Energy adaptations in human pregnancy: limits and long-term consequences[1–3]

Andrew M Prentice and Gail R Goldberg

ABSTRACT The very slow rate of human fetal growth generates a lower incremental energy stress than in any other mammalian species. This creates a situation in which adaptive changes in metabolic rate and in the amount of additional maternal fat stored during gestation can make a profound difference to the overall energy needs of pregnancy. Comparisons of women in affluent and poor countries have recorded mean population energy needs ranging from as high as 520 MJ to as low as −30 MJ per pregnancy. These energy costs are closely correlated with maternal energy status when analyzed both between and within populations, suggesting that they represent functional adaptations that have been selected for their role in protecting fetal growth. Although this metabolic plasticity represents a powerful mechanism for sustaining pregnancy under very marginal nutritional conditions, it must not be construed as a perfect mechanism that obviates the need for optimal nutritional care of pregnant women. The fact that fetal weight represents up to 60% of total pregnancy weight gain in many pregnancies in poor societies (compared with a well-nourished norm of 25%) indicates that the fetus is developing under suboptimal nutritional and physiologic conditions. It has long been recognized that this has immediate consequences for the offspring in terms of increased perinatal mortality. The more recent appreciation that impaired fetal growth may also precipitate longer-term defects in terms of adult susceptibility to noncommunicable and infectious diseases reinforces the view that pregnancy may be the most sensitive period of the life cycle in which nutritional intervention may reap the greatest benefits. *Am J Clin Nutr* 2000;71(suppl):1226S–32S.

KEY WORDS Energy adaptation, energy metabolism, pregnancy, fetal growth, women

INTRODUCTION

The subject of energy metabolism in human pregnancy has received extensive consideration over a period stretching back >60 y to early work that assessed the contribution of fetal metabolism to the overall energy costs of pregnancy (1). Over the intervening years, the emphasis of much of this work was on separating and quantifying the different components of gestational energy needs (2, 3) and on establishing appropriate recommendations for the energy requirements of pregnant women (4, 5). The intention of such work was to quantify average amounts, and deviations from these average values were generally viewed as undesirable biological or measurement noise that needed to be overcome by studying large samples of women to get a more precise estimate of the mean values (6).

We have taken the converse view that interindividual variations in the metabolic responses to pregnancy represent a biologically significant plasticity that has true adaptive value in enabling women to carry a pregnancy to term under a wide range of nutritional conditions (7). Because we discussed these issues in detail elsewhere (5, 8–12), this paper will provide only a brief summary of the theory of functional plasticity before considering the adaptive limits and the long-term consequences of any nutritional deprivation that exceeds these limits. It will become clear that concepts have moved far beyond the original view of the human fetus as a "perfect parasite" and that we now have a developing, but still rudimentary, understanding of the immensely complex hormonally orchestrated metabolic interplay between the competing needs of the fetus and those of the mother. Under conditions when nutritional supply is suboptimal, the final outcome will always represent a compromise. The full significance of the long-term sequelae of these compromises has only recently begun to be understood. Elsewhere in this issue, Godfrey (13) summarizes some of these long-term outcomes in his report on the latest developments in the "infant and fetal origins of adult disease" hypothesis. This paper extends the discussion with a particular emphasis on conditions of maternal undernutrition in developing countries.

A ZOOLOGIC PERSPECTIVE ON THE ENERGETIC STRESSES OF HUMAN REPRODUCTION

Before considering some of the specific aspects of energy metabolism in pregnancy, it is useful to consider women in a comparative zoologic perspective because this provides a probable explanation for the fact that human reproductive

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[2] Presented at the symposium Maternal Nutrition: New Developments and Implications, held in Paris, June 11–12, 1998.

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Am J Clin Nutr 2000;71(suppl):1226S–32S. Printed in USA.

metabolism displays some highly characteristic attributes not seen in other species.

A slow rate of fetal growth is a feature of primate reproduction, which is particularly pronounced in humans to allow time for the development of a complex brain (14, 15). The resulting long gestation results in very low nutritional stress per unit time because the mother can spread the incremental costs of creating the products of conception over an extended period. This has 2 important consequences: *1*) the daily incremental energy stress of human pregnancy is lower than for any other mammal when expressed relative to maternal metabolic body size (8), and *2*) the energy costs of maintaining the products of conception over a long gestation outweigh the costs of creating the products of conception by ≈4-fold in a well-nourished pregnancy (7). We believe that these factors place human reproduction in a distinct biological niche in which subtle adaptive changes in metabolism can have a highly significant effect on the overall energy costs of pregnancy, and hence on protecting fetal growth during adverse circumstances (7). In evolutionary terms, the survival value of such adaptive responses would exert a powerful selective drive that is absent in most other species in which the incremental costs of reproduction are so large that they overwhelm any marginal adjustments in metabolism and create an obligate need for a substantial increase in food intake. This is important in explaining why such metabolic plasticity has been reported only in humans and why it is such a significant feature of human reproduction.

ADAPTIVE MODULATIONS IN HUMAN ENERGY BUDGETS DURING PREGNANCY

Hytten and Leitch's (2) theoretic estimations of the overall energy costs of human pregnancy published almost 30 y ago have stood the test of time, have been experimentally validated as reasonable average values (5), and have been adopted by many national and international bodies as a partial basis for developing recommended energy intakes in pregnancy (4). The costs can be divided into 3 main components: *1*) the energy deposited as new tissue in the conceptus [placenta, uterus, breasts, amniotic fluid, expansion of blood volume, fetus (minus fetal fat) − total cost approximated at ≈20 MJ], *2*) the energy deposited as fat (averaging ≈150 MJ in a well-nourished pregnancy), and *3*) the energy required to maintain this new tissue (also estimated at ≈150 MJ in a well-nourished pregnancy).

The last of these components, maintenance energy needs, is estimated as the cumulative area under the curve represented by the rise in a mother's basal metabolic rate above the prepregnancy baseline metabolic rate. How different these curves can be is illustrated in **Figure 1**; average estimates from our studies in England and The Gambia are comparatively illustrated in the top panels. In the well-nourished English women, the basal metabolic rate began to rise soon after conception and continuously increased until delivery (9). In contrast, the undernourished Gambian women showed a pronounced suppression of metabolism that persisted well into the third trimester of pregnancy (16). This offset the later increase in basal metabolic rate

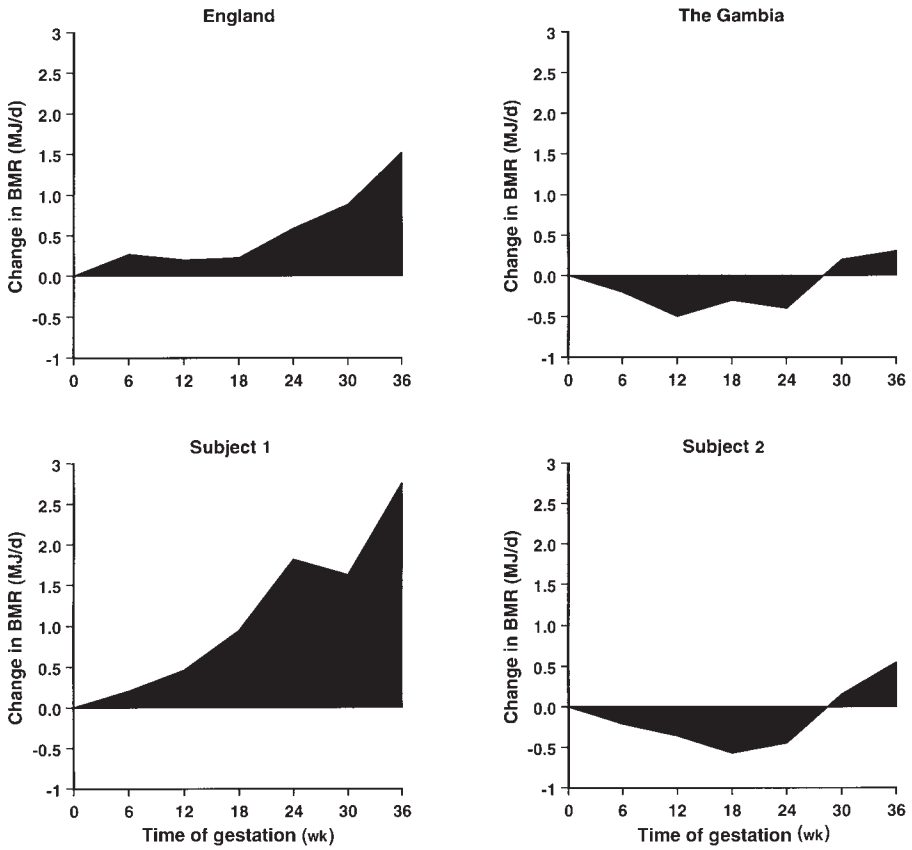

FIGURE 1. Changes in basal metabolic rate (BMR) during pregnancy in women from Cambridge, England (mean values) (9); in women from Keneba, The Gambia (mean values) (16); and in 2 individuals (subjects 1 and 2) from Cambridge (17).

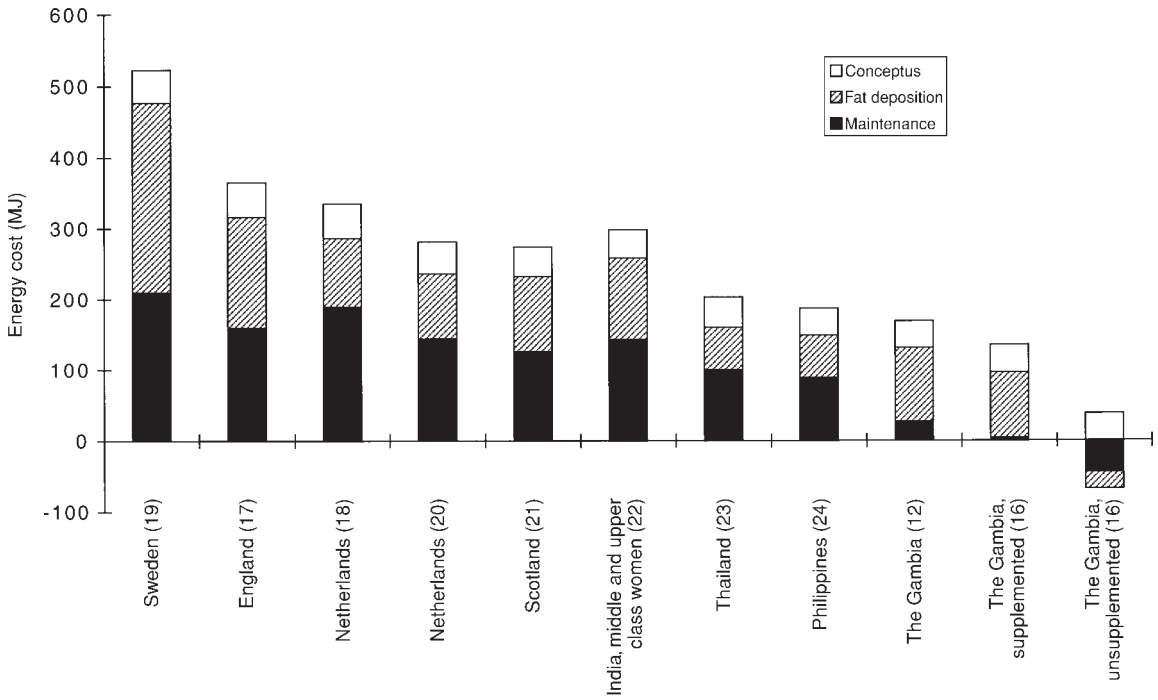

FIGURE 2. Total energy costs of pregnancy [conceptus (including fetal fat), fat deposition, and maintenance] in women from affluent and poor countries. The energy cost of the conceptus was estimated prorata according to birth weight. The supplemented women from The Gambia received balanced protein-energy supplements.

such that there was actually a slight net saving of energy over the entire gestation period. Gambian women who were participating in a high-energy dietary supplementation program experienced an amelioration of the energy-sparing decrease in metabolic rate (data not shown), suggesting an interaction between maternal energy status and the gestational metabolic response (16). After Lawrence et al's (16) initial observations, the remarkable decrease in metabolic rate in early gestation in Gambian women was confirmed in subsequent studies by Poppitt et al (12) and BJ Sonko (unpublished observations, 1998), indicating that it was not a chance finding.

A similar range in response can be seen between different women from the same nutritional setting (in this case England) in the lower panels of Figure 1. Elsewhere, we showed that thin women tend to show the energy-sparing type of response, whereas fatter women display the energy-profligate response (9). This finding was confirmed in a larger dataset of women from the Netherlands (18).

The combined costs of maintenance, fat deposition, and conceptus across 11 studies from 8 different countries drawn from emerging and affluent nations are illustrated in **Figure 2**. It can be seen that the energy cost of fat deposition also varies according to the state of affluence and is positively correlated with variations in maintenance requirements. This results in a very wide range of energy needs, from 523 MJ (125 000 kcal) in the Swedish women to −30 MJ (−7000 kcal) in the unsupplemented Gambian women. The average costs in the well-nourished groups were close to the current international assumption of 336 MJ (80 000 kcal).

We interpret these differences as representing a functional plasticity that offers survival value to the fetus under conditions of a suboptimal maternal diet. The relations that exist between the women's nutritional statuses and the metabolic costs of pregnancy are shown in **Figure 3**. The total costs of pregnancy were strongly correlated with the women's prepregnancy fatness ($r = 0.80$, $P < 0.01$) and with pregnancy weight gain ($r = 0.94$, $P < 0.001$). It is impossible to establish which of these factors is dominant in modifying the energy costs of gestation because they are themselves highly covariant ($r = 0.88$, $P < 0.001$). However, the within-country analyses from England and the Netherlands, which observed correlations between prepregnancy fatness and maintenance costs of pregnancy as discussed above, found no association between maintenance costs and pregnancy weight gain, suggesting that preconceptual nutritional status may be the critical factor.

We hypothesized previously that these relations suggest the existence of a mechanism that can monitor the mother's prepregnancy energy status and adjust the homeorrhetic changes in maternal metabolism accordingly (7). The subsequent discovery of leptin (25) provides a plausible mechanism by which peripheral energy status can be centrally monitored and might coordinate the metabolic responses to pregnancy.

It is clear that leptin plays a significant role in several components of the reproductive axis (26, 27) and current evidence suggests that it plays a key role in pregnancy (26, 28), including the modulation of fetal growth (29), although the precise reasons for the large increase in leptin concentration in pregnancy remain unknown (28, 30). In the nonpregnant state, circulating leptin concentrations are strongly influenced by body fat mass (31) and may be influenced by short-term energy status (26). In pregnancy, it appears that leptin may not correlate with maternal body fat (32), suggesting that its function may be modified.

Our hypothesis requires that low concentrations of plasma leptin, generated by either of these effectors, would signal the

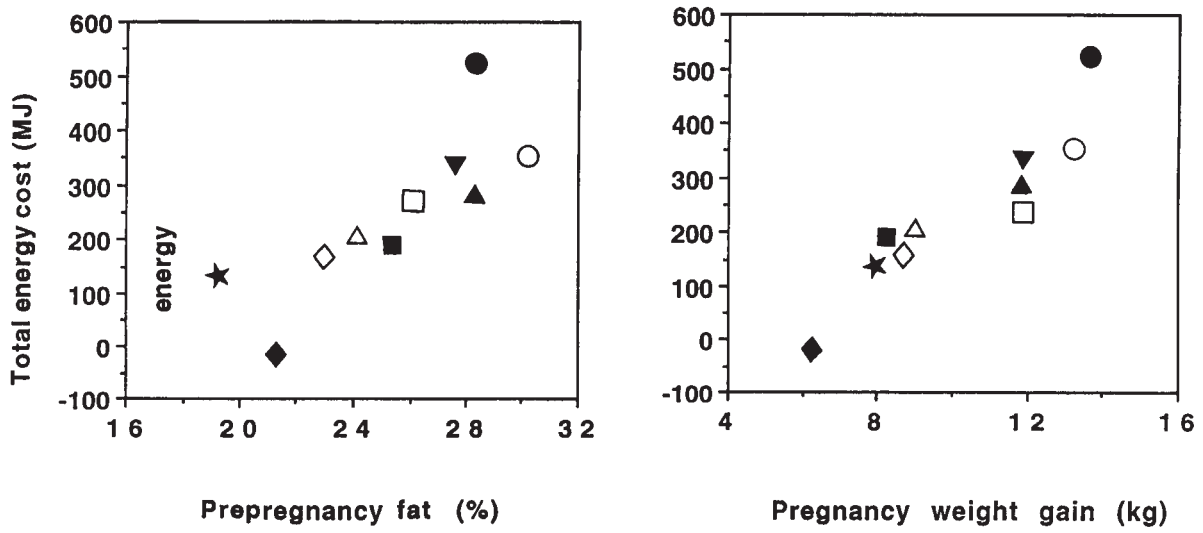

FIGURE 3. Intercountry correlations of the total energy cost of pregnancy with prepregnancy maternal fatness and pregnancy weight gain in women from Sweden (●, 19), England (○, 17), the Netherlands (▲, 18; ▼, 20), Scotland (□, 21), Thailand (△, 23), the Philippines (■, 24), The Gambia [supplemented and unsupplemented women (★, 16)], and The Gambia (◇, 12). Data from India were not included because data for percentage body fat were not reported. The supplemented women from The Gambia received balanced protein-energy supplements.

need to adopt frugal metabolic mechanisms after conception. Thus far, only one small study of 10 women has partially investigated this possibility (33, 34). In this study, Catalano (35) reports no correlation between changes in leptin and changes in either maternal fat mass or basal energy expenditure. However, this only addresses part of the question and there is a need for larger and more detailed studies to properly test this hypothesis.

LIMITS TO ENERGY-SPARING ADAPTIVE RESPONSES IN PREGNANCY

The above description portrays a cleverly coordinated biological system in which energy-sensitive modulations in metabolism help to sustain human pregnancies under highly marginal environmental circumstances. The danger with this portrayal is that it might be misinterpreted as suggesting that maintenance of optimal nutritional status in pregnant women is not a priority because the adaptive mechanisms of the women will cope.

We showed elsewhere that, when expressed relative to maternal body weight raised to the power 0.75 (traditionally used to scale metabolic body size), the CV for mean birth weights in the 11 studies cited here is only 3% (11). This indicates that the metabolic adjustments have, on average, assured a fetal weight that is proportional to maternal size. The key question, however, is, at what cost to the mother and the future health of her offspring?

Pregnancy weight gain is a critical component of this question. We showed above that it is intimately related to the overall costs of pregnancy, as would be anticipated. The issue of whether pregnancy weight gain drives, or is driven by, the metabolic changes is interesting but somewhat irrelevant in the present context because it is readily accepted that poor women consuming marginal diets have small weight gains, as illustrated by the data from 83 studies in **Figure 4**. Gestational weight gain ranged from 10% to 30% of prepregnancy weight. Note that these are average values, each of which has a wide interindividual range. It is clear that women from the poorer countries have much lower percentage weight gains despite having lower initial body weights. Absolute gains, therefore, show an even greater diversity. For instance, the mean (±SD) weight gain recorded from the Kenyan arm of the Nutrition Collaborative Research Support Program studies was 6.3 ± 3.4 kg (range: −5 to 14 kg) (36). This is in contrast with the US 1980 National Natality Survey, which recorded a mean weight gain of 13.8 kg (range: 0–23 kg) in women of moderate nutritional status (37). The proportions of women gaining <10 kg were as follows: 92% from Kenya and only 17% from the United States. Examples chosen

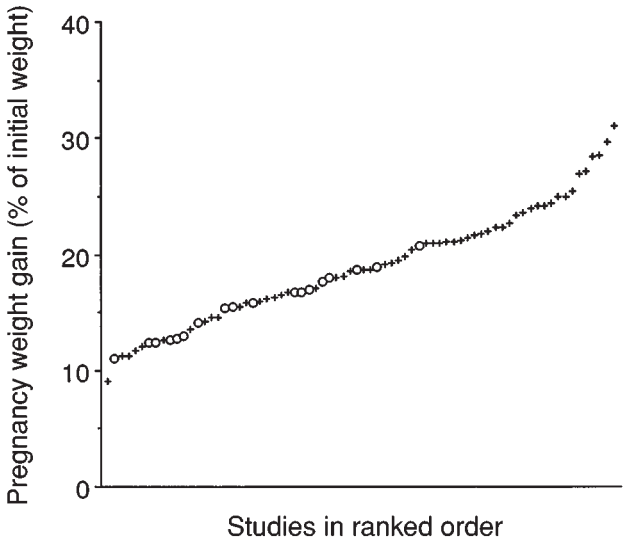

FIGURE 4. Pregnancy weight gain in affluent (+: North America, Europe, and Australia) and poor (○: Mexico, Kenya, The Gambia, Egypt, India, Ethiopia, Polynesia, Taiwan, Tanzania, Thailand, and the Philippines) countries, expressed relative to prepregnancy weight.

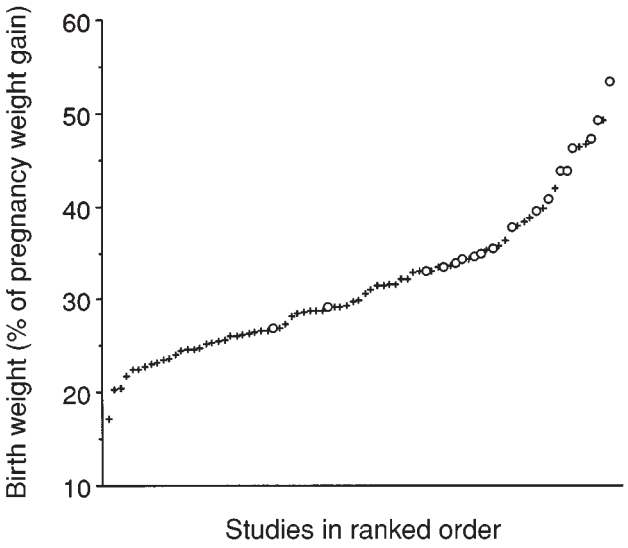

FIGURE 5. Birth weight in affluent (+: North America, Europe, Australia) and poor (○: India, Polynesia, Thailand, Tanzania, the Philippines, The Gambia, Ethiopia, Taiwan, India, Egypt, Kenya, and Mexico) countries, expressed relative to pregnancy weight gain.

from small Asiatic women from countries such as Bangladesh would show even bigger differences.

Small weight gains during pregnancy may have several consequences, which may or may not be mediated directly through an effect on birth weight. The relations between weight gain and birth weight are generally well known (37, 38) and are discussed elsewhere in this issue (39). It is clear that weight gain exerts a much stronger influence on birth weight in small, thin women than in well-nourished or overnourished women, in whom correlations are often weak or absent (37, 38, 40, 41). In the US studies by Abrams and Laros (38) the coefficient linking birth weight to maternal weight gain in underweight women was 22 g/kg. In our own Gambian studies, the coefficient was 33 g/kg weight gain after appropriate adjustments (42). This is a significant effect and can explain almost 200 g of the 500–600 g difference in mean birth weights between Gambian and English women. Other effects of weight gain may be more subtle and might be mediated through qualitative effects on fetal growth and development at different stages of intrauterine growth.

Birth weight as a proportion of gestation weight gain from the same datasets as used in Figure 4 are shown in **Figure 5**. In the affluent populations, fetal weight averaged ≈25% of total weight gain. This can presumably be accepted as the biological norm. In sharp contrast, the studies from developing countries show fetal weights that represent a much greater proportion of overall weight gain. We suggest that this indicates a state of stress in which the mother is having to make potentially damaging economies during gestation. Birth weight expressed as a proportion of weight gain in this way may be a useful index of nutritional adequacy in pregnancy.

To assess the potential significance of low weight gain, it may be useful to review the composition and function of the extra tissue deposited in pregnancy. Hytten et al (2, 43, 44) accumulated data from numerous sources to estimate the components of weight gain. For an average pregnancy in a well-nourished woman gaining 12.5 kg, they estimated the following breakdown: fetus, 3400 g; placenta, 650 g; uterus, 970 g; mammary tissue, 405 g; amniotic fluid, 800 g; expansion of blood volume, 1450 g; increased extracellular and extravascular water (in the absence of edema), 1480 g; and maternal fat, 3345 g. The first 6 of these are considered to be obligate changes, and only the last 2 may be optional. According to Hytten et al's estimates, the obligate changes would add up to 7800 g in an ideal pregnancy.

Clearly, there are tens of millions of pregnancies worldwide (perhaps as many as half of the total) in which weight gain falls far short, even of these obligate needs. The consequences of this deficit are not known in detail, but it is reasonable to speculate that it creates a metabolic milieu in which the fetus is struggling to derive the optimal nutrient supply and physiologic conditions in which to thrive.

LONG-TERM CONSEQUENCES OF NUTRITIONAL DEPRIVATION IN UTERO

The important work of Godfrey (13) and Barker (45), which indicates that many chronic adult diseases have their origins in fetal and infant nutrition, has refocused attention on early life as a critical period in human development. Barker's work shows that it is no longer tenable to assume that pregnancy has been successful if it produces a live baby free from congenital defects because an apparently healthy baby may have pathophysiologic or metabolic features that will emerge as adult disease after a long period of dormancy. In the context of undernourished poor women in the developing world, there are several components of the early programming of the disease process that merit special emphasis.

The first relates to the concept of the "thrifty phenotype," developed by Hales and Barker (46), in which it is proposed that fetuses subjected to early nutrient restriction become metabolically attuned to these conditions and sustain aspects of a thrifty metabolism for the rest of their life. If, as often happens in the rapidly emerging nations of the world, these conditions of early poverty are replaced by relative nutritional abundance in adult life, then thrifty phenotypes may be especially vulnerable to diseases of affluence, especially type 2 diabetes (47).

The second relates to our own discovery of a strong link between early life events and adult immunocompetence. In The Gambia, we showed that adults who were born during the annual hungry season are up to 11 times more likely ($P < 0.00009$) to die prematurely of infectious diseases than are those born during the harvest season (48). We hypothesize that this susceptibility is mediated through effects of intrauterine malnutrition on the developing immune system, although it is possible that other nonnutritional early life events may be responsible. If causality is related to early nutrient deficits, then the extremely strong association further emphasizes the profound importance of optimizing the nutrition of poor pregnant mothers.

CONCLUSIONS

The work described herein illustrates that the act of conception initiates a complex series of coordinated adjustments in energy metabolism. Human pregnancy is a period of much greater metabolic plasticity than is the nonpregnant state, and it can be assumed that this capacity for flexibility has been selected for is biological function in protecting fetal growth from the worst effects of maternal food shortage. However, despite these elegant adaptive processes, intrauterine growth retardation is highly prevalent in

poor communities and is known to be nutritionally mediated in many settings (42). Furthermore, there is evidence, based on the index of birth weight as a percentage of maternal weight gain, that the fetus has to struggle to maintain its growth trajectory and that this may have qualitative effects on the development of organs and physiologic systems that are not solely assessable through measures of birth size and anthropometric proportions. Evidence is rapidly accumulating that these programmed effects are more far reaching than imagined previously. This reemphasizes the crucial role of prenatal nutrition in community health. It suggests that pregnancy represents the most nutritionally sensitive period in the life cycle and the time at which nutritional interventions can reap the greatest benefits through improvements in maternal, fetal, and infant mortality, and through longer-term benefits in the health of adult populations, including intergenerational effects.

The issue of nutritional intervention in poor communities worldwide has been dogged recently by an academic nihilism generated by what are interpreted as disappointing results from intervention trials. Many of these trials (including some in the United States) were conducted in populations in which there was little a priori evidence of special nutritional needs, and many others were poorly implemented and evaluated. In almost all of these trials, birth weight was used as the main (and usually sole) outcome measure. The recent advances in our understanding of the importance of more subtle pathophysiologic defects related to intrauterine growth faltering open up a completely new horizon in which prenatal interventions should be judged on the basis of improvements in both short- and long-term function of the offspring as well as size. Our own recently published randomized control trial of prenatal supplementation in women from 28 Gambian villages achieved a highly significant reduction in stillbirths and perinatal mortality (42). If, as seems probable, the infants also derived longer-term benefits that will only emerge in adulthood, then the evidence in favor of such interventions would be powerful and would suggest an urgent need to establish scaled-up interventions in a variety of underprivileged populations.

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