

whether the same can be said of the efforts required to convince bureaucrats and agencies to fund longitudinal, observational research of the scope that will be needed to show the long term benefits of breast feeding—but I would welcome the opportunity to stand corrected.

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## Intrauterine factors, adiposity, and hyperinsulinaemia

*Thin babies with excess body fat may explain later adiposity in Indians*

The first world congress on fetal origins of adult disease was held in Mumbai, India, in 2001. The second congress was recently held in Brighton, United Kingdom. In spite of their diverse locations both these meetings were dominated by data from developed countries. This is largely a consequence of the extreme rarity of good historical records of birth size from developing countries. The recent insights emerging from prospective studies by Yajnik et al in Pune in India are therefore notable and deserve attention.<sup>1 2</sup>

The core of the theory of fetal origins of disease is that nutritional deprivation of the fetus during critical periods of development forces the baby to resort to adaptive survival strategies, which entail a resetting of the normal course of metabolic, physiological, and anatomical development. These adaptations become maladaptive if the organism encounters contrasting nutritional circumstances in later life. In relation to insulin action and diabetes Hales and Barker have described this phenomenon as the “thrifty phenotype.”<sup>3</sup> In the words of J V Neel, the initial proponent of the thrifty genotype hypothesis,<sup>4</sup> the thrifty phenotype is “rendered detrimental by progress” and leads to high rates of metabolic syndrome and type 2 diabetes.<sup>5</sup> Recently it has become apparent that it is the disharmony between fetal growth and later growth rates that seems to be the best predictor of the later pathology.<sup>6 7</sup>

A wide range of pathological and non-pathological factors influence fetal growth. Some of these are modifiable during pregnancy (smoking, alcohol, intake of nutrients), and others are essentially fixed at the moment of conception. One of these fixed influences is a mother's body size and composition. In the Indian studies pregnant women are very small.<sup>1</sup> In rural villages they average about 44 kg in mid-gestation, with a height of 1.52 metres and body mass index of 18 kg/m<sup>2</sup>. Under such circumstances maternal uterine constraint becomes a dominant regulator of fetal growth in order to protect the mother from having to deliver an inappropriately large baby. The importance of uterine

constraint has been known for many decades and was graphically shown by Walton and Hammond in their experiments crossing shire horse sires with Shetland pony mares that were much smaller. The uterine environment in the mare suppressed the inherited growth potential of the paternal chromosomes and produced appropriately small foals to allow natural delivery.<sup>8</sup> More recently the molecular biology of this process is emerging as a fascinating conflict between maternal and paternal influences that involves a range of imprinted genes, especially insulin-like growth factor-2 and its receptors.<sup>9</sup> The details aside it has become clear that maternal constraint must have a central role in fetal programming.

Together with Caroline Fall from David Barker's Medical Research Council group in Southampton, Yajnik and his team have used anthropometric measurements of babies to describe their morphology at birth. The picture that emerges is of Indian babies that are much smaller than those in Southampton in all respects except measures of body fat—especially central fat as judged by the subscapular skinfold thickness.<sup>1 2</sup> They describe this as the “thin-fat” baby syndrome and believe that it shows that the excess visceral adiposity of most Asian adults can be traced back to the neonate.

In collaboration with Yudkin at University College London Yajnik has shown that in the babies of urban mothers in Pune, insulin concentrations in the blood of the cord seem raised compared with the British babies and are correlated with subscapular skinfold thickness.<sup>2</sup> Later in childhood these thin-fat Indian babies can be shown to have profoundly impaired indices of insulin sensitivity, which are inversely correlated with birth weight.<sup>10 11</sup> These correlations with birth weight are importantly modified by both their postnatal growth rate and their achieved size in relation to their predicted size based on mid-parental height; with greater growth equating to worse insulin resistance (data presented by Yajnik at the recent Brighton congress). These findings emphasise the issues about disharmonious growth being a major contributor to later pathology.

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Much controversy remains about whether the diabetogenic inheritance of being small at birth is mediated through effects on insulin resistance or secretion, or both. The Indian group surmise that it is the extra adipose tissue mass that is driving insulin resistance, probably through its action as a quasi-endocrine organ,<sup>12</sup> but this remains to be proved.

The fetal origins theory is of greatest relevance to the developing world, and the implications of this work for global health are enormous. Around 95% of the world's growth retarded babies are born in developing countries, and a recent report from the World Health Organization and United Nations Food and Agriculture Organization (FAO) predicted that a global epidemic of obesity driven type 2 diabetes will soon dominate health care for chronic diseases, especially in Asia.<sup>13</sup>

So how should we try to intervene to limit the damage? The obvious response to the "small baby predicts later disease" paradigm is to propose dietary supplementation of mothers to produce larger babies. To a certain extent this seems sensible; we should probably act to prevent retarded fetal growth in mothers whose diet is so poor as to limit the baby's expected growth trajectory in relation to its parental and genetic inheritance, and to the maternal uterine environment. However, the picture is worryingly confounded by the issue of intergenerational maternal constraint. If we already have short thin-fat mothers producing small thin-fat babies, should we really be feeding them more? Possibly not if this results in augmented fetal growth which will be out of harmony with the baby's inheritance and future growth patterns. The resolution of this conundrum will require focused

investment in international studies on the regulation of early human growth and development.

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## Herbal medicines put into context

*Their use entails risks, but probably fewer than with synthetic drugs*

Recent reviews have rightly alerted us to the risk associated with herbal medicines.<sup>1</sup> This is necessary and important. But the more important question probably is—do the risks of herbal benefits outweigh their potential for harm? Therefore I will try to put herbal medicines into context and consider the benefit they might bring.

The potential benefits of herbal medicines could lie in their high acceptance by patients, efficacy, relative safety, and relatively low costs. Patients worldwide seem to have adopted herbal medicines in a major way. Survey data from the United Kingdom show that herbal medicine has been tried by about 30% of the British population.<sup>2</sup> The associated out of pocket expenditure was estimated to amount to £31m (US\$47.7m; €45m) in the United Kingdom<sup>2</sup> and £1.3bn in Germany.<sup>3</sup> Herbal medicines are used predominantly for minor and self limiting indications, with respiratory tract infections heading the list.<sup>3</sup> But even for those conditions the remarkable acceptance of herbal medicines can be a good thing only if they can be shown to do more good than harm at reasonable cost.

The efficacy of herbal medicines has been tested in hundreds of clinical trials, and it is wrong to say that they are all of inferior methodological quality. But this

volume of data is still small considering the multitude of herbal medicines—worldwide several thousand different plants are being used for medicinal purposes.<sup>4</sup> A recent overview included 23 systematic reviews of rigorous trials of herbal medicines.<sup>5</sup> Eleven came to a positive conclusion, nine yielded promising but not convincing results, and three were negative. The relative paucity of rigorous clinical trials is mostly due to the fact that, compared with the pharmaceutical sector, the herbal industry is small and can rarely afford the considerable expense of a clinical trial. Sadly the traditional use directive, which sets out to harmonise the registration of herbal medicines in the European Union,<sup>6</sup> lacks any incentive for companies to invest further into research. Public funds are only very rarely dedicated to research in this area.<sup>7</sup>

Even though herbal medicines are not devoid of risk,<sup>1</sup> they could still be safer than synthetic drugs. Between 1968 and 1997, the World Health Organization's monitoring centre collected 8985 reports of adverse events associated with herbal medicines from 55 countries.<sup>8</sup> Although this number may seem impressively high, it amounts to only a tiny fraction of adverse events associated with conventional drugs held in the same database.<sup>8</sup> However, the relative paucity could also