REVIEW ARTICLE

IMPLICATIONS OF THE THRIFTY PHENOTYPE HYPOTHESIS FOR THE HEALTH OF SOCIETIES UNDERGOING ACCULTURATION — LESSONS FOR SOUTH AFRICAN HEALTH PLANNING

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The Birth to Ten Study,[1-4] an ongoing study of children from birth in the Johannesburg area of South Africa, could highlight the importance of the thrifty phenotype hypothesis for emerging communities.[5,6] Unlike the thrifty genotype hypothesis[7-12] which holds that heritable traits derived from our hunter-gatherer lifestyle of yore are detrimental in times of plenty, the thrifty phenotype hypothesis proposes that humans are metabolically programmed during intra-uterine life to expect feast or famine. Those programmed for famine[13] who then become obese[5] are especially susceptible to development of the so-called metabolic syndrome including type 2 diabetes mellitus. The implications are clear. If the thrifty phenotype is true, then intervention during pregnancy will be able to remove the threat of diabetes mellitus; indeed among the inhabitants of the Micronesian island of Nauru increased caloric intake appears to have reduced the incidence of type 2 diabetes.[14] However, if the genetic basis of disease is true, little except for the passage of time or a radical change in lifestyle may alter the situation. The passage of time will allow this trait, which is no longer advantageous in terms of survival, to be outbred, while change of lifestyle will ensure that the environmental conditions conducive to development of the disease pattern are not achieved. In terms of evolution it is more likely that such a trait will merely be neutral and will remain present in the gene pool as it does not influence reproduction in the circumstances of modern management. Without any positive reason for the trait to disappear there is no selective pressure.

The other reason that the thrifty phenotype hypothesis is significant in this population is that low birth weight is common among the South African black population[15] and obesity is increasing far faster than in the South African white population.[16,17] Acculturation is significant among blacks aspiring to South African urban behaviour. Movement from rural to urban living is significant.[18]

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EFFECTS OF SOCIAL CHANGES

The effects of social changes within the black population are already obvious. The prevalence of obesity among black women between 15 and 64 years of age is 35%, much higher than the 18% prevalence among white women;[19] diabetes mellitus is currently at 7% and is set to reach 10% as with African Americans,[20,21] compared with 3.6% among white South Africans;[22,23] while hypertension is at 30% prevalence among black South Africans and only 15% among whites.[24] The only 'favourable' statistic is that white subjects have a mortality from cardiac disease of 55 per 100 000[25] and black South Africans 8 per 100 000,[26] with a lower incidence[27] of ischaemic heart disease. This observation has been noted among the Pima Indians of the Arizona and New Mexico desert as well, where hypertension does not predict cardiovascular disease,[28] and among the Nauru Islanders.[29-31] Only 20 years ago, myocardial infarction (MI) was unheard of in the black population[27] and now it is an expected presentation in the urban hospital setting.[32] Thus even the 'positive' statistic surrounding MI may be changing and would be expected to alter rapidly, as has the incidence of the other disorders.

GLUCOSE INTOLERANCE

The original hypothesis proposed that low birth weight was associated with an increased likelihood of glucose intolerance or diabetes mellitus.[5] This was later expanded to include the incidence of cardiovascular risk factors,[32-35] and thinness at birth was related to the likelihood of the 'metabolic syndrome' and insulin resistance.[36-40] The authors also demonstrated that other growth parameters such as adult height were related to tolerance.[41] Workers in other parts of the world, notably India,[42,43] and those studying the Pima Indians[44,45] and indirectly the Nauru Islanders,[14] have confirmed the relationship between birth weight and glucose intolerance.

The Birth to Ten study has followed 4 029 children from birth 10 years ago. For our data, a purely longitudinal cohort was selected from this group using the criteria of full-term birth, complete data on birth weight, and weight and height at 1, 5 and 7 years of age. All children were South African. Of the 468 subjects thus selected, a sample group of 152 children were chosen for study of the relationship of birth parameters and growth during childhood and dysfunction of the pancreas. Metabolic studies were performed at 7 years of age with parental consent and approval by the University of the Witwatersrand Ethics Committee.[46,47]

Of the Birth to Ten study cohort, 21 children (14%) were of low birth weight, i.e. below 2.5 kg, reflecting the prevalence of this phenomenon within the South African population. Glucose, measured at 30 minutes after a glucose load, related negatively to birth weight. Insulin secretion was also negatively related to birth weight at 7 years, but low-birth-weight children appeared to process proinsulin to completion more efficiently than the other children. This latter observation may represent the ultimate compensation by the beta cell. If this is so then it is perhaps indirect evidence that the presence of proinsulin and des[31,32] proinsulin have some physiological purpose that is sacrificed in the presence of insulinopenia. There are indications that proinsulin may have its own specific binding sites distinct from insulin.[48] Weight gain velocity from birth to 7 years of age correlated with measures of subcutaneous fat, body mass index (BMI) and insulin resistance calculated using homeostatic model assessment (HOMA). The associations were already significant at the age of 5 years, suggesting that too-rapid weight gain during childhood also represents an independent risk for the development of diabetes mellitus. In addition, children who become obese during childhood are more likely to become obese adults.[49-51] In those individuals of low birth weight who did not track within their weight centile, weight gain was in fat, not muscle tissue. Thus low-birth-weight individuals seem to be predisposed to fatness. Several studies[52-55] have highlighted the relationships between low birth weight and increased abdominal mass in children and adults. This study did not identify the anatomical sites of fat accumulation.

Recent unpublished work by our group has also shown that among low-birth-weight neonates (studied between 1 and 60 days of age) those with the lowest birth weight and/or insulin sensitivity have the greatest weight gain velocity.

Glucose and insulin correlated negatively with birth weight and positively with indices of obesity. In keeping with insulin's role as a growth factor, height is inversely related to glucose tolerance. As current height incorporates the body size information from heights at a younger age, these data highlight the relationship between glucose intolerance and stunting. Within the population from which these subjects were drawn the prevalence of stunting is 20% at the age of 2 years.[56] Studies of adults in the UK[33] have shown that hypertension is related to low birth weight. In South Africa, low birth weight has been correlated with a rise in systolic but not diastolic blood pressure.[57] Increased tissue sensitivity to cortisol, amplified by enhanced secretion of cortisol, is a feature of the familial predisposition to high blood pressure rather than a secondary effect of high blood pressure. It may be mediated by an abnormal glucocorticoid receptor, and it may contribute to the association between hypertension and insulin resistance.[58]

LOW BIRTH WEIGHT AND MATERNAL MALNOURISHMENT

Low birth weight or detrimental fetal programming may be caused by maternal malnourishment. Evidence for this is largely indirect, coming as it does from dietary deprivation studies of rats.[59] The only human study is of those conceived during the Dutch famine of 1945/46.[13] There was a greater incidence of glucose intolerance in those adults who were possibly exposed to undernutrition during intra-uterine life. Animal studies have also shown that deficiencies in specific components of the diet, such as threonine,[60] taurine, or total protein,[61,62] may be important.

Those who seek genetic explanations have suggested that glucokinase heterogeneity may cause low birth weight. In this view a fetus with reduced beta-cell glucokinase activity and consequent reduced insulin secretion will be small — the proposed altered glucokinase activity is then related to the development of adult diabetes (in keeping with the glucokinase defect related to a subset of maturity-onset diabetes of the young (MODY)).[63,64] This is not a convincing explanation given that only a small proportion of non-insulin-dependent diabetes mellitus (NIDDM) is explained by glucokinase deficiency. Reduction of placental 11-β-hydroxysteroid dehydrogenase 2 activity is another possible mechanism of low birth weight. This defect reduces inactivation of cortisol by conversion to cortisone. Activity of placental 11-β-HSD correlates with fetal weight. In rat experiments, inhibition of maternal 11-β-HSD has been shown to reduce birth weight.[65-68] Furthermore, reduction of maternal protein has been shown to reduce 11-β–HSD, increase placental glucocorticoid-inducible glutamine synthetase activity and cause hypertension and glucose intolerance in early rat adulthood.[69-71] Low birth weight has been related to elevated cortisol levels in adult men[72] and a low birth weight/placental weight ratio is strongly predictive of adulthood hypertension.[69]

Intuitively one assumes that maternal nutritional deprivation, possibly protein, possibly total caloric deficiency, is the major cause of low birth weight in South Africa.

It has been suggested that the effect of growth retardation is mediated through allometric control. That is, scarce nutrients are channelled to essential organs (e.g. the brain) to the detriment of others. In this scenario, both the liver[36] and the pancreas[43] are compromised. Certainly there are data suggesting a reduction of islets or beta cells in NIDDM. NIDDM is characterised by at least a 30% reduction in beta cells and a 10% increase in alpha cells.[72] Abnormal vascular development may be a possible mechanism whereby allometric growth is regulated and this is highlighted by results using protein-deprived pregnant rats in which the offspring displayed poor vascularisation of the pancreatic islets.[73,74] The high prevalence of albuminuria in the Nauru Islanders and the

Pima Indians also suggests that renal function may be compromised.[31,75] There appears to be a relationship between low birth weight and albuminuria.[75] It would be interesting to see whether this relationship includes hypertension and other components of the so-called metabolic syndrome.

Left ventricular mass has been found to correlate with birth weight. Thus although the cardium was thought to be 'protected' during maternal nutritional deprivation, this does not appear to be so.[76] This also begs the question whether the brain is fully protected.

Insulin sensitivity has been found to relate to muscle phospholipid fatty acid composition[77] in man. It has been proved that dietary protein reduction in pregnant rats reduces arachidonic acid as well as the activity of Δ5-desaturase in the offspring.[61] These results suggest that programming of long-chain polyunsaturated fatty acid desaturation leads to membrane changes and altered insulin sensitivity. Studies of Pima Indians report that reduced docosahexaenoic acid derived from dietary alpha linolenic acid results in insulin resistance.[78] A recent study[73] has also shown that cortisol levels are increased in adults of low birth weight and this may be another link between reduced fetal development and increased insulin resistance.

Other experimental work in rats has also suggested that the liver can be influenced by a maternal low-protein diet. In humans an indirect association has also been implied by measurement of abdominal circumference of newborns.[34,36,79,80] Alterations in fibrinogen, cholesterol and renin are associated with abdominal circumference.

In rats there are some data[81] to suggest that zoning in the liver is affected by maternal dietary protein deprivation. Zonation of the liver relates to the function of the hepatocyte. Thus the periportal hypatocytes which are exposed to 'fresh' blood are well oxygenated and supplied with substrate.

Gluconeogenesis occurs mainly within these cells. The perivenous hepatocytes are more involved in glycolysis and ketone body production. Biochemical alterations in hepatic function include increased phosphoenolpyruvate carboxykinase (PEPCK) activity in the periportal area and reduced glucokinase activity in the perivenous region which enhances gluconeogenesis and reduces glycolysis. Increased hepatic PEPCK activity has also been found to result from treatment of pregnant rats with dexamethasone during later pregnancy. The resulting offspring display increased hepatic glucorticoid receptor number and increased expression of PEPCK.[82] Altered hepatic phospholipid fatty acid composition has been described in the offspring of rats fed a low-protein diet during pregnancy.[83] In humans reduced lactic acid and adenosine triphosphate (ATP) production[84] from diminished glycolysis in muscle has been reported in low-birth-weight subjects.

CONCLUSION

In conclusion, increasing data support a maternal nutritional effect on the future adult health of the child. In South Africa both low birth weight and childhood/adult obesity are common. Although not explaining all cases of diabetes, the thrifty phenotype highlights a potentially burgeoning health problem and at the same time offers the opportunity to prevent this coincidence of processes in South Africa. The fact that all changes are 'fixed' by 5 years of age suggests that this offers the most fruitful time for intervention.

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