

Preface

In my beginning is my end.
– T. S. Eliot, #2 of Four Quartets

Eliot had no idea that his observations on the life cycle would start even before birth. And indeed, one's earliest beginning predicts both the timing and means to that end. The concept that obesity was inherent, and not just the sum result of the behaviors of gluttony and sloth was surmised early in the twentieth century, but began in earnest with the postulation of a "thrifty genotype" by James Neel in 1962. However, the field lay dormant for another 30 years, awaiting biological and genetic confirmation. To compound the biological directive, the notion that prenatal biological influences could impact postnatal outcomes for obesity dates to 1989, when David Barker, an epidemiologist from Southampton, UK, first made the observation that now bears his name, the Barker hypothesis. He noted that maternal nutrition impacted on the fetus, such that small for gestational age infants were predicted to be at increased risk for obesity and metabolic syndrome in the future. Thus, the precept of developmental programming to amend one's genetic predisposition was advanced.

In the interval 21 years since Barker's discovery, numerous observations have slowly amended these two complementary hypotheses. Leptin, the first gene that of the energy balance pathway, was discovered in 1994. While already deemed essential for adult body weight regulation, Richard Simerly, then at Oregon Regional Primate Center, showed in animal models in 2004 that leptin likely was molding our hypothalami even before we took a swig of baby formula. Leptin opened up our understanding of the energy balance pathway, including genes such as MC4R, and their role in the genetics of obesity. Recent genome-wide association scans suggest that genetic linkages to obesity are primarily in the CNS. We learned in the late 1990s that large for gestational age and premature infants also became obese; and in the early 2000s that maternal obesity and weight gain during pregnancy are also risk factors. Furthermore epigenetics, which led credence to the ability of experiential phenomena in the mother to affect genetic expression in the newborn, was already a hot discipline when Randy Jirtle's group at Duke discovered in 2003 that they could alter offspring weight and color coat in genetically determined *Agouti* mice through

altered maternal nutrition. This line of investigation has expanded exponentially ever since. The phenomenon of epigenetics has tied in very nicely with the above observations, explaining how vertical transmission of obesity can occur exclusive of DNA base changes. Lastly, data accrued by Retha Newbold at NIEHS and Bruce Blumberg at UC Irvine in 2005 found that environmental toxins not only contribute to obesity in adult animals but also program the liver and adipocyte during gestation. Moreover, each of these phenomena has been noted in human models. Lastly, we now recognize that developmental programming of obesity can be promulgated by actions in numerous target organs in the energy balance pathway. Actions on the hypothalamus can result in an altered energy setpoint; actions on the liver can result in an altered metabolic profile; and actions on the adipocyte can result in an altered storage capacity. These actions are not mutually exclusive, giving rise to phenotypes of hyperphagia (or not), insulin resistance (or not), and subcutaneous vs. visceral fat. Understanding these tissue-specific effects on these gestational perturbations will likely allow for understanding of the different obesity syndromes and their downstream co-morbidities.

Taken as a whole, these various phenomena clearly demonstrate that disruption of the normal energy balance paradigm during gestation has profound consequences for the offspring. These observations have led to a new branch of science and medicine: the Developmental Origins of Health and Disease (DOHaD). Given that (1) the obesity epidemic has gone global; (2) attempts at diet and exercise have failed to control the global obesity epidemic; and (3) we now have an epidemic of obese 6-month-olds, it is time to think “out of the box.” Is there an exposure that is causing this? Are pregnant women doing something to make their children fat? Are we promoting obesity before birth?

The purpose of this unique volume is to elucidate, in both animal and human models, the state-of-the-art evidence for each of these phenomena. The evidence, and indeed, our author roster, comes from around the world. Each of the sections of this volume (genetics, epigenetics, developmental programming, environmental obesogens) will start out with the role of pathogenetic mechanism in question in human obesity and will then follow up with the evidence in animal models. In this way, the strength and relevance of each of these pathogenetic mechanisms and their effects can be assessed.

It is hoped that by assembling each of these concepts in one volume, we will build a framework that will (1) inform physician and patient education into the causes of the obesity epidemic; (2) provide a nidus for further investigative efforts into the developmental nature of obesity and chronic disease; (3) provide a starting point for changes in policies to improve maternal–child health; and (4) provide data to assist public health officials to monitor and control environmental exposures, whether they be nutritional or toxicological.

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