Invited commentary

Fetal origins of adult disease

Several decades of research have demonstrated that significant contributions to risk of cardiovascular disease are made by adult lifestyle factors such as smoking, high consumption of saturated fats and salt, low levels of physical activity, and obesity. The more recent assertion that the risk of hypertension and coronary heart disease in adult life may be determined by an adverse environment before birth (Barker, 1994) has proved to be extremely controversial. Whilst this hypothesis is supported by a large number of retrospective epidemiological studies throughout the world, it remains true to say that such studies may be confounded by uncontrollable social and genetic factors.

Animal studies permit the investigation of the fetal origins of adult disease hypothesis in a more invasive manner, without the burden of such confounding factors. A number of such studies have been published, broadly supporting the hypothesis that fetal exposure to maternal undernutrition induces permanent alterations to cardiovascular control systems, manifesting as elevated blood pressure in adult life. As reviewed elsewhere, the feeding of low-protein diets, low-iron diets, high-saturated-fat diets and extremely-low maternal food intakes in rat pregnancy have all demonstrated the same general hypertensive effect (Langley-Evans *et al*. 1998). As yet, the precise nature of the mechanisms involved in the prenatal programming of hypertension remains unclear.

The paper by Holemans *et al*. (1999), in this issue, offers a different perspective to the problem. Pregnant rats underwent a 50 % reduction of normal food intake in the second half of gestation. At birth the pups either remained with mothers that had undergone food restriction, or were fostered to mothers that had been maintained on a normal diet. Although undernourished and growth-retarded before birth, the systolic and diastolic blood pressures of the 100-d-old offspring were similar to those of control rats exposed to maternal *ad libitum* intakes *in utero*. Although normotensive, some differences in responses to vasoactive agents were noted in the isolated arteries of the undernourished offspring. The effects of the NO inhibitor, Nω-nitro-L-arginine methyl ester, were similar in all groups of animals, but the arteries of undernourished offspring exhibited enhanced sensitivity to exogenous NO. These arterial preparations also differed in endothelium-dependent relaxation responses to bradykinin and acetylcholine, the responses being reduced relative to the vessels from control animals. The Holemans *et al*. (1999) paper concludes that the study does not support the hypothesis that intra-uterine undernutrition of the fetus programmes adult hypertension. The results do, however, indicate that prenatal nutrition can exert long-term effects upon the developing cardiovascular system. What remains to be resolved is the question of whether such effects predispose the individual to hypertension and end-stage disease.

Previous animal studies have demonstrated that in determining long-term blood pressure, the precise nature of the intra-uterine dietary manipulation may be critical (Langley-Evans *et al*. 1998). A mild restriction of protein within the maternal rat diet elicits 15–30 mm Hg elevations of systolic blood pressure in the 4-week-old offspring (Sherman & Langley-Evans, 1998). In contrast, a severe (70 %) restriction of total food intake in rat pregnancy (Woodall *et al*. 1996) induces only a 5–6 mm Hg elevation of pressure that manifests much later in life (30 weeks of age). In general, a balanced intra-uterine nutrient restriction, as applied by Holemans *et al*. (1999) and Woodall *et al*. (1996), produces a lesser effect upon later blood pressure than does the limiting of a specific nutrient in the diet (Langley-Evans *et al*. 1999). Given the findings of Woodall *et al*. (1996), where small elevations of blood pressure manifest in the undernourished offspring only beyond 30 weeks of age, it would be of interest to determine whether the alterations to arterial responses noted by Holemans *et al*. (1999) produce a similar late-onset hypertension.

Maternal food restriction to 50 % of *ad libitum* intake in the second half of pregnancy proved to be an effective means of inducing fetal growth retardation (Holemans *et al*. 1999). As with the form of undernutrition, the duration and timing of the undernutrition in pregnancy may also be an important determinant of later hypertension. Rats exposed to low-protein diets for any single week period of fetal life have elevated systolic blood pressure (Langley-Evans *et al*. 1999). The hypertensive effect of maternal protein restriction is greatest where undernutrition is targeted to the final week of gestation, but even this effect is less than that observed with animals that are undernourished throughout fetal development.

Whilst having no effect upon blood pressure, late-gestation food restriction in the rat alters the *in vitro* vascular responsiveness of arterial preparations from the offspring to a number of vasoactive agents (Holemans *et al*. 1999). Whilst of considerable interest and importance, these findings may not be indicative of the *in vivo* responses to such agents. As with all animal studies, caution must be taken in extrapolating from these findings to human disease states. Future studies, however, should evaluate the effects of NO inhibitors, exogenous NO and the endothelium-dependent relaxation agents in the intact animal. Extension of these studies to consider the renin–angiotensin system, which has been implicated in the intra-uterine programming of hypertension (Sherman & Langley-Evans, 1998), would also be desirable.

The altered *in vitro* vascular responses reported by Holemans *et al*. (1999) would appear to oppose one another,

in that NO would increase vascular resistance whilst bradykinin promotes vasodilatation. This illustrates the previously-observed point that just as the dietary stimuli that programme hypertension are varied, there are a number of different hormonal mechanisms operating in fetal life which appear to promote adult disease (Langley-Evans *et al*. 1998). With regard to the development of hypertension, intra-uterine environment-induced alterations to these responses may require further postnatal influences to elicit significant and permanent elevations of blood pressure. To date there is little or no research which has considered the interaction between prenatal and postnatal diet upon cardiovascular health. It might be postulated that the fetal environment predisposes an individual to later disease in a manner that is either independent of later lifestyle, or in a manner that requires a poor diet, high alcohol intake, smoking or obesity for manifestation of measurable symptoms. Indeed, the magnitude of the blood pressure elevation related to a low birth weight reported by Barker (1994) is well below the level associated with human disease. Typically a 3–5 mmHg higher blood pressure is noted for every 1 kg reduction of birth weight. Within the UK, most birth weights will fall within a 2 kg range (2·5–4·5 kg), giving the potential for a maximum 10 mmHg contribution of fetal factors to adult blood pressure. Interactions of pre- and postnatal factors must occur to increase significantly the risk of cardiovascular disease in the general population.

In summary, the paper by Holemans *et al*. (1999) has provided a valuable insight into the processes that underlie the fetal origins of adult disease hypothesis. The epidemiological findings of Barker and colleagues that birth weight and proportions at birth may predict later blood pressure (Barker, 1994) are clearly the first crude indications that a complex series of intra-uterine influences may permanently alter cardiovascular functions. These alterations may clearly manifest as hypertension in adult life, but may also be more subtle and require further environmental stimuli to produce human disease.

Simon C. Langley-Evans
Nene Centre for Healthcare Education
Boughton Green Road
Northampton NN2 7AL
United Kingdom

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