hence bone health, more recently it has become apparent that it has a range of other functions, including the regulation of both cell growth and differentiation, and the functioning of the immune system.

In a wide-ranging review, McCann and Ames [63] examined the considerable literature on the role of vitamin D in brain development. Various approaches including messenger RNA expression studies, autoradiography and immunohistology have indicated areas of the brain, including the hippocampus, as sites at which vitamin D acts. Such data are consistent with the suggestion that vitamin D influences proteins involved in ''learning and memory, motor control, and possibly even maternal and social behavior'' [63]. For example, the presence of vitamin D receptors was demonstrated in the hippocampus, sites capable of binding to DNA [64].

Rats born to vitamin D_3-deficient mothers were found to have a profoundly altered brain structure: the cortex was longer but not wider and the lateral ventricles were enlarged. There were reduced levels of ''nerve growth factor and glial cell line-derived neurotrophic factor and reduced expression of p75(NTR), the low-affinity neurotrophin receptor'' [65]. Such findings suggest that vitamin D_3 plays an important role during brain development. However, it remains to be seen if there is a clinical relevance for these findings in humans. It is surprising that as a low vitamin D status occurs frequently in pregnant women and infants it is a topic that has not received much consideration.

McCann and Ames [63] concluded that although there is ample biological evidence to suggest an important role for vitamin D in the brain's development and functioning, the effects are subtle and to date a causal relationship has not been fully established. However, after acknowledging that we do not fully understand the role played by vitamin D they argued for the supplementation of at-risk groups, for example nursing infants.

2.4.7 Choline

Although choline can be manufactured in the body, it is suggested that the amounts produced in this way may be insufficient so that an additional dietary source may be required. Choline has three major functions: it is a precursor for the neurotransmitter acetylcholine; it is a constituent of phospholipids that have a role in cell membranes; choline can also be converted into the methyl donor betaine.

During pregnancy choline is known to play a critical developmental role as it influences stem cell proliferation and apoptosis and thus the structure of the brain [66]. In addition, the higher levels of choline in the plasma of neonates suggest an important developmental function [67].

In adult rodents memory was better if towards the end of gestation they had been exposed to choline. If at this critical stage of brain development there had been a deficiency of choline memory was poorer when adult [68]. A systematic review of the animal literature, that related choline availability during gestation to subsequent neurological functioning, concluded that: ''choline supplementation during development results in improved performance of offspring in cognitive or behavioral tests'' [69]. Studies on animals suggest that choline influences the development of the hippocampus. The animal data have been described as ''compelling'' although we await relevant human data [70].

Although it is accepted that choline plays a role in brain development, the evidence is lacking that the level of intake influences the development of the human foetus. Relevant information comes from studies in which infant formulae were compared in which additional choline was and was not provided. A review of the topic failed to find evidence that adding choline helped cognitive development [67].

3 Short-term influences of diet on brain functioning

Although a deficiency during a critical stage in development may have a lasting impact on the brain, a generalization is that poor nutrition in later life will also have negative consequences although they may be reversed by a subsequently adequate diet. When the early stages of brain development have passed variations in diet still have the potential to influence behaviour.

3.1 Multivitamins and minerals

Although the traditional reductionist scientific approach has tended to consider one micronutrient in isolation there are reasons to take a broader approach. First, an exclusive deficiency of one nutrient will occur rarely, perhaps only when the local soil lacks a particular nutrient leading to a precise problem in an otherwise adequate diet. More often deficiencies will result from a generally poor diet with a consequent deficiency of several nutrients. Second, nutrients do not act in isolation: rather they have a role in a complex sequence of events, many of which require the provision of other micronutrients. As such the replacement of a single nutrient, even though there is a deficiency, may not be beneficial if it helps only one step in a sequence. The bottleneck may be simply moved on to the next metabolic stage that is inhibited by the deficiency of another nutrient.

A test of this suggestion was offered by SUMMIT [71] that in Indonesia gave mothers either a multimicronutrient supplement, or a combination of iron and folic acid, in a well conducted trial that involved 31 290 pregnant women. In those taking a range of micronutrients, rather than only iron and folic acid, there was an 18% greater reduction in child death and 14% fewer children with a low birth weight. Similarly in a Chinese study, preschool children were supplemented with vitamin A alone, vitamin A plus iron, or vitamin A with iron and six other micronutrients [72]. Although all three groups received vitamin A supplements, it was the sample who in addition received a range of micronutrients whose serum levels of retinol increased the most, although the levels of haemoglobin increased similarly in the three groups.

The suggestion that the multivitamin and mineral approach will be beneficial in terms of cognitive functioning was supported by a study in India. For a year, children aged 7–11 years ate school meals supplemented with chelated ferrous sulphate, vitamins A, B_2, B_6, B_{12}, folic acid, niacin, calcium pantothenate, vitamin C, vitamin E, lysine and calcium, and the performance on various tests was compared with a sample who did not eat meals prepared at school. The only biological measures reported related to iron status that improved in the experimental group whereas in the control group it declined. The performance on tests of memory and attention improved in those consuming the supplements although an overall measure of intelligence was not influenced [73]. Similarly in a double-blind trial, micronutrient supplements were given to Indian children aged 6–15 years from a middle class background [74]. Over a 14-month period supplementation improved attention but not intelligence, memory or school achievement.

3.2 Micronutrient supplementation in industrialized countries

Although a beneficial response to supplementation might be expected in developing countries it is more controversial

to suggest that it is needed in industrialized countries. Particularly as in large-scale trials micronutrient supplements have not been found to decrease age-related disease [75], some have drawn the conclusion that if the diet provides sufficient protein and calories then micronutrient intake will be adequate. It has, however, been argued that problems with psychological variables will often be the first to develop if there are sub-clinical deficiencies of micronutrients. In addition, changes in psychological functioning will be more rapid and hence more convenient to monitor than the development of disease [76]. For example, in a double-blind trial thiamine supplementation was found to improve mood, although as judged by the usual physiological index of bodily status, erythrocyte transketolase activation, the population was well nourished prior to supplementation [77].

The predicted susceptibility to minor changes in micronutrient status was suggested to reflect a high metabolic rate and the complexity of the brain's functioning; such that a behavioural output is the summated outcome of millions of metabolic processes, each of which may potentially depend on micronutrient status. It was suggested that even small improvements in micronutrient status, if they result in a large number of minor changes in metabolic efficiency, could have a cumulative effect. If such mechanisms exist then the complexity of the brain means that it should be the easiest organ in which to demonstrate a benefit from supplementation. At least in principle the almost instantaneous output of the brain will be easier to monitor than the slow progression of disease that may reflect nutritional status over many decades. There are two paradigms in which in industrialized societies psychological measures have been found to respond to multivitamin/mineral supplementation.

A great deal of controversy was generated by the report in 1988 that, in a randomized double-blind placebo-controlled study, the intelligence of children increased after taking a multivitamin/mineral supplement for 8 months [78]. The active supplement provided vitamins A, B_1, B_2, B_6, B_{12}, C, D, E, K, biotin, folic acid, pantothenic acid, calcium, chromium, copper, iodine, iron, magnesium, manganese, molybdenum, phosphorus, selenium and zinc. When 10 years later the topic was reviewed, 10 out of 13 studies had reported a positive response to supplementation although on occasions only in sub-groups [79].

Importantly, when the response had been found it was always with non-verbal measures of intelligence and never with verbally based tests. Two types of intelligence can be distinguished. Fluid intelligence can be assessed using non-verbal tests and is viewed as innate biological potential; that is basic reasoning ability. In contrast, crystallized intelligence can be assessed using verbal measures as it depends on specific information and vocabulary. Over a longer period, if the biological potential interacts with a stimulating environment an increase in crystallized intelligence will result. As a micronutrient supplement can only influence basic biology, and cannot of itself improve your vocabulary, the selective improvement in non-verbal intelligence suggested that this was a genuine phenomenon [79].

More recently, children in Australia and Indonesia were given multivitamin/mineral supplements, or omega-3 fatty acids, or both [80]. In Indonesian girls, and children of both sexes in Australia, micronutrient supplementation resulted in improved verbal learning, although neither general intelligence nor attention was influenced. Given the attention that omega-3 fatty acids have attracted it is interesting that they did not improve test performance (docosahexaenoic acid 88 mg/day and eicosapentaenoic acid 22 mg/day). It is also interesting that the findings were again found in apparently well-nourished Australian children.

Although the increasing number of positive findings in well-designed trials make the phenomenon difficult to ignore, with the limited data available there is little that can be concluded. The data suggest that it is a minority of children who respond, such that the comment that a poor diet is detrimental is a better summary than vitamins increase intelligence. For example children in Belgium kept a diet diary for 15 days [81]. It was those whose diets offered a low intake of a range of micronutrients that responded to supplementation, a minority of children who tended to come from less economically privileged areas and from schools for the less academically able.

The second area where there is evidence that a multivitamin/mineral supplement is beneficial is anti-social behaviour [82]. In a particularly well-designed study micronutrient supplementation improved the disciplinary record of young offenders [83]. As fatty acids, vitamins and minerals were provided it is unclear from this study which aspects of nutrition were influential as fatty acids by themselves have been shown to decrease aggressive behaviour [82]. However, multivitamin/mineral supplementation, without fatty acids, has also been reported to decrease aggressive behaviour. When a vitamin/mineral supplement (without fatty acids) was consumed under double-blind conditions the incidence of violence displayed by imprisoned juveniles decreased [84]. There was an association between an increased vitamin status, as judged by blood samples, and a decline in violence. It was suggested that an improved vitamin status indicated that it had been initially poor. The Dutch government responded to the British findings [83] by initiating their own study in collaboration with Radboud University in Nijmegen. For between 1 and 3 months, 116 young prisoners received micronutrient supplements while 105 received placebos. Although the study has not as yet been formally published, the Dutch Government has released the findings: those consuming the supplements were less aggressive. In those receiving the supplements the incidence of violence decreased by 34% although taking the placebo was associated with a 13% increase.

It is important that such findings have been also found outside of a prison. In a double-blind trial, the impact of

micronutrient supplementation (without fatty acids) was studied in school children, where violent and non-violent delinquency was monitored using school disciplinary records [85]. Over a 4-month period those who received supplements were less likely to be disciplined.

Thus, the study of measures of intelligence and aggressive behaviour has both provided a series of double-blind placebo-controlled trails in which multivitamins and minerals, with or without fatty acids, have been found to improve functioning. There are five well-designed studies that report a decrease in anti-social behaviour after consuming vitamin/mineral supplements. With the measures of intelligence, Benton [82] concluded that the topic was at an early stage and there was a need for large-scale trials that considered the composition of the supplement, the dietary styles of the children and the nature of the influence on cognition. Which of the nutrients in the multivitamin/mineral supplements were important, and at what dose, are questions that have not been addressed.

In conclusion, it is far too early to recommend specific changes in the diet of children. However, the increasing number of positive findings from well-controlled trials indicates that there are phenomena that should be systematically examined.

3.3 The timing and composition of meals

The energy required for brain functioning is also supplied by what we eat. Although received wisdom is that homeostatic mechanisms usually maintain blood glucose levels in the range that is needed for brain functioning [2], there is an increasing number of reports that the patterning of meals and their nutritional composition are influential.

The brain is the most metabolically active organ in the body and in the adult, whereas it represents about 2% of body weight, it is responsible for about 20% of basal metabolic rate. It is surprising that compared to other organs in the body the brain has very limited energy stores, yet it cannot decrease its requirements when supplies are low. The stores of glucose are limited, such that it is suggested that without replacement they will last about 10 min, although unless you have starved, or have eaten a diet devoid of carbohydrate for several days, the brain does not metabolize ketones [2]. The hormonal mechanisms that attempt to maintain blood glucose values within prescribed levels are suggested to be the result of evolutionary pressures that lead to the provision of a relatively constant supply of glucose to the brain. The existence of these homeostatic mechanisms can be used to argue that under most normal conditions the food consumed would not be expected to influence cognition. There are, however, reports that there are short-term reactions to the composition of meals, although it is not certain that the mechanism is the provision of glucose.

There are reasons for suggesting that children, rather than adults, may be more susceptible to the provision of glucose. When related to the size of the body, children have larger brains than adults, a reflection of rapid brain growth in the peri-natal period. In addition a given weight of brain tissue from a child uses more glucose than if it had come from an adult [86]. The use of glucose, *per* gram of brain tissue, increases up to 4 years where it requires twice as much energy as an adult [87]. A high rate of glucose utilization continues until about 9 or 10 years of age when it begins to decline, reaching the levels of an adult in the late teenage years. As a child's brain is both relatively bigger and more active than an adult's the possibility arises that they may be more dependent on regular meals. The possibility that the rate at which glucose is released into the blood may influence the functioning of children is supported by studies in which the effect of a glucose-containing drink has been examined. In the afternoon 9- to 11-year-old children had better memories and in class spent more time on task after a glucose drink rather than a placebo [88]. Similarly towards the end of the school day 7-year olds had an increased ability to sustain attention and were less likely to become frustrated after a glucose drink [89].

There has been a particular interest in the effect of breakfast on the behaviour of children. After reviewing the topic, Pollitt and Mathews [90] concluded that the ''data suggest that omitting breakfast interferes with cognition and learning, an effect that is more pronounced in nutritionally at-risk children than in well-nourished children''. For example the eating of breakfast rather than fasting improved the cognitive performance of 9–11-year-olds 1 h after the meal [91]. The ability to sustain attention was better an hour after eating breakfast in boys aged 9–12 years, although memory was unaffected [92]. However, in 12-year olds, half an hour after the meal but not later, eating breakfast cereal rather than fasting improved memory [93]. The impression from these early studies was that the benefits were short term, although more recently attention has been directed to the composition of the meal in an attempt to establish a meal that offers a longer-term improvement.

In young adults when breakfasts were compared that differed in the type of carbohydrate provided, if glucose was released more slowly memory was better in the late morning. [94]. Similarly when breakfasts of different macronutrient compositions were compared, better memory was associated with better glucose tolerance and the consumption of meals that more slowly released glucose into the blood [95, 96]. Similar findings have been reported in children. When iso-caloric meals that were designed to differ in their glycaemic load were consumed on different days, memory, attention and the time on task in the classroom were better when breakfast slowly released glucose [97]. Similarly, when the effects of breakfast cereals that differed in their glycaemic response were compared, 2 h after eating a low rather than high glycaemic load the former was associated with better attention [98].

One way of viewing these findings is that the cognitive functioning of a child benefits from a gradual release of energy. Consistent with this view is a study that related the

size of a child's breakfast, and whether a snack was subsequently eaten, to cognitive functioning [99]. The eating of a small breakfast, on average 61 kcal, was associated with spending less time performing schoolwork. However, in these 9-year olds the negative effects of a small breakfast were overcome by eating a mid-morning snack. In those who had eaten a larger breakfast the snack was without effect. Similarly in 7- to 9-year-old Indian children iso-caloric diets were consumed that differed depending on when during the morning the energy was consumed. A snack mid-morning improved memory in those from lower but not higher socio-economic backgrounds [100].

4 Discussion

Thus there is good evidence that a range of nutrients play important roles in brain development including iodine, iron, zinc, choline, vitamin B_{12}, folate and vitamin D. Zeisel [101] suggested that an examination of these nutrients will help us to identify other nutrients that are similarly important: that is those essential for cell division; those whose level of intake varies greatly between individuals and for which there is no, or at the most a limited capacity for biosynthesis.

There is ample evidence in developing countries that a nutritional deficiency during critical periods of brain development has a lasting impact on intellectual development [13, 30]. It is an immense problem with clear implications both for the individual and the economic prosperity of entire countries. The World Health Organization [102] listed deficiencies of iron, zinc and vitamin A among the top ten leading causes of death in developing countries. Even if those who are deficient do not display clinical symptoms their physical and cognitive development are likely to be impaired. The World Bank [103] considers fortification to be the most cost-effective way of dealing with these micronutrient deficiencies as no other ''technology available today offers as large an opportunity to improve lives and accelerate development at such low cost and in such a short time''. Fortification can take one of the three approaches. First, it can replace a nutrient that has been lost during food processing, for example the B-vitamins that are lost during milling. Second, the level of a nutrient can be raised above the level normally found in the food, for example adding additional calcium to milk. Third, nutrients that are not normally present can be added, such as the addition of iodine to salt. There are many examples of fortification throughout the developing world: for example, iodine is added to salt in three-quarters of developing countries with positive consequences for cognitive development. South Africa has developed a National Food Fortification Program of wheat, maize flour and sugar to which calcium, iron, zinc, vitamins A, B_1, B_2, B_3, B_6 and folate are added.

Although without any doubt food fortification has resulted in cost-effective widespread benefits, ideally the ultimate goal should be to provide an adequate supply of whole foods in their natural state. Whole foods contain many nutrients, many of which act synergistically: there is also the possibility that there are nutrients in natural foods that have not as yet been discovered.

There is less evidence in industrialized countries that micronutrient deficiencies have developmental consequences. Briefel *et al.* [104] considered the impact of using dietary supplements on the diet of American infants under 2 years of age. They concluded that in general infants can achieve a recommended level of intake from food alone. With most nutrients the incidence of an inadequate intake was at the most 2% of the sample although a low intake of vitamin E occurred more commonly. However, intakes above the ''Tolerable Upper Intake Level'' were found in both those taking and not taking a supplement; ''for vitamin A (97 and 15% of toddlers) and zinc (60 and 59% of older infants and 68 and 38% of toddlers) as well as for folate among supplement users (18% of toddlers)''. Such conclusions need to take into account that the standard against which nutritional adequacy is judged is defined by a ''particular indicator'': never are these indicators measures of cognitive functioning.

It is received wisdom that those planning to become pregnant should take a folic acid supplement to decrease the risk of neural tube defects. Potentially any micronutrient deficiency may be exacerbated during pregnancy making more general studies of supplementation with vitamins and minerals of interest. Relying on research mainly in developing countries a Cochrane review contrasted multimicronutrient supplementation during pregnancy with the consumption of two or fewer nutrients [105]. The taking of a multimicronutrient supplementation was associated with fewer low birth-weight babies and a lower incidence of maternal anaemia. However, these differences disappeared when a multimicronutrient supplementation was contrasted with a supplementation of iron and folic acid. These data reinforce the known importance of both iron and folate but did not suggest a general importance of other nutrients. Although this review did not consider the influence of supplementation during pregnancy on cognitive development the reported influence on birth weight may be significant. Consistently in industrialized countries higher birth weight has been related subsequently to better cognitive development [106–109]: a relationship that extends into the range of normal birth weights as it is not only a phenomenon associated with small premature babies. It is therefore important to establish factors that influence birth weight, with the hope that it can be increased with benefits for cognitive development. The adequacy of the nutrition of the pregnant mother is an obvious place to start. It is, however, important to keep these mechanisms in perspective as in industrialized countries the effects of normal birth weight are small relative to the influence of post-natal social factors [109]. However, the well-controlled study of Lucas [10–12] gives strong evidence that the nature of the diet of at least premature children can have a lasting influence on

cognitive functioning, although we await details of the active ingredients. At the very least these findings suggest the importance of the maternal diet during the later stages of pregnancy.

In industrialized countries, the evidence at present precludes making specific public health recommendations in the context of nutrition and cognitive functioning. Infants are recommended to take supplements of vitamins A, C and D by the United Kingdom Department of Health although this reflects more general developmental concerns: vitamin A will help vision and the skin, vitamin C is needed for bone growth and vitamin D for bones, teeth and general growth. As childhood advances, conventional wisdom has been that a balanced diet will supply sufficient micronutrients. The findings that multivitamin/mineral supplementation improves both behaviour [83–85] and intelligence scores [78–81] begin to question this assumption, although this is a controversial suggestion that requires the clarity that will only come from additional systematic study. It should be recalled that the government bodies that have drawn up the recommended dietary intakes of micronutrients have never used the achieving of optimal psychological functioning as a measure of adequate nutrition. Hence, the resulting recommended intakes may or may not allow the brain to function optimally; we simply do not know.

In summary, in developing countries there is overwhelming evidence that the adequacy of diet, particularly while the brain is rapidly growing, has significant and lasting implications for cognitive functioning. In contrast in industrialized countries there is little that we can conclude with confidence, although there is a series of well-designed studies that at least establish the principle that relatively minor differences in the diet have the potential to be influential.

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