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# COMMENTARY

# Birth Weight and the Fetal Origins of Adult Disease

**Commentary on the article by Oliver *et al.* on page 516**

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The sheep remains the animal in which it is possible to investigate fetal physiologic processes in detail: much of our knowledge of fetal development has been derived from this species, in particular in the use of the chronically instrumented preparation. Although relatively precocial at birth, sheep nonetheless share developmental features with the human that make them appropriate for investigating the mechanisms of human disease; for example, like the human the sheep has its full complement of cardiomyocytes and nephrons at birth. The ability to determine gestation precisely and to manipulate the diet or hormonal status of the pregnant ewe has led several groups to use the sheep to study the mechanisms underlying the fetal origins of adult disease. Needless to say, the length of gestation and the time to achieve maturity in the offspring make such studies prohibitively expensive and labor-intensive for both researchers and technical support staff. The studies from the Liggins Institute in Auckland published in this issue (1) are therefore of great importance, because in this study offspring of undernourished ewes were followed up to 30 mo of age postnatally.

The question addressed by the paper is the relative importance of birth weight *versus* maternal undernutrition in programming cardiovascular and metabolic function in the offspring. Although it is not unexpected that severe undernutrition produces an effect on birth weight, there is in fact evidence that supports the alternative hypotheses that programming mechanisms, initiated by unbalanced maternal nutrition, operate either through or independently of changes in fetal growth. Maternal undernutrition in late gestation may elevate maternal stress hormones such as glucocorticoids; in addition the challenge may alter the activity of the placental 11$\beta$-hydroxysteroid dehydrogenase barrier (2, 3), and both effects may elevate fetal plasma glucocorticoids levels. There is now a wealth of information that this elevation alters fetal growth, cardiovascular development and function, and metabolism (4, 5). If this constitutes the mechanism underlying fetal programming, then it should occur independently of changes in birth weight, for effects on fetal growth are only one of the panoply of effects of glucocorticoid exposure. The data from a range of animal models used would support this contention, as effects on postnatal blood pressure, resistance artery function, hypothalamic-pituitary-adrenal axis response, and glucose tolerance can be produced by nutritional manipulation in pregnancy (especially in early gestation) without necessarily producing effects on birth weight (6, 7). In contrast, the plethora of epidemiologic studies conducted across the globe has reinforced the concept that low (but not necessarily pathologically low) birth weight is associated with adult disease, especially hypertension and type 2 diabetes (8). Although most researchers concede that birth weight is a poor proxy for fetal growth and may give little insight into fetal adaptive processes, nonetheless these studies have reinforced the need for further investigations into the effects of processes operating during fetal development as determinants of later health and disease.

In the study of Oliver *et al.* (1), pregnant sheep were severely undernourished for 10 or 20 d from 105 d gestation (term = 146 d in this flock), and blood pressure and glucose tolerance were measured at 5 mo of age in both male and female lambs. At 30 mo of age, only ewes were studied, but at this age blood pressure, glucose tolerance, insulin sensitivity, and GH challenges were performed. Only singleton pregnancies were studied. As expected, the undernutrition reduced birth weight, but this was only significant in the group of lambs from ewes underfed for 20 d, and then only in ewe lambs. This may just be a feature of the power of the study, although the numbers of animals in each group (more than 10) were quite high for a study involving large animals. Sex differences in fetal endocrine responses to hypoxia (9) and effects of undernutrition on gestation (10) have recently been reported, and it is widely believed that, in humans, female fetuses are more mature at birth than males. We do not yet know whether such effects (which are relatively small) should be viewed as a sex-specific adaptation or differences in susceptibility to a potentially pathologic effect.

Despite the small effects on birth weight, the plasma glucose area under the curve after a glucose load and blood pressure increased with weight at 5 mo of age and with falling birth weight. This demonstrates how programming processes can operate against the background of "normal" growth, for after weaning body weights were not different among the groups. Only female lambs were studied at 30 mo of age (presumably related to the management problems associated with keeping

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larger numbers of sexually mature male lambs), and at this age plasma insulin and IGF-I levels were related to current weight and inversely related to birth weight. Plasma insulin responses to GH also increased with current weight. It is therefore clear that, *within* the groups, birth weight and postnatal growth (or at least current weight at study) are related to components of cardiovascular and metabolic control even in the absence of absolute differences in responses among the groups. Again, this reinforces the concept that programming mechanisms operate across the range of normal development in a population: epidemiologic studies show a correlation with birth weight in the population, made possible by the large numbers of subjects studied. In addition, those studies relating to men and women born in the middle of the last century would not be expected to include many intrauterine growth-retarded infants as their survival would have been low.

The effect of a late-gestation undernutrition challenge reported in this paper needs to be compared with those of a challenge in early gestation reported in previous studies cited (11–14), in which hypertension and enhanced hypothalamic-pituitary-adrenal axis responses have been shown, or those in which placental function was impaired throughout pregnancy by carunclectomy (15). The Auckland group has shown effects of such early undernutrition on fetal growth trajectories and responses to a late-gestation challenge (16–18). Much interest in this timing of a challenge has been fostered by the findings of Kwong *et al.* (19) in the rat that a preimplantation nutritional challenge affects early embryo growth and later blood pressure, and those of Dodic *et al.* (20) in the sheep that early pregnancy exposure to dexamethasone produces hypertension and other effects in the offspring. It is too early to conclude that common underlying mechanisms operate in all these studies, regardless of species, timing, and severity of insult. Indeed, it may be naïve to expect a single chain of cause and effect to operate in any case: a challenge occurring at a particular developmental stage may well not only induce an adaptive response at that time, but additionally determine the organism's response to a subsequent challenge, if it occurs. The same initial challenge may involve no or a different effect if it occurs at a different time, and may not influence the response to a subsequent challenge. Implicit in the fetal programming idea is the concept of a critical window of development during which a challenge may produce permanent effects. However, such effects may remain hidden and are graded, so that individuals show different degrees or no pathologic effects. Also implicit is the notion that the programming effects can be amplified or exacerbated by a subsequent challenge. This is revealed in the epidemiologic studies in which both birth weight and postnatal growth are predictors of coronary heart disease (21), and it is also evident in several of the animal studies (7).

The converse of these idea offers hope for new interventions, as appropriate advice tailored for individuals, *e.g.* on diet or body habitus, may help to reduce their risk of coronary heart disease and other chronic illness. We do not as yet know the extent to which we can relate the findings of Oliver *et al.* (1) to the development of pathology in the sheep; it may be that the ubiquitous biologic phenomenon of programming in response to, for example, a dietary challenge does not induce pathologic changes in all species. Indeed, even breeds of sheep may differ in this respect. Oliver *et al.* (1) used Romney Marsh–Dorset cross animals, a lowland strain, which might show different adaptive responses from strains bred to survive harsher conditions such as Welsh mountain sheep. The comparative physiology of programming in species, and between strains, will be a productive area for future research. But it will require the courage of funding agencies to commit resources to such lengthy and costly endeavors as that of Oliver *et al.* (1). The rewards, in terms of reduction of the burden of chronic disease across the globe, promise to be great.

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