International Journal of Obesity (2006) 30, S1–S3
 0307-0565/06 $30.00
www.nature.com/ijo

PREFACE

Propellers of growth trajectories to obesity and the metabolic syndrome

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International Journal of Obesity (2006) **30,** S1–S3. doi:10.1038/sj.ijo.0803512

'Children, no less than rockets, have their trajectories governed by control systems of their genetic constitution and powered by the energy absorbed from the environment'. This analogy between rockets and children, which encapsulates a fundamental property of human growth as a target-seeking function, was made by Tanner[1] in the mid-1980s – at a time when Reaven[2] was introducing the concept of Syndrome X to draw attention to the cardiovascular risks associated with insulin resistance and compensatory hyperinsulinemia. Neither Tanner nor Reaven would have anticipated that so many children are now being propelled along growth trajectories to the disease entities of Syndrome X – that is, towards type 2 diabetes and cardiovascular diseases, which we know now are driven by our obesigenic environment.

While the prevalence of obesity continues to rise in virtually all nations, so spectacular is the current surge in childhood obesity that the International Obesity Task Force (IOTF) now considers the epidemic of obesity to be accelerating out of control. At least 155 million school-age children worldwide are currently overweight, with 30–45 million classified as obese. In countries of the European Union alone, the number of children affected by overweight and obesity is now rising at 400 000 a year, and already one in four children is overweight – a new prevalence of 24%, which is already higher than the predicted peak for 2010. These grim figures forecast a deepening crisis in public health as children are being exposed to the potentially damaging metabolic and cardiovascular insults of excess fat gain during critical periods of growth and development. It is therefore not surprising that the limelight of research into understanding the etiology of obesity, and in developing effective strategies for its prevention, has now shifted towards the identification of environmental factors, events and growth patterns that very early in life predispose to later obesity and risks for Syndrome X – a term subsequently upgraded to the insulin resistance syndrome or metabolic syndrome. What are these early obesigenic environmental factors and growth patterns? How do they interact in propelling so many children to obesity and the metabolic syndrome? These are the fundamental questions that are addressed in this IJO supplement reporting the proceedings of the 3rd Fribourg Obesity Research Conference (FORC-2005) that was held in Fribourg, Switzerland, on the theme of 'Growing into Obesity and the Metabolic Syndrome'.

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Socio-cultural 'programming'

In their review about socio-cultural factors that are contributing to the surge in childhood obesity in Switzerland, Paolo Suter *et al.* emphasize how the drastic changes in lifestyle that have occurred during transition from the stone-age to the chip-age have led to early habit formation for sedentary behaviours that track from childhood into adulthood. Among the main culprits figure parents as poor models and the television set. Besides displacing physical activity and encouraging passive snacking, television also provides the most powerful medium for advertisements geared at sustainable habit formation for energy-dense foods and sugar-sweetened soft drinks. As Paolo Suter underlines, early habit formation and long-lasting 'learned behaviours' is now under the control of 'neuro-marketing' strategies – a frightening development in the 'programming' of childhood obesity.[3]

Developmental programming

There are of course several types of earlier exposures, which, at crucial points in brain development during fetal and neonatal periods, could permanently alter the nervous system. In his review on the developmental origins of obesity, James Young reminds us that impairments in autonomic innervation in the offspring owing to maternal

undernutrition or maternal protein deficiency have long been associated with global deficits in development of the central nervous system. Furthermore, hypothalamic–pituitary–adrenal activity can also be altered permanently by variations in glucocorticoid exposure, such as owing to maternal stress, maternal protein deficiency and neonatal overnutrition, all of which have been shown to lead to obesity in animal models. What is novel today is the convergence of data indicating that predispositions to later obesity can also be related to long-lasting alterations in sympathetic innervation and regulation of central sympathetic outflow in response to neonatal overnutrition, maternal intake of refined carbohydrates or exposure to cooler environmental temperature during pregnancy and lactation. Following an integrative analysis of these and other data, James Young argues that hyperinsulinemia during fetal and/or neonatal life, by inducing permanent changes in hypothalamic morphology and in the functional state of the sympathoadrenal system, may be a common predisposing factor in many of these circumstances associated with the development of obesity later in life. In particular, these arguments provide 'food-for-thought' about the extent to which dietary intake of refined carbohydrates during pregnancy and lactation may be contributing to the worldwide epidemic of childhood obesity via their effects on insulin secretion in the offspring.

Similarly, whether dietary fat levels and fat types in the maternal and infant diets may be of importance in programming towards later obesity are also fundamental questions that require scrutiny, particularly in the light of some rodent studies indicating that maternal high-fat feeding, or exposure to high levels of dietary n-6 fatty acids during pregnancy and lactation, leads to excess adiposity in the offspring. In a critical reappraisal of available data, Katherine Macé *et al*. conclude that although most epidemiological studies could not find any association between indices of fatness and the level of dietary fat intake in infants and children, the potential detrimental effects of maternal high-fat intake during gestation and lactation have yet to be robustly evaluated in population-based studies. They also raise the possibility that dietary-induced programming of obesity may also occur during weaning – a transition period between a high-fat diet (breast-milk or formula) to a low-fat (carbohydrate-rich) diet. This is particularly relevant as artificial feeding of rat pups on a high-carbohydrate diet during the lactating period leads to chronic hyperinsulinemia and later obesity. An intriguing question that arises, in the light of James Young's proposal above, is whether such programming of these pups fed in the cup might be attributed to the 'refined' nature of the carbohydrates.

Early growth patterns

The importance of early infancy as a critical period for predisposition to later obesity is also evoked by Marie-Françoise Rolland-Cachera *et al*., who in 1984 coined the term 'adiposity rebound' to refer to the age that corresponds to the second rise in the body mass index (BMI) after birth. The occurrence of adiposity rebound at a younger age (<5 years old rather than between 5 and 7 years old) is now recognized as an important predictor for a high BMI that tracks from childhood into adulthood. According to these authors, early infant exposure to diets that is low in fat and high in protein (i.e. the most satiating) may create a situation of relative energy deficit. The resulting slowing of weight gain during infancy, if followed by catch-up growth on a high-fat diet, could be an explanation for the premature adiposity rebound that leads to obesity. Indeed, early growth patterns of faltered growth followed by catch-up growth are also recognized to be strong predictors for later development of disease entities of the metabolic syndrome. However, as Johan Eriksson points out, there seem to be two distinct non-optimal growth patterns for later diseases: (*i*) an early age for adiposity rebound, which is associated with the development of both obesity and type 2 diabetes, and which is independent of birth size, and (*ii*) a pattern of growth that is characterized by a small birth size and thinness through infancy, followed by catch-up growth (in weight rather than in height) and which predisposes to coronary heart disease or type 2 diabetes.

In his explanation of how such non-optimal early growth followed by catch-up growth could lead to these diseases, Eriksson underscores the potential importance of impaired growth of organs and tissues that tracks into adulthood, with poor liver growth predisposing them to hepatic insulin resistance and dyslipidemia, and poor muscle growth resulting in reduced buffering capacity for glucose disposal and hence predisposing them towards insulin resistance. Indeed, in his review on fetal nutrition and later glucose homeostasis, Luc Tappy underscores the findings that reduced glucose oxidation and increased lipid oxidation can indeed be observed at early pubertal stages in non-diabetic children born small for gestational age, and that these impairments in substrate metabolism and in insulin sensitivity could be attributed not only to their lower lean body mass but also to their higher body fat content. He proposes a model in which the metabolic disorders and impaired growth in these individuals (born small for gestational age) are secondary to growth hormone resistance, with the consequential decrease in insulin-like growth factor-1 secretion leading to low growth rates and impaired glucose metabolism, and the increase in body fat leading to insulin resistance through increased plasma free fatty acids.

Thrifty phenotypes

Whatever the neuro-hormonal mechanisms (or indeed the mechanisms for genetic imprinting) that have been proposed to explain the roles of early nutrition and growth

pattern in susceptibility to later obesity and diseases, they are generally interpreted alongside the teleological arguments of an early adaptive response for a 'thrifty phenotype' turned maladaptive later in life. Thus, according to the thrifty phenotype hypothesis, originally put forward by Hales and Barker,[4] early pre- and post-natal life is a critical period during which environmental exposures that hinder growth (nutritional deficiencies or other insults) will lead to the programming of thrifty mechanisms that are adaptive during the period of limited supply of nutrients, but which contribute to increased risks for diseases during improved nutrition and catch-up growth later in life. But which components of catch-up 'growth' serve as vehicle for driving the expression of these thrifty mechanisms: catch-up in height, catch-up in lean tissue or catch-up in fat? In this context, there is now compelling evidence that the process of catch-up growth is characterized by a disproportionately higher rate of fat gain than lean tissue gain, and that hyperinsulinemia is an early feature of such preferential 'catch-up fat'. In their review on this topic, Dulloo *et al*. first focus upon the almost ubiquitous nature of the preferential 'catch-up fat' phenotype across the life cycle as a risk factor for obesity and insulin-related complications. They subsequently review the evidence indicating that such preferential catch-up fat is primarily driven by energy conservation (thrifty) mechanisms that operate via suppressed thermogenesis, with glucose thus spared from oxidation in skeletal muscle being directed towards *de novo* lipogenesis for storage in white adipose tissue. They also provide a molecular–physiological framework that integrates emerging insights into the mechanisms by which the thrifty metabolism that drives catch-up fat crosslinks with early development of insulin and leptin resistance during catch-up growth. Thus, the mechanisms by which body fat is acquired would seem to be at least as important as the consequences of excess fat *per se* in the pathogenesis of type 2 diabetes and cardiovascular diseases.

The 'cycling' girl

The increasing prevalence of overweight and obesity in children and adolescents, and the pressure from the media and society for a slim image (particularly in girls), is likely to generate an increasingly younger population that show repeated dieting and consequential weight cycling – that is, the phenomenon of 'yoyo' dieting that already inflicts more than 40% of women in Western societies. In their review on this topic, Jean-Pierre Montani *et al*. evaluate critically the importance of weight cycling as a risk factor for later cardiovascular diseases, and subsequently analyze the underlying mechanisms that center upon hypertension, visceral fat accumulation, changes in fatty acid composition, insulin resistance and dyslipidemia. These data are also analyzed within the framework of a new concept that is embodied in the 'repeated overshoot' hypothesis. According to this postulation, fluctuations of cardiovascular risk variables (such as blood pressure, heart rate, sympathetic activity, blood glucose and lipids) with probable repeated overshoots above normal values during periods of weight regain – and which are not fully compensated by undershoots during periods of weight loss – put an additional stress on the cardiovascular system when repeated over time. In other words, the oscillatory dynamics of these cardiovascular risk variables around their mean values in the normal physiological range could be as important as their elevated mean values in exerting stress on the cardiovascular system, and probably contribute to the overall cardiovascular morbidity of weight cycling.

Conclusion

This supplement contains a set of papers that integrates, from a perspective of system physiology and nutrition, the recent advances and emerging concepts about the multitude of environmental factors and growth patterns that confer susceptibility towards later obesity and the insulin resistance (metabolic) syndrome. It is hoped that in the coming years, the advancement of knowledge in this area will provide humans with the same degree of precision for early identification of children at risks as for predicting the trajectory of rockets.

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