

# From Inkerman Street to Australia

## The MEDICINE-Gilliland Fellowship

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Two years ago my colleagues and I spent a lot of time in Preston. In the area around Fulwood Park we walked down streets of terraced houses named after our colonial past, knocked on doors and examined men and women who had been born in the local maternity hospital, Sharoe Green. In the hospital remarkably detailed obstetric records have been preserved for more than fifty years, and we used them to relate fetal growth to cardiovascular disease in adult life.

Though surprised that the maternity hospital where they were born had renewed its interest in them, the inhabitants of Inkerman Street, Gordon Street, Mafeking Road readily agreed to help. An early analysis of the results showed that men and women who had had lower birthweight, in relation to the length of their gestation, now had higher blood pressure. This was interesting, but we knew it already. What was new was that those who had had lower birthweight in relation to the weight of their placentas also had higher blood pressure. The trends were strong, the differences large: the *BMJ* spent weeks trying to find the catch before they gave up and published the paper. Other surveys have since confirmed the results. What do they mean?

Fellows of the Royal College of Physicians know little about the placenta, let alone what causes it to be disproportionately large in relation to the size of the baby. So I sought help from our sister college across the park. Though Fellows of the Royal College of Obstetricians and Gynaecologists know much about the placenta, they too know little about what makes it disproportionately large. Couples conceive, it was explained to me, in order to produce a baby, not a placenta, and concern for the former has overshadowed interest in the latter. Books were recommended to me. They were unhelpful—though I did learn that one

president of the College (in the last century) was absolutely certain that the ovary had nothing to do with menstruation.

And so to Oxford and to Geoffrey Dawes. His unit was once the world repository of knowledge about fetal growth and produced a generation of fetal physiologists. Most, however, have gone on to Australia and New Zealand. It became clear that I would have to go there too. A word with Carol Seymour, a form filled in, a brief delay and I was buying the ticket to Sydney, the first stop on my journey.

I learnt nothing about the placenta in Sydney. But I didn't expect to. I went there because Professor Wilcken does interesting work on apolipoprotein B in children and because I wanted to see the Opera House. I made it my first stop because I was once told that circular journeys are best made clockwise. A consultant physician told me that, when I was his registrar, and we were planning a ward round. I have done ward rounds clockwise ever since and I find it works well. The same consultant also told me to beware of men who walk with a springy gait. This has proved less useful, though the dog who bit me in Preston was owned by a man with a springy gait.

I saw Sydney in a day. At 7.30 am a guest lecture; then the Opera House and the art gallery—where the unknown artist, Sydney Lymeburner, now dead of drink, has recently been discovered. I continued to Auckland.

I learnt a lot about the placenta in Auckland. Professor 'Mont' Liggins, though retired, works on. He showed me the converted bicycle shed where he did the experiments on sheep that made him famous and an FRS. He is known for his work on the physiological adaptations made by the fetal seal when its mother dives. When discussing this with him I was careful to conceal my ignorance. All physicians use the techniques for this on social occasions when they see former patients whose faces are familiar but whose illnesses are forgotten. On this occasion, however, my dissimulation was rapidly penetrated by Jane Harding, a paediatrician who once worked at Oxford. In one wonderful afternoon she taught me the essentials of feto-placental physiology.

It rained on the following day, again. Having revised the notes I made with Jane, I went to meet Peter Gluckman, the professor of paediatrics. He told me about the effects of growth factors on the fetus. We discussed thin babies, short babies and symmetrically small babies. It is becoming clear that the physiology, metabolism and diseases of these babies when they become adults are profoundly different. Peter's wife

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Judi told me about the difficult months when home repairs forced them to share their bedroom with their fax machine. The instantaneous transmission from across the world, usually at night, of manuscripts, overdue bills and invitations to conferences in Bogota, though a wonder of our times, proved bad for married life.

Boarding the plane to Melbourne I found myself without a seat. But the man sitting resolutely in mine turned out to be on the wrong plane. He was a New Zealand senator trying to get to Sydney. His departure left local passengers wondering about their leaders. On the flight local wine was in abundance and I chardonnayed my way into the elegant centre of Melbourne. The taxi driver did not know where the hotel was, though he did not tell me so. He was Greek and did not speak English. We drove around for a while speaking in our own languages until we passed a large hotel, for the third time, and I got out.

Professor Geoffrey Thorburn was once deputy director of the Oxford unit. My brief presentation of our findings provoked a strong response from his colleagues. At the MRC Unit in Southampton we are used to strong responses. Stand up and say that coronary heart disease originates neither in improvident living, nor in genetic inheritance, but in fetal adaptations to the mother, and accusations of subverting the public health are unloosed like filopodia from a gastrulating embryo. The strong response of the Melbourne physiologists was, however, one of surprise: not surprise at our findings but surprise that doctors had taken so long to realise what had been obvious to biologists for decades.

The fetus is highly sensitive to the environment afforded by the mother and adapts to it. This is the phenomenon called 'phenotypic plasticity'. The result of adaptation is permanent modification of gene expression, or reduction in cell numbers of particular tissues, or change in organ structure and function. Such permanent effects are called 'programming' and are now thought to underlie cardiovascular disease. Throughout the afternoon and evening discussion continued, during which it was pleasing to meet Roger Short, once a fellow MRC director, who has escaped and found happiness in Australia.

By this stage of the trip I could hold my own in discussion of the placenta. But no-one had yet told me what had made it disproportionately large. My hosts directed me to the Institute of Agriculture. Surprisingly, Australia is unsuitable for sheep. It is hot, yet they wear woollen coats. There is drought and famine for half the year yet they take nine months to gestate and lactate. Determining when it is best to expose ewes to the suboptimal nutrition that inevitably accompanies some part of the reproductive cycle is a major focus of agricultural research. At the Institute Professor Egan and his colleagues showed me data which to them were commonplace but were to me a revelation. If a ewe is deprived of food in early pregnancy, the placen-

ta will enlarge—an adaptation which presumably serves to increase nutrient extraction from the mother. If a period of deprivation in early pregnancy is followed by abundance in later pregnancy, the enlarged placenta can lead to improved fetal growth.

The implications for sheep rearing in Australia are obvious. The implications for human reproduction are beguiling. Does undernutrition in early human pregnancy induce placental growth? Is nausea and sickness in early pregnancy therefore beneficial? What are the preconditions for hypertrophy, since some babies born after malnutrition have small placentas? I went to Adelaide with high expectations. If anyone knew, I was told, it would be Professor Jeffrey Robinson, obstetrician, trout fisherman, wine connoisseur and formerly, of course, at Oxford.

I was not disappointed. The studies which Jeffrey has carried out with Julie Owens have shown how the effects of early pregnancy undernutrition depend on pre-pregnant nutritional state. In sheep the small fetus with the big placenta, the Preston baby that develops high blood pressure, can be produced at will, by manipulation of the mother's pre- and early pregnant diet. Importantly there are many clues to the mechanisms by which maternal undernutrition can influence fetoplacental growth.

No-one who studies the development of the fetus 'can fail to be filled with a sense of wonder and delight', Lewis Wolpert wrote in the 'Triumph of the Embryo'. And wonder and delight were a feature of my trip. So was frustration. With clear evidence that cardiovascular disease, diabetes and other disorders originate in fetal life, progress depends on advances in maternal nutrition and developmental biology. Some answers must come from Australia and New Zealand, where there is a unique concentration of expertise. But the groups there are seriously underfunded, even in comparison with ourselves, and additional money is unlikely to be found within these countries. Will funding sources in Britain help? A meeting in London is planned for September.

I returned home by way of Java, where many pregnant women are undernourished. In 1983 Professor Jane Kusin and colleagues at Airlangga University carried out a randomised controlled trial of energy supplementation during the last trimester of pregnancy—surprisingly the only such trial ever done. Supplementation has no effect on birthweight, but it increased post-natal growth rates in early childhood. The children born during the trial are now ten. Are those whose mothers were supplemented still taller? Do they have lower blood pressure, better insulin production?

I met Jane in Surabaya, in a hotel whose colonial splendour had faded; though a string quartet still played in the lounge, mingling Bach with Japanese chatter. We drove out to the villages in Madura, where the trial was carried out, and wrote a grant application to the Wellcome Trust in a café in the nearby town.

Our writing disturbed flies who spread themselves thickly on the paper, and the smell of dead fish was distracting. The application, however, was successful.

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