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The Program Organizing Committee prepared a program “highlighting various current developments in Paediatric Endocrinology and Diabetology”. The meeting consisted of 4 Plenary Lectures, 8 Symposia with 3 speakers each, 10 Free Communication sessions with 6 Oral Presentations each, 4 Satellite Symposia with 4 speakers each, 10 Clinical Focus Sessions with 6 Oral Presentations each, 12 Meet the Expert Seminars, 3 Poster Sessions with approximately 200 presentations each, 2 Interactive Sessions, and 2 New Technology sessions. Many activities focused on molecular pathophysiology with relevant clinical implications.

The purpose of the meeting was to have an opportunity to participate in interactive sessions, short communications, and in guided poster rounds. The programme was attractive for clinical researchers, basic science researchers, practicing clinicians, fellows in training, medical students and other professionals interested in paediatric endocrinology. It resulted in an important update in multiple aspects of paediatric endocrinology.

A selection of some of the activities will be commented.

PLENARY LECTURES
Abstracts and comments on most of the plenary lectures follows.

DNA damage repair, cancer, ageing and life span extension
Hoeijmakers, Jan 1; Garinis, G 1; van der Plujim, I. 1; Mitchell, J. 1; Andressoo, J-O. 1; Diderich, K. 1; Lalai, A. 1; de Waard, H. 1; Beems, R.B. 1; van Steeg, H. 1; Niedernhofer, L. 2; van der Horst, G.T.J. 1
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A wide variety of lesions is continuously induced in our genes causing numerous alterations in DNA including adducts, different types of single and double strand breaks and interstrand crosslinks. These arise from ubiquitous, noxious exogenous agents (UV- and X-radiation, chemicals), natural metabolites produced by respiration (e.g. reactive oxygen species) and from intrinsic chemical instability of DNA. To protect the vital genetic information a network of genome care-taking mechanisms has evolved. Of these a set of DNA repair systems constitute a key component. Nucleotide excision repair (NER) removes helix-distorting lesions in a complex ‘cut and patch’ reaction. There are two sub-pathways. Global genome NER operates genome-wide and is critical for preventing mutations. Transcription-coupled repair (TCR) counteracts the cytotoxic
effects of DNA injury by rescuing gene expression blocked by DNA damage. Inherited NER defects are associated with sun (UV) hypersensitive syndromes, including xeroderma pigmentosum (XP, highly cancer-prone), and the severe neuro-developmental conditions Cockayne syndrome (CS) and trichothiodystrophy (TTD, characterized by brittle hair). Mutations in the multifunctional NER/TCR XPB and XPD helicases are associated with an extreme clinical heterogeneity, ranging from XP to XP combined with CS and TTD. Defects in the NER and crosslink repair endonuclease, ERCC1/XPF, cause XP or XP with multi-system dysfunction. Mouse models have provided important insights into the impact of the NER sub-pathways on human health and the complex genotype-phenotype relationship. XPDTTD mice, with a partial defect in both global and TCR are only moderately cancer-prone, but exhibit wide spread premature ageing. XPDXP/CS mutant mice are highly predisposed to cancer, with a milder ageing phenotype. Complete repair deficiency in TTDxXPA mice aggravates many premature ageing symptoms, reducing life span to ~3 weeks. Mutations in the ERCC1 gene induce a distinct set of accelerated ageing features, with a rate of onset depending on the severity of the mutation. The correlation between repair defect severity and clinical manifestation provides strong evidence for the DNA damage theory of ageing. The authors propose that endogenous oxidative lesions compromise transcription, inactivate genes, and trigger apoptosis/senescence inducing ageing. Very cytotoxic interstrand cross-links may also cause cell death, senescence and features of ageing. In contrast, lesions or defects in genetic stability mechanisms causing enhanced levels of DNA damage-induced mutagenesis correlate with increased carcinogenesis. Microarray analysis has revealed the involvement of the IGF1/GH somatotrophic axis that controls metabolism and anti-oxidant systems in the organismal response to intrinsic cytotoxic DNA damage. This pathway has also been linked with life span extension.

Aging and the IGF system

Beside GH, insulin, age and nutrition, individual circulating IGF-I concentrations are influenced by a number of genetic factors. Twin studies have shown that at least 38% of the interindividual variability in circulating IGF-I levels is genetically determined. About 1 Kb upstream of the promoter region the IGF-I gene contains a polymorphic region composed of multiple CA-repeats. For other genes it has been found that the amount of protein that is formed from a gene is inversely related to the number of CA repeats. In the Rotterdam Study, a population based study in a population aged 55 and over, 10 different alleles were observed in this polymorphic region near the promoter of the IGF-I gene. This IGF-I gene polymorphism was associated with the age-related decline of serum IGF-I levels. In the Rotterdam Study the authors observed an optimum in IGF-I levels and final body height for the 192-bp and 194-bp allele of the IGF-I gene. This IGF-I genotype was not associated with both the risk of new type 2 diabetes and myocardial infarction. Moreover, although they did not find differences in survival between IGF-I genotypes in the whole study population, in subjects with type 2 diabetes patients and prior myocardial infarction survival time was significantly lower in the variant carriers of this IGF-I gene polymorphism when compared to subjects with the wild type. In an other study they observed that variant carriers of this IGF-I gene polymorphism had a decreased risk to develop prostate cancer suggesting that genetically determined chronic exposure to low IGF-I levels has a protective effect on the risk for prostate cancer in normal elderly men. In conclusion, it is at present not
known whether IGF-I also may influence human longevity. The studies reported above suggest that genetic variability in the genes responsible for IGF-I regulation plays a major role in IGF-I bioactivity and that this IGF-I bioactivity plays a role in the pathogenesis of cardiovascular disease, diabetes and cancer.

**How the hypothalamus controls glucose production**

Obici, Silvana, United States

Recent evidence highlights the important role of the brain in the control of glucose homeostasis. Hypothalamic centers sense the availability of peripheral nutrients via redundant and overlapping nutrient-induced peripheral signals such as leptin and insulin and via direct metabolic signaling. Indeed, insulin action in the hypothalamus leads to suppression of glucose output. Circulating insulin acutely suppresses glucose production via direct action on liver and, after its transport across the blood-brain barrier via activation of neural circuits in the hypothalamic arcuate nucleus. Insulin-mediated activation of insulin receptor substrate (IRS), PI3K and $K_{ATP}$ channels are required steps for the transmission of an efferent neural input to the liver. The hypothalamic insulin signal is conveyed via a synaptic relay to the motor nucleus of the vagus in the brainstem and reaches the liver via vagal efferent fibers.

Hypothalamic leptin also acts on hepatic glucose fluxes. Leptin, upon binding its receptor in the arcuate nucleus, activates two distinct signaling pathways: Jak/STAT and IRS/PI3K. The activation of leptin in the arcuate nucleus leads to stimulation of proopiomelanocortin (POMC)-positive neurons and inhibition of NPY/Agrp-positive neurons. The acute central effects of leptin on hepatic glucose fluxes can be divided into those mediated by the activation of the melanocortin pathway, which causes increasing of hepatic gluconeogenesis, and those that are melanocortin independent that lead to a reduction of glycogenolysis. The neural and molecular pathways conveying hypothalamic leptin signaling to the liver are still under investigation.

The hypothalamic sensing of macronutrients integrates multiple hormonal and metabolic homeostatic signals. Both glucose and FFAs can influence the intracellular levels of long-chain fatty acyl-coenzyme A (LCFA-CoAs). The brain senses circulating nutrients (glucose, fatty acids), hormones (insulin, leptin), and other signals from a variety of peripheral organs (adipose tissue, pancreas, gut) and controls glucose homeostasis by promoting glucose use and suppressing glucose production. In obesity and DM2, the brain fails to correctly perceive and respond to the peripheral signals of nutrient availability. Therefore, responding to nutrient availability, these hypothalamic regions in turn exert a negative feedback not only on food intake, but also on endogenous glucose production. Disruptions in the mechanisms of CNS nutrient sensing alter these homeostatic responses and contribute to the pathophysiology of obesity and type 2.

**Endocrinology of sleep**

Van Cauter, Eve, United States

Sleep is an important modulator of neuroendocrine function and glucose metabolism in children as well as in adults. In recent years, sleep curtailment has become a hallmark of modern society with both children and adults having shorter bedtimes than a few decades ago. In this presentation, we will review the impact of sleep on neuroendocrine function and metabolism and discuss laboratory evidence indicating that sleep curtailment in young adults is associated with a constellation of metabolic and endocrine alterations, including decreased glucose tolerance, decreased insulin
sensitivity, elevated sympa-tho-vagal balance, increased evening concentrations of cortisol, and disturbances of the neuroendocrine regulation of hunger and appetite. We will also review epidemiologic evidence associating short sleep with increased body mass index and diabetes risk in children and young adults. Altogether, the evidence points at a possible role of decreased sleep duration and quality in the current epidemic of obesity and diabetes in children as well as adults.

Poor or insufficient sleep has an adverse effect on glucose regulation because, 1. brain glucose uptake is reduced, 2. sympathetic nervous activity is elevated and 3. beta cell responsiveness is decreased.

In normal pubertal boys, the sleep period is associated with, 1. increased testosterone release, 2. increased growth hormone release, and 3. increased prolactin release.

In conclusion, in this increasingly prevalent syndrome, a feedforward cascade of negative events generated by sleep loss, sleep fragmentation, and hypoxia are likely to exacerbate the severity of metabolic disturbances. Chronic sleep loss, behavioral or sleep disorder related, may represent a novel risk factor for weight gain, insulin resistance, and Type 2 diabetes.

**Immunopathogenesis of diabetes mellitus type 1**
Roep, Bart
Netherlands
Type 1 (insulin-dependent) diabetes mellitus results from a T-cell mediated autoimmune destruction of the pancreatic beta-cells in genetically predisposed individuals. The knowledge of the immunopathogenesis has increased enormously in the last two decades. The contribution of T-cells in the pathogenesis is beyond doubt. Therapies directed against T-cells have been demonstrated to halt the disease process and prevent recurrent beta-cell destruction after islet transplantation. Less is known about the nature and function of these T-cells, the cause of the loss of tolerance to islet autoantigens, why the immune system apparently fails to suppress autoreactivity, and whether (or which) autoantigen(s) are critically involved in the initiation or progression of disease. The contribution of dendritic cells in directing the immune response is clear, while the contribution of B-cells and autoantibodies is subject to reconsideration. Autoreactive T-cells have proven to be valuable tools to study pathogenic or diabetes related processes. Measuring T-cell autoreactivity also provided critical information to determine the fate of islet allografts transplanted to type 1 diabetes patients. Cellular autoimmunity is a difficult study subject, but it has been a worthwhile quest to unravel the role of T-cells in the pathogenesis of type 1 diabetes. The challenge for the future is to determine which factors contribute to the loss of tolerance to beta-cell antigens, and to define what measures T-cells can provide to suppress autoreactivity, since it is becoming increasingly evident that T-cells provide a two-edged sword: some T-cells may be pathogenic, but others can regulate the disease process and thus form new targets for immunointervention.

**Low birth weight and Type 2 diabetes: fetal programming or shared genes**
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United Kingdom
Fetal growth is conventionally considered to reflect the maternal environment. Therefore the association of low birth weight with subsequent Type 2 diabetes has been assumed to reflect programming of the fetus by the intra-uterine environment. At present there is little direct evidence in man of a specific maternal environmental insult
that “programs”. Other explanations such as genetic susceptibility both altering intrauterine growth and also predisposing to diabetes should be considered. The fetal insulin hypothesis proposes that genes that reduce insulin secretion or action will reduce insulin-mediated growth of the fetus, and hence birth weight, as well as predispose to diabetes latter in life. Key evidence for this comes from our observations in families with glucokinase mutations. A maternal mutation increases birth weight by >500g by increasing fetal insulin secretion as a result of maternal hyperglycaemia while a fetal mutation reduces birth weight by > 500g by reducing fetal insulin secretion. Observations in other types of monogenic diabetes supported the critical role of genetically determinants of fetal insulin secretion. Evidence is not just from rare single gene disorders: reduced birth weight is found in the offspring of men who latter develop Type 2 diabetes. Mutations in Kir6.2, hepatocyte nuclear factor (HNF)1beta, and HNF4alpha can also cause diabetes and also greatly alter birth weight. Gain-of-function mutations in Kir6.2 (KCNJ11), which is the pore-forming subunit of the ATP-sensitive K(+) channels, that couple beta-cell metabolism to electrical activity, an essential role in the control of insulin secretion. HNF4alpha cause maturity-onset diabetes of the young (MODY). These offer novel mechanisms for the association of both increased and reduced fetal growth with Type 2 diabetes. Ultimately whether the association of altered fetal growth and subsequent diabetes is the result of genetic predisposition or programming will be resolved when our understanding of the molecular basis of these two processes improves. Until that time it is not appropriate to assume that birthweight is always the result of altered maternal environment or that associations with birthweight always reflect programming.

SYMPOSIA

Epimutation of the telomeric domain on chromosome 11p15 is a major and specific cause of Silver-Russell syndrome

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Silver-Russell syndrome (SRS) is characterised by severe intrauterine and postnatal growth retardation with spared cranial growth, dysmorphic features and frequent body asymmetry. It is clinically heterogeneous and diagnosis may be subjective. Maternal disomy for chromosome 7 is found in about 7% of the cases. Our group has recently identified hypomethylation of the telomeric domain of the 11p15 region (including the H19 and IGF-II genes) as a mechanism leading to SRS.

The objective was to assess the 11p15 methylation status in a large group of SRS and of non SRS small for gestational age (SGA) patients and to perform (epi) genetic-phenotypic correlations.

Forty-two SRS and 87 non SRS SGA patients were included. The diagnosis of SRS was retained when the mandatory criterion of intrauterine growth retardation was associated with at least 3/5 major criteria: relative macrocephaly, postnatal growth retardation, asymmetry, prominent forehead, feeding difficulties. None of the 87 non-SRS SGA displayed an abnormal methylation pattern at 11p15. Twenty-six (62%) SRS displayed
hypomethylation of the telomeric domain of 11p15. Birth weight and height were lower (p<0.001) in the abnormal 11p15 SRS group (abSRS) than in the normal 11p15 SRS group (nlSRS) (-3.3 vs. -2.2 SDS and -4.6 vs. -3.1 SDS). Postnatal BMI was also lower (p<0.005) in the abSRS (-2.4 vs. -1.6 SDS) whereas cranial circumference was higher (p<0.05; -0.76 vs. -1.5 SDS). Asymmetry and relative macrocephaly were much more frequent in the abSRS (69% vs. 27%, p<0.01, 100% vs 62.5, p<0.001). The number of major diagnostic criteria was also higher in the abSRS (92% with at least 4 major criteria vs. 54% in the nlSRS, p<0.01). All patients had biparental inheritance of chromosome 7. Hypomethylation of the 11p15 telomeric domain, resulting in down regulation of IGF-II, is a major and specific cause of SRS. Evaluation of the 11p15 region is very contributive to assess the diagnosis.

**Ultra high-resolution whole-genome comparative genome hybridization applied to patients with anomalies of gonadal development**

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Despite the fact that a number of genes known to be involved in sex-determination have been identified, the genetic basis of the majority of human cases with errors of sex determination is not explained. In some cases of 46,XY females and rare cases of XX-SRY negative males structural chromosomal changes have been identified (9p, 11p, Xp22 and 1p33). These rearrangements have been used to identify novel genes involved in mammalian sex-determination (e.g. DAX-1). Ultra-high resolution oligo microarray comparative genome hybridization (CGH) offers the possibility of discovering subtle changes in copy number in the human genome that may contribute to genetic diversity and in some cases mediate genetic disease. Here, we describe high-resolution oligonucleotide array analysis of 18 patients of Caucasian ethnic origin, who presented with various anomalies of gonadal development. We used the high capacity microarrays that contains 385,000 probes on a single glass slide. This feature density enables a median probe spacing of 6,000 bp. In the 18 individuals a total of 89 copy number differences representing 56 unique loci were identified. In addition, the analysis defined the breakpoint of a previously reported XX SRY-negative male with a distal Xp deletion (breakpoint distal to the ZNF673 gene). We also identified a previously unreported 46,XY female with gonadal dysgenesis and autism associated with a deletion of distal 9p (breakpoint within the GASC1 gene). Of the 56 unique loci showing copy number changes, 32 had been previously reported as copy number polymorphisms and the remaining 24 novel copy number changes were observed in only a single individual and have not been previously observed. Some of these variants may contribute to the pathologies. The novel changes include an intragenic deletion in a receptor tyrosine kinase in a patient presenting with 46,XY gonadal dysgenesis, coarctation of the aorta, congenital nystagmus and behavioural anomalies and a partial duplication of a novel kinesin gene in a patient with pseudoprecocious puberty.

**Introduction: purpose of the consensus meeting. A new nomenclature**

Hughes, Ieuan

United Kingdom

The Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology joined forces to plan and implement a Consensus document on the management of intersex disorders. A total of 50 international experts representing genetics,endocrinology,paediatric surgery and gynaecology,psychology,sociology and patient advocacy groups gathered to formulate
answers to a series of questions representing the spectrum of challenges posed by the investigation and management of an infant with ambiguous genitalia. The Faculty was divided into 6 Working Groups whose brief was to cover the following topics from an evidence base as far as was possible: Genetics and Nomenclature; Brain Programming; Investigation and Medical Management; Surgical Management; Psychosexual and Psychosocial Issues; Outcome Data. A key product of the Consensus has been the unanimous decision to revise the nomenclature and terminology currently used by health professionals. A modern lexicon was devised to reflect progress in the molecular aspects of sex development and to employ precision in applying definitions and diagnostic labels. Some currently used terms such as intersex are perceived as pejorative by patient support groups and pseudohermaphroditism is confusing and non-informative. An all embracing term of Disorders of Sex Development (DSD) is recommended for use which is defined by congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. On this basis, it is possible to formulate a classification system for DSD which is aetiological and functionally based and can be used by a range of biomedical scientists. This radical change in nomenclature must now be tested in practice and subsequently evaluated as to its benefit for health professionals and families with DSD.


**Pediatric Endocrinology of Chronic Diseases, Cytokines & their effect on growth & Puberty**

**Cytokines and their effects on steroidogenesis, inflammation and the HPA axis**

**Bornstein, Stefan**

**Germany**

The adrenal gland, as the main effector organ of the HPA axis, is a major site for both the synthesis and the action of numerous cytokines. Especially, inflammatory cytokines, like IL-1, IL-6, TNF and IL-18 play a key role in the immuno-adreno-cortical communication, during physiological as well as pathological situations. Thus, in cases of severe inflammation a coordinated response of the adrenal and immune system is crucial for survival. Previously, we have demonstrated a novel link between the innate immune system and the endocrine stress response, involving Toll-like receptors (TLRs). In our studies, we have shown that TLR-2 and TLR-4 are expressed in human and mice adrenals. TLR-2/4 deficiency was associated with an impaired adrenal corticosterone response in the knockout mice, in addition to marked cellular alterations in adrenocortical tissue. Furthermore, TLR-2 and TLR-4 deficient mice have an impaired stress response following inflammatory stress, induced by bacterial cell wall compounds. This defect appears to be associated by a decrease in systemic and intraadrenal cytokine expression and release. In conclusion, Toll-like receptors and cytokines play a crucial role in the immune-adrenal crosstalk. This close functional relationship needs to be considered in the treatment of inflammatory diseases requiring an intact adrenal stress response. This is also of high clinical importance, since there exists a high rate of TLR2 and TLR4 polymorphisms in humans and anti-cytokine based therapies are widely used in several autoimmune / inflammatory diseases.

**Cytokines and their effect on growth plate chondrocytes**
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Sweden  
Children with chronic inflammatory conditions, such as Crohn's disease or rheumatoid arthritis, experience impaired longitudinal growth. Although the inflammatory responses are different in various diseases, they can be characterised by a common spectrum of genes and endogenous mediators involved, including growth factors, inflammatory cytokines, chemokines, matrix metalloproteinases, and toxic molecules such as nitric oxide or free radicals. The cytokines that have been most studied for their ability to regulate bone and cartilage function are interleukin 1 (IL-1), tumour necrosis factor (TNF)- and interleukin-6 (IL-6). These cytokines may influence growth in children with inflammatory diseases by acting systemically and/or locally in the growth plate. We have shown that IL-1 and TNF- act in synergy locally in the growth plate to suppress longitudinal growth, an effect that can be partially reversed by insulin-like growth factor-I. IL-1 and TNF- inhibit the expression of a number of genes encoding chondrocyte-specific matrix molecules, including collagen types IX and XI and aggrecan proteoglycan. IL-1 decreases alkaline phosphatase activity during hypertrophy and suppresses the normal increase in cell size and type X collagen expression, suggesting inhibition of chondrocyte differentiation. TNF- induces apoptosis in cultured chondrocyte and has also been shown to reduce proteoglycan synthesis in fetal mouse metatarsals. Today, there are new commercially available biologic response modifiers that can be used to treat chronic inflammatory conditions. These include etanercept (TNF-inhibitor) and anakinra (IL-1 receptor antagonist). New data will be presented showing that etanercept and anakinra are both capable to prevent cytokine-induced growth retardation in cultured fetal rat metatarsal bones. Selective targeting of inflammatory cytokines has the potential to rescue growth in patients with chronic inflammatory diseases.

Promoting growth in children with chronic disease  
Ahmed, S. Faisal  
United Kingdom  
Short stature and growth retardation are commonly reported in children with chronic inflammatory disease. In addition, most studies that have examined final height in adults with childhood onset chronic inflammatory disease show a reduction. Although the underlying mechanisms for growth retardation are not fully understood, it is likely that factors such as poor nutrition, abnormalities of sex steroid and the growth hormone (GH)/insulin like growth factor-1 (IGF-1) axis, and the chronic use of glucocorticoids are important contributory factors. However, central to the impairment of growth in these children is the modulatory role of disease severity and pro-inflammatory cytokines on the above factors. Cytokines may affect the child’s growth either through systemic mechanisms or at the local level of the growth plate. Off-label use of recombinant human growth hormone in children with poor growth and chronic inflammatory disease has been encouraged by reports of an improvement in height velocity which may lead to a cessation of height deterioration but not complete recovery. Anti-TNF therapy has the potential to improve growth through a range of mechanisms. Whilst, addressing delayed puberty may itself lead to growth promotion, there is currently little evidence to support this practice in children with chronic inflammatory disease. Monitoring for abnormalities of growth requires an understanding of linear growth and puberty and a facility to measure and interpret the measurements. Its management requires close cooperation between the endocrinologist and the primary disease clinician who can address the child’s nutritional and disease control status. Other benefits of growth
promoting therapy on outcomes such as lean mass and bone mineral content should not be assessed without correction for changes in height. Growth promotion with rhGH or sex steroids is best performed within the umbrella of a clinical trial.