

# Preface

*We fat all creatures else to fat us, and we fat ourselves for maggots. Your fat king and your lean beggar is but variable service, two dishes, but to one table; that's the end.*

Hamlet. A tragedy by William Shakespeare (1599/1601).

There is more to our state of adiposity than simply what quality of meal we are offering the maggots upon our demise. Obesity brings with it greater risk of non-communicable diseases such as cardiovascular disease, diabetes, musculoskeletal disorders and cancer. It no longer seems likely that the escalating incidence of obesity and these related diseases can be mitigated by just changing adult lifestyle and diet. Now the concept of a developmental origin of health and disease (DOHaD) is firmly part of scientific, clinical and health policy activities aimed at understanding and reducing the risk of non-communicable diseases. But the focus of the field has moved from small babies and maternal undernutrition to the other end of the nutritional spectrum, maternal obesity and the future life of the larger baby. It seems that obesity begets obesity, and so the cycle continues, as is evident from the more than doubling of the worldwide prevalence of obesity since 1980 [1]. The time is ripe for this book.

The chapters are authored by undisputed leading scientists, clinicians and policy makers in this field. In these chapters, the authors set out their ideas and provide an up-to-date synthesis of the current thinking about the problem of parental obesity, the ideas of intergenerational programming, and the physiology behind it. We hope that this book will therefore appeal to a broad readership of students, clinicians, researchers and health policy makers who either seek an introduction to the area of DOHaD or have a specific interest in the pathogenesis of obesity.

In this book, the spotlight is on critical periods in development when obesity might affect offspring physiology, sometimes even before a mother conceives or is aware that she is pregnant. These effects appear to have a legacy across several generations. In Chap. 2, Gaillard and Jaddoe draw upon their considerable experience and data from the observational Generation R study, and in Chap. 3 Patel and Poston write from the perspective of their

recent randomized control trial (RCT) of a diet and physical activity intervention (UPBEAT). In both chapters, the authors call for more RCTs to understand intergenerational programming. The impact of maternal obesity on offspring physiology is multifaceted and linked to disease of the cardiovascular system and metabolism, to allergic diseases (see Chap. 15) and to cancer (Chap. 13). The importance of early critical windows is emphasized by research (Chap. 5) showing the potential for the environment around time of fertilization (pre-implantation) to have a lasting impact on offspring physiology. Indeed many contributors to this book recommend that in order to break the ‘intergenerational cycle’ of obesity, interventions should target obesity in the preconception period as well as throughout pregnancy. Nevertheless, others argue for a better evidence base, since there may be negative implications of dietary restriction/weight loss or exercise before or around time of conception (Chap. 7). Part of this evidence base is likely to concern the 16 million women 15–19 years old who give birth each year, about 11% of all births worldwide [2]. The way in which weight gain and obesity during pregnancy in the young, still-growing mother affects offspring is more complex (Chap. 4) and the use of the sheep as a model for this has produced important mechanistic insights.

“Women are responsible not only for the health of their own offspring but also for the cost to the community of an unhealthy future population. . . . Women are caught in a pincer movement between those seeking to protect the fetus and those concerned with the social and economic cost or burden of ill health” wrote Ray Noble (2006) [3]. Therefore, it is timely that research into the influence of paternal obesity on offspring physiology has burgeoned (Chap. 6). Obese fathers are more likely to father an obese child with impaired glucose metabolism, an effect which may then extend into the next generation. These observations have the potential to shift at least some of the burden of responsibility for lifestyle intervention pre-pregnancy from the mother to the father.

To understand causality in human observational studies of maternal obesity and impact on offspring, more sophisticated study designs and detailed maternal-offspring outcome measurements are now needed (Chaps. 2 and 3). However, over the course of this book the reader will discover that substantial advances in understanding the mechanisms and pathways linking parental obesity to offspring physiology are being made using animal models. As with drugs, overeating may involve a chronic cycle of intoxication (‘positive reinforcement’) and the emergence of withdrawal anxiety over time that perpetuates disordered eating. The physiological evidence described in Chaps. 9 and 10 that pregnancy high fat diet/obesity alters both maternal behaviour towards her offspring and leads to altered food preferences in them, along with heightened risk of mental ill-health, increased anxiety, social behavioural deficits and impaired memory and learning is of real concern.

Current knowledge is expanding on the mechanistic basis of the imbalance between appetite and satiety, and of adipogenesis-lipogenesis in the offspring of mothers with high fat intake during pregnancy (Chap. 11). Leptin, an adipokine peptide hormone produced by fat cells, can cross the blood-brain barrier and in offspring of maternal obesity/high fat pregnancies its action in the hypothalamus is implicated not only in the dysfunction in appetite/satiety pathways (Chap. 11), but also in cardiovascular dysregulation and hypertension (Chap. 14). Furthermore, the mechanisms underlying insulin resistance in offspring of high fat fed and obese mothers are likely to involve changes in insulin sensitivity in skeletal muscle and liver (Chaps. 7 and 8). Nonalcoholic fatty liver disease (NAFLD), whereby fat accumulates in the liver, is the hepatic manifestation of the metabolic syndrome. There is now considerable evidence to suggest that NAFLD in offspring is primed by high fat diet and obesity during pregnancy (Chap. 12). The disease can progress in severity and lead to the development of fibrosis and cirrhosis, and may be linked to hepatocellular carcinoma. The increased risk of malignancy in offspring of obese pregnancies is an emerging field of research and the most persuasive evidence to date is from rodent studies in which the incidence of mammary tumours in female offspring is heightened (Chap. 13).

Throughout the book, and summarized in Chap. 16, contributors highlight epigenetic mechanisms that may help to explain the intergenerational cycle of obesity and physiological dysregulation. It is clear that the advances in the knowledge of epigenetic mechanisms have brought ‘environmental sense’ to the world of genomics. In addition, the microbiome has provided a new mechanistic perspective on the intergenerational programming of obesity and physiology. Evidence of the susceptibility of the early life microbiome to programming by maternal diet, antibiotic exposure, mode of delivery and breastmilk offers an exciting avenue for understanding how the changes in the early life environment (such as maternal obesity and weight gain) influence the health of the next generation and possible future interventions (Chap. 17).

The importance of parental obesity as a major risk factor for non-communicable diseases is apparent from the outset of this book. The reader gets a sense of the urgency for action if adolescents and young adults are to have a better future, the cost associated with non-communicable diseases is to be reduced, and if the intergenerational programming of obesity is to be halted (Chap. 1). Many of the contributors to this book have synthesized the current state of research into the mechanisms linking parental obesity to altered offspring physiology, and suggest targets for future interventions. Realizing the potential of such interventions is important but enormously challenging and, as the reader will appreciate from Chap. 1, this must be done within a coordinated policy scheme at international, national and local government level.

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