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# President's Report

Dear All,

It is an honor for me to take on the role of APPES President for the next 2 challenging years.

I joined APPES back in 1999 as a fellow student when the number of APPES members was only 182, and it has increased over the years. The number of APPES members to date has reached 452 members. Looking at this progress, it is a very impressive achievement done by the past Presidents. At this opportunity I would like to express my gratitude to the leadership of our past Presidents, Wayne Cutfield and Xiaoping Luo and the hard work of all the council members who have helped make APPES one of the biggest organisations in the world, in terms of population and country size.

APPES always strives to better serve, not only our members, but also pediatricians in general and, most importantly, the children around the globe. Global inequality has been the issue in many fields and countries despite the globalization around the world. Globalization has yet to give equal opportunities and outcomes to those certain developed and developing countries. Opportunity to do research varies from country to country despite the population and size of the country. This leads to a slow development of the children care in many countries. In the millennium of development, we have to work hand in hand and move toward a better care for the children (in the Asia Pacific region)

I am also pleased to report the appointment of the new council and would like to express my deepest appreciation to the following council members to take on their new roles:

- Immediate Past President: Xiaoping Luo (China)
- President Elect: Reiko Horikawa (Japan)
- Secretary: Suttipong Wacharasindhu (Thailand)
- Treasurer: Craig Munns (Australia)
- Pik-To Cheung (Hong Kong)
- Fatimah Harun (Malaysia)
- Viji Bhatia (India)
- Han-Wook Yoo (Korea)

- Byung Kuy Suh (Korea)
- Vũ Chi Dũng (Vietnam)
- Nalini Shah (India)
- Melinda Atienza (Philippines)
- Jun Fen Fu (China)
- Chair of SPC: Paul Hofman (New Zealand)
- Fellows Meeting Convenor: Maria Craig (Australia)

Together with the wonderful and devoting new council members, I am excited and eager to see APPES continue to grow in size, capability and have more regional influence.

We will have in the coming 2 years' agenda to further promote APPES, increase collaboration in research between member countries as well as non-member countries and strive to provide pediatric endocrinology service with equal quality standard to all regions in the Asia Pacific. We will persistently reach out to look for opportunities to extend our international network and to connect with other international organisation around the world to achieve our ambitious goals and objectives.

Our program will start with the Annual Fellows Meeting from the 9—12 November, crossing over with the first APPES CME meeting in Vietnam on 12 & 13 November 2011

It is also my great pleasure to announce that the next APPES Biennial Science Meeting will be held in Bali, Indonesia. A formal bidding was undertaken in July 2010 and opened to all member countries. The decision was made during the APPES meeting in Xi'an and announced to all APPES members.

Finally, I am looking forward to seeing you all at the APPES meetings and wish you a successful and productive year in 2011.

Sincerely yours,

Aman Pulungan  
APPES President



Aman Pulungan  
APPES President

# COUNCIL NEWS

## EXECUTIVE



Aman Pulungan  
President  
Indonesia



Xiaoping Luo  
Immediate Past President  
China



Reiko Horikawa  
President Elect  
Japan



Suttipong Wacharasindhu  
Honorary Secretary  
Thailand



Craig Munns  
Honorary Treasurer  
Australia

## COUNCIL MEMBERS



Vijayalakshmi Bhatia  
India



Pik To Cheung  
Hong Kong



Han-Wook Yoo  
South Korea



Fatimah Harun  
Malaysia



Nalini Shah  
India



Melinda Atienza  
Philippines



Jun Fen Fu  
China



Byung Kuy Suh  
Korea



Vũ Chi Dũng  
Vietnam



Paul Hofman  
Chair Scientific Pro-  
gram Committee  
New Zealand



Maria Craig  
Convenor,  
Fellows Meetings  
Australia

## CO-OPTED MEMBERS



Chris Cowell  
Chair, Global Inequalities  
Subcommittee  
Australia



Geoff Ambler  
Webmaster  
Australia

# APPES 12th Fellows Meeting

The 12<sup>th</sup> APPES Fellows' Meeting was held in association with the Chinese Medical Association from November 14th to 17th, 2010 in Xi'an. One of the Four Great Ancient Capitals of China, Xi'an has more than 3,100 years of history. The course was attended by 42 paediatric endocrine fellows from 13 countries across the Asia Pacific region, including Australia, China, Hong Kong, India, Indonesia, Japan, Malaysia, Korea, Philippines, Singapore, Taiwan, Thailand and Vietnam. The fellows' meeting was held immediately prior to the APPES Scientific Meeting and we were therefore fortunate to have a number of invited plenary and symposium speakers join the faculty. Most fellows stayed on for the APPES ASM, so for almost one week, they were immersed in comprehensive learning across many areas of paediatric endocrinology, in fascinating historical surroundings. It was also a wonderful opportunity to interact with colleagues and make new friends.

We were pleased to have a strong, experienced international faculty including Prof Scott Rivkees, Prof Kim Donaghue, Prof Viji Bhatia, Prof Reiko Horikawa, Prof Han-Wook Yoo, Prof Wayne Cutfield, A/Prof Paul Hofman, A/Prof Pik-To Cheung, Dr Aman Pulungan, A/Prof Chris Cowell, A/Prof Craig Munns, Prof Louis Low (who has been on faculty for every APPES fellows' school), and A/Prof Maria Craig (Scientific Convenor). The meeting was generously supported by Merck-Serono, Pfizer (who provided travel grants) and APPES. The format of the workshop consisted of interactive case presentations by fellows, small group discussions, lectures by the faculty and a quiz. The standard of case presentations by fellows was extremely high and we were fortunate to learn from each other about the diverse presentation of paediatric endocrinology across the region. Congratulations to Dr Song Hai Lim from Singapore who was awarded the best presentation for his case of "Familial Glucocorticoid deficiency" and to Dr Ganesh Jevalikar from India who achieved the highest score in the APPES quiz, by a clear margin. Whilst we all had a busy time learning, we also took some time out to experience some of China's extensive history and visit the Terracotta warriors.

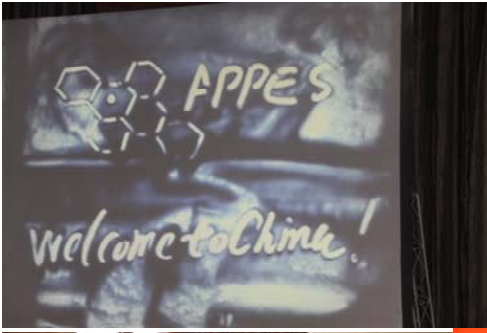
Thanks to all of the fellows for your hard work in preparing and presenting cases, and your enthusiastic participation in the small discussion groups. Thank you also to the faculty for your commitment to teaching, the excellent, up to date lectures and comprehensive teaching materials. Finally special thanks to Katy, Lyndell and Alicia for your wonderful organisation.

This year's meeting will be in Hanoi, Vietnam from 9th to 12th November 2011, immediately prior to the inaugural APPES advanced course/CME update for consultants on the weekend of 12th/13th November (the morning of Saturday 12th November will be joint sessions for fellows and consultants). Further details regarding both meetings including how to apply will be on the APPES website in March 2011.

Maria Craig  
Fellows School Convenor



# PHOTOS FROM APPES MEETING, XI'AN, CHINA



# PHOTOS FROM APPES MEETING, XI'AN, CHINA



# AWARD PRESENTATIONS

The following presentations were made during the opening ceremony of the 2010 APPEs Scientific Meeting In Xi'an, China

## LIFE MEMBERSHIP



A/Prof Chris Cowell is Director of the Kids Research Institute at The Children's Hospital at Westmead, Sydney, Australia and is a Senior Staff Specialist in the Institute of Endocrinology and Diabetes at the Children's Hospital at Westmead. He has been Director of Clinical Research at CHW since 2005. A Clinical Associate Professor of the University of Sydney, A/Prof Cowell trained as a paediatric endocrinologist in Toronto and Sydney and has extensive clinical experience in diabetes, growth, obesity related metabolic syndrome and disorders of bone metabolism. His major research interests are the prevention of metabolic complications of obesity in teenagers, and the effects of disease states on bone mass and bone geometry. He has published more than 200 articles in leading journals that include the New England Journal of Medicine, the Journal of Clinical Endocrinology and Metabolism and the Journal of Bone and Mineral Research.

Chris is undoubtedly one of the regions most highly regarded paediatric endocrinologists which gave him the mana to bring his vision of a regional paediatric endocrine society to reality back in the mid 1990's. Through his passion and single minded determination he established APPEs with strong support from Louis Low, Mena Desai and Chanika Tuchinda . Chris and Louis were the unofficial "parents" of APPEs and nurtured the society through it's early years to become the strong regional society it is today. To paraphrase Winston Churchill "never before has some much been owed to so few". Chris you almost single-handedly established our society and for that every one here owes you an enormous debt of gratitude.

## TEACHING AWARD



Prof Suttipong Wacharasindhu is Professor in Pediatric Endocrinology at the Chulalongkorn Hospital in Bangkok. He also is a member of the Expert Committee of Endocrine and Metabolism, The Royal College of Pediatricians of Thailand, serves as Assistant Director for Risk Management, King Chulalongkorn Memorial Hospital, Bangkok, is Chairman of The Patients' Rights and Ethics, King Chulalongkorn Memorial Hospital, Thai Red Cross Society; Coordinator of International Communication Office of Pediatric Endocrine Societies (COPES) and in addition he has served as APPEs Honorary Secretary since 2006.

In amongst all this work, Prof Suttipong has consistently shown that he is not only one of the best pediatric endocrinologists in Thailand, but also an excellent human being with very good human relationships. His colleagues, fellows and students praise him as a very good teacher with excellent teaching skills. Prof. Suttipong is so keen to update the knowledge in pediatric endocrinology and DM consistently and with his experience resulting in a good teaching approach to the problems. His ability to finish the jobs within short periods of time with determination, diligence and responsibility has always been observed.

Prof. Suttipong is also an excellent administrator with success. He had received "Awards of Recognition for Outstanding faculty Member 2008" .

Prof. Suttipong had just been declared to be Head, Department of Pediatric, Faculty of Medicine, Chulalongkorn University this October.

# Highlights

# 6th Annual Biennial Scientific Meeting APPES

Xi'an, China, 17–20 November 2010

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The 6th Biennial Scientific Meeting of the Asia Pacific Paediatric Endocrine Society was held in Xi'an, China from 11–14 November. Xi'an is the birthplace of the Chinese nation with its first Emperor QinShiHuangDi creating the empire by successfully integrating 7 separate states. His impact on civilisation lives forever with the amazing discovery of the Terracotta Warriors in 1974 and his mausoleum which has not yet been opened. Xi'an was capital of China for 1100 years during 13 dynasties. The history and culture of China was highlighted in a cascade of amazing cultural performances at the opening ceremony including calligraphy artists, acrobats, sand painters and dancers. **Professors Xuefan Gu, Louis Low**, Co-Chairs of the LOC, **Ms Lan Zhao**, Secretary-General Shanxi Health Bureau, **Professor Guoming Qi**, Vice-President of the Chinese Medical Association and **Professor Xiaoping Luo**, President of APPES and CSPEM, welcomed over 557 participants from 22 countries/regions and stressed the importance of the meeting to improve knowledge, research and training as well as the opportunity to renew friendships and collaborations.



## Controversies in hyperthyroidism management

**Scott Rivkees (Yale, USA)** provided a comprehensive overview of contemporary management of Graves' disease in children and teenagers whilst highlighting the unravelling of the liver toxicity of propylthiouracil (PTU) and the subsequent recommendation for withdrawal for its use in children and adults. Graves' disease is uncommon, 1/10,000 in children, females:males 3:1, versus 1/1000 in adults. The overall remission rate is low in young people, approximately 15% in prepubertal subjects and 30% in adolescents with good prognostic factors including small thyroid, older age and low thyroid stimulating immunoglobulins (TSI) at diagnosis (Fig. 1).

Anti thyroid drug therapy was introduced in 1947 with PTU followed by methimazole (MMI) in 1950. In 2008, 1/3 of children with Graves' disease in the USA were on PTU when a series of case reports established that PTU causes liver failure in approximately 1/2000 and is the 4<sup>th</sup> most common cause of drug related liver transplant in children. Reversible liver disease occurs in 1/200 children treated with PTU. As there are no predictors for PTU induced liver disease, it should never be used as first line therapy in children. Recent evidence suggests that PTU is potentially hepatotoxic in adults including during pregnancy. PTU has been shown to be teratogenic in mice with dose dependent skull and heart defects that have not been seen with MMI. Studies are underway to determine if it is teratogenic in humans.

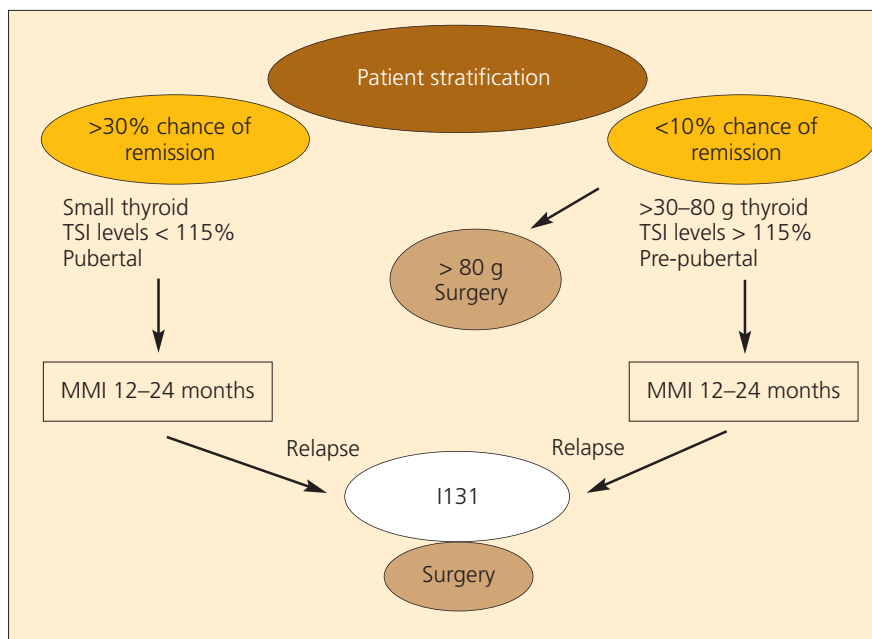


Fig. 1: Therapeutic options for children with Graves' disease.

Methimazole is effective in a once daily dose. Side effects are dose dependent so it is important to use as low a dose as possible; infants, 1.25 mg; age 1–5 yrs, 2.5–5 mg; 5–10 yrs, 5–10 mg; 10–18 yrs, 10–20 mg. At Yale, the MMI adverse events for last 100 patients include 17% minor, 2% major – joint pain, allergic reactions (Stevens Johnson syndrome). If there is a side effect, definitive treatment with surgery or radioactive iodine (RAI) is required – do not use PTU. There is no evidence of remission on medical therapy beyond 2 years and thus the options for therapy need to be balanced based on prognostic factors at diagnosis, the age of the patient (Fig. 1) and other long term risks of medical therapy. These include progressive thyromegaly and the increased life time risk of thyroid cancer, 0.9% which is 10 to 20 fold higher than patients treated with surgery or RAI because of the presence of the remaining thyroid tissue which has malignant potential.

Surgery is the oldest form of definitive therapy, Professor Kocher being awarded the Nobel prize in 1909. Professor Rivkees recommended subtotal surgery leaving 2–4 g of tissue. Subtotal surgery is associated with an appreciable risk of relapse, 20 to 40% but this has to be balanced against potential serious side effects of surgery

that are more common with total thyroidectomy. He emphasised the need for surgery to be performed by a surgeon who has a high volume of thyroid surgery, >30 cases/year.

RAI is the alternate definitive therapy and the goal of RAI therapy needs to be hypothyroidism, not euthyroidism for dosing (Table 1). It is not effective if thyroid gland is >80 g. The risk of long term cancer to the thyroid and to the whole body has been addressed in several studies. Professor Rivkees commented that he was not aware of reports of cancer if the I131 dose was >150 uCi/g of thyroid tissue. A 36 year retrospective study in a small number of children had projected a slight increase in cancer risk if treated with 15 mCi at age 5 and so it was recommended not to use RAI in this age group.

Table 1: Contemporary I131 dose. After Rivkees et al. *Pediatrics* 2003;111(4Pt 1):745–9.

- Goal: Hypothyroidism; I131 dose: >150 uCi/g  
- (125 Gy; 12,500 Rads; 5.5 MBq/g)
- Associated with >95% cure rate with single dose
- The bigger the gland, the higher the dose needed.
 

10–30 g:	150 uCi/g
31–60 g:	200–250 uCi/g
61–80 g:	300–400 uCi/g

Professor Rivkees summarised the major points of his lecture;

- MMI is definitely preferable to PTU
- Prolonged ATD is an option...
- Surgery is an option if done by a high volume surgeon
- RAI can be used in children
- PTU ? use only in first trimester of pregnancy

## Management in DSD

Charmian Quigley (USA) reviewed the terminology of disorders of sex development (DSD) and gave us a practical approach to their presentation, diagnosis and management. She addressed issues such as disclosure of diagnosis to the patient and family bearing in mind age and cultural factors. She touched on gender of rearing and suggested that non-urgent surgery should be minimised.

Dr Quigley focused on 46XY DSD illustrating with cases the varying presentations according to age-group and genital phenotypes. She suggested tests to work up 46XY DSD should include a karyotype, 17OH-P, testosterone and AMH level (Fig. 2). AMH is useful in confirming the presence of testes, establishing sertoli cell function and if present in normal levels effectively excluding complete gonadal dysgenesis.

She emphasized the importance of serum and urinary steroid profiles in the neonatal period with particular attention borne to the timing of postnatal gonadotropin and sex steroid surge – “mini-puberty”. She highlighted the distinctive contrast between postnatal hormonal profiles of infants with complete AIS (CAIS) and those with partial AIS (PAIS). Infants with CAIS are more likely to have blunted LH responses and undetectable testosterone levels. Those with PAIS are more likely to have exaggerated testosterone levels. Both will have brisk HCG responses but those with CAIS are more likely to have blunted responses to GnRH stimulation [1]. This suggests that the hypothalamus requires expression of an androgen receptor that retains at least some degree of function for “mini-

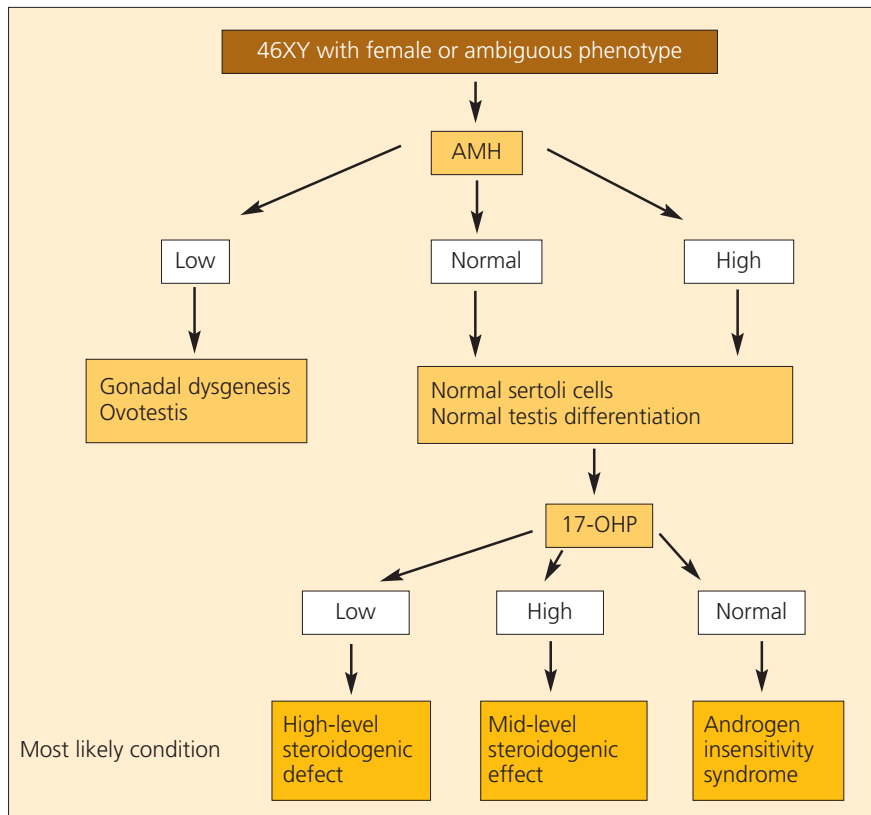


Fig. 2: A diagnostic algorithm for 46XY DSD.

puberty” to become evident. Whereas infants with both CAIS and PAIS had brisk testosterone responses to human chorionic gonadotropin, indicating normal testicular responses to gonadotropins [2].

She concluded stressing that gender identity is multi-factorial involving genetic, hormonal, environmental, psycho-social and cultural factors. There may be significant benefit in empowering parents to provide information to the child and involving families with adequate peer support groups.

### Congenital adrenal hyperplasia (CAH)

Tomohiro Ishii (Japan) reviewed the evidence for screening of congenital adrenal hyperplasia (CAH). CAH remains a medical emergency and in virilised infant females a psychosocial emergency. He outlined the available screening testing modalities through the Guthrie card, their advantages and limitations (false positive results due to stress, fetal adrenal steroids and differences in antibody specificities, and

false negative results due to antenatal maternal glucocorticoid exposure). Second tier screening tests including gas or liquid chromatography mass spectrophotometries were also outlined. He suggested that screening for CAH was cost efficient and beneficial [3] and should become widely used.

Sonia Grover (Australia) gave a gynaecologist’s perspective of affected females with CAH and varying degrees of virilisation. She encouraged us to carefully consider with each patient what would be considered “best outcomes” in terms of gender role, identity and assignment. She reviewed evidence on genital surgery, close relationships, sexual enjoyment and fertility. Surgical cosmetic outcomes and anatomical results are dependent on the expertise of the surgeon and delaying surgery such as vaginoplasty until adolescence may result in CAH patients being operated under the care of surgeons with little CAH experience. Referral should be made to highly skilled surgeons familiar with CAH in centres of excellence. There was consensus that disclosure though

complete, should be approached in a gradual manner.

Paul Hofman (New Zealand) and Dr Grover pointed out no population based CAH studies are available. However, current evidence suggests although CAH affected females frequently display less feminine role behaviour in childhood, most have female-typical gender identity [4]. Toy play appears to be related to degree of prenatal androgen exposure [5]. Gender identity was not strongly influenced by early androgen exposure, nor predicted by childhood gender related behaviour or genital appearance. Gender dysphoria was uncommon in CAH (~5%) but was more frequent than in the general population, the reason for which is not well understood [6]. Therefore, he recommended that gender assignment in affected females should always be female.

Adjustment and quality of life studies suggest good psychosocial adjustment which were not related to genital appearance at birth or age of genital surgery [7]. Cognitively, there were no observed differences in intelligence quotient. However, CAH affected females appeared to have higher spatial abilities than sisters without CAH, whereas boys had the same trend with unaffected brothers.

### AVP and oxytocin as social hormones

Richard Ebstein (Singapore) presented fascinating data on effects of arginine vasopressin (AVP), oxytocin (OT) and their receptors on social behaviours across vertebrates including humans. AVP and OT may be necessary in establishing basic human interactions including trust, empathy and stress.

Are we hardwired to trust, give, be generous, monogamous or not? AVP appears to influence anxiety levels in socially stressful situations and mediates stress responses including cortisol release. Dr Ebstein presented data on AVP as a social hormone whose effects are particularly notable when performing in front of an audience. In addition, AVP and OT appear to influence subjects’ ability to perform

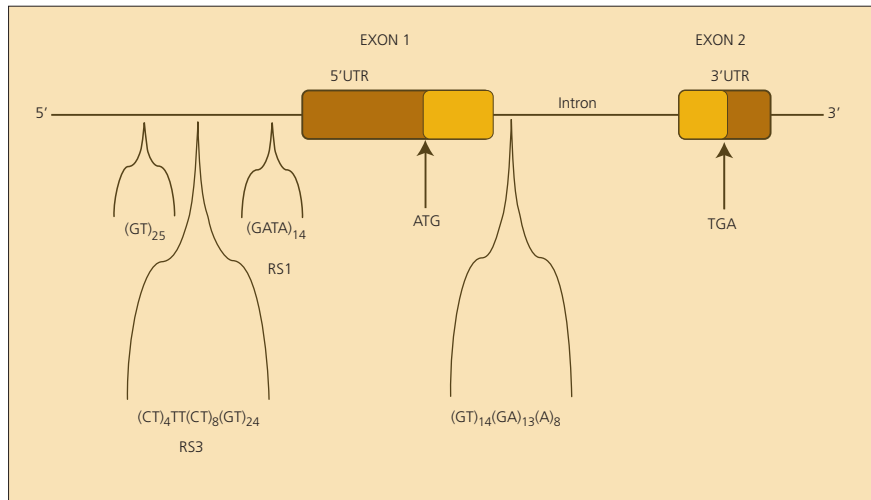


Fig. 3: Location of AVPR1a microsatellite repeats. The start site of protein synthesis is represented by ATG. Located on chromosome 12 q. (After Thibonnier et al. 2000)

higher theory of mind tasks, “mentalize”, interpret facial expression and empathize. AVP and OT appear to act in opposing manners in these respects. Intranasal administration of AVP impairs the ability to interpret facial expression, more markedly in males. On the other hand, higher OT levels correlate with higher levels of affection between mothers and their infants. OT may also play a significant role in neurocognitive development through effects on “mirror neurones” which allow learning through observation – “mimicry”. These observations are in

keeping with reports that OT may have a beneficial role in autistic spectrum disorders (ASD).

Dr Ebstein further discussed the role of genetic expression of the AVP receptor 1a (AVPR1a) which is controlled by the length of a promoter region microsatellite, the longer the repeat the greater the expression (Fig. 4). Social experiments using behavioural economic paradigms, “games”, studying altruism and generosity demonstrated an association between generosity and longer microsatellite repeats adjacent to the AVPR1a. In Vole

studies, the length of the promoter is the decisive neurogenetic difference defining dramatically different social behaviors in two closely related species. In male voles a longer promoter resulted in a monogamous and more caring social behaviour, whereas short promoters resulted in polygamous and “colder” social behaviours.

Finally, social behaviour is modified by sex hormones. Testosterone levels in both men and women positively correlated with “selfishness” (Fig. 5). So are we hard wired to be monogamous or polygamous? Is being divinely empathetic or severely autistic extreme on either end of the subtle endocrine continuum? Should endocrinology expand into the paradigm of neuropsychosocial endocrinology? We are encouraged to think broadly about the broad neuro-bio-psycho-social and emotional effects our therapies may have for individuals and their social sphere.

## Bone symposia

Jung Sub Lim (Korea) reviewed the literature on the use of dual energy X-ray absorptiometry (DEXA) in assessment of bone mineral densitometry (BMD). He emphasized the need for adequate BMD technique (eg. patient alignment) and standardized measures for age, gender, height, weight and bone age.

Craig Munns (Australia) presented a comprehensive review of bone health assessment including definitions of osteoporosis in childhood as bone density Z-score  $< -2$ , in combination with a clinically significant fracture.

In addition to DEXA, assessment of bone health should include relevant serology Ca, Mg, PO<sub>4</sub>, ALP, PTH and Vit D, lateral thoraco-lumbar spine X-ray, bone age, bone volumetric density through peripheral quantitative computerised tomography and transiliac bone biopsy (underutilised at present). Other important factors include level of activity and pubertal stage. Causes of secondary osteopaenia including immobility and inflammatory states need to be considered. Ensuring adequate vitamin D and calcium

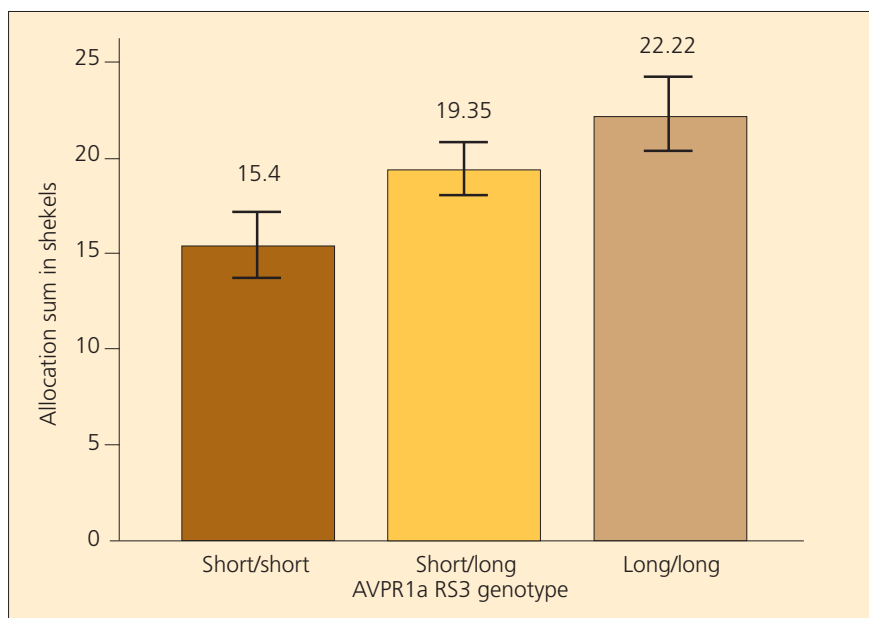


Fig. 4: Average giving rate by short/long AVPR1a genotype. Long AVPR1a promoter sequence was associated with greater rate of giving. One-way ANOVA:  $n = 203$ ,  $F = 3.456$ ,  $p = 0.033$ . Post-hoc analysis using a Tukey HSD test showed a significant difference between short/short versus long/long ( $p = 0.025$ ).

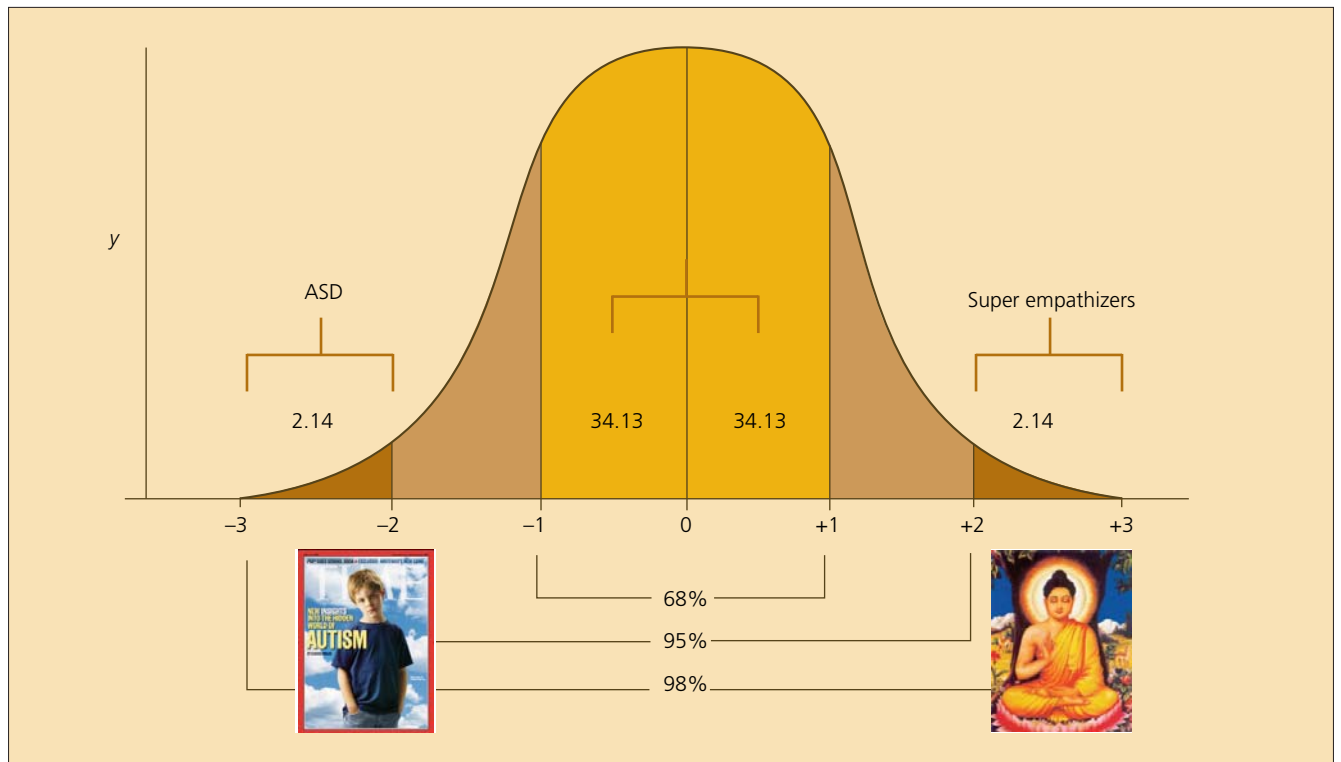


Fig. 5: The possible spectrum of empathy related to social hormones.

supplementation, appropriate progression through puberty and minimisation of exogenous osteotoxic drugs are important starting points. Therapy should include mobilisation and increased physical activity whenever possible as muscle strength is most important in bone remodelling and greater bone diameter leads to increased bone strength. The use of whole body vibration training is currently being assessed.

Bisphosphonate therapy may be considered in certain clinical scenarios such as fractures and painful limbs in children with osteoporosis unable to mobilise. Intravenous bisphosphonate therapy seems to be superior to oral bisphosphonates with regard to muscle force and bone effects [8].

Intravenous bisphosphonate therapy is beneficial in children with moderate to severe osteogenesis imperfecta (OI) and resulted in improved muscle and bone strength, better gross motor function [9, 10] and decreased bone pain [11]. Repeated cycles of intravenous pamidronate therapy lead to increased bone density and decreased fracture rates in patients with OI. Potential adverse effects include reduced bone

turnover and delayed bone healing, metaphyseal lines, acute phase reactions and respiratory distress [13–15]. Histomorphometric data demonstrates gains in cortical thickness and trabecular bone volume [12]. Overall, the benefits of pamidronate therapy outweigh potential risks and Pamidronate therapy has become the standard of care for patients with OI [12]. Bisphosphonate therapy in these children should be undertaken in centres with expertise in the field and a coordinated multidisciplinary team (medical, surgical and allied health professionals).

So when should pamidronate be discontinued? Although the majority of BMD gain occurs in the first 2 to 3 years of pamidronate therapy, discontinuation results in significant decreases in BMD. These effects are more pronounced at the radial metaphysis than at the diaphysis and are dependent on growth. It is possible this may produce zones of localized bone fragility after pamidronate treatment is stopped in growing children [16].

**Linda DiMeglio (USA)** presented an update on osteopetrosis. She illustrated the different autosomal recessive (AR)

and autosomal dominant (AD) types of osteopetrosis with cases and discussed their pathophysiology, treatment modalities and prognoses. Gene mutations leading to AR osteopetrosis include T-cell immune regulator 1 (TCIRG1), chloride channel 7 (CLCN-7) and receptor activator of nuclear factor-ligand (RANK-L). AD osteopetrosis related defects include carbonic anhydrase II (CAII) deficiency and CLCN-7 mutation.

The AR type also referred to as “malignant” is associated with cranial nerve entrapment resulting in early palsies, blindness and deafness, long bone fractures, infections (pneumonias and osteomyelitis) and sleep apnoea. The natural history is progressive anaemia, leukopaenia, hypocalcaemia and death from infection and marrow failure in the first decade of life. Bone marrow transplant is the treatment of choice in AR osteopetrosis.

Interestingly although most autosomal dominant “benign” forms of osteopetrosis have incomplete penetrance and are thought to be mild; the phenotypic expression, even within kindreds, is quite varied and may be severe [17]. Increasing bone resorption

.Table II: Assessment tools and therapeutic options for osteopetrosis.

Assesment tool	Therapeutic option	Potential side effects
<ul style="list-style-type: none"> <li>• Full blood count and differential</li> <li>• Ca, PO<sub>4</sub> and PTH levels</li> <li>• Creatine kinase (CK-BB), tartrate-resistant acid phosphatase (TRAP) and x-rays (spine, femur)</li> <li>• Periodic ophthalmologic examination</li> <li>• Consider serial scans of orbits if optic nerve entrapment is suspected +/- decompressive surgery</li> <li>• Hearing screening</li> </ul>	<ul style="list-style-type: none"> <li>• High dose calcitriol (up to 32µg/day) with low calcium diet [18]</li> <li>• Interferon gamma [19]</li> <li>• Bone marrow transplant</li> </ul>	<ul style="list-style-type: none"> <li>• Hypercalcaemia, hypercalciuria, nephrocalcinosis</li> <li>• Toxicity</li> <li>• GVHD, immunosuppression – only proven in AR osteopetrosis</li> </ul>

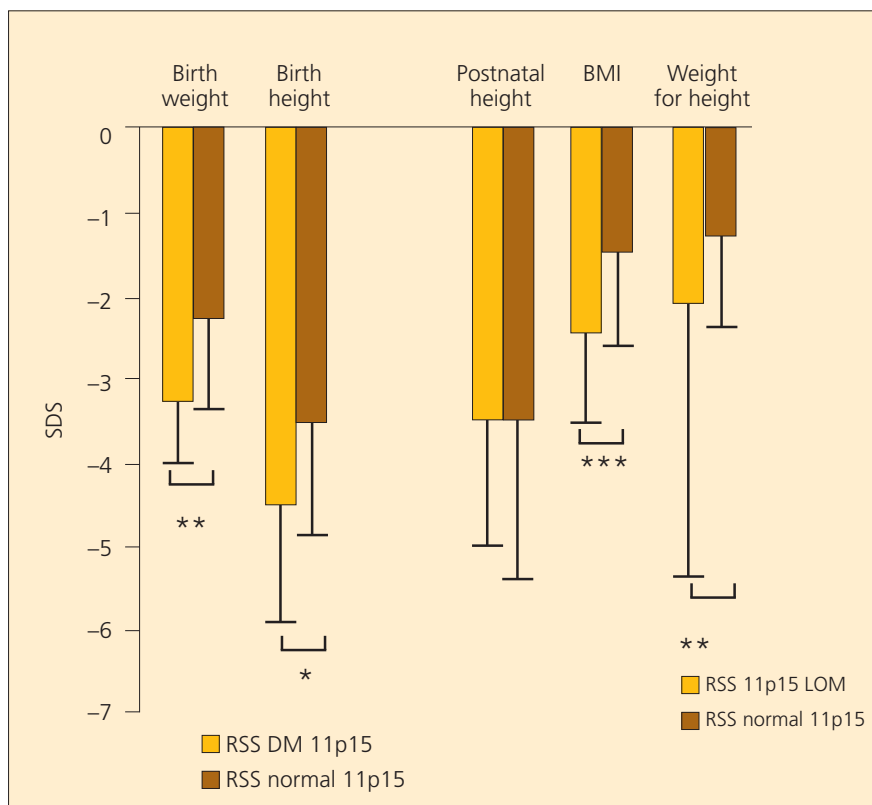
with medical therapy is difficult and all therapies are potentially toxic. Dr DiMeglio suggested bone marrow transplant should be considered in AD types based on the severity of the clinical phenotype. Useful assessment tools and potential therapeutic options are listed in *Table II*.

## Epigenetics in childhood disorders

**Irene Netchine (France)** and **Wayne Cutfield (New Zealand)** reviewed recent data on the effects of epigenetics on intra- and extra-uterine growth and body composition. Epigenetic effects refer to environmentally driven variations in gene

expression through processes including DNA methylation and histone modification. Genomic imprinting is an epigenetic phenomenon by which particular genes are expressed in a parent-of-origin-specific manner.

Dr Netchine shared data on epigenetic changes observed in overgrowth and undergrowth syndromes. Beckwith-Wiedemann syndrome (BWS) can be caused by epigenetic changes in the imprinted regions of 11p15. Russell-Silver syndrome (RSS), considered the mirror phenotype of BWS, has been associated with maternal uniparental disomy for chromosome 7 (mUPD7) in 5–10% of cases. Dr Netchine identified a loss of methylation (LOM) of 11p15 imprinting center region 1 (ICR1) domain, including IGF-II. Her group went on to study a total of 127 small for gestational age (SGA) patients, 58 of which were diagnosed with RSS. Interestingly, 63.8% of those with RSS had partial LOM of the 11p15 ICR1 domain and 5.2% had mUPD7. Those with more obvious clinical features including body asymmetry and low BMI were more likely to have 11p15 ICR1 epimutation (*Fig. 6*). This suggests that a major cause of RSS, particularly in those with failure to thrive, is epigenetic LOM in the 11p15 ICR1 loci [20].



*Fig. 6: RSS epigenotype/phenotype correlation. RSS with 11.15 epimutation have a more severe IUGR and a lower BMI at 2 years of age.*

She also pointed out that lower methylation correlated with lower birth weight and that children with RSS were at higher risk of the metabolic syndrome. With increasing under-

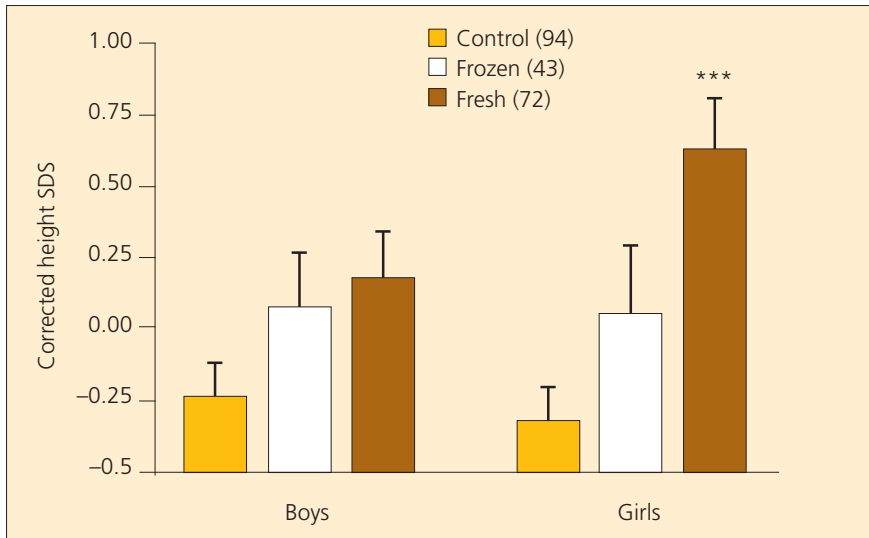


Fig. 7: Influence of IVF in childhood growth. (After Miles HM et al *J Clin Endocrinol Metab* 2007).

standing of the molecular mechanisms for RSS, genotype-phenotype correlations may become more apparent. RSS may be helpful in providing insights into the Barker Hypothesis.

Professor Cutfield reviewed data on the effects of intra- and peri-natal nutrition. He compared and contrasted the growth and metabolism patterns in several cohorts of patients: i) conceived through *in-vitro* fertilisation (IVF), ii) SGA, iii) pre-term and iv) post-term. Children born through IVF from fresh embryos were taller than those born from frozen embryos. Children from both IVF groups were taller than those naturally conceived (Fig. 7). Recent data suggests that IVF improves not only childhood growth but also improves metabolic profiles [21].

So when can epigenetic changes take place? Parents born preterm have greater body fat than control subjects, a pattern replicated in their offspring. This supports epigenetic changes can be inherited. Animal models demonstrate that growth media can affect gene expression; whilst follow up studies demonstrate differences in metabolic profiles of children with intrauterine growth restriction [22]. Thus the intra-uterine environment is important. Finally, neonatal nutrition can further modify subsequent body composition and insulin sensitivity patterns. Infants consuming higher carbohydrate containing meals in the first 2–3 months of life had higher body

mass indices in childhood. The post-natal environment may influence not just our immediate phenotype but epigenetically modify later metabolic profiles.

Dr Cutfield surmised that the period of sensitivity to programming of growth and metabolism extends from preconception until at least early infancy. However, the triggers and mechanisms that lead to programmed metabolic disease from early life events remain unclear. At present there are limited human studies and cohorts such as offspring from IVF conception and SGA (pre-term and post-term) should be prospectively and carefully followed up.

### Update on growth and growth hormone therapy

Pinchas Cohen (USA) introduced his talk with a fascinating hypothesis that

the tall stature of the Terracotta Warriors was representative of the top 1% of the Chinese population in the era they were made. The mean height of the male population at that time of the first Emperor was  $163 \pm 7$  cm and the mean height of the Terracotta Warriors is 179 cm with a range between 166–188 cm – this theory proposes that not only were their faces and hair styles representative of “real” warriors but also their height. In a range of randomised controlled trials in children with growth hormone deficiency and those with idiopathic short stature (Fig. 8), Professor Cohen and colleagues have demonstrated that there is a wide range of sensitivity to growth hormone, the most sensitive being children with the most severe

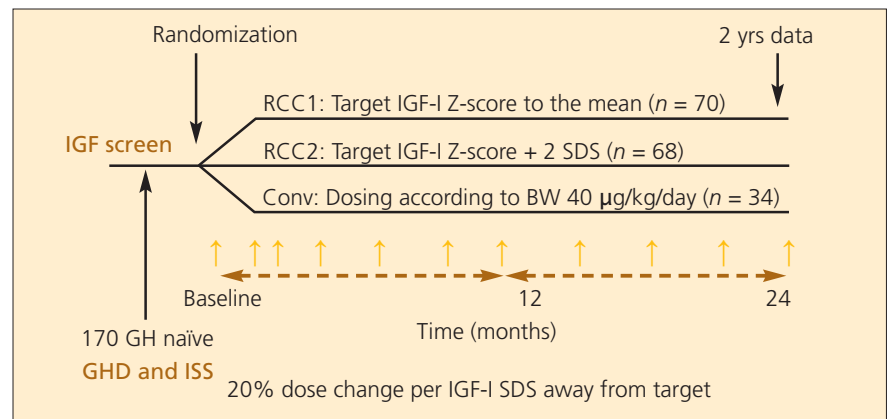


Fig. 8: Study design (NN2051): IGF-based dosing (after Cohen et al. *JCEM* 2007).

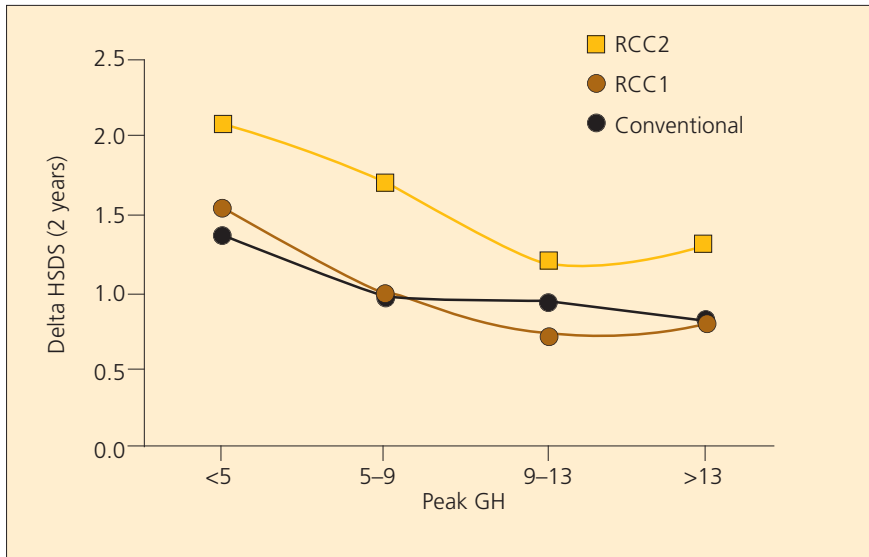


Fig. 9: Two-year Height SDS change. (After Cohen et al. JCEM 2010)

GHD (Fig. 9). They have demonstrated in a 4 year Randomised Controlled Trial (RCT) in children with GHD comparing 3 doses of 25, 50 or 100 µg/kg/day, the two higher doses achieved the 50<sup>th</sup> height percentile for the population whereas the low dose only achieved height on the 3<sup>rd</sup> percentile after 4 years. There was no acceleration of puberty with the higher doses.

In a further study (RCC1 in Fig. 8) in which the target response was an IGF-I value on the 50<sup>th</sup> percentile for the population standards, it was found that in children with GHD, 40% required a GH dose < 25 µg/kg/day, a finding

reinforcing the extreme sensitivity of some children with severe GHD. On the other hand, for children with Idiopathic short stature (ISS), much higher GH doses were required to achieve an IGF-I on the 50<sup>th</sup> percentile. Furthermore, given the same IGF-I value, the height SDS gained is greater in the GHD children compared to those with ISS, (Fig. 10). Thus ISS children have a combination of reduced GH and IGF-I sensitivity.

Charmian Quigley (USA) provided an update on growth hormone therapy for children with SHOX haplo insufficiency. The SHOX gene is located on Xp22.3

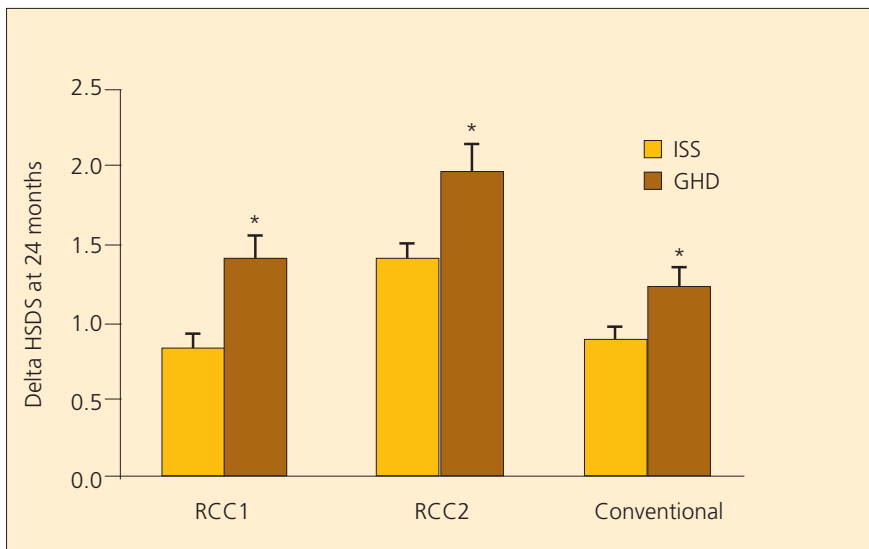


Fig. 10: Delta height SDS for GHD and ISS patients with IGF deficiency titrated to target IGF levels in the NN 2051 study. (After Cohen et al. JCEM 2010).

and Yp11.3 and does not undergo X inactivation. There is a dose dependency of SHOX in relation to stature, duplication of SHOX is associated with tall stature and haplo insufficiency as occurs in Turner syndrome and SHOX deficiency is associated with short stature. SHOX deficiency occurs in approximately 2% of children with ISS and should be investigated in all children with disproportionate short stature such as short trunk and arm span in association with other clinical features including high arched palate, micrognathia, cubitus valgus, madelung deformity and genu valgum. Growth hormone therapy has been demonstrated to improve height velocity and height SDS over 2 years in a randomised control trial published in 2007. A follow-up of 14 of the older subjects from this study who have now reached final height demonstrated their height SDS increased from -3.2 to -1.9 and 36% had a final height > -2SDS. This response is similar to that seen in Turner syndrome and with limited data, there was no difference in response between the girls and boys. There have been no significant adverse events and in particular, no change in body proportions. Thus the preliminary data indicate that growth hormone using doses similar to that in Turner syndrome may be effective both in the short and long term in children with SHOX deficiency.

Jeffrey Baron (USA) gave a fascinating insight into growth plate biology describing how chondrocytes progress through their stages of proliferation, differentiation, secretion of cartilage matrix and finally their re-modelling into bone tissue. This process is under complex regulation by paracrine, endocrine and transcriptional factors. With increasing age, the growth plate undergoes senescence; a developmental program that includes a gradual decrease in proliferation rate and structural involution. He presented a model of decreased rate of senescence which helps explain catch-up growth in individuals who have had growth inhibition such as in hypothyroidism, nutritional deficiency, or cortisol excess and a model of increased rate of senescence explaining catch down growth such as in oestrogen excess (Fig. 11).

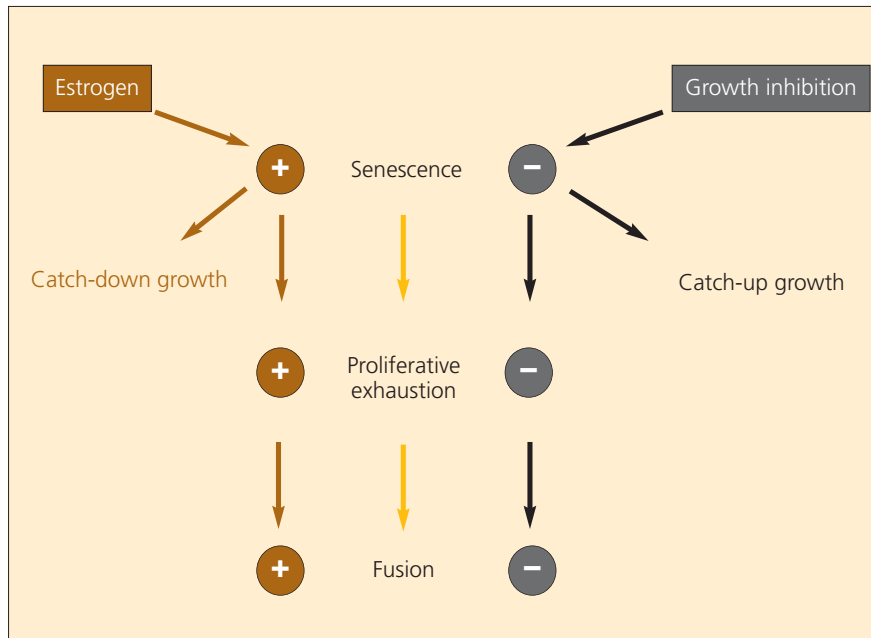


Fig. 11: Model of increased and decreased rate of chondrocyte senescence.

## AHSCT in type 1 diabetes

Autologous nonmyeloablative hematopoietic stem cell transplantation (AHSCT) has recently been used to preserve beta cell function and achieve insulin independence in patients with type 1 diabetes (T1DM) [23, 24]. AHSCT, which combines chemotherapy and stem cell infusion, may act to suppress immune mediated islet cell destruction and facilitate endogenous mechanisms of beta cell regeneration. The establishment of beta cell tolerance may occur through depletion of diabetogenic effector cells, regeneration of regulatory T cells, alternations in cytokines levels and changes to T- or B cell repertoires.

In this plenary lecture, **Guang Ning (China)** reported results of AHSCT in 45 patients with T1DM and 51 with type 2 diabetes who were all dependent on insulin for blood glucose control, with BMI < 28 kg/m<sup>2</sup>. The age range was 16–65 years, mean duration 6.2 years and mean insulin dosage 43 IU/day. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m<sup>2</sup>) and granulocyte colony stimulating factor (10 µg/kg/day), collected from peripheral blood by leukapheresis and cryopreserved. Cells were injected intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin (4.5 mg/kg).

Primary end points were safety and changes in exogenous insulin requirements (daily dose and duration of usage). Secondary end points were HbA<sub>1c</sub>, C-peptide levels and GAD antibody titres.

During follow-up, 16 patients became insulin free (3 with T1DM, 13 with T2DM) and daily insulin requirements decreased significantly in those who remained on insulin (26 patients reduced insulin dose greater than 50%). In 12 patients, insulin dose increased following

transplant. Fasting and post prandial C-peptide and C-peptide AUC increased significantly post transplant. Individual differences in efficacy were observed; factors influencing response included degree of residual beta cell function and glycaemic control. GAD antibody titres appeared to influence response: there was a significant negative relationship between GAD and fasting C-peptide levels. Adverse effects included nausea, diarrhoea, anorexia, fever, leucopenia and platelet reduction.

Professor Ning concluded that the results of his trial confirm that high-dose immunosuppression and AHSCT is safe and effective. There remains a need for continued follow up of patients undergoing AHSCT to evaluate safety and efficacy. Further research should also elucidate the immunomodulatory and other mechanisms of action of this promising therapy. The potential impact of AHSCT in China is likely to be substantial, with an estimated 92 million adults affected by diabetes in Chinese adults, of whom around 5 million have T1DM.

## Vitamin D deficiency in mothers and children

Vitamin D deficiency (VDD) in mothers and children is increasingly recognised in both developing and developed



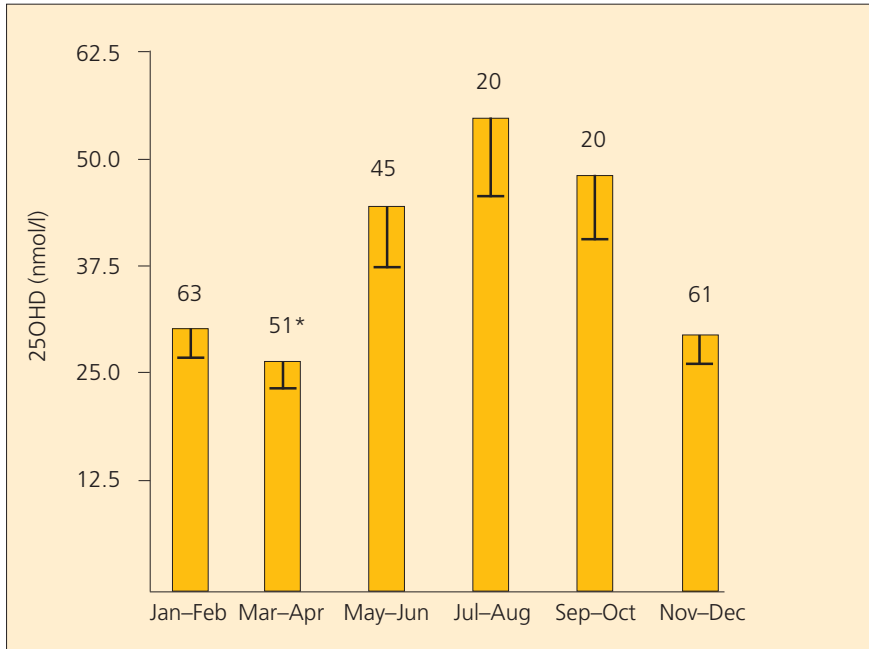


Fig. 12: Mean (+ SD) vitamin D levels in adolescents and pregnant women from rural India (\* $p < 0.01$  vs Jul-Aug) (After [28]).

countries and the adverse consequences of deficiency are extensive. **Viji Bhatia (India)** reminded us of the severe consequences of VDD and hypocalcaemia, including neonatal seizures [25, 26] and increased risk of pneumonia in young children [27]. Non-calcitropic actions of vitamin D include immunomodulation, prevention of infection (such as tuberculosis), anti-neoplastic (breast, colon, prostate), and possible prevention of type 1 and type 2 diabetes.

Inadequate sun exposure and dark skin are major risk factors for VDD. Notably, brown skin needs at least three times longer UV exposure than white skin. In a rural low socioeconomic community in India, 89% of adolescent girls and 74% of pregnant women had VDD (Fig. 12, 25OHD < 50 nmol/l). [28]. Duration of sun exposure lower in adolescent girls vs women, however only 15% of skin surface exposed in adolescents and 9% in pregnant women. In contrast, boys appeared to be relatively protected from VDD (only 27% had VDD), this may be due to spending more time outdoors and preferential nutrition. Calcium intake was also low (221 mg/day in girls, 214 g/day in pregnant women). Unfortunately milk is a premium product and is expensive in rural India.

Professor Bhatia presented data on vitamin D supplementation during pregnancy. In a pilot study of antenatal cholecalciferol supplementation in rural India, pregnant women were randomised to either no cholecalciferol (Group A) or 60,000 U (Group B) in the fifth month of gestation or 120 000 U each in the fifth and seventh gestational months (Group C). 25OHD was low at baseline (median 32 nmol/l) but

increased significantly at delivery only in group C (from 40 nmol/l at baseline to 53.4 after delivery,  $p < 0.001$ ). Only 40% of women in Group C achieved 25OHD at delivery >50 nmol/l. She concluded that 120,000 U of cholecalciferol in the fifth and seventh months of gestation is effective in raising 25OHD at delivery [29]. Supplementation also resulted in beneficial effects on neonatal anthropometry, ALP and calcium.

Professor Bhatia reviewed recent studies and current recommendations for prevention of VDD and treatment of rickets. Vitamin D2 (ergocalciferol) and D3 (cholecalciferol) have equivalent bioavailability, however D2 is metabolised more quickly in rickets, so D3 is preferred for replacement. Due to faster response, the oral route is preferred over IM. For routine supplementation, either D2 or D3 are appropriate. In adult males, the total amount of vitamin D from all sources (supplement, food, tissue stores) needed to sustain 25-hydroxycholecalciferol is approximately 4000 IU per day [30]. A single dose of 100,000 U vitamin D3 causes a rapid rise in serum vitamin D level, with a plateau at 90 days [31] (Fig. 13). Adults from high risk communities appear to need 2,000 units per day (or 50,000 to 100,000 units every 2 months). In adolescents, vitamin D3 at doses

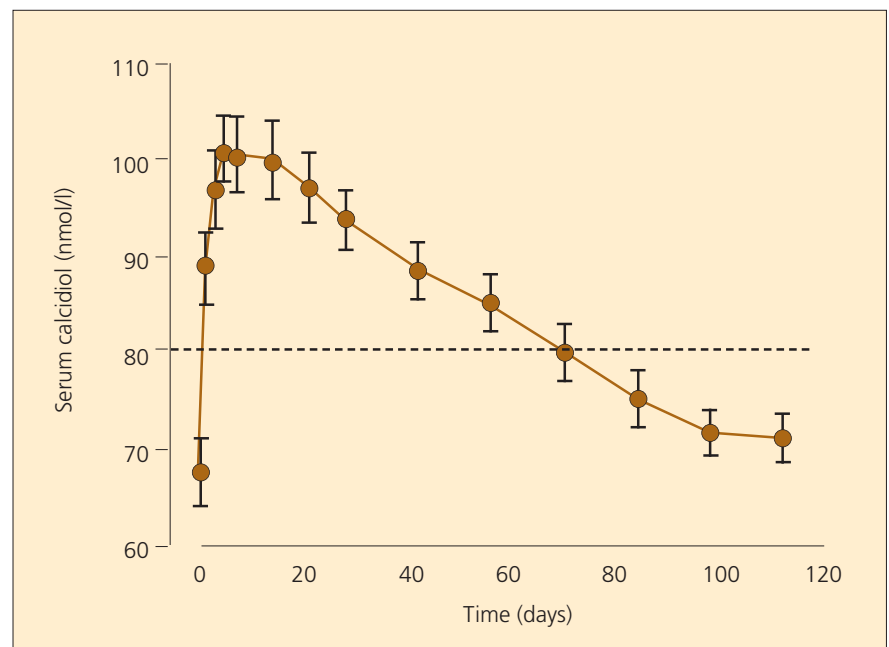


Fig. 13: Effect of single oral dose of 100,000 units of vitamin D3 in 30 subjects. (After [31]).

equivalent to 2,000 IU/day (14,000 IU per week) for 1 year is safe and results in desirable vitamin D levels [32]. In young children, 400 units is recommended for supplementation [33], while doses of 60,000 units per month, or 300,000 units as a single dose, have been shown to be safe in adults. In the setting of low dietary calcium intake, vitamin D requirements are increased and replacement doses required are greater [34].

In summary, VDD is rampant even in tropical countries and has a broad range of implications. Whilst it appears that vulnerable populations may need pharmacological supplementation, more dosing studies needed to quantify adequate replacement.

## Diabetes complications – an update on screening and management

In an outstanding plenary lecture, **Kim Donaghue (Australia)** outlined current knowledge and recent advances in the pathogenesis, genetics, epidemiology, screening and management of microvascular complications in diabetes. She outlined the different risks of complications in young people with type 1 vs type 2 diabetes; microalbuminuria and nephropathy are more common in type 2 [35], even after adjusting for other risk factors (ethnicity, HbA<sub>1c</sub>, duration, lipids, BMI, inflammatory markers) [36]. Abnormal liver function and hypertension are common, and adolescent girls with type 2 diabetes demonstrate preclinical abnormalities of cardiac structure and function [37].

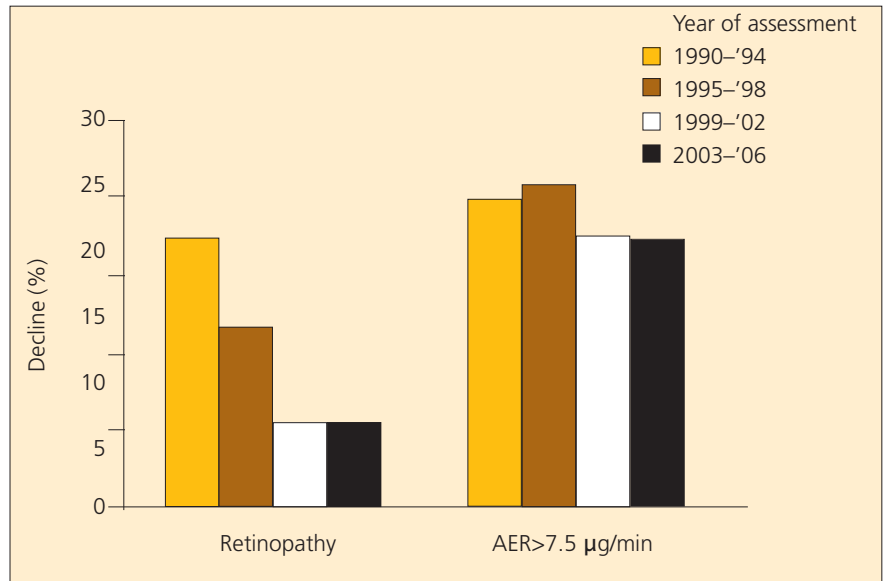


Fig. 14: Decline in retinopathy in adolescents with type 1 diabetes (duration < 5 years, age 11–17 yr, 1990–2006 (After Cho Y et al., in press).

Technological advances in diagnostic tools and imaging, along with results from clinical intervention trials, have enhanced our understanding of the pathophysiological basis of microvascular disease. The sum total of glycooxidation burden may be measured using skin autofluorescence and ultrasound of the plantar fascia to measure its thickness. These non-invasive measures of tissue collagen glycation have been associated with an increased risk of retinopathy, early elevation of albumin excretion (a precursor to microalbuminuria) and nerve abnormalities [38]. Interestingly, a polymorphism in the gene for Paroxonase-1 (an HDL-bound antioxidant enzyme) appears to afford some protection [39].

Novel measures have been developed recently to quantify structural and functional changes in retinal blood vessels. In adolescents with diabetes, changes in arteriolar calibre, tortuosity, optimal deviation and fractal dimension may identify individuals at increased risk of retinopathy [40] and other complications such as early elevated albumin excretion (presented in the Kaichi Kida oral session, Benitez P et al., abstract # OR1–4). Retinal vascular changes may reflect endothelial dysfunction, critical to the initiation of vascular disease.

Corneal confocal microscopy is a novel tool that has recently been used to non-

invasively to diagnose and stratify the severity of human diabetic neuropathy [41]. Established tools, such as thermal threshold and vibration testing, have been used by Professor Donaghue's group for the assessment of neuropathy in adolescents over the past two decades. Heat discrimination deteriorates over time, with a protective effect of the aldose reductase gene Z+2 polymorphism [42]. The autonomic nervous system can be examined using pupillometry (abnormalities predict future development of microvascular complications [43]), heart rate variation.

In parallel with changes in management and glycaemic control, there has been a reduction in retinopathy and nephropathy in adolescents with type 1 diabetes in recent decades (Fig. 14) [44], although this may have reached a plateau. Some complications, such as neuropathy, have not declined, higher rates of obesity with accompanying systemic inflammation may be implicated. It is of note that adults who survive after 50 years of with type 1 diabetes are lean, and those without complications are more physically active with better lipid profiles.

Professor Donaghue reviewed current guidelines for complications screening in type 1 diabetes, including retinopathy screening every 1–2 years using fundal photography or mydriatic ophthalmoscopy, annual nephropathy

screening using timed overnight albumin excretion or spot urine albumin to creatinine ratio, annual neuropathy screening and blood pressure measurement and lipid screening every 5 years [45].

Recent trials have demonstrated that antihypertensive treatment reduces complications, including primary prevention of retinopathy (DIRECT Study). ACE inhibitors reduce progression of microalbuminuria and increase the rate of regression in adults, but their use cannot currently be recommended in adolescents who are normoalbuminuric and normotensive. The results of the Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AddIT) [46], currently underway, will provide important data on the potential renal and cardiovascular protective effects of ACE inhibitors and statins in high-risk adolescents (with early elevation of AER).

### Type 1 diabetes and cardiac function

Adolescent girls with type 1 and type 2 diabetes have a blunted exercise stroke volume (SV), reduced aerobic capacity and impaired diastolic filling compared with non-diabetic controls (Fig. 15).

In this interventional study of adolescents with type 1 diabetes **Silmara Gusso (New Zealand)** from the Liggins Institute reported the results of a study examining the effects of 20 weeks of exercise training on left ventricular function (LVF) and femoral leg blood flow (FLBF) in adolescents with type 1 diabetes. At baseline, systolic blood pressure (BP), heart rate at rest and during maximal exercise were higher (compared with non-diabetic adolescents), while  $VO_2$ max was lower. Stroke volume (SV) at rest was lower in type 1 patients compared with controls, and there was an impaired SV response to exercise. After 20 weeks of training (compliance 85%), body fat percentage was significantly lower compared with the control adolescents with type 1 diabetes (who did not undergo training). There was no change in  $HbA_{1c}$  but a 10% decrease in insulin dose. At rest and during acute exercise, heart

rate and systolic BP decreased, and  $VO_2$  max increased, compared with no change in the diabetic control group. Exercise training improved the left ventricular response to acute exercise (improvement in SV, end diastolic volume, end systolic volume); specifically the increase in exercise SV was achieved by a decrease in end-systolic volumes. In contrast, femoral leg blood flow did not change with training.

The authors concluded that short term exercise training improves cardiac but

not peripheral vascular function in adolescents with type 1 diabetes. Exercise training should be encouraged in this population.

### Circadian dysrhythmia in endocrinology

This fascinating session by Scott Rivkees provided new insights into disorders of circadian rhythms. The hypothalamic suprachiasmatic nuclei (SCN) contain a biological clock that is responsible for

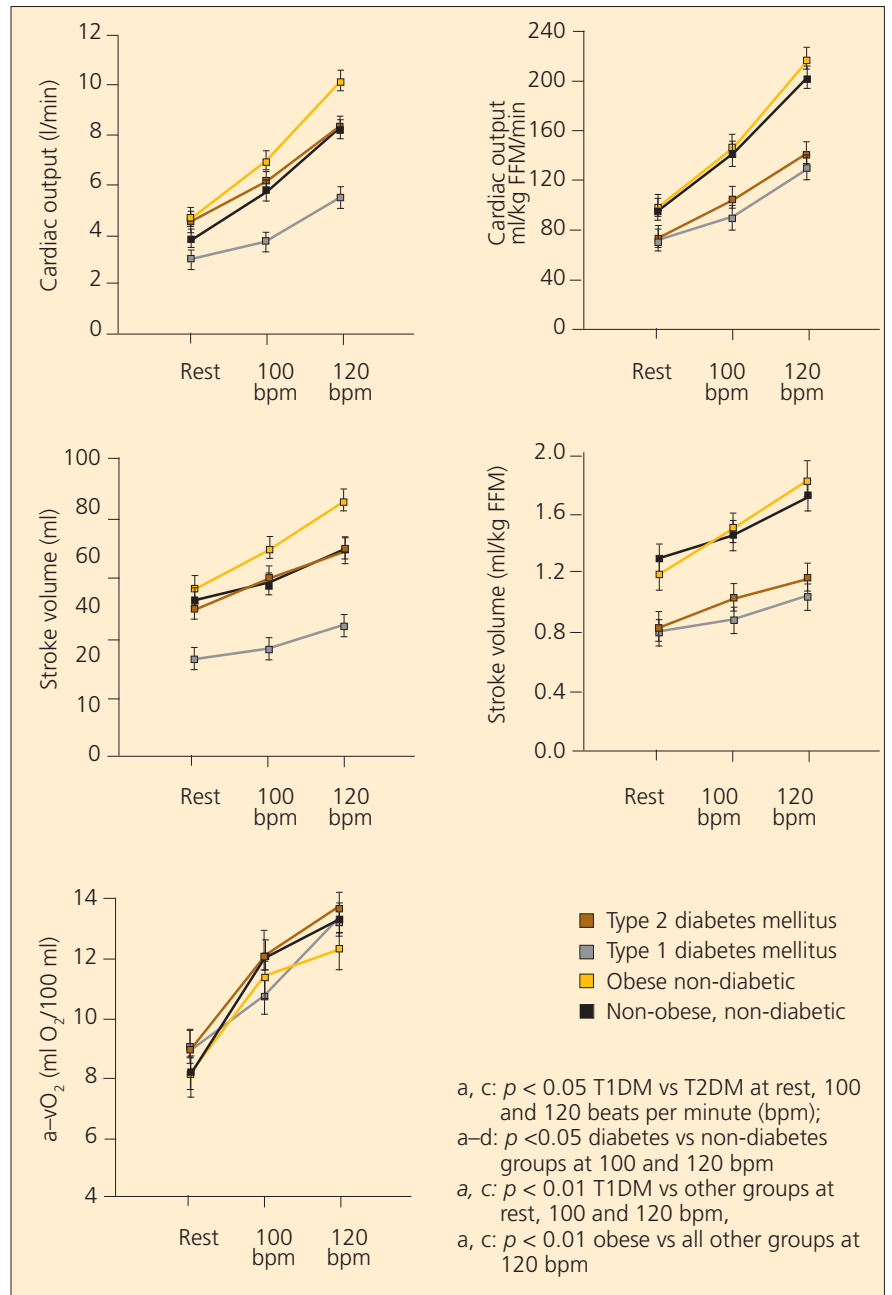


Fig. 15: Haemodynamic data. Cardiac output (a, b), stroke volume (c, d) and  $a-vO_2$  (e) in T2DM, T1DM, obese non-diabetic and non-obese non diabetic adolescents. Data are mean  $\pm$  SE. After Gusso *S Diabetologia* 2008.



generation of circadian rhythms, such as the sleep-wake cycle and rhythms in temperature and hormone production. The SCN contain ~10,000 neurones and each cell within the SCN has the capacity to oscillate individually. These oscillations are generated by rhythms in gene and protein expression. The circadian timing system develops prenatally and progressively matures postnatally, with rhythms in sleep-wake and hormone secretion developing after the age of two months. The system is regulated by photic information; SCN are normally inactive at night, but if exposed to light will cause an increase in metabolic activity. The human biological clock contains melatonin receptors [47] and melanopsin (located in retinal ganglion cells) is an important photoreceptive molecule that is involved in the regulation of circadian rhythms.

Circadian timing system disorders include those affecting the eye (eg optic nerve hypoplasia and blindness) in which lighting intensity and cycling may be impaired. Amongst children with optic nerve hypoplasia, 30% have abnormal rest-activity rhythmicity patterns – predictors include severe vision impairment, abnormal pupillary responsiveness, developmental delay and multiple hormonal deficiencies [48]. SCN lesions (congenital, tumours, genetic) also lead to disordered circadian timing. Desynchronization of the biological clock phase with the

outside world leads to ‘jet-lag’ or adolescent insomnia. Finally, many illnesses are influenced by the time of day, including respiratory (eg asthma), cardiovascular disease, migraine, epilepsy and SIDS.

Actigraphy is a quantitative measure used in the evaluation of circadian disorders; abnormal patterns include arrhythmic (‘all over the place’), as observed in cases of optic nerve hypoplasia, or free-running (where the clock is not reset every day). However, there is poor correlation between parental reports and actigraphy [49].

Some children with septo-optic dysplasia and sleep disruption are deficient in melatonin [50], which binds to the SCN. Melatonin has been successfully used in the treatment of biological clock lesions in both children and adults.

## References

1. Quigley CA, Bellis AD et al. Historical, clinical, and molecular perspectives. *Endocr Rev* 1995;16(3):271–321.
2. Quigley CA. The postnatal gonadotropin and sex steroid surge – insights from the androgen insensitivity syndrome. *J Clin Endocrinol Metab* ;87(1):24–8.
3. Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. *Pediatrics* 2006;117(5 Pt 2):S287–95.
4. Berenbaum SA, Bailey JM. Effects on gender identity of prenatal androgens and genital appearance: evidence from girls with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2003;88(3):1102–6.
5. Nordenstrom A, Servin A et al. Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by CYP21 genotype in girls with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2002;87(11):5119–24.
6. Meyer-Bahlburg HF, Dolezal C et al. Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. *Arch Sex Behav* 2004;33(2):97–104.
7. Berenbaum SA, Korman Bryk K et al. Psychological adjustment in children and adults with congenital adrenal hyperplasia. *J Pediatr* 2004;144(6): 741–6.
8. Rauch F, Munns CF et al. Risedronate in the treatment of mild pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Bone Miner Res* 2009;24(7):1282–9.
9. Munns CF, Rauch F et al. Effects of intravenous pamidronate treatment in

- infants with osteogenesis imperfecta: clinical and histomorphometric outcome. *J Bone Miner Res* 2005;20(7):1235–43.
10. Rauch F, Travers R, et al. The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. *J Clin Invest* 2002;110(9):1293–9.
11. Falk MJ, Heeger S et al. Intravenous bisphosphonate therapy in children with osteogenesis imperfecta. *Pediatrics* 2003;111(3):573–8.
12. Glorieux FH. Experience with bisphosphonates in osteogenesis imperfecta. *Pediatrics* 2007;119 Suppl 2:S163–5.
13. Munns CF, Rauch F et al. Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. *J Bone Miner Res* 2004;19(11):1779–86.
14. Munns CF, Rauch F et al. Respiratory distress with pamidronate treatment in infants with severe osteogenesis imperfecta. *Bone* 2004;35(1):231–4.
15. Rauch F, Travers R et al. Sclerotic metaphyseal lines in a child treated with pamidronate: histomorphometric analysis. *J Bone Miner Res* 2004;19(7): 1191–3.
16. Rauch F, Cornibert S et al. Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. *Bone* 2007;40(4):821–7.
17. Waguespack SG, Hui SL et al. Autosomal dominant osteopetrosis: clinical severity and natural history of 94 subjects with a chloride channel 7 gene mutation. *J Clin Endocrinol Metab* 2007;92(3):771–8.
18. Key L, Carnes D et al. Treatment of congenital osteopetrosis with high-dose calcitriol. *N Engl J Med* 1984 16;310(7):409–15.
19. Key LL, Jr., Rodriguiz RM et al. Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med* 1995;332 (24):1594–9.
20. Netchine I, Rossignol S et al. 11p15 imprinting center region 1 loss of methylation is a common and specific cause of typical Russell-Silver syndrome: clinical scoring system and epigenetic-phenotypic correlations. *J Clin Endocrinol Metab* 2007;92(8):3148–54.
21. Miles HL, Hofman PL et al. In vitro fertilization improves childhood growth and metabolism. *J Clin Endocrinol Metab* 2007;92(9):3441–5.
22. de Zegher F, Ibanez L. Prenatal growth restraint followed by catch-up of weight: a hyperinsulinemic pathway to polycystic ovary syndrome. *Fertil Steril* 2006 Suppl 1:S4–5.
23. Voltarelli JC, Couri CE et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 2007;1568–76.
24. Couri CE, Oliveira MC et al. C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 2009;301:1573–9.

25. Balasubramanian S, Shivbalan S, Kumar PS. Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. *Indian Pediatr* 2006;43:247–51.
26. Robinson PD, Hogler W et al. The re-emerging burden of rickets: a decade of experience from Sydney. *Arch Dis Child* 2006;91:564–8.
27. Muhe L, Lulseged S et al. Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* 1997;349:1801–4.
28. Sahu M, Bhatia V et al. Vitamin D deficiency in rural girls and pregnant women despite abundant sunshine in northern India. *Clin Endocrinol (Oxf)* 2009;70:680–4.
29. Sahu M, Das V et al. Vitamin D replacement in pregnant women in rural north India: a pilot study. *Eur J Clin Nutr* 63:1157-9, 2009
30. Heaney RP, Davies KM et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003;77:204–10.
31. Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Clin Nutr* 2008;87:688–91.
32. Maalouf J, Nabulsi M et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *J Clin Endocrinol Metab* 2008;93:2693–701.
33. Thandrayen K, Pettifor JM. Maternal vitamin D status: implications for the development of infantile nutritional rickets. *Endocrinol Metab Clin North Am* 2010;39:303–20.
34. Thacher TD, Fischer PR, et al. Early response to vitamin D2 in children with calcium deficiency rickets. *J Pediatr* 2006;149:840–4.
35. Eppens MC et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 2006;29:1300–6.
36. Maahs DM, Snively BM et al. Higher prevalence of elevated albumin excretion in youth with type 2 than type 1 diabetes: the SEARCH for Diabetes in Youth study. *Diabetes Care* 2007;30:2593–8.
37. Whalley GA, Gusso S et al. Structural and functional cardiac abnormalities in adolescent girls with poorly controlled type 2 diabetes. *Diabetes Care* 2009;32:883–8.
38. Craig ME, Duffin AC et al. Plantar fascia thickness, a measure of tissue glycation, predicts the development of complications in adolescents with type 1 diabetes. *Diabetes Care* 2008; 31:1201–6.
39. Gallego PH, Craig ME et al. Association between p.Leu54Met polymorphism at the paraoxonase-1 gene and plantar fascia thickness in young subjects with type 1 diabetes. *Diabetes Care* 2008;31:1585–9.
40. Cheung N, Rogers S et al. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. *Diabetes Care* 2008;31:1842–6.
41. Tavakoli M, Quattrini C et al. Corneal confocal microscopy: a novel noninvasive test to diagnose and stratify the severity of human diabetic neuropathy. *Diabetes Care* 2010;33:1792–7.
42. Thamotharampillai K, Chan AK et al. Decline in neurophysiological function after 7 years in an adolescent diabetic cohort and the role of aldose reductase gene polymorphisms. *Diabetes Care* 29:2053-7, 2006
43. Maguire AM, Craig ME et al. Autonomic nerve testing predicts the development of complications: a 12-year follow-up study. *Diabetes Care* 2007;30:77–82.
44. Mohsin F, Craig ME et al. Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002. *Diabetes Care* 2005;28:1974–80.
45. Donaghue KC, Chiarelli F et al. Microvascular and macrovascular complications associated with diabetes in children and adolescents. *Pediatr Diabetes* 2009;10 Suppl 12:195–203.
46. Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AdDIT). *BMC Pediatr* 2009;9:79.
47. Reppert SM, Weaver DR, et al. Putative melatonin receptors in a human biological clock. *Science* 1988;242:78–81.
48. Rivkees SA, Fink C et al. Prevalence and risk factors for disrupted circadian rhythmicity in children with optic nerve hypoplasia. *Br J Ophthalmol* 2010;94:1358–62.
49. Rivkees SA. Rest-activity patterns in children with hypopituitarism. *Pediatrics* 2003;111:e720–4.
50. Webb EA, O'Reilly MA et al. Rest-activity disturbances in children with septo-optic dysplasia characterized by actigraphy and 24-hour plasma melatonin profiles. *J Clin Endocrinol Metab* 2010;95:E198–203.



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An invitation is extended to all APPES members to submit news for the newsletter.  
The newsletter will be published 4 times a year.

If you would like to submit articles or photos, please do so via email on [appes@willorganise.com.au](mailto:appes@willorganise.com.au)

## Future Events

### 2011

30 April - 3 May, 2011  
LWPES Annual Meeting  
Denver, Colorado

September 25 - 28, 2011  
50<sup>th</sup> ESPE Meeting  
Glasgow, Scotland  
[www.espe2011.org](http://www.espe2011.org)

October 19 - 22, 2011  
ISPAD 36th Annual Meeting  
Miami, USA

December 4 - 8, 2011  
World Diabetes Congress  
Dubai, United Arab Emirates  
<http://worlddiabetescongress.org/>

### 2012

September 20 - 23, 2012  
51<sup>st</sup> ESPE Meeting  
Leipzig, Germany

November 2012  
APPES Scientific Meeting  
Bali, Indonesia  
[www.appes.org](http://www.appes.org)

### 2013

September 18 - 21, 2013  
9<sup>th</sup> Joint ESPE/LWPES Meeting  
Rome, Italy

## Save the Date



**APPES Fellows Meeting**  
9—12 November 2011

**APPES Continuing Medical Education (CME) Meeting**  
12—13 November 2011

**Hanoi, Vietnam**

For more details, contact the APPES Secretariat:  
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