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GROWTH AND DEVELOPMENT CONTRACT SESSION

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In 2003 the Centre of Research Excellence (CoRE) for Growth and Development was formed. The purpose is to conduct research into growth and development, focussing particularly on the issues of pre – and post natal growth and its implications for human health.

The medical challenges for the developed world are those associated with the nutritional environment, obesity and the associated illnesses of diabetes and cardio – vascular disease. There is evidence linking the propensity for these diseases to the nutritional status of the fetus in the first trimester of pregnancy and the interaction of this status with nutrition in the immediate post – natal period. In this respect the problem differs from the issues considered by animal production. Here the last trimester of pregnancy has received the most attention, and few domestic animals live long enough for cardio – vascular problems to arise. Nevertheless the skills and methods of investigation developed by animal scientists can be applied to these new problems

Animal production research and medical science have much to offer each other, but with a few notable

exceptions this potential has not been realised. A cursory look at the references listed by the authors in this contract shows little evidence of contact. One of the goals of the CoRE is to promote this interaction. This contract session with the New Zealand Society of Animal Production has two goals. First, to make animal scientists aware of the questions facing medical scientists with respect to early growth and development, the focus of the CoRE effort. Second, to encourage individuals to make contact and build future networks with the aim of developing joint projects.

Progress in managing the diseases of obesity would have a remarkable effect on human well being. New Zealand has a unique opportunity to combine the knowledge underpinning its powerful agricultural industry with the world class medical science represented at the Liggins Institute to address these problems. The potential is enormous, although naturally building such co-operative ventures takes time. This contract session is a beginning.

BRIEF COMMUNICATION

Sheep nutrition, fetal growth and human health

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Keywords: fetus; nutrition; growth; programming.

It has long been known that impaired size at birth is associated with a high mortality and morbidity, both around the time of birth and subsequently. This is true in domestic animals, wild animals and humans. However recent recognition in human populations that babies born small are at increased risk of a number of adult diseases, including coronary heart disease and diabetes, has added weight to the importance of research in this field (Barker, 1998). In domestic animals such as sheep it is not hard to demonstrate that limited maternal nutrition results in reduced size at birth. However the dogma has always been that this is not true in humans, and that only exposure to the most severe of famine conditions will result in reduced birth size (Kramer, 1987). Furthermore, trials of nutritional supplements in human pregnancy have resulted in minimal effects on size of the offspring (Kramer, 2002). This apparent species difference is more readily understood if it is kept in mind that fetal growth is regulated by fetal nutrition, but that

maternal nutrition is not the same as fetal nutrition. Nutrition reaches the fetus via a long “supply line” which begins with the maternal diet and metabolism and is affected by the uterine vasculature and placental transport capacity before finally reaching the fetus (Bloomfield & Harding, 1998). Common clinical causes of impaired fetal growth involve interruption of the supply line, resulting in fetal undernutrition even in the presence of normal or indeed excellent maternal nutrition (Harding, 2003).

Many children born small show rapid growth after birth to obtain normal adult stature. However a proportion of infants born small do not show this catch-up growth and remain permanently stunted. Those who do not catch-up also appear to have increased morbidity (Harding & McCowan, 2003) (Karlberg & Albertsson-Wikland, 1995). Thus the factors that determine the potential for later catch-up growth or otherwise are of critical importance. It is at least 30 years since Mellor

and colleagues demonstrated that fetal sheep exposed to maternal undernutrition for a relatively brief period of time in late gestation showed prompt catch-up growth when the restriction was relieved, whereas more prolonged maternal undernutrition resulted in irreversible growth failure of the fetus (Mellor & Murray, 1982). Our own attempts to repeat these studies revealed that not all fetuses slowed their growth in the face of an apparently consistent maternal nutritional insult. We were able to demonstrate that fetuses growing rapidly in late gestation slowed their growth in response to maternal nutritional restriction, whereas those growing slowly in late gestation were able to continue this slow growth in the face of nutrient restriction (Harding, 1997b). We hypothesised that this slow growth pattern in late gestation was established early in pregnancy.

Further studies involved maternal undernutrition in sheep from 60 days before until 30 days after mating. These studies involved individual feeding of ewes to obtain a standard reduction in body weight to ensure that individual differences in metabolic rate and feed conversion did not add variance to the data. Using this approach we have demonstrated that undernutrition around the time of conception results in profound changes in the late gestation fetus. A slow growth trajectory is established which persists out to term and allows continued growth in the face of a brief late gestation nutritional insult (Harding, 1997a) (Oliver *et al.*, Submitted for publication). Fetal metabolism is altered in a way that suggests altered placental function (Oliver *et al.*, submitted for publication) (Harding & Gluckman, 2001). Fetal insulin secretion is increased in response to an arginine but not a glucose challenge in late gestation, suggesting early maturation of the fetal pancreatic beta cells after periconceptual undernutrition (Oliver *et al.*, 2001). There is also evidence of early maturation of the fetal hypothalamic/pituitary/adrenal axis with an early rise in cortisol, ACTH and prostaglandins leading to preterm delivery (Bloomfield *et al.*, 2003) (Bloomfield & Harding, submitted for publication, Kuramasamy *et al.*, submitted for publication).

All these data suggest that nutritional events around the time of conception have profound effects on later fetal growth and maturation. The mechanisms underlying the signals that the embryo must receive about maternal nutritional status are not yet clear. However possibilities include maternal responses to pregnancy and altered placental structure and function. These possibilities are currently being investigated. Furthermore, it is not yet clear if these effects have long term consequences. Detailed follow-up studies of the offspring, even into the second generation, will be required to clarify these effects. In view of the apparent relevance of these findings to human health more work is urgently required in this area.

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