The concept of fetal programming was introduced by Professor David Barker in the late 1980s based on his studies of birth weight and its correlation with death from cardiovascular diseases in adult life.\(^1\) Although this hypothesis was initially met with criticism, it has grown to be well accepted since the mid-1990s.\(^2\) However, the mechanisms underlying the link between a suboptimal intrauterine environment, the early postnatal period and health in adult life have been difficult to determine. Two outstanding fetal physiologists have made significant contributions to our understanding of the mechanistic links between alterations in the intrauterine environment and health in adult life: Professors Eugenie Lumbers and Caroline McMillen. Their remarkable contributions were celebrated recently at the Australian Early Origins of Hypertension Workshop, a satellite to the International Society for Hypertension meeting in September 2012. Forty national and international experts gathered to share their work, particularly as it relates to aspects of the contributions made by Caroline and Eugenie. Some of the studies discussed at the meeting are presented in this themed issue.

Eugenie Lumbers graduated with an MBBS from University of Cambridge and was subsequently awarded a Doctorate in Medicine from that university. In 1971, she became the first female recipient of the NHRMC CJ Martin Fellowship that led her to the Nuffield Institute for Medical Research in Oxford (1972–1973). On her return to Australia and appointment as a Senior Lecturer in 1974, she established her own laboratory at the University of New South Wales (UNSW) and has been consistently funded by the Australian Research Council, the National Health and Medical Research Council, Australian Kidney Foundation and the National Heart Foundation. In 1992, Eugenie was awarded a Vice-Chancellor’s Award for Teaching Excellence. In 1993, she served on the Prime Minister’s Advisory Committee for Women in Science and Technology. In 1999, Eugenie became a Scientia Professor, the first female Scientia Professor at UNSW. In 2002, she was elected to the Australian Academy of Science and received the Centenary Medal of Federation. In 2002, she was elected a Fellow of the Royal Society of Australia. In 2012, she was awarded an Order of Australia.

Professor Lumbers’ research has been broad-based: she has studied both cardiovascular and fluid and electrolyte physiology in the adult, the fetus and the newborn.\(^3\)\(^,\)\(^4\) She has been particularly interested in the role and actions of the renin–angiotensin system (RAS), in both animal models and humans. She discovered inactive renin\(^5\) (prorenin) and, with Brian Morris, demonstrated that it was activated by proteases.\(^6\) Most of her work in some way relates to the development ofthe cardiovascular system and kidney, including development of neural control of the circulation\(^7\) and programming.\(^8\) Eugenie has also made contributions to fetal gene therapy. Her current interests are related to the roles of the renin–angiotensin system in human placentaion and in pregnancy-associated hypertension,\(^9\) as well as programming of renal diseases. She also has interests in the role of cardiac function in preterm neonatal hypotension.\(^10\) Eugenie is also studying the repositioning of drugs that block the renin–angiotensin system as potential anticancer drugs.

Caroline McMillen graduated with a BA (Hons) and Doctor of Philosophy at Oxford University before completing her medical degree at the University of Cambridge. She moved to Australia to take up a Lectureship at Monash University, and was appointed as Chair and Head of Physiology at the University of Adelaide in 1992. She served as Dean of the Faculty of Science and as Director of the Research Centre for the Early Origins of Adult Disease at the University of Adelaide and was appointed as Pro/Deputy Vice Chancellor Research and Innovation at the University of South Australia (UniSA) in 2005. Caroline’s most recent appointment in 2011 is as Vice Chancellor at the University of Newcastle (New South Wales). Her research has been supported by the Australian Research Council and National Health and Medical Research Council for over 20 years. She was ranked in the top 1% of all Web of Science authors for the last decade in the subject area of Biology and Biochemistry.

Caroline has published seminal papers on the development of neuroendocrine control of cortisol in the developing fetus, dissecting the impact of fetal growth restriction on the developmental capacity of the cells in the pituitary, which are responsible for the stimulation of cortisol synthesis and secretion.\(^11\) Caroline’s early work on the effects of placental insufficiency on the sympathoadrenal system,\(^12\) and on fetal growth, draw together the key components that link intrauterine growth retardation because of placental insufficiency (the major cause of IUGR in Western nations) as a key link in the DOHAD concept.\(^13\) Caroline’s group made the observation...
that leptin acted in the brain of the fetus to cause a change in fat development.14 Furthermore, she showed that all of the appetite-regulatory neuropeptides were present in the brain of the sheep before birth; she proceeded to investigate the responses of the ‘fat-brain’ axis to exposure to excess nutrients in late gestation in fetal and postnatal life.15 Caroline has pioneered a unique animal model in which embryos are transferred in early life from an obese ewe to a ewe of normal body weight to show that exposure to maternal obesity during a period before and for 1 week after conception alone can result in an increase in the total mass of fat, particularly visceral fat, in her offspring.16 The work of her group on the periconceptional programming of epigenetic changes in the stress axis of the offspring17,18 and her current work on the epigenetic programming of changes in the insulin signaling and growth pathways within the liver and muscle after early nutritional restraint19 are typical of Caroline’s prescience in her field.

The papers presented in this themed issue reflect the main topics of research that Eugene and Caroline have focused on, some from their collaborators, and others from their mentees. The issue begins with two reviews that outline the impact of maternal hypoxia,20 and maternal overnutrition,21 on cardiovascular health. Giussani and Davidge20 describe the impact of prenatal hypoxia on the development of the cardiovascular system, leading to an increased risk of cardiovascular diseases in adult life. Importantly, to reflect the direction in which the field is now moving, they also describe possible interventions to prevent cardiovascular diseases. Furthermore, the physiological, structural and molecular consequences of maternal overnutrition on tissues such as the heart, kidney and skeletal tissue and, consequently, risk of cardiovascular diseases are reviewed by Blackmore and Ozanne.21 Gugusheff et al.22 show that cross-fostering offspring that were exposed to a ‘junk food’ diet throughout gestation onto control dams during lactation can prevent increased fat intake and fat mass, but the effect is sex dependent. Probyn et al.23 show that maternal alcohol consumption during pregnancy decreased surfactant protein B and increased fibrosis in the lung in adulthood. While Boyce et al.24 show that vitamin D supplementation during pregnancy and weaning results in an increase in renin mRNA expression in the kidney of offspring as adults.

The periconceptional period has also been identified as an important time period where maternal health can influence the health of her offspring. Lie et al.25 show that periconceptional undernutrition in sheep alters the expression of molecules involved in cardiac growth and metabolism, with differential effects in singletons and twins. Furthermore, in the same model of periconceptional undernutrition, Zhang et al.26 show that both periconceptional undernutrition and undernutrition in only the first week of pregnancy reduce glucocorticoid receptor mRNA expression in the pituitary gland, which may program an increased stress response in the offspring.

Fetal growth restriction was the first known cause of fetal programming of cardiovascular health. Macko et al.27 use the maternal hyperthermia model of fetal growth restriction to show that before growth restriction, there is an increase in fetal plasma noradrenaline that suppresses insulin secretion from the pancreas. Meyer-Gesch et al.28 used a model of uterine space restriction to induce fetal hypoxemia, hypoglycemia and growth restriction, resulting in delayed development of the kidney. While Lie et al.29 use the carunclectomy model of fetal growth restriction in sheep to show that 21 days after birth, there are changes in the protein abundance of molecules involved in lipid accumulation in omental fat that may explain the increased risk of visceral adiposity in individuals that are born growth-restricted.

Together, this collection of articles covers the main themes of research that Eugene and Caroline continue to focus on, highlighted by the contributions that they and their mentees have made to this issue. We look forward to following their continuing body of work.

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