Original Article

Will feeding mothers prevent the Asian metabolic syndrome epidemic?

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Evolutionary pressures have probably amplified the mechanisms for minimizing the impact of environmental factors through compensatory maternal mechanisms. Nevertheless, experimentally there are clear long-term programming effects of manipulations to the maternal diet on the likelihood of neural-tube defects associated with folate deficiency The fat/lean ratios of the newborn, and subsequent development, seem to be linked to amino acid or folate supply. An altered balance in the hypothalamic–pituitary–adrenal axis, which experimentally has profound effects on brain development, is induced by low-protein maternal diets. Such diets are linked to a reduced pancreatic capacity for insulin production and to an altered hepatic architecture, with a change in the control of glucose metabolism. Human studies suggest that what happens in pregnancy is modified by the child's diet in the first months of life. Low birthweight is linked to early stunting, and predisposes to abdominal obesity and metabolic syndrome in later life. Metabolic syndrome amplifies the risks of diabetes, hypertension, coronary heart disease and probably some cancers. Mothers with gestational diabetes are themselves prone to early type 2 diabetes and produce heavier babies prone to childhood obesity and adolescent type 2 diabetes. There is increasing evidence of an intergenerational effect, with big babies being prone to excess weight gain, which then, in girls, predisposes them to diabetes in pregnancy, which, in turn, promotes an accelerating cycle of early diabetes in subsequent generations. Essential fatty acids and fat soluble vitamins are important, but we need early interventions and monitoring systems to justify coherent policies.

Key words: Fetal programming, low birth weight, maternal nutrition, metabolic syndrome

Introduction

It is now many years since McCance and Widdowson undertook their classic experiments on pigs and rodents to reveal how, by manipulating the diet of pregnant animals, it is possible to alter permanently the whole array of mechanisms that control the size of the body, and subsequent responses to later dietary changes and nutritional and physiological manipulations.[1] I was privileged to witness some of McCance and Widdowson's experiments, to engage them in the teaching of students at the London School of Hygiene (LSHTM) in the early 1970s, and to have them discuss their own and our new work as I established the new MRC Dunn Clinical Nutrition Centre in Cambridge. At that time, it was clear to us all that what they had discovered could lead to profound insights for humans, particularly as the remarkable studies by the Medical Research Council unit in Aberdeen had established the fundamental principles of maternal physiology and nutrition as summarized years later by one of the senior staff members.[2] This Aberdeen work was taken as a basis for understanding the supposedly normal physiological responses to pregnancy and, with it, a clear understanding of the resilience of the mother. A concept emerged that highlighted the enormous evolutionary pressures on survival, which must have ensured a most remarkable array of mechanisms for protecting the fetus from environmental and nutritional stresses. Maternal metabolic responses appeared to ensure the best possible array of nutrient flow to the fetus, given the ability of women to sustain pregnancies under adverse of circumstances. Thus, a question arose whether humans were unusually well adapted to coping with nutritional and other stresses in pregnancy; if so, humans would not be as vulnerable as other species.

Slowly, more experimental work began to emerge with Stewart *et al*. engaging in meticulous experiments showing the intergenerational impact of persistently adverse diets,[3] which matched new analyses from Angus Thompson, successor to Duguld Baird, presented to us at the LSHTM. Thompson was able to analyse data from three successive generations of women all born and monitored in the Royal Infirmary in Aberdeen. His analyses not only showed the importance of maternal size in terms of both weight and height before pregnancy, and the value of a 12 kg or so

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weight gain in pregnancy, but also how grandmaternal height seemed to contribute to the birthweight of grandchildren. It has taken us 30 years to catch up with some of these earlier, simple analyses.

Therefore, Barker's hypothesis, as it is frequently termed,[4] simply put into a modern disease-based context ideas that were routine in the nutritional world. Indeed, Barker's proposals were preceded by the proposition that cardiovascular deaths in Norway could be predicted from the records of infant mortality at the time of their childhood.[5] Nevertheless, Barker generated a new approach by collecting evidence of disease and metabolic risk factors in adults and relating these to meticulous records collected on the same individuals when they were born. This later led to prospective studies on babies and their development. Since the early days, when crude birthweight was considered a reasonable index of nutritional experience, the analyses have evolved beginning with an emphasis on the weight-for-length of infants as a better predictor, then with more importance being assigned to the head and abdominal circumferences as indices of differential organ growth at different stages of pregnancy. Now, with the advent of scanning techniques, fascinating insights into the differential growth of lean tissue and fat in different organs is emerging, and how these fetal growth rates respond to different maternal diets is being examined.

Prevalence of low birthweight

The differences in the prevalence of low birthweight (LBW) infants (weighing less than 2.5 kg) are substantial across the world with Asia (not Africa) having by far the highest prevalences. South-East Asia has the greatest problem, with half the children in Bangladesh born weighing less than 2.5 kg (approximately 28% of all Indian babies are of LBW).[6] This means that 12.3 million children are of LBW in Asia, with 9.3 million considered to have intrauterine growth retardation (IUGR) because they are of LBW, despite being born at more than 37 weeks of gestation; therefore, the remaining three million LBW babies are classified as having been born prematurely.[7] These rates compare with 6% of LBW (2% IUGR–LBW) in China, 11% (6% IUGR–LBW) in Vietnam and the Philippines, and 8% (4% IUGR–LBW) in Indonesia and Malaysia. Whereas originally the high prevalence of small babies was seen as understandable, given the relatively short stature and slim build of Asian women, now it is becoming ever more evident that these anthropomorphic features are an intrinsic response to generations of dietary deprivation and other environmental circumstances, such as the endemic parasitism and other infective scourges of Asia.

Handicap of low birthweight

Wherever the children are born, LBW has been clearly linked to a series of handicaps, and this high prevalence is, in prevalence terms, associated with high rates of stunting and underweight physiques in preschool children across the globe.[6] This association is not surprising, considering that LBW babies must show an unusually high compensatory growth rate after birth not to be small for their age later on.

Determinants of low birthweight

Maternal size is the crucial determinant of infant size throughout the animal kingdom, so it is not surprising that a mother's overall weight is a good predictor of her child's birthweight. Detailed analyses of the determinants of birthweight, for the World Health Organization, showed the major importance of maternal prepregnancy weight.[8] Both height and weight-for-height contributes, and this reflects not only maternal current nutritional state, as revealed by weight-for-height, but also lifelong nutritional wellbeing, which makes a major contribution to final adult height. Thus, the absolute weight of a woman is more important than her body mass index for reasons that may well be associated with her mass of lean tissue, with its turnover of amino acids and all of the associated nucleotides, other constituents and micronutrients, the whole array of which the fetus needs for its own growth. Subsequent maternal weight gain is also associated with infant size at birth, so immediate and long-term nutritional inputs for mothers are both of major importance, and this means that the best predictor of birthweight turns out to be maternal final pregnancy weight. Therefore, the worst predictors for LBW babies are associated with women of short stature who are also slim before pregnancy and who only put on modest amounts of weight; their risk of a IUGR baby is then more than fourfold higher than normal. However, interestingly, the World Health Organization expert group, on surveying the global data, were compelled to categorize the data into different regions to take account of very different maternal weights, pregnancy weight gains and birthweights in different countries. Nevertheless, it is still clear that women in the lowest global quartile of prepregnancy weight (i.e. <40 kg) have a 2.5-fold increased risk of an IUGR baby; this applies to half the women in western India and almost no women in the USA.[7] It has been estimated that 50% of all IUGR in rural areas of developing countries is attributable to small maternal size at conception and poor weight gain, without considering other nutritional issues. Malaria also makes an important contribution, as do other maternal infections that cause a loss of appetite, nutrient losses and poor absorption, abnormal placental function and fetal infections.

Food supplements and the avoidance of low birthweight

The issue of food supplements and the avoidance of LBW has been re-evaluated recently by Allen and Gillespie,[7] for the Asian Development Bank, who made use of a recent Cochrane database analysis,[9] and an analogous systematic review.[10] However, a more detailed study of the research, and of critical reviewer comments on randomization and other procedures, leads to somewhat different conclusions from the bald summary of the evidence that focuses narrowly on the rigid criteria set for valid randomized trials. First, it should be recognized that well-fed Asian women nurtured during pregnancy in a hygienic environment and

with their parasitism treated have a far lower prevalence of premature delivery, IUGR and LBW babies than most Asian mothers who are confronted with microbially contaminated drinking water and an absence of sanitation. There seems little doubt that a great contributor to the high prevalence of LBW in Asia is poor environmental hygiene and that this limits the potential impact of nutritional adequacy. In practice, both dietary inadequacy and infective load are so great that half of the women in the Indian subcontinent are anaemic, with pregnant women having an astonishingly high prevalence of frank anaemia (88%) and a maternal death rate that in developed countries would produce an immediate outcry. When we pointed this out in a United Nations report on how to combat the persistent nutritional problems of childhood malnutrition,[6] we were surprised to discover that the death rates in Asian mothers had not been highlighted before; UNICEF immediately changed their strategy to include the problems of the mother as well as her child, and the new development policy of the Asian Bank explicitly incorporated a mother and child orientated strategy.

It must be remembered that current trials and statistical analyses are still crude in their ability to discriminate the interactions of nutritional inadequacy and infections in determining contributors to the ill-health of populations living in difficult circumstances. The anaemia rate in pregnant Indian women is so extraordinary that, when compared with non-Asian women in any circumstance, a selective explanation must be sought. Undoubtedly, the anaemia has a major component of iron deficiency, but folate deficiency is also endemic in societies world famous for their insistence on the benefits of vegetarianism. The problem of iron deficiency is markedly accentuated by the pervasive parasitism, so the greatest reductions in anaemia rates occur when both parasitic treatment and iron supplementation are used, as shown in Indian women working on a tea plantation estate. Therefore, there are much greater benefits when a combination of measures is used and it cannot be assumed that benefits seen when providing nutrient supplements to the most nutritionally deficient populations of developed countries will also be evident in societies with high levels of infection (where there is often a poor response to nutritional measures). In addition, if overall maternal heights and prepregnancy weights are important predictors of birthweight, then finding modest effects of supplements in pregnancy cannot test the true contribution of nutrition to this problem. Such trials simply describe the potential immediate effects of interventions in pregnant women.

A standard Cochrane analysis revealed that, in 14 trials, birthweight was improved if a balanced protein and energy supplement was given. There was a 32% (borderline significant) reduction in the percentage of small for gestational age (SGA) babies, a 21 g per week greater maternal weight gain and a 32 g increase in birthweight.[10] Significant falls in the stillbirth rate were also found in three out of four protein trials. Allen and Gillespie properly emphasize the need to consider trials carefully before dismissing an effect,[7] and highlight the value of carefully conducted Gambian studies, which showed a marked effect in women who were actually monitored for their additional intake and provided with 4.26 mJ, 22 g protein, 56 g fat, 47 mg calcium and 1.8 mg iron daily in the form of biscuits.[7] It is widely recognized that in other trials women living within their communities in practice often share their supplements with the family, thus reducing the selective potential impact of the supplement. However, in general it is evident that within trials it is the most disadvantaged women who benefit most. Table 1 summarizes the effects of supplements in Gambian women; it is clear that the greatest benefit came in the hungry season, when women were normally losing weight and producing smaller babies.[11] Supplements provided during this season had very marked effects. In smaller studies of Asian women within the UK,[12,13] those who had the lowest weights showed the greatest benefits. Thus, Allen and Gillespie are correct to take a more discriminating view of the data on supplementation.

The timing of the supplement is also important, and findings have often been counterintuitive. Animal research workers have known for years that the early phase of pregnancy is a critical time, with nutritional effects being

Table 1. Low birthweight (LBW) and mortality in rural Gambian women supplemented in the second half of pregnancy

	Control group	Intervention group
Maternal postdelivery body mass index	20.7 ± 2.3	21.3 ± 2.8
No. days prenatal supplementation	0	8.2 ± 31
Average birthweight increase (g)	–	136
Hungry season	–	201
Harvest seasons	–	94
Increased head circumference (mm)	–	3.1**
% LBW		
Hungry season	18.5	11.6**
Harvest season	15.9	10.7**
All year	17.0	11.1***
% still births	2.35	1.00*
% neonatal deaths	3.92	2.36*
% deaths at 1–11 months	3.82	3.78

*$P < 0.05$; **$P < 0.01$; $P < 0.001$.

mediated via the ovum or during the early phase of development and implantation. Human longitudinal analyses in Guatemala showed the highest gains in birthweight (62 g) occurring with nutrient supplementation during the second rather than the third trimester of pregnancy; an outcome independent of prepregnancy weight.[14] These findings amplify the importance of early nutritional state, but also show that important nutritional improvement can occur after implantation in humans.

Selective nutrient supplementation

It appears that additional protein given on its own may be a handicap, not an advantage, when supplementing mothers. This was found in Chilean and New York studies, and highlights the potentially important role of protein metabolism.[7] Animal experiments have clearly shown that the amount of protein eaten during pregnancy can have profound effects on the future size and metabolism of offspring, without necessarily leading to a reduction in birthweight. Thus, it is clear experimentally that birthweight as such is only a crude indication of whether or not the fetus has been programmed for metabolic changes induced by alterations in maternal protein metabolism and the uterine supply of the constituents needed for lean tissue growth. Hales *et al.* showed in a rodent model that the amount of protein in maternal diet induces changes in the structure of the liver and in the enzymatic capacity for gluconeogenesis and glycolysis, which, in conjunction with an effect on pancreatic size and function, can completely alter glucose metabolism in offspring.[15] This is not an effect that necessarily involves an alteration in the selective expression of particular genes. It does reflect a change in organ cellular structure with a subsequent alteration in the capacity of particular cells and organs to function. In addition, it has clearly been shown that there may be selective changes in gene expression mediated though alterations in promoter activity associated with specific genes. Thus, Seckl and Walker and McCormick *et al.* have generated an extraordinary range of experiments, with detailed molecular analyses, which highlight the way in which maternal protein intake, as well as the immediate postnatal handling of animals, can alter the induction of selective subtypes of glucocorticoid receptors, not only in the brain, but in a multitude of tissues.[16,17] This research has also shown that the enzyme 11β-hydroxysteroid dehydrogenase type 1 activity, now considered responsible for the reversible interconversion of active glucocorticoids, is differentially expressed in many tissues and can amplify glucocorticoid action in the liver, adipose tissue and the brain. Thus, the generation of local corticosteroids within tissues, and their receptors, can be permanently programmed by both early dietary events and the physical and emotional stresses immediately after birth. It has also been shown by Langley-Evans and Jackson that a low maternal protein intake induces hypertension in rat offspring.[18] This phenomenon is, in part, mediated by an increase in fetal cortisol levels stemming from a reduction in placental capacity to degrade the circulating maternal corticosteroids.[19] Thus, a lower maternal protein intake reduces the placental hydroxysteroid dehydrogenase activity, thereby increasing the overflow of maternal corticosteroids into the fetus. This in turn, in late pregnancy, seems to either directly, or through associated changes, alter the whole setting of the hypothalamic–pituitary–adrenal (HPA) axis so that a higher prevailing circulating corticosteroid level is, by the fetus, treated as the normal required concentration to which the HPA feedback system should respond. Therefore, the animal is programmed to have a more responsive adrenal secretory system, with additional corticosteroid secretion reflected in greater insulin resistance and probably in the selective channelling of stored energy to central rather than peripheral fat depots. In addition, a maternal low-protein diet alters the kidney nephron number and function in the fetus, which may also be a key factor in the enhanced propensity to higher blood pressure in offspring.[20]

Folate requirements and fetal programming

A number of studies have considered the role of folate in fetal growth and metabolism, and a Cochrane analysis has showed that folate supplements not only increase, as expected, the serum and red-cell folate concentrations in maternal blood and reduce the prevalence of low haemoglobin levels in late pregnancy, but may also increase birthweight.[21] However, more detailed analyses of early studies with folic acid (e.g. in South Africa) show that women on monotonous diets have far fewer LBW babies when given folate. Thus, it is all too easy to dismiss, in crude Cochrane analyses, the impact of nutrients, if the difference in benefit that might be expected to occur in folic-acid-deficient women compared with well-nourished women is not discriminated. In addition to increasing the size of babies in deficient women, folic acid supplements also seem to reduce the risk of premature delivery and limit the risk of ante-partum haemorrhage and the need for Caesarean section. There also appears to be, in one large study, reasonable evidence that higher folate intake reduces the risk of pre-eclampsia.[22–24]

All investigators would now accept that folic acid has a marked effect in limiting the propensity to neural tube defects (NTD), particularly in women with the common genetic subtype of 5,10-methylenetetrahydrofolate reductase activity. A series of multiple trials have been conducted that have produced convincing evidence, but recently Wald *et al.* have highlighted the fact that the current advice for women to take 400 μg/day folic acid before and during early pregnancy to combat NTD may be too little because it only reduces the risk by 36%.[25] Depending on the prevailing intake of folic acid, an additional supplement of 5 mg may be needed to reduce the risk by approximately 85%. However, this level is probably geared towards women with unusual genotypes who have a particular susceptibility to NTD, and almost certainly does not reflect the normal needs of folic acid for promoting fetal development of lean tissue and size at birth. The Indian studies of Rao *et al.* have shown the marked association between lean growth rate and birth size, depending on maternal folate status; this is crucially

dependent on whether mothers eat appreciable quantities of fresh green vegetables and/or take additional milk, which may providing them with vitamin B_{12} as well as more essential amino acids.[26]

These data suggest that there is a high prevalence of folate deficiency in the Indian subcontinent, despite the dominance of vegetarianism in the region. This deficiency reflects not only the surprisingly small intakes of vegetables and fruit, but also the common practice of prolonged cooking, presumably in response to the need to limit the impact of the almost universal microbial contamination of food.

Zinc deficiency has also been highlighted as a potentially deficient micronutrient in pregnancy, with zinc deficiency leading to a limit on cell division, inadequate development of immuno-competence and the induction of hormonal alterations. Allan and Gillespie note that birthweight was higher in the supplemented group in several trials and that premature birth was found to be less frequent in three out of 10 trials.[7] Again, observations in women with poor zinc intakes or below-average plasma zinc concentrations, are those that seem to show the best effects of additional zinc, but there are now many major international trials underway to look at the combined effects of micronutrients, rather than a specific mineral in limiting the growth of the fetus. The other micronutrients that have been studied in some detail are vitamin A, calcium and iodine. Additional vitamin A in Asia, where mild to moderate deficiency still persists, limits urinary tract infections, diarrhoea and dysentery as well as pre-eclampsia, eclampsia and anaemia in the mother, and may limit perinatal mortality. Experimental studies suggest a very important role for maternal vitamin A in programming the long-term function of the lung in offspring, so current analyses, which depend upon crude measures of the immediate perinatal effect of improved vitamin A status, may be too limited to show its overall value. Cochrane analyses show that higher calcium intakes do limit the risks of hypertension, pre-eclampsia and eclampsia, and even lower the blood pressure of the neonate; this being seen particularly in women on lower calcium intakes.[27] However, pharmacological amounts of calcium (i.e. 1–2 g/day) seemed to be required to produce this response. More convincing evidence comes from iodine supplementation in iodine deficiency areas, which used to be a huge international problem. Studies in Papua New Guinea and the Democratic Republic of Congo have shown that in severe deficiency states, supplementary iodine reduces infant mortality by 30% and has the classic benefits of limiting cretinism and other iodine-deficiency disorders.[28,29]

Essential fatty acids

Trials of the value of essential fatty acid supplements are considered of limited significance in the analyses by De Onis *et al*., but detailed consideration of the extraordinary importance of n-3 fatty acids for brain development, the control of cellular processing through the incorporation of n-3 fatty acids in membranes, and in the n-6/n-3 balance of prostanoid synthesis, means that there is no doubt that the essential fatty acids are a crucial requirement in pregnancy.[10] Essential fatty acids are also involved in the prostaglandin-mediated induction of labour, so it is not surprising that n-3 fatty acid supplements have been found in some studies to lengthen the time of pregnancy; therefore, inducing bigger babies.[30] Campbell *et al*. and Haggarty *et al*. discovered the remarkable induction of selective placental lipase and protein-binding systems, which ensure that n-3 fatty acids, liberated from maternal depot fat turnover, are selectively trapped by the placenta in preference to other fatty acids, immediately available from dietary-derived chylomicra or other large triacylglycerol fractions in the plasma, which reflect the recent intake of dietary fats.[31,32] In vegetarian diets in developed countries, omega 3 fatty acid intake is very limited because omnivore women only derive modest amounts of n-3 from vegetable sources, the greatest intakes coming from fish consumption and the fatty acids that are found in eggs and animal sources by virtue of animals feeding either on grass or fish meal.[33] Lucas has emphasised the crucial role of n-3 fatty acids in the myelination process and in brain development that occurs in late pregnancy and early neonatal life, so it is no wonder that the provision of n-3 fatty acids through adequate maternal nutrition and breast milk is so crucial to long-term brain development and function.[34] We do not know whether the smaller head circumference of babies, and indeed of adults, in malnourished Asian communities reflects the poor intake of n-3 fatty acids. Certainly, from discussions with agricultural directorial colleagues regarding policy developments in horticulture, it is clear that there has been a systematic attempt to limit the amounts of n-3 fatty acids in plants bred for food purposes, because these fatty acids readily become rancid; therefore, limiting the shelf life of foods. Therefore, since the World War II, plant breeders have been systematically limiting the n-3 composition of food sources, whilst amplifying the n-6 content in recognition of the supposed benefits of 'polyunsaturated fatty acids' for limiting heart attacks. This is a vivid indication of the way in which crude human nutritional assessments can lead to huge changes in the food chain, which may induce changes inadvertently that are disadvantageous, rather than beneficial to health.

General health care and adolescent pregnancy

In all the discussions on the value of good maternal nutrition, it is important to recognize that smoking cessation is profoundly important and can reduce the prevalence of LBW by about 20%. Anti-malarial prophylaxis for women living in endemic areas of malaria is also important and can increase the average birthweight by 112 g, which is much more than the increase normally seen with nutrient supplementation studies. Alan and Gillespie have also highlighted the greater likelihood of IUGR in babies born to women who are engaged in strenuous work or who stand for a very long time at work.[7] This feature is seen even in affluent countries such as the USA, but it is not clear as yet whether there would be substantial benefits if women in Asia did not have to continue to do strenuous work throughout their pregnancies.

An additional major hazard in Asia relates to the problem of adolescent pregnancy. Whereas pregnancy is unusual in girls below the age of 18 in Indonesia, in India and other adjacent countries, the prevalence of pregnancy in young adolescents is very high. Already at least 25% of adolescent girls in the developing world have had their first child by the age of 19 years and it is very clear that maternal mortality rates are far higher in younger adolescents, whether this is assessed in Asia, Africa or the Caribbean. In rural northern India, despite the legal age of marriage being 18 years, the average age of conception is 15.3 years. Yet the evidence suggests that full pelvic maturation may not be complete until women are in their early twenties in the developing world.

Wallace *et al*. have clearly shown, in sheep experiments, the extraordinary impact of pregnancy in adolescence when the main maternal drive is to store nutrients to serve the needs of the mother rather than the fetus.[35] Thus, additional feeding leads to a worsening of fetal outcome because the anabolic drive in the mother deprives the fetus of nutrients. Only when the mother is mature does the classic full physiological adaptation of pregnancy enable the remarkable selective channelling of nutrients from the mother to the placenta, and the full functioning of all the induced selective enzymes geared to trapping essential nutrients needed for fetal growth.

Given the cultural acceptance of adolescent pregnancy, the Asian community may be facing an even greater problem as the Westernization of the diet induces a sudden reduction in the age of menarche, which can amount to 2 years within a single generation. It is then possible that the problems of adolescent pregnancy will become even greater because conception will be physiologically possible at an even earlier age.

Nutrition transition and its selective handicaps in relation to maternal nutrition

There have been astonishing changes in the nutritional state of the world, as the majority of developing countries have moved, within a single generation, from a state of marginal deficiency to a Westernization of diet. Resulting changes, including a sudden spurt in growth and an increase in adiposity, may be seen, on the whole, as beneficial. However, it now looks as though this may be the worst possible combination of events. Pre-existing intergenerational programming of the current population to expect a life of semistarvation must now cope with the new phenomenon of a much more plentiful energy-dense but nutrient-dilute diet. The human species has adapted over millennia to cope with marginal food intakes by producing smaller babies with different organ structures geared to making the maximum use of very limited nutrient intakes. The ability to cope with high protein, fat, sugar and salt intakes has probably never been an evolutionary pressure. However, now children who are born relatively small, but who then experience an acceleration in growth as they benefit from improved sanitation, immunization and a limitation in infections, show worrying evidence that they are selectively handicapped by this disjunction in prenatal and postnatal nutrition.[36] Western foods are high in protein, fats, sugar and salt, which are precisely those components for which the human species has, in evolutionary terms, developed selective taste buds to identify. Thus the umami, essential fatty acid, sweet and salt sensitive taste receptors in the tongue are geared to identify these foods in deprived early human communities, which may have been short of protein, essential fats, energy and, in ancient times, salt. However, within the last 50 years, food industrial and catering responses to taste panel assessments of preferred foods have inevitably led to the development of energy-dense convenience foods that satisfy these primeval taste signals.

Yajnik's studies in India show that infants that are born small and grow rapidly in childhood are those with the highest insulin resistance and a propensity to diabetes.[30] If the resetting of the HPA axis is a prevailing feature of the populations of the developing world, this may explain the extraordinary prevalence of Cushing's disease-like features of hypercorticolism in Chinese and other Asian children and adults who become obese. The prevalence of abdominal obesity seen in Hispanic, African and Asian populations who are gaining weight may also reflect the impact of hypercorticolism, insulin resistance and the selective channelling of energy stores to abdominal fat. It has been known for decades that children in the developing world have much smaller peripheral fat stores with smaller triceps skinfold thicknesses, but reasonable subcutaneous skinfold measurements. It used to be thought that this was an ethnic-specific phenomenon, but it may well have reflected the HPA axis setting for higher cortisol secretion rates in deprived societies. Therefore, as children and adults gain weight, they will inevitably lay down their fat abdominally and develop the metabolic syndrome which is now so prevalent in developing countries.

Given the escalating rates of excessive weight gain in the developing world, and the unusual propensity of these societies to develop abdominal obesity and metabolic syndrome, it is very likely that rates of diabetes across the world are going to be far greater than currently predicted. Women are now producing ever larger babies. Women who are overweight before pregnancy are much more likely to develop gestational diabetes and glucose intolerance, and this in turn increases the likelihood of having bigger babies with a propensity to childhood obesity and a very early, and now increasingly frequent, adolescent onset of type 2 diabetes. Figure 1 displays the transition from a malnourished society to a new environment where the double handicap of energy-dense foods and obesity is accompanied by micronutrient deficiency with persisting fetal malnutrition, and an exceptional susceptibility to diabetes and probably to other chronic diseases in early adult life

Therefore, we are facing one of the biggest public health challenges ever confronted. The infective plagues and pandemics of influenza, HIV and the re-emergence of malaria and tuberculosis are significant, but the complex-

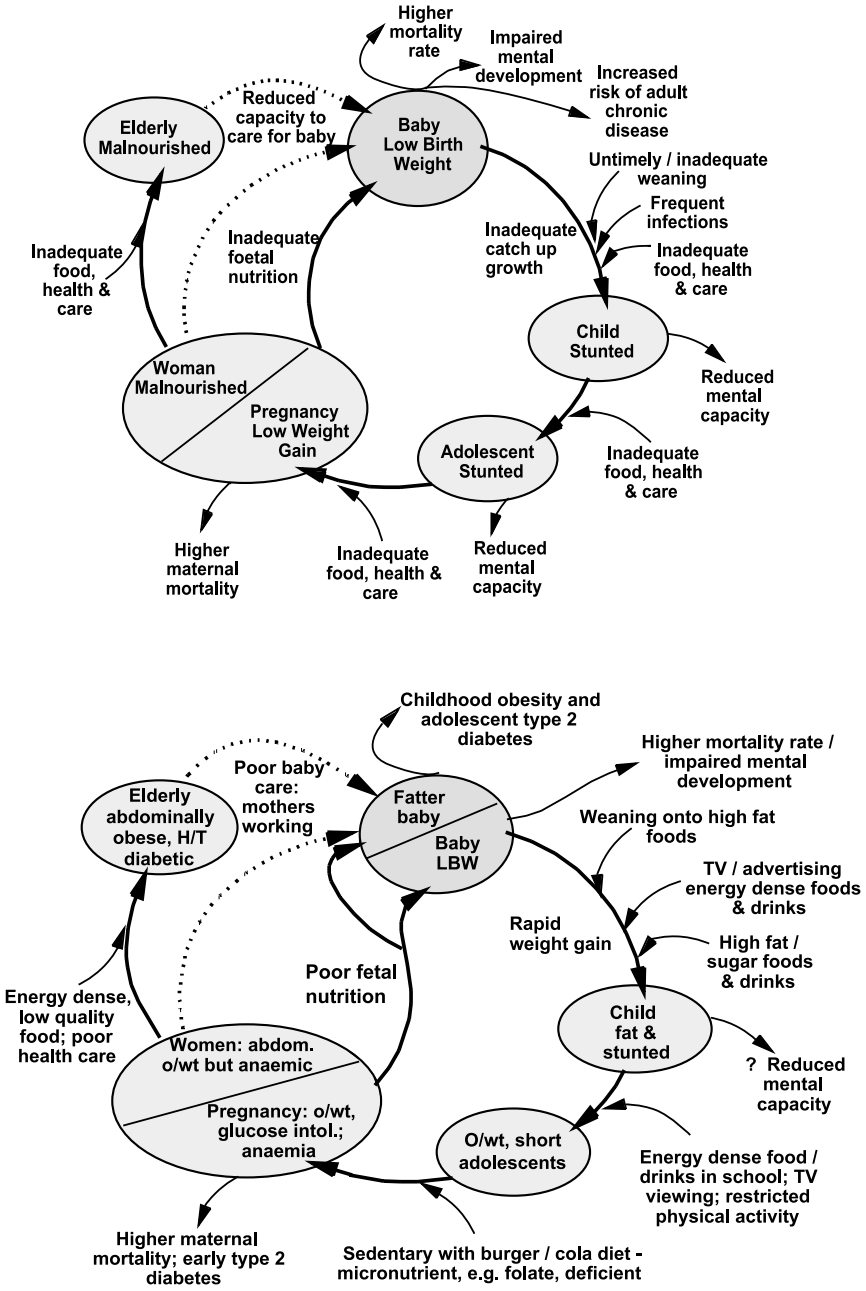

Figure 1. The transition from intergrational malnutrition to abdominal adiposity and diabetes.

ity and persistence of chronic diseases in the developing world are likely, over the next 20 years, to overwhelm even these scourges. We certainly need to develop preventive policies for limiting excessive weight gain, with all its implications for the food supply, the production and marketing of food and the provision of appropriate environments for physical activity. However, a critical issue for us to consider now is whether the majority of the world's population is in a state of super-sensitivity to an excess of food. Maternal and fetal nutrition should be considered as a major priority, along with the need to assess how best to improve fetal nutrition and limit the next generation's susceptibility to chronic disease. We need to increase the well-being of young girls in adolescence and early adulthood and optimize maternal nutrition so that offspring are less handicapped. In theory, it could be anticipated that perhaps three generations will pass by before *Homo sapiens* has adapted to producing babies programmed to expect plentiful supplies of food. However, in the current transition, there are girls and young women who are much more likely to develop gestational diabetes. We are already faced with the double handicap of persisting maternal and childhood malnutrition and escalating rates of hypertension, diabetes and other chronic diseases, such as cancers. Therefore, we now must add the challenge of maternal nutrition to the portfolio of action needed to combat adult chronic disease and a life-cycle approach to public health policies now becomes crucial.

References

1. McCance RA, Widdowson EM. Nutrition and growth. Proc R Soc Lond (Biol) 1962; 156: 326–337.
2. Hytten FE, Leitch I. Physiology of Human Pregnancy, 2nd edn. Oxford: Blackwell Scientific, 1971.
3. Stewart RJC, Sheppard H, Preece R, Waterlow JC. The effect of rehabilitation at different stages of development of rats marginally malnourished for 10–12 generations. Br J Nut, 1980; 43: 403–412.
4. Barker DJP. Mothers, Babies and Disease in Later Life. BMJ Publishing Group, London, 1994.
5. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med 1977; 31: 91–95.
6. James WPT, Norum K, Smitasiri S, Swaminathan MS, Tagwirye J, Uauy R, Ul Haq M. Ending Malnutrition by 2020: an Agenda for Change in the Millennium. Final Report to the ACC/SCN by the Commission on the Nutrition Challenges of the 21st Century. Supplement to the Food and Nutrition Bulletin September/October 2000. Tokyo: UNU International Nutrition Foundation.
7. Allen L, Gillespie S. What Works? A Review of the Efficacy and Effectiveness of Nutrition Interventions. Manilla: ACC/SCN Geneva in collaboration with the Asian Development Bank, 2001.
8. World Health Organization. Physical Status. The Use and Interpretation of Anthropometry. Technical Report Series 854. Geneva: WHO, 1995.
9. Kramer MS. Balanced Protein/Energy Supplementation in Pregnancy. Oxford: Cochrane Library, 1999.
10. De Onis M, Villar J, Gulmezoglu M. Nutritional interventions to prevent intrauterine growth retardation: evidence from randomized controlled trials. Eur J Clin Nutr 1998; 52: S83–S93.
11. Ceesay SM, Prentice AM, Cole TJ, Foord F, Poskitt EME, Whitehead RG. Effects on birthweight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. BMJ 1997; 315: 786–790.
12. Viegas OA, Scott PH, Cole TJ, Eaton P, Needham PG, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. I. Unselective during second and third trimester. Br Med J 1982; 285: 589–592.
13. Viegas OA, Scott PH, Cole TJ, Eaton P, Needham PG, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. II. Selective during third trimester only. Br Med J 1982; 285: 592–595.
14. Li R, Haas JD, Habicht J-P. Timing of the influence of maternal nutritional status during pregnancy on fetal growth. Am J Hum Biol 1998; 10: 529–539.
15. Hales CN, Desai M, Ozanne SE, Crowther NJ. Fishing in the stream of diabetes: from measuring insulin to the control of fetal organogenesis. Biochem Soc Trans 1996; 24: 341–350.
16. Seckle JR, Walker BR. Minireview: 11 β-hydroxysteroid dehydrogenase Type 1 – a tissue-specific amplifier of glucocorticoid action. Endocrinology 2001; 142: 1371–1376.
17. McCormick JA, Lyons V, Jacobson MD, Noble J, Diorio J, Nyirenda M, Weaver S, Ester W, Yau LJ, Meaney MJ, Seckl JR, Chapman KE. 5′-heterogeneity of glucocorticoid receptor messenger RNA is tissue specific: differential regulation of variant transcripts by early-life events. Mol Endocrinol 2000; 14: 506–517.
18. Langley-Evans SC, Jackson AA. Increased systolic blood pressure in adult rats caused by fetal exposure to maternal low protein diets. Clin Sci 1994; 86: 217–222.
19. Edwards CRW, Benediktsson R, Lindsay RS, Seckl JR. Dysfunction of placental glucocorticoid barrier: link between fetal environment and adult hypertension. Lancet 1993; 341: 355–357.
20. Hoet JJ, Hanson MA. Intrauterine nutrition: its importance during critical periods for cardiovascular and endocrine development. J Physiol 1999; 514: 617–627.
21. Mahomed K. Folic acid supplementation in pregnancy. Cochrane Database Systematic Reviews 2000; 181.
22. Baumslag N, Edelstein T, Metz J. Reduction of incidence of prematurity by folic acid supplementation in pregnancy. Br Med J. 1970; 1: 16–17.
23. Kulier R, De Onis M, Gülmezoglu AM, Villar J. Nutritional interventions for the prevention of maternal morbidity. Int J Gynaecol Obstet 1998; 63: 321–346.
24. Vollset SE, Refsum H, Irgens LM, Emblem BM, Tverdal A, Gjessing HK, Monsen ALB, Ueland PM. Plasma total homocysteine, pregnancy complications and adverse pregnancy outcomes: The Hordeland Homocysteine Study. Asia Pac J Clin Nutr 2000; 17: 962–968.
25. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet 2001; 358: 2069–2073.
26. Rao S, Yajnik CS, Kanarde A, Fall CH, Margetts BM, Jackson AA, Shier R, Joshi S, Reye S, Lubree H, Desai B. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune Maternal Nutrition Study. J Nutr 2001; 131: 1217–1224.
27. Purwar M, Kulkarni H, Motghare V, Dhole S. Calcium supplementation and prevention of pregnancy induced hypertension. J Obstet Gynaecol Res 1996; 22: 425–430.
28. Pharoah PD, Buttfield IH, Hetzel BS. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 1971; i: 308–310.
29. Thilly CH, Delonge F, Lagasse R, Bourdoux P, Ramioul L, Berquist H, Ermans AM. Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. J Clin Endocrinol Metab 1978; 47: 354–360.
30. Olsen SF, Sorensen JD, Secher MJ, Hedegaard M, Henriksen TB, Hansen HS, Grant A. Randomised controlled trial of effect of fish oil supplementation on pregnancy duration. Lancet 1992; 339: 1003–1007.
31. Campbell FM, Gordon MJ, Dutta-Roy AK. Placental membrane fatty acid-binding preferentially binds arachidonic and docodsahexaenoic acids. Life Sci 1998; 63: 235–240.
32. Haggarty P, Page K, Abramovich DR, Ashton J, Brown DS. Long chain polyunsaturated fatty acid metabolism and transport across the perfused human placenta. Placenta 1997; 18: 635–642.
33. Lakin V, Haggarty P, Abramovich DR, Ashton J, Moffat C, McNeill G, Danielian PJ, Grubb D. Dietary intake and tissue concentration of fatty acids in omnivore, vegetarian and diabetic pregnancy. Prostaglandins, Leukot Essent Fatty Acids 1998; 59: 209–220.
34. Lucas A. Programming by early nutrition in man. In: Brock GR, Whelan J, eds. The Childhood Environment and Adult Disease. John Wiley & Sons, Chichester, 1991.
35. Wallace JM, Aitken RP, Cheyne MA. Nutrient partitioning and fetal growth in rapidly growing adolescent ewes. J Reprod Fert 1996; 10: 183–190.
36. Yajnik C. Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease. Proc Nutr Soc 2000; 59: 1–9.