The theme of the Meeting was TRANSLATING BASIC SCIENCE INTO CLINICAL PRACTICE, hence the President of ESPE 2012, Dr. Wieland Kiess, said that following this theme presentations "will combine the richness of basic science and clinical practice in paediatric endocrinology and related sciences. The topics range from basic concepts of human evolution and mechanisms of obesity to meet the expert sessions on how to treat the child with disorders of puberty or the thyroid."

"The ESPE Annual Meeting which is held in different European cities and countries, is recognized worldwide as a meeting of high scientific and educational quality. It is currently attended by approximately 3,000 delegates".

PLENARY LECTURES

Summaries of some of the Plenary Conferences will be reproduced.

PL1-1: The evolution of human childhood

Jean-Jacques Hublin
Leipzig, Germany

In the course of evolution, humans have developed a unique way to give birth, to grow and to reproduce. In part this pattern results from the adaptive challenge represented by the exceptionally large size of our brain in relation to our body mass. During the last 2.5 million years this encephalic development, unrivaled among other primates, allowed the constant increase of social and technological complexity characterizing the human lineage. However, growing neonates with such a big brain required major obstetrical adjustments for bipedal primates of which the pelvic anatomy is highly constrained. The brain is also a very expensive organ in terms of metabolic costs. This is particularly problematic during the early phase of the individual development, from conception to weaning, when the mother carries the burden of fueling the growing brain of her child. From an evolutionary perspective, these two issues were resolved by delaying our development and by extending the volumetric growth of our brain during the first years of life. From a nutritional point of view humans also developed unique adaptations, including an early age for weaning. This allows the mother to share the burden of the developing children with other adults of the social group. It also results in a shorter birth interval and peculiar patterns of the women’s reproductive life. Our cognitive abilities, social complexity, and some of our psychological traits are direct consequences of these adaptations. Conversely they can also be seen as the conditions making the unique growth pattern of humans possible.

PL2-4: Long term outcomes of childhood obesity
Jennifer L. Baker  
Copenhagen University Hospital, Institute of Preventive Medicine, Copenhagen, Denmark

**Background:** Currently we are in the midst of a childhood obesity epidemic. Even if the levels are stabilizing in many countries, far too many children remain excessively heavy and at risk of ill health. Although concurrent health and social consequences are well-documented, less is known about long-term outcomes. **Objective:** To examine the evidence supporting (or refuting) the presence of long-term health and social consequences of childhood obesity. **Methods:** An overview of the current literature as well as emerging results from on-going studies will be presented. **Results:** There is support for negative long-term consequences of excess childhood weight with the health outcomes of various forms of cancer, coronary heart disease, stroke and other diseases. Additionally, there are negative associations between childhood obesity and the social outcomes of educational attainment and socio-economic status.  

**Conclusions:** Despite great interest in this area, results from research on long-term outcomes of childhood obesity are only beginning to emerge. Taken together, the evidence suggests that there is great cause for concern about the future health of the large numbers of children affected by the obesity epidemic.

**PL4-5: Isolated glucocorticoid deficiency caused by immunoreactive but biologically inactive ACTH**  
Mark E. Samuels1; Nicole Gallo-Payet2; Sandra Pinard2; Caroline Hasselmann1; Fabien Magne1; Lysanne Patry1; Lucie Chouinard2; Jeremy Schwartzentruber3; Anissa Djerimi1; Edgar Delvin1; Cheri L. Deal1; Guy Van Vliet1; Jacek Majewski3; Johnny Deladoey1  
1Endocrinology Service and Research Center of Sainte-Justine University Hospital, University of Montreal, Pediatrics, Montreal, Canada; 2Endocrine Unit, University of Sherbrooke, Medicine, Sherbrooke, Canada; 3McGill University and Genome Quebec Innovation Centre, Human Genetics, Montreal, Canada

**Background:** A 4 year-old girl, born to healthy unrelated parents, presented with hypoglycemia (1.8 mmol/L) without electrolyte abnormalities and was found to have very low serum morning cortisol (37 nmol/L) and very high serum ACTH level (379 pmol/L). Our working diagnosis was glucocorticoid deficiency due to ACTH resistance, but MC2R and MRAP were normal. The patient was obese and had red hair (like her mother), but POMC was not studied initially because of the high ACTH. However, whole exome sequencing revealed that the patient is a compound heterozygote for two POMC mutations: one is in the 5’ UTR, creating a new out-of-frame ATG which, if translated, would lead to inactivation of that allele; this mutation has been reported in a homozygote with undetectable plasma ACTH; the second is a missense mutation in a conserved residue in the protein-coding region of the gene (POMC p.R145C), in the ACTH hormone sequence itself (ACTH p.R8C). **Hypothesis:** The p.R8C ACTH mutant is an immunoreactive but bioinactive ACTH form. **Methods:** Whole exome sequencing, Sanger sequencing, peptide synthesis, ACTH immunoradiometric assay, binding and activation assays in HEK293 cells expressing human MC2R (hMC2R). **Results:** Using synthetic wild-type and p.R8C mutant ACTH, we showed that the laboratory assays used in clinical practice detected the mutant peptide which, in functional tests, failed to
activate the ACTH receptor (absence of cAMP production).  **Conclusion:** This is the first documented case of glucocorticoid deficiency with POMC mutations that result in the secretion of an ACTH molecule with decreased bioactivity but normal immunoreactivity. Exome sequencing led to the correct etiological diagnosis in this patient in whom genes known to cause ACTH resistance had been found to be normal. Thus, POMC mutations should be considered in patients presenting with glucocorticoid deficiency from apparent ACTH resistance.

**PL4-6: Co-adaptation of the vitamin D receptor (VDR) and colour-determining genes to latitude during humans' venture out of Africa**

*Dov Tiosano*1; *Laura Audi*2; *S Climer*3; *W Zhang*3; *M. Fernandez-Cancio*2; *R. Gershoni-Baruch*4; *M ElKholy*5; *A Templeton*3; *Ze'ev Hochberg*1

1Meyer Children's Hospital, Faculty of Medicine, Technion-Haifa Institute of technology, Pediatric Endocrinology, Haifa, Israel; 2Vall d’Hebron Research Institute, CIBERER, Pediatric Endocrinology, Barcelona, Spain; 3Washington University, Computer Science and Engineering, Biology, Biomedical Engineering, Statistical Genomics, Genetics, St. Louis, United States; 4Meyer Children's Hospital, Genetics, Haifa, Israel; 5Ain Shams University, Pediatrics, Cairo, Egypt

**Context:** As modern humans ventured out of Africa, they received significantly less UVB radiation, and had to adjust their skin color for vitamin D generation. We hypothesized that as humans ventured out of Africa the VDR gene co-adapted with skin color (SC) genes to changing latitude and UVB exposure. **Methods:** To this end, we extracted DNA from 751 subjects from a range of geographical latitudes and skin colors, and determined 68 SNPs from SC genes (MC1R, TYR, TYRP1, OCA2, SLC45A2, SLC24A5, KITLG) and from the VDR gene. **Computation:** A new method of identifying associations among SNPs was used called BlockBuster. It calculates a vector correlation that can attain multiple associations among SNPs and deal with underlying genetic heterogeneity. It detects haplotypes within small genomic regions and identifies multilocus genetic states that frequently occur within individuals in a population. **Results:** 4/22 VDR gene SNPs, all in the 5’ promoter region, are rare in Sub-Saharan Africa, but virtually fixed in all other populations, whereas coding region and 3’ UTR SNPs have no such distinction power. Four SNPs of SLC24A5, SLC45A2, MC1R, all in the coding regions of SC genes, clustered in non-random associations with the VDR 5’ promoter SNPs. The frequency of this cluster was 0.021 in Sub-Saharan Africa (latitude 0-8N), 0.276 in Egypt and Yemen (15-29N), 0.571 among Israeli Moslems and the Maghreb (31-33N), and 0.855 in Europeans (40-50N); the 8 SNPs in a 4-gene cluster correlated strongly with latitude, R^2 =0.873, p=3.7E-5. **Conclusions:** A selective sweep favoring the VDR promoter haplotype happened almost as soon as Homo sapiens migrated out of Africa. When the VDR promoter haplotype combined with four SNPs in SC genes, a higher order cluster correlated strongly with latitude. Thus, the newly-described high frequency VDR promoter haplotype interacted with SC genes to produce fine-scale adaptation to northern latitudes and decreasing UVB irradiation along the route out of Africa.

**PL5-8: Height determination and chondrocyte development**

*Keiichi Ozono*
Background: Skeletal dysplasia is a disorder of skeletal development characterized by abnormality in shape, length, a number and mineral density of bone. Skeletal dysplasias or dysostosis are classified into more than 400 different names of diseases. Enchondral bone formation is a coordinated event involving the proliferation and differentiation of chondrocytes and the eventual replacement by bone. Impaired enchondral bone formation leads to skeletal dysplasia, and different mutations in the same gene may cause the opposite phenotypes: short and tall stature. For example, FGFR3 (fibroblast growth factor receptor 3) is responsible for achondroplasia and CATSHL syndrome. Acromesomelic dysplasia, type Maroteaux characterized by dwarfism and short limbs is caused by loss-of-function mutations in the NPR-B (natriuretic peptide receptor-B) gene. However, gain-of-function mutations in NPR-B gene have not been reported. Objective: The aim of the study is to explore the NPR-B gene mutation in patients with tall stature.

Patients and methods: The proband was a 15-year-old boy with tall stature and large toes. His mother and grandmother had the same symptoms. We analyzed the genes including FGFR3, CNP (C-type natriuretic peptide), NPR-B and NPR-C. Results: A novel missense mutation of the NPR-B gene was identified in the affected members of the family. When expressed in HEK293A cells, the mutant NPR-B generated intracellular cGMP even in the absence of CNP, which further increased on treatment with CNP to levels higher than that in cells expressing wild-type NPR-B. Transgenic mice in which the mutant NPR-B was expressed in chondrocytes exhibited a similar phenotype to that observed in the patients. Conclusions: The constitutive active gain-of-function mutation of NPR-B associated with the elevated levels of cGMP in growth plates leads to the elongation of long bones. Our findings reveal a critical role for NPR-B in skeletal growth in both humans and mice. CNP may mediate the effect of growth hormone on chondrocyte proliferation and differentiation.

PL6-9: New insights into disorders of gonad development using whole genome analysis
Andrew Sinclair1; Stefanie Eggers1; Sultana Faradz2; Katherine Smith3; Melanie Bahlo3
1Murdoch Children’s Research Institute, Royal Children’s Hospital, Melbourne, Australia; 2Diponegoro University, Center for Biomedical Research, Faculty of Medicine, Semarang, Indonesia; 3The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Background: Disorders of Sex Development (DSDs) are congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. The cause of these problems is most often a breakdown of the complex network of gene regulation responsible for proper development of testes or ovaries in the embryo. Most DSD patients have an unknown etiology and cannot be given an accurate diagnosis. Objective: To identify the underlying mutation or small insertions/deletions in gonad determining genes of patients with DSD. Methods: We have used whole exome capture and massively parallel sequencing (MPS), to identify small insertions/deletions and point mutations in patients affected by DSD. For example, we analysed one family that had two different DSD phenotypes. Of the family members sequenced: six were
unaffected, three had 46,XY complete gonadal dysgenesis and four had premature ovarian failure (POF). We used a recently developed method to perform linkage analysis on this family using genotypes extracted from the MPS data. Due to the power of this large family, we quickly obtained a unique linkage peak on chromosome 9.

**Results:** The strategy of combining whole exome sequencing and linkage analysis using MPS data led to the rapid identification (within 2 days) of a novel three base pair, in frame deletion in exon six of NR5A1 (SF1) in all the affected individuals. The three base pair deletion was confirmed by Sanger sequencing. NR5A1 has a key role in steroidogenic pathways and gonad development. The deletion removes a single amino acid and causes major disruption to the secondary and tertiary structures of protein, affecting the function of the DNA binding domain such that it can no longer regulate downstream genes, ultimately causing the two DSD phenotypes seen in this family.

**Conclusions:** This example shows the tremendous power of massively parallel sequencing approaches, especially when combined with linkage analysis of a large family. In this instance it led to a rapid identification of the disease-causing mutation and appropriate diagnosis.

**NEW PERSPECTIVES**

Summaries of some New Perspective Conferences will be reproduced
**NP1-44: Digital microfluidics: a new technology for disease screening in the newborn**

*David S. Millington*
Duke University Medical Center, Durham, United States

There is increasing need for diagnostic technology that is applicable to screen for inherited metabolic disorders both in the newborn screening laboratory and at the point of care, where sample volumes are limited. Digital microfluidics (DMF), a "lab-on-a-chip" technology, provides an elegant and cost-effective solution for performing various enzymatic activity and other types of assay from extracts of dried blood spots and whole blood volumes of less than 1 µL. In principle, droplets from reagent and sample reservoirs are manipulated on a circuit board entirely under software control. A multiplex fluorometric enzyme assay for five lysosomal storage disorders (Pompe, Fabry, Gacher, Hunter and Hurler disease) on up to 48 specimens has been developed on the DMF platform. Results from unaffected and known affected dried blood spot samples, as well as quality controls, compared well with standard fluorometric assays performed in a clinical laboratory. A significant advantage of DMF is that assays are completed in less than 3 hr, compared with 24 hr by the standard method, and the volumes of sample and reagents consumed are far less than in conventional assay methods. The system has been tested under pilot conditions in newborn screening centers in the US and has successfully detected patients with Fabry and Gaucher disease. Other DMF assays that have been successfully demonstrated include a DNA based assay for T-cell receptor excision circles (TREC) for detection of T-cell depletion syndromes including severe combined immune deficiency (SCID), and a point-of-care test for hyperbilirubinemia. The technology holds promise for moving newborn screening to the point of birth, which is the only rational option for countries that lack a centralized system for collecting and analyzing newborn specimens, and could save time, cost and lives in the existing programs of developed countries.

**NP1-45: Lipidomics: new tools and applications**

*Manuel Mayr1; Christin Stegemann2*
1London, United Kingdom; 2King’s College London, Cardiovascular Division, London, United Kingdom

**Background:** The conventional reductionist approach to research investigates individual candidate factors or linear signaling pathways but ignores more complex interactions in biological systems. **Objective and hypotheses:** Lipidomics in combination with other molecular profiling technologies, such as proteomics, can be used to integrate biological information in disease-specific networks that drive pathophysiological changes. **Methods:** A chip-based robotic nanoelectrospray platform interfaced to a triple quadrupole mass spectrometer was adapted to analyze lipids in tissue sections and extracts from human endarterectomy specimens by shotgun lipidomics. **Results:** Eighteen scans for different lipid classes plus additional scans for fatty acids resulted in the detection of 150 lipid species from 9 different classes of which 24 were detected in carotid endarterectomies only. Further analyses focused on plaques from symptomatic and asymptomatic patients and stable versus unstable regions within the same lesion. Polyunsaturated cholesteryl esters with long-chain
fatty acids and certain sphingomyelin species showed the greatest relative enrichment in plaques compared to plasma and formed part of a lipid signature for vulnerable and stable plaque areas in a systems-wide network analysis. In principal component analyses, the combination of lipid species across different classes provided a better separation of stable and unstable areas than individual lipid classes. **Conclusions:** A combination of -omics technologies explores different aspects of disease but the different pillars of observations facilitate the data interpretation and increase the confidence in the findings. Ultimately, a systems biology approach may advance our understanding of cardiovascular disease processes at a “biological pathway” instead of a “single molecule” level and accelerate progress towards disease-modifying interventions.

**NP2-46: Promises of iPS cell technology for monogenic diseases of the beta cell**

_Timo Otonkoski_
University of Helsinki, Childrens Hospital, Helsinki, Finland

Recent development in cellular reprogramming technology has made it possible to derive induced pluripotent stem (iPS) cells from somatic cells (see this site [www.endopedonline.com.ar](http://www.endopedonline.com.ar) Number 37 [March 2012], Subject Reviews, Argentine Society for Clinical Investigation. **SYMPOSIUM: STEM CELLS**). This provides new possibilities for patient-specific cellular models to study pathogenetic mechanisms in cells which would otherwise be impossible to obtain. The major open question in such development is, whether it is possible to generate genetically intact physiologically functioning differentiated cells from the iPS cells. Pluripotent reprogramming is associated with an increased level of genomic instability. However, particularly since the emergence of non-integrating methods, it appears that this is not a major problem. iPS derived pancreatic beta-cells would be an important tool for diabetes research and therapeutic exploration. Currently it is possible, by mimicking the inductive signals or embryonic pancreas development, to induce relatively pure populations of pancreatic endocrine progenitor cells from human ES and iPS cells. Many of these cells express insulin and/or glucagon but the cells are functionally immature. However, after engraftment in immunodeficient mice, the progenitors undergo further maturation. In order to establish a platform for stem cell based modelling of beta-cell diseases, we have established iPS cells form patients with permanent neonatal diabetes (PNDM) and studied their differentiation into pancreatic islet-like cells. Preliminary data suggest that this approach may be suitable to recapitulate developmental defects associated with pancreatic hypoplasia and beta-cell death due to insulin mutations. The combination of in vitro-differentiation and genomic sequencing may be a powerful tool to identify new causes of PNDM. In addition, through this approach it is possible to correct the pathogenic mutation by gene targeting, followed by functional testing of the corrected cells.

**NP2-47: Next generation iPS cell technologies for modelling disease**

_Tristan McKay1; Amandine Breton1; Juliette Delhove1; Daniel Foxler2; Tyson Sharp2_
1William Harvey Research Institute, Queen Mary UNiversity of London, Centre for Endocrinology, London, United Kingdom; 2Barts
Cancer Institute, Queen Mary University of London, Molecular Oncology, London, United Kingdom

The capacity to reprogram somatic cells to a state of pluripotency is proving to be a step change in delivering authentic in vitro models for the study of diseases that affect diverse visceral tissues not least in endocrinology. Induced pluripotent stem cells (iPSC) generated from a single patient skin biopsy can self-renew indefinitely providing a limitless supply of cells and have the capacity to differentiate into virtually any cell-type under the right conditions. This technology breakthrough was achieved by genetically modifying cells to express high levels of 4 critical genes already identified as important in the maintenance of pluripotency. However, the process has proven to be highly inefficient and this genetic cocktail has been shown to cause substantial chromosomal and epigenetic instability that can compromise the iPSc ability to differentiate and the integrity of those differentiated cells. We have used new approaches to modulate the activity of a group of small RNAs called microRNA who's critical role in the maintenance of pluripotency is becoming ever more apparent. We have shown that by reducing the gene expression of a newly described modulator of specific microRNA activities we are able to generate iPSc with far greater efficiency than the classical approach, moreover with reduced transgene activity and thus increased efficacy. We propose that this new methodology will further enable the study of complex diseases in diverse fields.

**SYMPOSIA**

Summaries of some Conferences within Symposia will be reproduced.

**IGF-I as an oncogene**

**S1-12: Nuclear IGF-1 receptors in tumour cells**  
Olle Larsson  
Stockholm, Sweden

Recently we demonstrated that IGF-1 receptor undergoes SUMOylation, leading to its nuclear accumulation and gene activation by binding to enhancer regions. The levels of nuclear IGF-1R (nIGF-1R) is much higher in neoplastic cells compared to normal cells, suggesting important roles of nIGF-1R in cancer. nIGF-1R interacts with the transcription factor LEF1 and contributes to expression of LEF1-target genes independent of beta-catenin and IRS-1. nIGF-1R also associates with Histone 3 (H3) and modifies H3 via tyrosine phosphorylation. This triggers events involved in induction of epigenetic control of transcription. Thus, in addition to binding to enhancer regions, nIGF-1R may regulate transcription epigenetically and function as a co-factor for transcription factors.

**S1-13: IGFBPs/ALS: more than just IGF carrier proteins**  
Horacio Domené  
CONICET, Centro de Investigaciones Endocrinológicas (CEDIE), Buenos Aires, Argentina
Insulin-like binding proteins (IGFBPs) 1 to 6 form binary complex of high affinities with IGF-I and –II, while acid-labile subunit (ALS), with no affinity to IGFs, binds binary complexes of IGFs with IGFBP-3 or -5 to form heterotrimers of 150 kDa. These complexes maintain IGF-I into the vascular compartment, protecting IGF-I and IGFBP-3 for degradation by proteases. Besides acting as simple carrier proteins, IGFBPs regulate the amount of IGF-I available to interact with IGF1 receptors. IGFBPs may also act as modulators of cell growth by IGF independent mechanisms. Some Antiproliferative actions of IGFBP-3 appear to be independent of IGFs, as the apoptosis induced trough the recently reported IGFBP-3R. Although mice models of individual IGFBPs KO show modest phenotypes, triple null mice for IGFBP-3, -4 and -5 have a significant reduction in IGF-I levels and reduced adult sizes. The ALS-KO mice presents a mild growth deficit despite a marked reduction in the circulating levels of IGF-I and IGFBP-3, showing increased hepatic and gastric tract tumors at advanced age. Knock-in mouse models of mutated IGF-I with reduced affinity for IGFBPs have low serum IGF-I and high GH levels, presenting increased body size and selective organomegaly. Only IGFALS gene defects have been characterized in humans, because patients with inactivation of IGFBP1 to 6 genes have still to be identified. Human ALS deficiency presents mild growth retardation, despite severe IGF-I deficiency, probably related to the preserved autocrine/paracrine action of IGF-I. In animal models and epidemiologic studies in humans, high IGF-I and low IGFBP-3 levels have been positively associated to increased cancer risk. While in GH insensitivity and GH deficient patients, IGF-I deficiency appear to protect against cancer development, in ALS deficiency, where local IGF-I production is preserved, increased insulin and GH secretion and reduced IGFBP-3 levels may hypothetically result in a favorable milieu to tumor progression. Careful follow-up is required to evaluate long-term consequences in these patients.

S3. Cushing Syndrome and Disease

S3-17: Recent advances in the genetics of the various forms of Cushing syndrome

Constantine Stratakis

National Institutes of Health, Program in Developmental Endocrinology & Genetics, National Institute of Child Health and Human Development, Bethesda, United States.

The majority of benign lesions of the adrenal cortex (AC) leading to Cushing syndrome (CS) are linked to one or another abnormality of the cyclic (c) AMP signaling pathway. Benign adrenocortical causes of CS include the common and sporadic cortisol-producing adenoma (CPA) and a spectrum of corticotropin (ACTH)-independent, and almost always bilateral, hyperplasias. Macro-hyperplasias are more common among older patients, whereas micro-hyperplasias are frequent among children and young adults. Massive macronodular adrenocortical disease (MMAD) or ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) describes a heterogeneous group of disorders that are associated with aberrant G-protein-coupled receptor (GPCR) expression (E). Abnormal GPCR-E has been found in CPAs; a small number of both MMADs and CPAs harbor somatic GNAS (Gsa) mutations. AIMAH can also be found in the context of McCune-Albright syndrome. Micro-hyperplasias are either pigmented (the classic form being that of primary pigmented nodular adrenocortical disease or PPNAD)
or non-pigmented (NP-MAH) and isolated (i) or in the context of other syndromes (Carney complex - CNC). Both CNC and iPPNAD are caused by germline PRKAR1A mutations; somatic mutations of this gene that regulates cAMP-dependent protein kinase (PKA) are also found in 10-20% of all CPAs and abnormalities of PKA are present in most MMADs. NP-MAH forms of adrenal hyperplasia and some CPAs are associated with phospohodiesterase (PDE)-11A and PDE-8B sequence defects. Other PDEs may be involved, too. From all the above, it is clear that increased cAMP signaling leads to tumors in AC. Mouse models of PRKAR1A deficiency also show that increased cAMP signaling leads to tumors in AC and other tissues. Whole-genome transcriptome profiling of tumors from humans and mouse models identified Wnt signaling as the main pathway activated by abnormal cAMP signaling, along with cell cycle abnormalities. Most recently, we further demonstrated that activation of Wnt-signaling is a somewhat generic endpoint of cAMP/PKA activation, even in bone. We conclude that cAMP signaling aberrations are essential in the pathogenesis of benign cortisol-producing lesions of the AC, especially micronodular hyperplasias.

**S3-18: Clinical evaluation of the patient with suspected Cushing syndrome**

*Helen Storr*

London, United Kingdom

Endogenous (non-iatrogenic) Cushing's syndrome is a rare life-threatening disorder caused by prolonged exposure to excessive glucocorticoids. In approximately 75—80% of paediatric cases, the disorder is secondary to an ACTH-secreting pituitary adenoma (Cushing's disease, CD). Paediatric Cushing's syndrome (CS) is a very rare clinical problem, which is associated with significant morbidity and presents the tertiary paediatric endocrinologist with major diagnostic and therapeutic challenges. The clinical progression of CS in children usually takes place over many years and may go unrecognised by family, carers or family doctors. Recognition of features which might alert the clinician to the diagnosis of CS is of crucial importance. In our CD series the mean length of history 2.5 ± 1.7 yr (0.3-6.6 yr) and 64% pts have a history of >2 yr. Most children and adolescents have a typical cushingoid appearance and all our paediatric CD patients had a change in facial appearance. A more subtle or subclinical presentation or cyclical features are uncommon. Almost all CD patients have weight gain, in our CD series 78% have BMI SDS ≥ 2.0. All our CD patients have evidence of growth failure and 38% patients have short stature (Ht SDS ≤ -2.0). Additionally, paediatric CD is characterised by a male preponderance in prepubertal years, with a change in sex distribution at the time of puberty. Prepubertal virilisation is frequent in CD patients and was noted in 86% of our CD patients. Pubertal patients also had low LH and FSH suggesting impaired pituitary-gonadal axis function. Striae were noted in 48% patients, being more frequent in the older patients. Additional features were: hypertension (48%), emotional lability/depression (60%), fatigue (62%) and headaches (48%). A diagnostic protocol for investigation is required which broadly follows the model for adult patients. Most paediatric endocrinologists have limited experience managing children or adolescents with CS and thus benefit from close consultation with adult colleagues.

**S3-19: Recent therapeutic advances for Cushing syndrome in children**
Cushing’s syndrome remains one of the most fascinating, and often the most complex, of problems in neuroendocrinology. While it is relatively uncommon in adults, it appears to be extremely rare in childhood, so it is important that centres which have extensive experience in its management share their conclusions. Clearly, in cases of adrenal adenoma or carcinoma these need to be surgically removed, where possible laparoscopically except for adrenocortical carcinoma. Primary pigmented nodular adrenal dysplasia, either as an isolated finding or in patients with Carney Complex, requires bilateral adrenalectomy. For Cushing’s disease, the initial treatment of choice is transsphenoidal surgery, which in our hands has a cure plus remission rate of 78%, increasing when performed following tumour localization by petrosal sinus sampling. In adults, recent data suggest a recurrence rate, even with apparently curative surgery, of ~10% at years and up to 20% at 20 years, but limited follow-up in children has shown no recurrences to date. Radiotherapy is often very effective for surgical failures, providing normal cortisol levels often within one year. Medical therapy with metyrapone and/or ketoconazole is useful, and intravenous etomidate can be life-saving where parenteral therapy is essential. The glucocorticoid antagonist mifepristone may also have a place. In terms of pituitary-directed therapy, the multiligand somatostatin analogue pasireotide has shown to normalise cortisol levels in 20-30% of adult patients, although the induction of hyperglycaemia is of some concern, and it is unlikely to be licensed for use in childhood. In other situations bilateral adrenalectomy may be attractive as an immediately curative option for hypercortisolaemia, and the onset of Nelson’s syndrome is uncommon. It is very important to treat short stature vigorously with GH replacement where this has been identified, and in some cases induction of pubertal delay with GnRH analogues will extend the time for optimisation of growth.

Understanding Primordial Dwarfism

S10-38: The clinical geneticist's approach to a child with primordial dwarfism

Andrew Jackson
Edinburgh, United Kingdom

Primordial dwarfism is a group of human single-gene disorders with extreme global growth failure. Reduced growth starts from early in development, with substantial reduction in size observed at birth and continuing postnatally, such that final adult stature may be as little as 1 metre. In contrast to other forms of dwarfism, significant microcephaly is present, with head circumference reduced proportionately, or more severely than height. This group of conditions includes Seckel syndrome, Microcephalic Osteodysplastic Primordial Dwarfism (MOPD) types I and II, and Meier-Gorlin syndrome. Eleven genes have now been identified for microcephalic primordial dwarfism, encoding proteins involved in fundamental cellular processes including centrosome function (CEP152, PCNT, and CENPJ), genome replication (ORC1, ORC4, ORC6, CDT1, and CDC6), DNA damage response (ATR, CTIP), and mRNA splicing (U4atac). In this talk I will outline a
clinical approach to primordial dwarfism along with the phenotypes of these conditions and provide an overview of the underlying cellular mechanisms that have been implicated to date.

S10-39: Mutations of the pericentrin gene as a cause of primordial dwarfism
Anita Rauch
Zürich, Switzerland
Abstract text has not been submitted.

A recent publication by the Speaker on the subject follows:
Best Pract Res Clin Endocrinol Metab. 2011 25:125-30. The shortest of the short: pericentrin mutations and beyond. Rauch A. Institute of Medical Genetics, Schorenstrasse 16, Schwerzenbach-Zurich, Switzerland. Anita.rauch@medgen.uzh.ch

Abstract. Microcephalic or Majewski’s osteodysplastic primordial dwarfism type II (MOPD II) represents the most common type of primordial dwarfism. Adult height is typically about one meter and short stature is becoming mildly disproportionate over time with mild skeletal anomalies. Mental development is usually borderline or within the low normal range but cerebrovascular events that are common in childhood can result in significant cognitive impairment and cerebral palsy. Despite cerebrovascular insults, cardiomyopathy and early onset type 2 diabetes contribute to early mortality and morbidity. Common minor clinical features are truncal obesity, high pitched voice, microdontia and pigmentary changes. MOPD II is caused by autosomal recessive loss of function mutations in the PCNT gene encoding for a key centrosomal protein. There is clinical overlap with the so called Seckel syndrome, a heterogeneous group of entities with at least four different gene loci known to date.

S10-40: Seckel syndrome: mutations in the CEP 152 gene
Bernd Wollnik
Cologne, Germany
Abstract text has not been submitted.

A recent publication by the Speaker on the subject follows:

Abstract. Functional impairment of DNA damage response pathways leads to increased genomic instability. Here we describe the centrosomal protein CEP152 as a new regulator of genomic integrity and cellular response to DNA damage. Using
homozygosity mapping and exome sequencing, we identified CEP152 mutations in Seckel syndrome and showed that impaired CEP152 function leads to accumulation of genomic defects resulting from replicative stress through enhanced activation of ATM signaling and increased H2AX phosphorylation.