

PREFACE

This book is dedicated to two colleagues and friends who sadly passed away, Henriette A. Delemarre-van de Waal in 2014 and Michel L. Aubert in 2015. Both were very active researchers in the field of puberty regulation and, for Henriette, as a clinician, clinical management of pubertal disorders. They both contributed to this field with a vast amount of excellent scientific research. After her medical training in Leiden and paediatric training in Amsterdam (Vrije Universiteit Medical Center, VUMC), Henriette A. Delemarre-van de Waal was a fellow in paediatric endocrinology with Prof. Leo Van den Brande in Utrecht, but continued her clinic in Amsterdam. She prepared her PhD thesis on the induction of puberty by pulsatile GnRH administration in patients with hypogonadotropic hypogonadism, which she defended in 1984 cum laude. She soon became internationally known for this subject and continued to be involved in it for several decades. Along the same lines, she studied the effect of GnRH treatment on testicular descent in cryptorchid boys, GnRH analogue treatment of precocious puberty and oxandrolone treatment in boys with constitutional delay of growth and puberty. In the meantime, she had a very successful academic career. In 1987, she was appointed Associate Professor and, in 1994, Professor of Paediatric Endocrinology at VUMC. In 2008, she became Professor of Paediatrics and Department Chair in Leiden. To better understand the regulation of pubertal development, Henriette initiated many studies in human and animal models. A unique longitudinal study on diurnal and nocturnal LH and FSH secretion in healthy adolescents gave insight into the physiology of puberty onset, and studies on LH and FSH secretory profiles were also performed in patients with abnormal pubertal development, for instance due to exposure to cyclophosphamide. From 1991 to 1992, she took a sabbatical year to work in the research group of Dr. Robert Steiner at the University of Washington, Seattle (USA), where she learned to work at the bench. This led to excellent papers, for example on the expression and sexual dimorphism of galanin mRNA in GHRH neurons in the rat. This certainly made her a more all-round investigator, having learned the techniques and challenges of laboratory experiments. Back in Amsterdam, she initiated various studies on animal models, such as on the effect of intrauterine restriction in the rat. Henriette had a very good eye for human models that could help elucidate the pathophysiology of certain conditions and provide insight into normal physiology. Besides children born small for gestational age and children growing up in poor conditions in Indonesia and South Africa, other examples included twins (which helped to dissect the genetic component of many body functions), obese children, children born after in vitro fertilization and adolescents with gender dysphoria. She was also eager to use novel techniques. For example, she studied the association between various genetic polymorphisms and epigenetic markers versus growth and body composition, and used advanced functional MRI and EEG tools to study brain development after prenatal growth retardation, and in obese or transsexual children. Michel Aubert studied biochemistry from 1960 to 1965 at the Swiss Institute of Technology in Lausanne and received a master's degree in chemistry and biochemistry at the Federal Polytechnic School of Zürich in April 1965. From 1965 to 1971 he was a Research Fellow at the Institute of Clinical Biochemistry, Department of Internal Medicine, University of Lausanne

School of Medicine (Prof. A. Vannotti and J.P. Felber), where he defended in May 1970 his PhD thesis in biochemistry on radio-immunoassays of polypeptide hormones in plasma, the critical evaluation of the different steps of the assays, and finally their application in clinical endocrinology and gynaecology. From 1971 to 1975 he went to San Francisco as a Postdoctoral Research Fellow in the Paediatric Endocrine Unit, Department of Paediatrics, University of California, San Francisco (USA; Professors Melvin M. Grumbach and Selna L. Kaplan). There he made collaborative studies with Professors C.H. Li, 'Hormone Research Laboratory', and W.F. Ganong (Department of Physiology, University of California, San Francisco) on growth hormone molecular conformation and activity in radioreceptor assays and radioimmunoassays. At the same time, he developed his interest in developmental endocrinology as shown by his numerous publications on the ontogenesis of human foetal pituitary hormones and hypothalamic factors. During this period, he also became a consultant at the National Pituitary Agency (Baltimore, Md., USA). In 1975, Michel Aubert returned to Switzerland as a Research Associate at the Division of Biology of Growth and Reproduction, Department of Paediatrics, University of Geneva School of Medicine. In 1977, he received his 'Privat-Doctent'. The same year, he became a lecturer at the Department of Biochemistry, University of Geneva School of Sciences. In 1979, he received the Bizot Prize of the University of Geneva for his research. In 1987, he was appointed Associate Professor, at the Department of Paediatrics, University of Geneva School of Medicine. He received the ESPE Research Award in 1997 for his work on the sexual maturation of the rat: 'The search for a neuromodulator that controls the onset of puberty'. In the Division of Biology of Growth and Reproduction, Michel Aubert created and developed a basic research laboratory which soon became internationally recognized. His research themes were the neuroendocrine aspects of growth and development, the neuroendocrine regulation of feeding, intrauterine growth retardation and the 'programming' hypothesis. However, his main research topic remained the control of sexual maturation in rats, studying the ontogeny from foetal to adult life of hypothalamic GnRH and pituitary GnRH receptors, their effects on gonadotropin secretion, their number and activity modification after castration and replacement therapy. Michel Aubert participated intensively in the studies of measurement of GnRH and melatonin and their metabolites in biological fluids, and the role of melatonin and circadian rhythms in the control of the onset of sexual maturation in the rat, in the oestrous cycles of female rats as well as in humans. Furthermore, Michel Aubert studied the role of GRF, growth hormone, IGF-1, opiates, NPY, leptin, nutrition and fasting on the sexual maturation of the rat and the possible role of these hormones and factors on the development of obesity, in relation to the 'programming' hypothesis. After starting as a biochemist, he became a biologist in developmental endocrinology. Both Henriette and Michel were very successful in obtaining grants for scientific projects, and supervised more than 30 fellows and PhD students. Almost all these projects were directly or indirectly related to puberty. However, their interest became broader. Henriette as a pediatric endocrinologist made interesting studies performed on bone mineral density, endocrine development and growth hormone treatment of pre-term infants, health-related quality of life and cryptorchidism. An important research line was aimed at investigating the effects of restricted intrauterine and early postnatal growth in childhood and adolescence in terms of blood pressure, insulin sensitivity and secretion, microvascular function, cardiovascular risk factors and renal function. Although he retired officially in 2005 from the University of Geneva, Michel Aubert was asked by the National Scientific Research Foundation to develop in the Division of Development and Growth of the Department of Paediatrics a new research

programme on the rat in association with the National Research Programme 50 entitled 'Endocrine Disruptors: Importance for Human Beings, Animals, and Ecosystems'. He directed the studies on the prenatal effects of low caloric diet, nicotine and bisphenol A on the islet cells, adipogenesis, neonatal brain metabolism and development, as well as sexual maturation. His last original research was the study of a botulinum toxin-derived targeted secretion inhibitor that downregulates the GH/IGF1 axis, which might be of clinical relevance for the treatment of GH hypersecretion syndromes. While each career is primarily determined by the personality of the scientist, Henriette's and Michel's careers can also serve as an illustration of the evolution of puberty research over the last 35 years: diagnostic and therapeutic use of pituitary hormones, translational studies on rodent models, incorporation of the concept of foetal 'programming' under the influence of nutrition, and a search for neurobiological and neurodevelopmental mechanisms through imaging techniques in humans and in rodents. Colleagues and friends will long remember their scientific contributions and personality.

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The translational perspective on puberty that was so nicely promoted by Henriette A. Delemarre-van de Waal and Michel L. Aubert sets the scene for this book. Up-to-date concepts from animal and human physiology and pathology are bridged here towards a better understanding and management of pubertal disorders. Normal and abnormal pubertal development are examined in three perspectives: the role of genetic factors, the role of environmental factors including nutrition and therapeutic issues in disorders of puberty. This outlook is framed along current key concepts in paediatric endocrinology such as interaction between genetic and environmental factors and developmental programming. The added value of this book involves several aspects. Among others, different experts share views on similar critical issues (weight of genetic versus environmental factors, impact of environmental factors in relation to critical periods in development, etc.). This enables the reader to identify areas of consensus and controversy, and make their own judgement. Also, each chapter involves a section drawing lessons for clinical management in an attempt to have readers link basic research, physiology and pathophysiology with the clinical management of pubertal disorders. We would like to express our gratitude to the contributors for the outstanding work they have provided and for constructive discussions during our editorial review. We are confident that basic scientists, clinical scientists and practitioners will find in this book a unique and inspiring resource for scientific research and clinical practice.

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