Preface

Like other living creatures, human beings are ‘plastic’ in early life: their growth and development are moulded by the environment. Although the growth of the fetus is driven by the generative programme contained in its genome, it is limited by the supply of nutrients from the mother. There are many reasons why it may be advantageous, in evolutionary terms, for the body’s structure and function to remain plastic in early life and this is a general phenomenon of early development.

The human baby responds and adapts to the nutrients it receives by altering its production of hormones and the sensitivity of its tissues to them, by changing its metabolism, and by redistributing its cardiac output to protect key organs, especially the brain. Slowing of growth is adaptive because it reduces the requirements for substrate. Unlike physiological adaptations in adulthood, those made during development tend to lead to life-long changes in the structure and function of the body – a phenomenon sometimes referred to as programming. It is as though the baby receives from its mother a forecast of the nutritional environment it will encounter after birth and changes its physiology and metabolism accordingly.

The plasticity of human development has been known for a long while. Only recently, however, has evidence appeared suggesting that the origins of important chronic diseases of adult life, including coronary heart disease, stroke and type 2 diabetes may lie in fetal responses to the intra-uterine environment. The ‘fetal origins’ hypothesis proposes that these disorders originate through adaptations which the fetus makes when it is malnourished. A feature of the early findings, which came mainly from epidemiological studies, was the strength of the associations between small body size at birth and later disease. Important biological effects must underlie such associations, and it soon became evident that these effects could be replicated experimentally in animals, usually by reducing the mother’s food intake around the time of conception and during pregnancy.

This book focuses on the links between early growth and type 2 diabetes, more specifically the insulin resistance syndrome, in which insulin resistance and impaired glucose tolerance are combined with hypertension and dyslipidaemia. Ten years ago, a study in Hertfordshire, England, showed for the first time that people who had had low birthweight were more insulin resistant and had higher rates of type 2 diabetes in later life. This association has been confirmed in studies in Europe, the US and other countries. We now need to understand the processes that underlie it, and this is the subject of this book.

The first chapter by Hales & Barker describes the ‘thrifty phenotype’ hypothesis. It proposes that type 2 diabetes originates in poor nutrition.
in fetal life and infancy, which lead to insulin resistance and accompanying changes in glucose and lipid metabolism. The baby thereby becomes adapted to poor nutrition and is ‘thrifty’. For so long as it continues to be poorly nourished during childhood and adult life, these adaptations are beneficial. With increased food intake, decreased energy expenditure and the development of obesity, however, the adaptations are no longer beneficial. Increased insulin resistance, combined with a reduced capacity to secrete insulin because of impaired pancreatic β-cell development, lead to impaired glucose tolerance, and ultimately to the insulin resistance syndrome and type 2 diabetes.

A key issue is to what extent does the association between low birthweight and type 2 diabetes reflect poor nutrition or other environmental influences in early life, and to what extent does it reflect genetic influences. Lindsay & Bennett argue for the importance of genes and restate the ‘thrifty genotype’ hypothesis. 40 years ago, Neel proposed that predisposition to type 2 diabetes might arise through genetic variations that were favourable in times when malnutrition was widespread but became unfavourable as nutrition improved. Caroline Fall addresses the rising epidemics of type 2 diabetes that are now occurring in the non-industrialised world. Are the poorer peoples of the world doomed by their genetic inheritance? Or can the adverse effects of increasing energy intakes be offset by improved fetal and infant nutrition? Whatever the answer there is no doubt that obesity is a driving force in these epidemics and we need to know more about the gene–environment interactions which underlie it. These are discussed in the next chapter by Andrew Prentice.

In discussion of nutrition in early life, the distinction between fetal and maternal nutrition is sometimes not made, and maternal nutrition is simply equated with the mother’s diet in pregnancy. In the next chapter I describes how a mother’s ability to nourish her baby is established during her own fetal life and by her nutritional experiences in childhood and adolescence, which determine her body size, composition and metabolism. While the supply of nutrients to the fetus is known to be the major influence that regulates its growth, Frayling & Hattersley argue for the importance of genetic influences in determining the links between size at birth and later disease.

A strength of the fetal origins hypothesis is that it is supported by experimental findings. Experiments show that even minor modifications to the diet of female animals before and during pregnancy may be followed by life-long changes in the offspring in ways that can be related to human disease – for example altered glucose-insulin metabolism and elevated blood pressure. This is the subject of the next five chapters. Bertram & Hanson describe animal models that have been used to study programming. Fowden & Hill review programming of the endocrine
pancreas. Metabolic programming is reviewed by Susan Ozanne, while Christopher Byrne describes the programming of two hormonal axes that modulate insulin action, the hypothalamic-pituitary-adrenal axis and the growth hormone-insulin-like growth factor axis. The long-term consequences of the abnormal intra-uterine environment associated with maternal diabetes are described by Van Assche, Holemans & Aerts.

Finally, Eriksson, Lindström & Tuomilehto return us to public health. Research into the thrifty phenotype hypothesis has two goals. One of them is to determine whether the rising epidemics of type 2 diabetes can be lessened by improving the body composition and nutrition of girls and young women and by protecting the growth of young children. The other goal is the earlier detection and better treatment of the disease. To realise both goals, clinicians, basic scientists and epidemiologists must join forces. My thanks go to the contributors to this book, who have done just that in order to write it. Thanks also to my colleagues, Shirley Simmonds and Pam Freeman, who helped with the editing, and to Gill Haddock who produced the book.

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