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PREFACE

Pathogenesis of the worst killers of the 21st century

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The trend towards obesity has reached epidemic proportions around the globe, and for the first time in the history of mankind, the prevalence of obesity has exceeded that of malnutrition. Whether obesity *per se* should be considered a disease is debatable, but it is undeniable that it provokes the development of debilitating conditions, in particular type 2 diabetes and hypertension, both of which are high risk factors for cardiovascular diseases. According to the current World Health Organization (WHO) population statistics, 40 – 60% of obese patients eventually develop type 2 diabetes and have high blood pressure, 60 – 90% of individuals with type 2 diabetes are (or had been) obese, and hypertension is a major contributor for cardiovascular morbidity and mortality in patients with obesity and type 2 diabetes. With nearly half of all deaths in Western countries related to cardiovascular diseases, the steady progression of obesity worldwide is expected to elevate cardiovascular diseases as the worst global killer of the twenty-first century.

This supplement of the *International Journal of Obesity* reports the proceedings of a one-day conference, held at the University of Fribourg, during which scientists from Swiss universities and industry exchanged views and perspectives about pathways towards obesity, and pathways from obesity to metabolic diseases. It might *a priori* seem paradoxical for so much interest about fatness in a small country where the prevalence of obesity is thought to be among the lowest in the world. However, as Yves Shultz and Virgile Woringer argue in their critical assessment of obesity in Switzerland, there is a lack of objective information on the prevalence of overweight or obesity in this country. They draw attention to the fact that, in Switzerland and in other European countries where National Surveys rely upon subjects' interviews (and hence self-reported weight and heights rather than measured values), the overweight/obesity prevalence is largely underestimated.

Whatever its exact prevalence, the trend towards obesity in Switzerland, like in many parts of the world, is fast moving in the upward direction. In his plenary lecture about the pathways to obesity, Eric Jéquier reviews the cardinal features of the 'nutrient balance' theory which has been a main focus of his research in human energy metabolism during much of the 1990s. This theory embodies the importance of increased fat in the diet and lack of physical activity as the two most important factors which contribute to explain the rising prevalence of obesity. There are, however, many individuals exposed to these same 'obesigenic' environments who, apparently without conscious effort, do not become overweight or obese, thereby underscoring the possibility that the extent to which a given individual develops or resists obesity reside in the interaction between his/her genetic makeup and the environment. Although there has not been any major breakthrough in the identification of genes that could be implicated in the heritability of common obesity, remarkable progress has been made over the past few years in the understanding of molecular pathways involved in body weight regulation. In a second plenary lecture on the molecular pathways to obesity, Karl Hofbauer reviews these spectacular discoveries, notably that of leptin and the leptin – melanocortin system, factors controlling adipocyte differentiation, and the identification of mitochondrial carriers that apparently possess uncoupling properties. He underlines the fact that our understanding of the precise organization and hierarchy of the regulatory networks is, however, far from complete, and presents an integrative view of the complex interactions of neural and hormonal factors in the control of energy intake, storage and expenditure, and their role in the pathophysiology of obesity.

The symposium that follows on the theme of pathways from obesity to metabolic diseases was co-chaired by Francoise Jeanrenaud-Rohner and Ulrich Keller. The first speaker, Jean-Pierre Montani, addresses the pathways from obesity to hypertension within the conceptual framework that obesity, hypertension and cardiovascular diseases contribute to three corners of a vicious triangle. While overweight predisposes to hypertension and thus to an increased prevalence of cardiovascular diseases, this in turn weakens the heart, tires the cardiac patient and thus favours inactivity and further weight gain. The pathogenesis of obesity-induced hypertension is reviewed from an integrative analysis of how factors induced or potentiated by obesity, including leptin, FFA, TNFα, renin – angiotensin and endothelial dysfunction, lead to sympathetic overactivation, vasoconstriction and sodium retention. In the subsequent analysis of pathways from obesity to type 2 diabetes, Jean-Pierre Felber and Alain Golay reassess the relationships between obesity and diabetes, the early appearance of insulin resistance in the development of obesity, the elevation of plasma FFA as a major factor at the origin of insulin resistance in obesity, and how insulin resistance and insulin deficiency are closely related in a dual regulatory cycle.

They also discuss the practical application of pathophysiological information — about partial reversibility of the evolution of obesity towards diabetes — for the prevention of diabetes in obese subjects. The last part of the symposium directs attention to emerging evidence that, independently of excess weight, large fluctuations in body weight at some point earlier in life represent an independent risk factor for cardiovascular diseases. High cardiovascular morbidity and mortality have been reported in men and women whose weight fluctuated earlier in young adulthood (because of diseases, malnutrition or voluntary slimming), or much earlier in life because of foetal or neonatal growth retardation. In addressing the pathways from weight fluctuations to metabolic diseases, Dulloo *et al* focus on the phenomenon of accelerated fat recovery or 'catch-up fat' after weight loss or growth retardation. The arguments are put forward that during weight recovery on our modern refined foods, the mechanisms of adaptive thermogenesis that regulate catch-up fat are pushed beyond the limits for which they were meant to operate and turn maladaptive, with consequences for enhanced susceptibilities towards skeletal muscle insulin resistance and overactive sympathetic activity.

The proceedings of this one-day conference therefore reflect current concepts and hypotheses which constitute molecular–physiological research into the area of weight regulation, obesity and obesity-related metabolic diseases in some of the Universities in Switzerland. We are all pleased that there are many young scientists interested in the field, both in academia and in industry. We hope that they will share with us their own views and contributions on the subjects in our future obesity meetings. In the meantime, we would like to thank all those who helped us in organizing this first Fribourg Obesity Research Conference (FORC), the plenary lecturers, the symposium speakers and chairpersons, and the young scientists who have presented their posters with great enthusiasm (their abstracts are also included in this supplement). May we take this opportunity to thank the Swiss Physiological Society, Swiss Society for Nutrition Research and Swiss Association for the Study of Obesity, as well as all the sponsors from Industry, for their contributions and encouragements towards the organization and publication of this conference.

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