
33rd Meeting of the

**British Society for
Paediatric Endocrinology
and Diabetes**

16-18 NOVEMBER 2005

Bristol Marriott Hotel City Centre, Bristol, UK

Programme & Abstracts

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Bristol Marriott Hotel City Centre, Bristol, UK

LOCAL ORGANISING CONVENOR

Dr Liz Crowne, Consultant Paediatrician, Bristol

BENEFACTORS

Eli Lilly & Co Ltd, Ferring Pharmaceuticals Ltd, Ipsen UK Ltd,
Novo Nordisk Ltd, Pfizer Ltd and Serono Ltd

Also supported by the Child Growth Foundation and the Turner Syndrome Support Group

www.bsped.org.uk

WELCOME

Welcome to Bristol for the 33rd Annual Meeting of the BSPED.

This year's meeting is being held at the Bristol Marriott City Centre Hotel, a 4 star hotel situated close to the recently redeveloped Bristol docklands. Bristol is a historic city, with many intriguing, traditional and occasionally 'off the wall' things to do and see. Its harbour side location lined with attractions, boats, restaurants and museums is well worth visiting as is the Georgian village/suburb of Clifton with Brunel's famous suspension bridge. If you get a chance to explore Bristol the large selection of restaurants, cafes and bars provides something for every taste and budget.

I hope we have produced an exciting and varied programme and make no apologies that this reflects the interests of the organisers! The two afternoon symposia on Thursday have an oncological theme, the first a Rare Endocrine Tumours symposium with contributions from clinical genetics, endocrine surgery and adult endocrinology and the second a Late Effects symposium. I am delighted that Professors Stephen Shalet and Mike Stevens, leading experts in the field will be able to give us their view of current developments. On Friday we have a plenary session on Type 1 Diabetes prevention with keynote speakers Professors John Todd, Polly Bingley and Dr Colin Dayan. We also have an adrenal clinical management session starring Professor Martin Savage and Dr John Achermann and an Obesity Symposium with presentations on obesity surgery and appetite regulation. In addition there will be three oral presentation sessions, an attended poster session and both endocrine and diabetes nurse specialist sessions held in parallel during Friday morning. It is a packed schedule and I hope should provide a stimulating two days in Bristol.

The annual dinner will be held on the evening of Thursday 17 November 2005 at the Royal West of England Academy (RWA), which is one of five Royal Academies of Art in the UK and has HM Queen Elizabeth II as its patron. It is a registered charity which has been self-supporting for over 150 years and possesses an outstanding Grade II listed building, galleries and permanent fine art collection.

We look forward to seeing you all at this years meeting.

Yours Sincerely



Liz Crowne

Local Organising Chair – BSPED 2005, Bristol

Conference Secretariat

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Date and Place of Meeting

The 33rd Meeting of the British Society for Paediatric Endocrinology and Diabetes will be held on 16-18 November 2005 at the Bristol Marriott Hotel City Centre, 2 Lower Castle Street, Old Market, Bristol, Avon, BS1 3AD. Telephone number: +44 (0)117 9294281, Fax number: +44 (0) 117 9276377.

BSPED CME Day

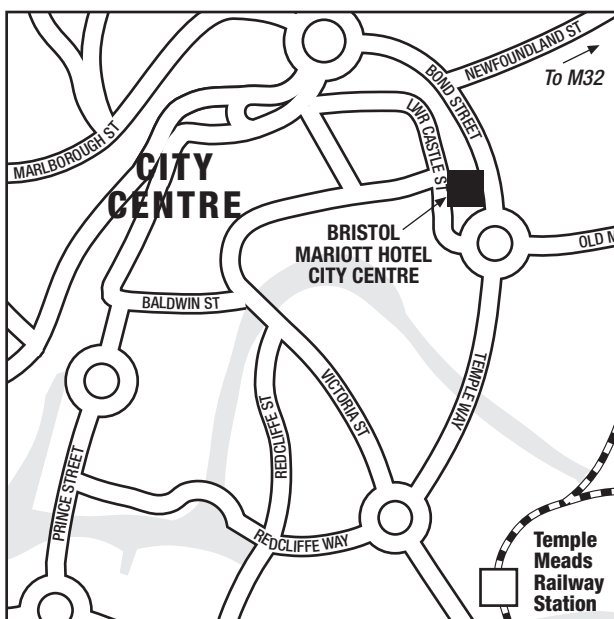
The BSPED CME day will take place on Wednesday 16 November 2005 from 11.00-17.00. This is the first annual BSPED CME day approved event, which shall occur on the day preceding the annual scientific meeting of the society, at the UBHT Education Centre, Upper Maudlin Street, Bristol BS1 8AE, UK. Over a period of 4 years it will cover the entire syllabus of paediatric endocrinology. The course content will be aimed at paediatric endocrinologists (in training as well as those seeking an update) and paediatric endocrine nurses. The faculty members will consist of UK paediatric endocrinologists.

Further details regarding this day are available from S Faisal Ahmed: Email: gcl328@clinmed.gla.ac.uk or telephone: + 44(0)141 2010571 (direct) + 44 (0)141 2010243 (secretary).

Location

The venue of the BSPED annual meeting will be the Bristol Marriott Hotel City Centre, which is situated in the centre of Bristol close to the main business and shopping areas. Some accommodation is available at this venue, but there are also alternative city centre hotels nearby.

Bristol has excellent transport links within easy access of the Bristol Marriott Hotel City Centre. Bristol Temple Meads Train Station is situated approximately 10 minutes walk from the hotel and provides frequent services to and from all major UK cities. In addition Bristol Airport is a 10 km taxi ride from the hotel and is served by several budget airlines, such as Easy Jet and British Airways that



fly from cities all over the UK. If driving, Bristol is located at the top of the M32, which you can join at J19 on the M4 motorway.

Parking is available at the adjacent NCP Car Park at a price of £7.50 per 24 hours as a delegate and/or hotel resident.

Registration fees

The late registration fee for BSPED Members is £290 and £310 for non-members; in addition reduced registration fees are available for junior doctors, nurses and students. These fees include lunch on both the 17 and 18 November 2005 and the Welcome reception at the Bristol Marriott Hotel City Centre, but does not include the Annual Dinner.

Name Badges

Name badges will be provided at the registration desk and must be worn at all times for admission to all scientific sessions.

Poster sessions

Posters will be displayed from 12:30 - 13:45 on Thursday 17 November and from 12:30 - 13:30 on Friday 18 November 2005 in the Bristol Suite Foyer. There will be conducted poster tours at 13.15 - 13.45 on Thursday and 13.00 - 13.30 on Friday if you wish to join.

The Annual General Meeting of the BSPED

The Annual General Meeting of the BSPED will be held on Thursday 17 November 2005 from 17:15 - 18:15 in Bristol Suite 2 & 3.

Nurses' Session

The Nurses' sessions will take place on Friday 18 November 2005 from 09:30 - 12:30 in the Rome Suite. The first of the two sessions will be the Endocrinology nurses sessions: Puberty, which will be followed by the Nurses business meeting and coffee. The second will be the Diabetes nurses session: Eating disorders in Type 1 Diabetes.

CPD Approval

CPD approval from the Federation of the Royal College of Physicians of the UK has been given for this meeting. Delegates may claim 12 points for full attendance of the meeting. If you want to claim your CPD points you must sign the register on the registration desk at the meeting before 16:00 on Friday 18 November 2005. You will need your GMC number.

Social Programme

The Welcome Reception, generously supported by Serono Limited, will take place on Wednesday 16 November 2005 at 18:45 following the Serono Satellite Symposium at the Bristol Marriott Hotel City Centre in the Rome Suite Foyer. All delegates are invited to join us for a drink. The Annual Dinner will take place at the Royal West of England Academy, Queen's Road, Clifton, Bristol

on the evening of Thursday 16 November 2005. The evening will begin with pre-dinner drinks followed by a three course dinner. The price to attend this evening is £45 per person and there may be a limited number of tickets available from the registration desk. Shuttle buses will be provided from the Bristol Marriott Hotel City Centre to the Royal West of England Academy. A timetable of coaches to the dinner will be available at the registration desk during the meeting.

Catering

A buffet lunch will be served on Thursday 17 November and Friday 18 November 2005 in Bristol Suite 1, which is situated next door to the main meeting room. Tea and coffee will also be available in this room during specified break times.

Serono Satellite Symposium

Serono Limited are holding a satellite symposium entitled 'Entering a new era in managing growth hormone deficiency' on Wednesday 16 November 2005 from 17:30 - 18:45 in the Rome Suite.

Benefactors

We are grateful to the following benefactors for their support of the BSPED: Eli Lilly & Co Ltd, Ferring Pharmaceuticals Ltd, Ipsen UK Ltd, Novo Nordisk Ltd, Pfizer Ltd and Serono Ltd

Accommodation

Accommodation is available either at the Bristol Marriott Hotel City Centre or at a number of other hotels located nearby in the city centre. Availability at the Bristol Marriott Hotel City Centre is limited and is based on a first come first served basis. If you would like to book one of these rooms please contact the hotel reservations direct on +44 (0)117 9294281 quoting the name of this meeting (BSPED 2005). The cost of a single occupancy room is £130.00 bed and breakfast.

If you would prefer to stay at an alternative hotel in Bristol City Centre you can book accommodation online through Conference Bristol at: <http://www.conferencebookings.co.uk/> or on the booking form enclosed in the preliminary programme. If you choose to book online please use the following event reference: BRSBSPED2005 when prompted.

Conference Bristol can also be contacted directly by telephone +44 (0)117 9462200 or email: conference@bristol-city.gov.uk. Please quote BSPED 2005.

Please note that BioScientifica Ltd are not responsible for accommodation bookings.

Wednesday 16 November 2005

	ROME SUITE	ROME SUITE FOYER
12.00		
12.15		
12.30		
12.45		
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14.00		
14.15		
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15.00		
15.15		
15.30		
15.45		
16.00		
16.15		Registration
16.30		
16.45		
17.00		
17.15		
17.30		
17.45	Serono Satellite Symposium: Entering a new era in managing growth hormone deficiency	
18.00		
18.15		
18.30		
18.45		
19.15		Welcome Reception <i>(GENEROUSLY SUPPORTED BY SERONO LTD)</i>
19.30		
19.45		
20.00		

TIMETABLE

Thursday 17 November 2005

	BRISTOL SUITE 2 & 3	BRISTOL SUITE 1	BRISTOL FOYER
08.00			
08.30			Registration
08.45			
09.00	Welcome and Oral Communication 1: Growth and neonatal endocrinology		
09.15			
09.30			
09.45			
10.00			
10.15			
10.30			
10.45		Tea and coffee	
11.00	Oral Communication 2: Steroid/Bone/Late effects		
11.15			
11.30			
11.45			
12.00			
12.15			
12.30		Lunch and posters	
12.45			
13.00			
13.15			
13.30			
13.45	Rare Endocrine Tumour Symposium		
14.00			
14.15			
14.30			
14.45			
15.00			
15.15			
15.30		Tea and coffee	
15.45	Late Effects Symposium		
16.00			
16.15			
16.30			
16.45			
17.00	Annual General Meeting		
17.15			
17.30			
17.45			
18.00			
18.15			
19.30	Annual Dinner at Royal West of England Academy, Clifton, Bristol		

Friday 18 November 2005

	BRISTOL SUITE 2 & 3	BRISTOL SUITE 1	BRISTOL FOYER	ROME SUITE
08.00				
08.30				
08.45			Registration	
09.00				
09.15	CTU Feedback			Endocrinology Nurses' Session: Puberty
09.30				
09.45	Prevention of Type 1 Diabetes			
10.00				
10.15				
10.30				
10.45				
11.00				
11.15		Tea and coffee		Nurses' Business Meeting
11.30				
11.45	Clinical Practice Session- HPA access			Diabetes Nurses' Session: Eating disorders in type 1 diabetes
12.00				
12.15				
12.30				
12.45		Lunch and posters		
13.00				
13.15				
13.30				
13.45	Obesity/Type 2 Diabetes Symposium			
14.00				
14.15				
14.30				
14.45	Oral Communication 3: Diabetes and obesity			
15.00				
15.15				
15.30				
15.45				
16.00				
16.15				
16.30				
16.45	End of Meeting			
17.00				
17.15				
17.30				
17.45				
18.00				
18.15				
19.30				

Wednesday 16 November 2005

- 11:00 – 17:00** **BSPED CME Day**
UBHT EDUCATION CENTRE, BRISTOL
- 16:00 – 17:30** **Registration for the BSPED Meeting**
ROME SUITE FOYER
- 17:30 – 18:45** **Serono Satellite Symposium:**
Entering a new era in managing growth hormone deficiency
ROME SUITE
- 17:30 Opening remarks
- 17:35 The SGA phenotypes throughout foetal, postnatal and adult life
Pierre Chatelain (Lyon, France)
- 17:55 Pharmacogenomics applied to growth hormone disorders
Peter Clayton (Manchester)
- 18:15 Entering a new era of device technology
Herve Dumas (Serono International, Geneva)
- 18:30 Discussion
- 18:40 Summary and closing remarks
- 18:45 – 19:45** **Welcome reception**
ROME SUITE FOYER
(GENEROUSLY SUPPORTED BY SERONO LIMITED)

Thursday 17 November 2005

- 08:00 – 09:00 Registration**
BRISTOL SUITE FOYER
- 09:00 – 10:30 Welcome and Oral Communication 1: Growth and neonatal endocrinology**
BRISTOL SUITE 2 & 3
Chairperson: Christine Burren (Bristol)
- OC1 09:00 The dwindling influence of growth hormone with advancing age: - molecular studies in skin fibroblasts from children and adults
Whatmore AJ, Karperien M, van Duyvenvoorde HA, Wit JM & Clayton PE
- OC2 09:15 The influence of IGF-I, IGFBP-3 and leptin on growth during the first two years in extremely premature infants
Whatmore AJ, Patel L, Cavazzoni E, Wales JK, Gibson AT & Clayton PE
- OC3 09:30 The effect of ceramide on chondrocyte growth dynamics
MacRae VE, Farquharson C & Ahmed SF
- OC4 09:45 Activation of a GH receptor pseudoexon is associated with a broad spectrum of growth hormone insensitivity phenotypes
David A, Camacho-Hübner C, Akker S, Rose S, Alvi S, Butler G, Savage MO, Clark AJL & Metherell L
- OC5 10:00 Mutations in cullin 7, a cofactor for ubiquitination, cause the 3M intra-uterine growth retardation syndrome
Clayton PE, O'Sullivan J, Glaser A, Oliveira MH, de Alcantara MRS, de Almeida Barretto ES, Kingston H, Read A, Cormier-Daire V & Scambler PJ
- OC6 10:15 Early insulin treatment in very low birth weight babies assessed by continuous glucose monitoring
Beardsall K, Ong KKL, Ogilvy-Stuart AL, Ahluwalia JS, Thompson MH & Dunger DB
- 10:30 – 11:00 Tea and coffee**
BRISTOL SUITE 1
- 11:00 – 12.30 Oral Communication 2: Steroids/bone/late effects**
BRISTOL SUITE 2 & 3
Chairperson: Catherine Hall (Manchester)
- OC7 11:00 Use of continuous subcutaneous hydrocortisone infusion to maximise control in a patient with congenital adrenal hyperplasia
Bryan SM & Hindmarsh PC
- OC8 11:15 Association of an Fc receptor-like 3 haplotype with autoimmune Addison's disease suggests an alternative pathogenic allele at the locus
Owen CJ, Eden JA, Jennings CE, Wilson V, Cheetham TD & Pearce SHS
- OC9 11:30 The effect of the novel glucocorticoid receptor ligand, AL-438 on growth plate chondrocytes and longitudinal bone growth
Owen HC, Miner JA, Ahmed SF & Farquharson C

-
- OC10 11:45 Longitudinal changes in bone mineral content (BMC) and body composition (BC) with chronic kidney disease (CKD)
Rashid R, Neil E, King D, Hagerty C, Beattie TJ, Murphy AV, Ramage IJ, Maxwell H & Ahmed SF
- OC11 12:00 Increased adiposity, raised C-reactive protein and cardiovascular risk markers in postpubertal survivors of leukaemia after bone marrow transplantation
Yeap ML, Elson R, Cornish J, Oakhill A & Crowne EC
- OC12 12:15 Correlation between clinical and biochemical features on sperm donation and sperm quality in underage minors with cancer
Alexander S, Gomes S, Wafa R, Bahadur G & Spoudeas H
- 12:30 – 13:45 Lunch and posters**
BRISTOL SUITE 1 AND BRISTOL SUITE FOYER
- 13:45 - 15:15 Rare Endocrine Tumour Symposium**
BRISTOL SUITE 2 & 3
Chairperson: Caroline Brain (London)
- S1 13:45 Current management issues in MEN
Steven Ball (Newcastle Upon Tyne)
- S2 14:15 A surgeon's perspective of MEN
Barney Harrison (Sheffield)
- S3 14:45 Multiple endocrine neoplasia - managing rare endocrine tumours in childhood and adolescence
Victoria Murday (Glasgow)
- 15:15 – 15:45 Tea and coffee**
BRISTOL SUITE 1
- 15:45 - 17:15 Late Effects Symposium**
BRISTOL SUITE 2 & 3
Chairperson: Helen Spoudeas
- S4 15:45 Current issues in late effects: endocrinology
Stephen Shalet (Manchester)
- S5 16:30 Current issues in late effects of treatment for cancer: the oncology perspective
Michael Stevens (Bristol)
- 17:15 – 18:15 Annual General Meeting of the BSPED**
BRISTOL SUITE 2 & 3
- 19:30 – 23:00 Annual Dinner**
ROYAL WEST OF ENGLAND ACADEMY, CLIFTON, BRISTOL
-

Friday 18 November 2005

- 08:30 – 09:00 Registration**
BRISTOL SUITE FOYER
- 09:00 – 09:30 CTU Feedback**
BRISTOL SUITE 2 & 3
Chairperson: Jeremy Kirk (Birmingham)
David Dunger (Cambridge)
- 09:30 – 11:00 Prevention of Type 1 Diabetes**
BRISTOL SUITE 2 & 3
Chairperson: David Dunger (Cambridge)
- S6 09:30 Genetics of Type 1 diabetes
John Todd (Cambridge)
- S7 10:00 Prediction of Type 1 diabetes mellitus
Polly Bingley (Bristol)
- S8 10:30 Towards a vaccine for Type 1 diabetes
Colin Dayan (Bristol)
- 09:30 – 11:00 Endocrinology Nurses Session: Puberty**
ROME SUITE
Chairperson: Nicky Nicoll (Bristol) & Ruth Elson (Bristol)
- 09:30 Investigation of puberty: How do you interpret the results?
Louise Bath (Edinburgh)
- 09:45 Presentation 2
Diane Barstow (Newcastle upon Tyne)
- 10:00 Presentation 3
Pauline Musson (Southampton)
- 10:15 Presentation 4
Ethel McNeill (Glasgow)
- 10:30 Precocious Puberty - Comprehensive Care
Tanya Urquhart (Sheffield)
- OC19 10:45 Treatment of precocious puberty with GnRH analogues: an audit of nurses' perceptions of clinical practice
Davies KM, Storr HL, Casey AM, Kirk JM & Savage MO
- 11:00 – 11:30 Nurses business meeting and coffee**
ROME SUITE
- 11:00 – 11:30 Tea and coffee**
BRISTOL SUITE 1
- 11:30 – 12:30 Diabetes Nurses Session: Eating disorders in Type 1 diabetes**
ROME SUITE
- 11:30 Diabetes and anorexia nervosa
Noeleen Lovell (Bristol)

- 12:00 Psychological management of eating disorders in diabetes
Patricia Tallis (Bristol)
- 11:30 - 12:30 Clinical Practice Session**
BRISTOL SUITE 2 & 3
Chairperson: Stafford Lightman (Bristol)
- S9 11:30 Adrenal failure in the newborn: a role for genetic analysis?
John Achermann (London)
- S10 12:00 Investigation of the pituitary-adrenal axis in suspected Cushing's syndrome
Martin Savage (London)
- 12:30 - 13:30 Lunch and posters**
BRISTOL SUITE 1 AND BRISTOL SUITE FOYER
- 13:30 - 14:30 Obesity / Type 2 Diabetes Symposium**
BRISTOL SUITE 2 & 3
Chairperson: Julian Shield (Bristol)
- S11 13:30 The role of sleep in metabolism
Sharad Taheri (Bristol)
- S12 14:00 Obesity surgery: effective cure for obesity-related Type 2 diabetes
Justin Morgan (Bristol)
- 14:30 - 16:00 Oral Communication 3: Diabetes and obesity**
BRISTOL SUITE 2 & 3
Chairmen: Carlo Acerini (Cambridge)
- OC13 14:30 Fasting and postprandial Peptide YY response in adolescents with obesity
Wickramasuriya BPN, le Roux CW, Ghatei MA, Bloom SR & Matyka K
- OC14 14:45 Mature subcutaneous and visceral adipocyte concentrations of adiponectin are highly correlated in normal-weight children and inversely related to Body Mass Index standard deviation score
Sabin MA, Holly JMP, Shield JPH, Turner SJ, Grohmann MJ, Stewart CEH & Crowne EC
- OC15 15:00 Lower physical activity in childhood diabetes
Lou YY, Trevelyan N, Wooton S & Betts PR
- OC16 15:15 Cognitive behavioural therapy for adolescents with Type 1 diabetes
Allen RJ, Indoe D, Tallis PM & Crowne EC
- OC17 15:30 Abnormalities of thyroid function at diagnosis of Type 1 diabetes mellitus: relationship with diabetic ketoacidosis
Saroha V, Didi M & Blair JC
- OC18 15:45 The practical transfer from injected insulin to oral glibenclamide in permanent neonatal diabetes mellitus due to activating mutations in KCJN11
Wickramasuriya BPN, Barrett TG, Carter S, Clark PMS, Etisham S, Hakeem V, Hattersley A, Pearson ER, Shaw NJ & Tinklin TS
- 16:00 Close of meeting

S1**A Surgeon's Perspective of M.E.N**

BJ Harrison

Department of Surgery, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK.

An endocrine surgeon is a physician who operates and whether treating adult or paediatric patients should be part of a multidisciplinary team. Even in the absence of a family history he / she should have a high degree of suspicion that a child with an endocrine tumour that can occur in MEN or other familial syndromes may be the index case in a previously undiagnosed kindred.

In young patients with genetically determined medullary thyroid cancer the key to a good outcome is a preoperative diagnosis and an appropriate first operation - total thyroidectomy / lymphadenectomy performed by an experienced surgeon. The appropriate operation will depend upon the specific familial syndrome, the age of the patient and the disease extent at presentation.

The surgery of pheochromocytoma / paraganglioma in young patients will in many cases be performed by a minimally invasive route. The surgeon should be the team member most familiar with the pre / peri / post / operative care of patients with this disorder. The surgical strategy will depend upon the presence of unilateral/bilateral disease and the age of the patient.

Familial parathyroid and pancreatic disease are rare in the paediatric age group. The dilemma for the multidisciplinary team relates to the timing and extent of surgery, which must strike a balance between the potential morbidity of an intervention and early / late recurrence of the disorder.

S2**Current management issues in MEN**

SG Ball

School of Clinical Medical Sciences; University of Newcastle.

The Multiple Endocrine Neoplasia (MEN) syndromes are autosomal dominant, familial cancer syndromes characterised by multiple and metachronous neoplasia of endocrine tissue. There can be additional, non-endocrine features.

Progress in molecular diagnostics means that we are now placed to integrate clinical, biochemical and genetic data to develop a coordinated approach to screening, staging and management tailored to an individual.

This presentation will discuss the basis for such a coordinated approach, and highlight the challenges to specialist services that such an approach may raise.

S3**Multiple Endocrine Neoplasia-Managing rare endocrine tumours in childhood and adolescence**

VA Murday

Ferguson Smith Department of Clinical Genetics, Yorkhill Hospital, Glasgow.

All endocrine tumours in childhood are rare and it is now clear that most individuals who develop these tumours have a genetic susceptibility. The management of these individuals is multidisciplinary and specialised. It is important that the correct genetic diagnosis is made, that the appropriate endocrine and surgical management is employed and smooth transfer to adult services is ensured.

Multiple endocrine neoplasia type 1 and 2 are examples of the susceptibility disorders and illustrate how guidelines may be used to improve management of these patients and their families.

Children may present through family history follow up, symptomatically from an endocrine tumour or as a result of a non endocrine associated feature/s.

Genotyping is important and will affect management choices. Prophylactic surgery is important in preventing malignancy and improving prognosis for affected individuals.

S4**Current issues in late effects: Endocrinology**

SM Shalet

Endocrine Dept., Christie Hospital, Manchester, UK.

Relatively few endocrine systems are completely spared from the impact of cancer treatment; the major damage is caused by radiation (XRT) and chemotherapy (CT). Endocrine sequelae include isolated GH deficiency(D), panhypopituitarism, XRT-induced hypothalamic obesity, precocious puberty, hypothyroidism, hyperthyroidism, thyroid tumours, hyperparathyroidism, infertility, hypogonadism and osteoporosis.

Recent studies have revealed that XRT induces 1) quantitative damage to the h-p axis leading to amplitude-dependent dampening of GH secretion with relative preservation of non-pulsatile secretion, 2) activation of the hypothalamic-pituitary-adrenal axis with increased cortisol concentrations and production rates in those not rendered ACTHD, but it does not induce TSHD before GHD.

Testing for XRT-induced GHD may need to differ from that used for other aetiologies of GHD; cancer survivors with XRT-induced GHD benefit from GH replacement in adult life as well as in childhood; indeed the benefit in terms of quality of life match those seen in any other adult patient group with alternative causes of GHD. Therefore there is a service issue about continuity of endocrine care for a GHD adult survivor of childhood cancer who attends a paediatric oncology clinic but needs adult endocrine input to management.

Additional areas of recent interest in this field include the possible benefits of somatostatin analogues for XRT-induced hypothalamic obesity, the treatment of CT-induced bone loss with bisphosphonates, the relatively low XRT dose required to induce premature ovarian failure, the proof of principle human experience of re-implanting ovarian strips leading to conception, and the establishment of the dose-response curve for thyroid XRT and thyroid cancer.

S5

Current issues in late effects of treatment for cancer: the oncology perspective

M Stevens

Institute of Child Life and Health, University of Bristol, Bristol, UK.

Survival from cancer in childhood has improved significantly over the past 30 years. As survival has improved, there has been an increasing need to assess quality of survival and to make provision for actual, or potential, medical and psychosocial problems in an increasing population of survivors.

There is good evidence that adverse health outcomes associated with childhood cancer and its treatment may arise many years after completion of therapy. It has been estimated that as many as 70% of adult survivors of cancer in childhood experience problems relating to their treatment and such data motivate many paediatric oncologists to recommend indefinite surveillance for the survivors under their care. In practice, however, this is not consistently implemented and there is little in the literature about the perspective of survivors themselves.

Systematic surveillance provides the opportunity to gain new knowledge but brings with it an obligation to educate survivors about the potential impacts of their cancer diagnosis and its treatment on their subsequent health, and to provide appropriate follow-up care. The alternative to systematic surveillance is selective follow up - based on the judgement of the professional (physician), or by the choice of the survivor. In either case, the decision whether or not to offer or to accept follow up must be based on valid information about likely risks and the opportunity for useful interventions. The development of a large research programme in the United States (the Childhood Cancer Survivors Study), and a similar study in the UK, will help inform the evidence base for surveillance of long term survivors.

The challenge for the future will be to identify, prospectively, those with specific risks and to implement appropriate and acceptable programmes for surveillance and intervention. Current approaches to this goal will be discussed.

S6

Genetics of Type 1 diabetes

JA Todd

University of Cambridge and Wellcome Trust Sanger Institute, Cambridge, UK.

It is evident that at least 90% of cases of type 1 diabetes (T1D) involve an immune-associated disruption of pancreatic beta-cell function that is genetically determined. The penetrance of this inherited programme is heavily influenced by multiple environmental factors, which may well include diet, microbial exposures, and maternal-foetal interactions. The identity of four susceptibility loci is known: the HLA class II genes, HLA-DRB1, -DQB1 and -DQA1, insulin (INS), CTLA4 and PTPN22 (encoding lymphoid specific phosphatase, LYP). The known structures, functions and patterns of expression of these molecules and their allelic variants indicate that T1D probably originates in the thymus from birth (or before it) via HLA class II-peptide interactions, in which expression of INS and its precursors is a key determinant of susceptibility. The CTLA-4 and LYP molecules are both established negative regulators of T cell activity, expansion and homeostasis, indicating that their subtle, but important, allelic deficiencies in function and expression increase the risk of a susceptible HLA class II-restricted T cell repertoire leading to beta-cell destruction. There are probably dozens, if not hundreds, of susceptibility loci remaining to be found: on-going mapping indicates effects at CD25 gene region and the HLA-B locus. Disease susceptibility genes can be used to stratify T1D aetiology: we have shown that in the subset of T1D patients with evidence of anti-thyroid autoimmune disease the effects of CTLA4 allelic variation are much more pronounced than in isolated T1D. Whole-genome association analyses have recently become feasible and it is anticipated that other disease mechanisms can be identified in the near future. Aside from disease stratification and elucidation of mechanisms, susceptibility genes can also be used to select individuals at risk of T1D for participation in future clinical trials to prevent the disease.

S7

Prediction of Type 1 diabetes mellitus

PJ Bingley

Department of Clinical Science at North Bristol, University of Bristol, Bristol, UK.

Testing and clinical application of interventions to prevent or delay the onset of type 1 diabetes will depend on measuring risk in unaffected individuals. Genetic markers in isolation identify infants from the general population at high relative risk of type 1 diabetes but, in the UK, the highest risk HLA class II genotype is associated with only 1.7% absolute risk of diabetes by age 5 and 5% by age 15. However, in infants with two affected family members or an HLA-identical diabetic sibling, the same genotype confers 50% risk of diabetes by age 10, or of islet autoimmunity by age 5. Autoantibodies to islet antigens - islet cell antibodies (ICA) and antibodies to insulin, GAD and IA-2 - provide the mainstay of prediction. These first appear in infancy, and positivity for multiple islet autoantibodies is a robust and sensitive marker of high risk. A relative aged < 25 with three or more antibodies has > 60% risk of type 1 diabetes within 5 years, and long term studies suggest that all individuals with multiple antibodies will eventually develop diabetes. Autoantibody affinity and other characteristics promise even more precise quantification of short-term risk and improved specificity in the general population. Glucose-stimulated insulin secretion measured in an intravenous glucose tolerance test, particularly considered together with insulin

resistance, further delineates short-term risk. Finally, impaired glucose tolerance in an antibody positive individual implies impending diabetes. Using these tools, infants are identified for trials of interventions to prevent autoimmunity on the basis of genetic susceptibility, relatives with multiple antibodies for interventions to slow the ongoing autoimmune response, and antibody positive individuals with IGT for testing potentially more toxic interventions. Risk assessment strategies for type 1 diabetes, integrating demographic, genetic, immune and metabolic markers, are flexible and sophisticated, and provide a model for other multifactorial disease.

S8

Towards a Vaccine for Type 1 Diabetes

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More than other autoimmune disease, type 1 diabetes should be preventable for the following reasons: (i) The insulin-producing β cells of the pancreas are only gradually destroyed by self-reactive T cells over a period of many years (ii) the latent interval between the establishment of highly predictive stable patterns of humoral autoimmunity and disease onset often extends over years or even decades, providing an extended window of opportunity for intervention to prevent disease onset (iii) Early studies with immunosuppression demonstrated the potential for delaying β cell damage but these agents proved too toxic to be a generally applicable intervention.

In animal models, administration of short peptides corresponding to T cell target sequences (peptide immunotherapy) has been shown to be a simple and effective method of restoring tolerance and reversing disease in animal models of Type 1 diabetes. Increasing evidence suggests that this works by inducing regulatory T cells that actively suppress the autoreactive T cell clones. However technical difficulties in identifying T cell target sequences in humans have hampered the application of peptide immunotherapy in man. Professor Mark Peakman's group at King's College London in collaboration with ourselves have developed a novel approach to identifying candidate sequences from all three major β cell autoantigens, comprising a combination of microelution of naturally processed autoantigenic peptides from human HLA-DR4 molecules, followed by testing for disease-related reactivity in sensitive *in vitro* T cell (ELISPOT) assays. Using this strategy, we have shown that Type 1 diabetes onset is distinguished by the presence of circulating effector memory (interferon- γ secreting) CD4 T cells recognizing a discrete cluster of islet peptides. In addition, we can detect potential regulatory (IL-10 secreting) T cell responses to these peptides in over 60% of healthy individuals. These islet peptides therefore fulfil criteria for selection as candidate vaccines for diabetes immunotherapy.

S9

Adrenal failure in the newborn: a role for genetic analysis?

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Adrenal failure is an important differential diagnosis in the neonatal period in babies with failure to thrive, weight loss and prolonged jaundice, especially when electrolyte disturbances (hyponatraemia, hyperkalaemia) are detected. Whilst initial management focuses on appropriate resuscitation, fluid and salt replacement and steroid treatment, it is also important that the aetiology is considered at an early stage as re-addressing the specific cause can be difficult once the child is established on steroid replacement. The past decade has seen significant advances in our understanding of the genetic aetiology of several forms of adrenal failure that present in early life, and adopting a genetic approach has several benefits such as predicting the need for mineralocorticoid replacement, determining the risk of associated features such as hypopituitarism, and for counselling the likelihood of recurrence in the family. For example, genetic causes of secondary adrenal hypoplasia include those associated with hypopituitarism (e.g., HESX1, LHX4), isolated ACTH deficiency due to mutations in Tpit, or as part of an obesity syndrome (e.g., POMC or PC-1). ACTH resistance can occur due to mutations in the ACTH receptor gene (MC2R), aladin (AAAS) in Triple A (Allgrove) syndrome (addisons, alacrima, achalasia), or in the accessory protein MRAP. Primary adrenal hypoplasia most commonly occurs in an X-linked form (due to mutations in DAX1) but can occur in a poorly understood recessive form (sometimes due to changes in SF1) or as part of the IMAGe complex. Finally, although the genetic basis of steroidogenic defects was thought to be fairly well established (e.g., CYP21, HSD3B2), recently described changes in StAR, CYP11A and P450 oxidoreductase have re-written some of the rule books, highlighting the importance of keeping an open mind in this field of paediatric endocrinology.

S10

Investigation of the pituitary-adrenal axis in suspected Cushing's syndrome

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Paediatric Cushing's syndrome (CS) is rare, but presents an important diagnostic challenge. CS is characterised by weight gain, growth failure, osteoporosis etc and caused by excess circulating glucocorticoid (cortisol-like) concentrations due to endogenous secretion or exogenous administration. The diagnosis of CS is based on demonstration of abnormalities of the pituitary-adrenal axis. The 2 aetiological categories of CS are ACTH-independent and ACTH-dependent CS. In ACTH-independent CS, the primary abnormality is in the adrenal gland, eg adrenocortical tumour and primary nodular adrenal hyperplasia, or exogenous glucocorticoids. ACTH is suppressed by negative feedback and is UNDETECTABLE. In ACTH-dependent CS, caused by Cushing's disease (pituitary ACTH-secreting corticotroph adenoma) or ectopic ACTH syndrome the stimulus for cortisol secretion comes from ACTH which is DETECTABLE.

Investigation consists of 2 basic stages, first the demonstration of CS, and secondly the identification of the precise aetiology. To demonstrate CS, we use UFC x 3, serum cortisol circadian rhythm (9,18,24,9 hrs), sleeping midnight cortisol should be <50 nmol/L and LDDST- either 1 mg at night followed by 09.00 cortisol which should be <50 nmol/L or 0.5 mg 6 hrly (9,15,9,3 etc x 48 hrs) where the 48 hr cortisol should be <50 nmol/L.

Differentiation of ACTH-independent from ACTH-dependent CS depends on; accurate measurement of 09.00 plasma ACTH x 2, a HDDST, which will have no effect on ACTH-independent cortisol secretion, but cause >50% suppression of cortisol in Cushing's disease, and a CRH test which will have no effect except in Cushing's disease where there will be an increased cortisol response. No single investigation is diagnostic of CS. The diagnosis is made from the cumulative information from a number of tests. For this the child should be formally admitted to allow a defined protocol to be performed.

S11

The role of sleep in metabolism

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Sleep is an active complex process whose precise physiological functions are unknown. The importance of sleep to neurocognitive function and psychological wellbeing is increasingly appreciated. Recently, however, attention has focussed on the interactions between sleep and metabolism. Animal models have shown that total sleep deprivation results in increased appetite. Importantly, large population studies have identified that short sleep duration is associated with increased body mass index (BMI) across multiple age and ethnic groups. A recent study has identified sleep duration at 30 months as a factor contributing to childhood obesity at age 7 years. Adult studies have identified an association between sleep duration, insulin resistance, and diabetes. The mechanisms for these associations are not precisely known, but the observed relationships are independent of potential confounding factors, including sleep-disordered breathing. Alterations in metabolic hormones may be involved. Two opposing hormones in appetite regulation are leptin and ghrelin. Leptin is released by adipocytes to signal the extent of nutritional stores; leptin therefore suppresses appetite. Ghrelin is a peptide hormone released by the stomach that acutely signals hunger to the hypothalamus. A recent large population study and small human laboratory study report that short sleep duration results in increased ghrelin and low leptin, two hormonal changes that together increase the drive for food intake. In the laboratory study, sleep restriction resulted in increased appetite for high calorie food. These studies have opened up a new field of enquiry into metabolic regulation. Children's sleep is increasingly curtailed by school start time and schoolwork, television, internet, video games, and now mobile phones. This sleep loss may contribute to the development of obesity. Investigating the mechanisms involved in the interaction between sleep and metabolism is likely to provide novel avenues for addressing the obesity epidemic.

S12

Obesity surgery: effective cure for obesity-related type 2 diabetes

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Over 1 in 4 Britons are obese- approximately four times as many as 25 years ago. Obesity rates in children mirror this rise leading to obesity being described as the epidemic of the 21 century. obesity carries an increased risk of developing hypertension, Type 2 diabetes, Heart disease, stroke and cancers of the breast, prostate and colon.

The best way to loose weight is by diet and exercise but only 5% of obese people maintain weight loss after dieting. Drug therapies have similar disappointing long term results. Weight loss surgery is the only treatment that has been proven to produce sustained and significant weight loss. NICE has recommended that surgery is considered to aid weight loss in selected patients. The UK has been slow to respond to the need for obesity surgery. World-wide some 146,301 bariatric procedures were performed in 2003, 103,000 in the USA. In the UK the number was less than 500.

Weight loss surgery is increasingly being performed laparoscopically for both bypass and restrictive procedures. Laparoscopic gastric banding (LGB) has been shown to be safe, effective, reversible and adjustable. Mortality from LGB in adults is 0.05% compared to 10% for Roux-en-Y gastric bypass. Weight loss usually stabilises at 2-3 years with

50-60% of excess weight lost. Long term follow-up is essential to get good results. Dramatic improvement in serious medical comorbidity's accompanies the weight loss especially those associated with the metabolic syndrome. There is improvement in insulin sensitivity and pancreatic beta cell function leading to remission of type 2 diabetes in approximately 70% of patients. Hypertension, dyslipidemias, sleep apnoea, asthma, GORD, and fertility are improved by LGB.

Complications of the technique have decreased with time and experience. a full multidisciplinary team is required to optimise outcome in the long-term.

OC1**The Dwindling influence of Growth Hormone with advancing age: Molecular studies in skin fibroblasts from children and adults**

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Growth Hormone (GH) levels peak in puberty and decline thereafter. Changes in body composition, exercise capacity and other aspects of aging can be partly related to this decline in GH. Therefore, whilst the GH signalling pathways remain the same, their relative contribution may change with age. GH binds to its receptor and stimulates the JAK/STAT and MAPK pathways. Evidence suggests that the JAK/STAT5 pathway regulates IGF-I production. There is limited data on changes in GH signalling with age, or how abnormalities in the IGF-I axis may affect signalling.

We have investigated the effects of GH on the phosphorylation/activation of both STAT5b and MAPK in fibroblasts derived from normal children and adults, and from two adult subjects with identified abnormalities in their IGF-I axis (one mutated IGF-I and one mutated IGF-I receptor).

Fibroblasts were treated with GH (200ng/ml) for 0-60min or with EGF (10ng/ml) for 15min. Proteins were blotted for total and phosphorylated MAPK and STAT5b.

GH stimulated MAPK phosphorylation within 5min in child (max mean 405% at 15min) and adult controls (max 217% at 10min) and in IGF-mutant derived cells (max 159% at 10min).

Whilst markedly increasing Stat5 phosphorylation in child control cells (mean peak 261% at 5 min), GH only weakly stimulated STAT5 in 1 of 4 experiments in adult controls. In contrast, in cells derived from the IGF mutants, GH weakly increased Stat5 phosphorylation in 5 out of 7 experiments (mean 120% at 10 min). EGF treatment increased phosphorylation of both MAPK and STAT5b in all fibroblasts. CONCLUSIONS: 1) MAPK signalling was seen in all cells (Child control > adult control > adult mutant), 2) STAT5b signalling was markedly diminished in adult controls compared to child controls and 3) There was no obvious change in signalling components as all cells responded to EGF.

Therefore, JAK/STAT signalling is age-dependent.

OC2**The influence of IGF-I, IGFBP-3 and leptin on growth during the first two years in extremely premature infants**

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OBJECTIVE: To determine the contributions of plasma IGF-I, IGFBP-3 and leptin on growth of extremely premature infants over the first two years of life.

STUDY DESIGN: A longitudinal study was undertaken in preterm infants (gestation 24-33 wk). Weight (Wt), crown-heel length (CHL) and head circumference (HC) were measured and expressed as standard deviations scores (SDS) at birth (n=54), expected date of delivery (EDD) and 6, 12 and 24 months post-EDD (n=29). Serum IGF-I, IGFBP-3 and leptin were measured. To reflect overall hormone output, area under the curve (AUC) for hormone levels during the study was calculated and expressed as AUC/day over 4 time periods: birth-EDD, EDD-200d, EDD-350d and EDD-700d. Relationships between growth parameters and hormone output were examined. Statistical significance was defined as P less than 0.01. Ethical committee approval was obtained.

RESULTS: Mean Wt and CHL SDS were lower at EDD than at birth (P<0.001). Thereafter catch-up in Wt was seen by EDD+6m and in CHL by EDD+24m. Serum IGFBP-3 levels, but not IGF-I or leptin, on day 1 correlated with birth Wt SDS (r=0.46, P=0.002), CHL SDS (r=0.41, P=0.01) and HC SDS (r=0.44, P=0.004). Wt SDS at EDD was determined by AUC IGF-I, IGFBP-3 and leptin (birth-EDD), with leptin being the best predictor in multiple regression (r=0.65, P<0.0001). Wt at EDD+24m was determined solely by AUC leptin (EDD-700d) (r=0.62, P=0.002). CHL SDS at EDD was determined by AUC IGFBP-3 and leptin (birth-EDD), with IGFBP-3 being the best predictor (r=0.54, P<0.0001). CHL SDS at EDD+24m was determined by AUC IGF-I and IGFBP-3 (EDD-700d) with IGFBP-3 being the best predictor (r=0.47, P=0.01).

CONCLUSIONS: All growth measurements at birth were associated with IGFBP-3 levels in these extremely preterm infants. IGFBP-3 output over the first 2 years influenced linear growth over the same period while leptin output influenced weight gain.

OC3**The effect of ceramide on chondrocyte growth dynamics**

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Abnormal growth patterns are commonly observed in children suffering from chronic inflammatory diseases. These disorders are associated with the increased production of pro-inflammatory cytokines, which inhibit growth plate chondrocyte dynamics. These effects may be mediated by ceramide, a sphingosine-based lipid second messenger, which is elevated in a number of chronic inflammatory diseases. To test this hypothesis, we determined the effects of C2-ceramide (40mM), a cell permeable ceramide analogue, on the growth of the ATDC5 chondrogenic cell line and on cultured fetal metatarsals. In ATDC5 cells, C2-ceramide significantly induced apoptosis (caspase-3 activity) (63%; P<0.05) and significantly reduced proliferation ([³H]-thymidine uptake), (62%; P<0.05). C2-

ceramide also significantly reduced cell number (protein content), (65%; $P < 0.05$) and proteoglycan synthesis (alcian blue uptake) (28%; $P < 0.05$). To examine whether IGF-1 could ameliorate the inhibitory effects of C2-ceramide on ATDC5 proliferation, cells were exposed to C2-ceramide plus/minus IGF-1 (10 nanograms per millilitre) for 24h. C2-ceramide in the presence of IGF-1 significantly increased proliferation compared to C2-ceramide alone (988%; $P < 0.05$), although proliferation following this recovery (936 dpm) was significantly lower than treatment with IGF-1 alone (2929 dpm; $P < 0.05$). C2-ceramide significantly reduced fetal metatarsal growth over an 8-day period (31% decrease vs control at day 8; $P < 0.05$). IGF-1 treatment significantly ameliorated these inhibitory effects (46% increase in length; $P < 0.05$), although growth of these bones over the 8-day period was significantly lower than that of metatarsals treated with IGF-1 alone ($P < 0.05$). C2-ceramide appears to exert detrimental effects on growth plate chondrocyte dynamics, with limited IGF-1 mediated recovery. Comparable inhibitory effects have also been observed in murine ATDC5 cells and metatarsals treated with TNF-alpha and IL-1-beta. These pro-inflammatory cytokines may mediate their effects through ceramide, influencing the growth of children with inflammatory diseases through a local effect at the growth plate.

OC4

Activation of a GH receptor pseudoexon is associated with a broad spectrum of growth hormone insensitivity phenotypes

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Inherited growth hormone insensitivity (GHI) is caused by mutations in the GH receptor (GHR). Classical GHI, known as Laron syndrome, is characterized by short stature and dysmorphic facial appearance. However, some patients present with short stature and normal facial appearance, and they are classified as having non-classical GHI.

We first described four related non-classical GHI patients with the presence of a mutation in a GHR intronic sequence, resulting in the activation of a pseudoexon and the inclusion of an additional 36 amino acids in the GHR extracellular domain. We have now analysed more than 50 GHI patients and screened those with no mutations in the GHR coding exons (19) for the presence of the pseudoexon mutation. Genomic DNA has been isolated from peripheral blood leucocytes, amplified by polymerase chain reaction (PCR) and sequenced.

So far we have identified 7 patients from 3 families with the same mutation (A to G at the 5' splice site). They all have elevated baseline and stimulated GH levels, and showed no response to GH treatment. Five patients belong to the same family. They have normal facial features. Height range from minus 3.9 to minus 5.6 SDS and IGF-I levels are in the low or low-normal range for age. One unrelated patient has 'Laron-type' facial features and is severely affected. Her height is minus 5.9 SDS with a very low serum IGF-I: 6.2 ng/ml. A second unrelated patient has 'Laron-type' facial features. His height is minus 5.0 SDS and IGF-I levels are in the low-normal range for age.

In conclusion, activation of the pseudoexon in the extracellular domain of the GHR can lead to phenotypes ranging from mild to severe GHI. Therefore, screening for the presence of this mutation should be carried out in both classical and non-classical GHI patients without mutations in the coding region.

OC5

Mutations in Cullin 7, a Cofactor for Ubiquitination, cause the 3M Intra-uterine Growth Retardation syndrome

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3M syndrome is characterised by severe intra-uterine and post-natal growth failure. Patients have a characteristic triangular facial appearance and disproportionate short stature with tall vertebral bodies and over-tubulation of long bones. The condition bears some resemblance to the Russell Silver syndrome, but is transmitted as an autosomal recessive trait. It has been proposed that heterozygous carriers demonstrate mild phenotypic manifestations of the condition.

3M syndrome has been reported in a wide range of populations. We identified the condition within a very large, highly consanguineous pedigree in North-East Brazil that was under study because of a high incidence of severe isolated GH deficiency due to homozygous mutation in the GHRH-receptor gene. Autozygosity mapping in this and other families with multiple affected sibs identified a locus on chromosome 6p21.1. Genetic analysis refined the interval of interest, and sequencing of individual genes in this region led to the identification of pathogenic mutations within Cullin 7 (Huber et al Nat Genet In press).

Cullin 7 is one member of a family of proteins involved in cell cycle regulation, including acting as a scaffold for the assembly of the E3 ligase enzyme complex that leads to the ubiquitination of substrate protein as a prelude to degradation in 26S proteasomes. The Brazilian 3M subjects carry a missense mutation in exon 25 of Cullin 7 creating a premature stop codon (4717C>T, R1573X). This region is necessary for ROC1 recruitment and binding, and thus formation of the E3 ligase complex.

These investigations demonstrate that mutations in Cullin 7 cause 3M syndrome and suggest that a defect in ubiquitination generates both pre- and post-natal growth retardation.

OC6**Early Insulin Treatment in Very Low Birth Weight Babies assessed by Continuous Glucose Monitoring**

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INTRODUCTION: Hyperglycaemia is a common occurrence in very low birth weight (VLBW<1500g) babies admitted to neonatal intensive care. Although insulin is used to treat hyperglycaemia there are no widely accepted protocols due to concerns about hypoglycaemia.

AIM: A pilot study to investigate the role of early insulin treatment during the first week of life, in VLBW babies.

METHODS: Infants were recruited within 24 hours of birth (n=16) and randomised to standard neonatal care or early insulin treatment. The study intervention involved starting insulin (0.05u/kg/hr) within 24 hours of delivery, with 20% dextrose titrated aiming to maintain normoglycaemia for 7 days. Control babies received standard clinical care. Data on glucose control was collected in all babies using continuous subcutaneous glucose monitoring (Medtronic MiniMed Continuous Glucose Monitoring System). Babies were weighed and leg length measured on days 1 and 7. Ethics approval and informed parental consent were obtained for this study.

RESULTS: Mean (SD) gestation and birth weight for infants treated with insulin and controls were 26.2 (2.47) weeks and 26.89 (2.73) weeks, 0.79kg (0.26) and 0.73kg (0.16) respectively. CRIB scores mean (range) 7 (2-9) and 7 (1-17). In the control group 6 babies (75%), developed hyperglycaemia that required treatment with insulin infusion. Babies randomised to control had a median of 35.9% of the time hyperglycaemic (>10mmol/l) compared to those treated with early insulin 7.6% (p=0.035). The normoglycaemic period (sensor glucose 4-8mmol/l) in the intervention arm was 56.3% compared to 36.6% in the control group (p=0.027). Hypoglycaemia was not increased in the early insulin arm (p=0.746). There was a trend to increased weight and a significant increase in leg length in the early intervention group (p<0.05).

CONCLUSION: Hyperglycaemia is a frequent complication in infants born <1500g. The use of early insulin in the VLBW infant can improve glucose control and has the potential to improve anabolism.

OC7**Use of continuous subcutaneous hydrocortisone infusion to maximise control in a patient with congenital adrenal hyperplasia**

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Poor control in adolescent patients with congenital adrenal hyperplasia - CYP21 deficiency is often observed. We describe a 16-year-old boy who required frequent high doses of oral hydrocortisone in order to maintain plasma cortisol concentrations of 300 nmol/l, but inadequate to suppress the ambient serum 17 hydroxyprogesterone (17OHP) (400 nmol/l) and androstenedione concentrations (24.9 nmol/l). Pharmacokinetic and dynamic studies revealed a reduced cortisol half life of 40 min (normal range 60-80 min), reduced oral bioavailability of 75% (normal range 90%-100%) but normal suppression of ACTH secretion with overnight dexamethasone.

Normal circadian rhythm of cortisol was mimicked with an intravenous hydrocortisone infusion regimen totalling 50 mg per day. Complete suppression of serum 17OHP concentrations were obtained over the first 24 hours. Bioavailability of subcutaneous versus intravenous hydrocortisone was determined to be 100% and a programme of subcutaneous hydrocortisone (Efcortisol, Sovereign, UK) delivery was commenced using the Medtronic Minimed 712 infusion pump (Paradigm). Over 12 months, serum 17OHP concentrations remained suppressed (< 2 nmol/l), and androstenedione concentrations reduced (2.3 nmol/l). Serum testosterone rose from 4.5 nmol/l to 15.5 nmol/l. Symptoms suggestive of hydrocortisone insufficiency disappeared.

Illness/emergency replacement regimens are possible on the Paradigm, however the patient was advised to carry an emergency kit in case of pump failure. Insertion sites should be changed every three days to ensure good absorption. Skin erythema at insertion sites appears dependent on delivery rate volumes. Treatment funding and patient enthusiasm/compliance are considerations. Glucocorticoid excess weight gain in the initial phase is possible.

Continuous subcutaneous hydrocortisone delivery may prove a useful adjunct to the management of patients with CYP21 deficiency. Intervention should be considered in those who display a rapid clearance of hydrocortisone from the circulation (not uncommon during puberty) and those where frequent high oral doses of hydrocortisone fail to achieve adequate control.

OC8**Association of an Fc receptor-like 3 haplotype with autoimmune Addison's disease suggests an alternative pathogenic allele at the locus**

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The common autoimmune endocrinopathies are caused by susceptibility alleles at several genetic loci including MHC, CTLA4, PTPN22 and probably several others. Many of these susceptibility alleles are shared between several different autoimmune disorders including type 1 diabetes, autoimmune thyroid diseases and rheumatoid arthritis. In recent months a novel susceptibility locus was identified in the 5' end of the Fc receptor-like 3 (FCRL3) gene in Japanese patients with rheumatoid arthritis, Graves' disease and SLE. The putative

susceptibility allele (FCRL3_3C), at position minus 169 relative to the transcription start site, was associated with a higher promoter activity and with increased NFkappaB promoter binding in gel-shift studies, suggesting a direct functional role.

We have examined a 4 marker FCRL3 haplotype, encompassing the markers reported to be associated with autoimmunity, FCRL3_3 to FCRL3_6, in UK subjects with autoimmune Addison's disease (n=104), Graves' disease (n=616) and in healthy controls (n=469). Genomic DNA was genotyped using a primer extension-MALDI-TOF assay (Sequenom) or by PCR-RFLP. Analysis was performed using haploview and unphased software. Ethical approval was obtained.

There was tight linkage disequilibrium between the 4 markers studied with pairwise D' values of between 0.93 and 1.0. Surprisingly, the putative susceptibility allele, FCRL3_3C, was present in a decreased number, of 37.4% of the Addison's disease alleles, as compared to 47.8% of the control alleles; p=0.007; odds ratio 1.54 (5-95% 1.13 to 2.10). Alleles of the three other FCRL3 markers were also associated with Addison's disease with p values ranging from 0.02 to 0.008. The four marker FCRL3 haplotype showed association with Addison's disease with a global p value of 0.02 (unphased). In contrast, no marker showed association with Graves' disease. These results confirm that FCRL3 is an autoimmune disease susceptibility locus in Caucasians too, but suggest the 'disease' allele is other than the promoter minus 169 FCRL3_3C.

OC9

The Effect of the Novel Glucocorticoid Receptor Ligand, AL-438 on Growth Plate Chondrocytes and Longitudinal Bone Growth

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Glucocorticoids (GC) are commonly used for immunomodulation as well as steroid replacement. Long-term use can, however, result in side effects including growth retardation in children due to their actions on growth plate chondrocytes. Recently, a non-steroidal anti-inflammatory agent (AL-438) that acts through the glucocorticoid receptor (GR) has been described. Studies with AL-438 have shown it retains full anti-inflammatory efficacy but has reduced negative effects on osteoblasts compared to those elicited by prednisolone (Pred) or dexamethasone (Dex). We have used the chondrogenic ATDC5 cell line to compare the effects of AL-438 with those of Dex and Pred on chondrocyte proliferation and differentiation. During chondrogenesis, Dex and Pred (10-6M) exposure for 24h resulted in a reduction in cell proliferation (30.3% and 18.8% respectively (p<0.05)), whereas exposure to AL-438 (10-6M) had no effect. Proteoglycan synthesis was also reduced after exposure to Dex or Pred for 96h (56% and 53.9% respectively (p<0.05)) but not after AL-438 exposure. Gene expression levels of collagen type II, collagen type X and aggrecan were lower in Dex treated cells, but were unchanged in Pred or AL-438 treated cells. LPS-induced IL-6 production in ATDC5 cells was significantly reduced by Dex or AL-438 (10-6M) (58.1% and 55.4% respectively; p<0.05) showing that AL-438 has similar anti-inflammatory efficacy to Dex in these cells. Foetal mouse metatarsals incubated with Dex or AL-438 (10-6M) paralleled control bone growth until day 12 when Dex treated bones were significantly shorter (22%; p<0.01) than control bones. AL-438 treated metatarsals continued to parallel control bone growth. These results indicate that the adverse effects of Dex or Pred have on chondrocyte proliferation and bone growth were attenuated following AL-438 exposure. This suggests that AL-438 has a reduced side effect profile on chondrocytes compared to other GCs, and this could prove important in the search for new anti-inflammatory treatments for children.

OC10

Longitudinal Changes in Bone Mineral Content (BMC) and Body Composition (BC) with Chronic Kidney Disease (CKD)

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OBJECTIVES: To examine longitudinal changes in BMC and BC (defined as Lean mass(LM) and Fat mass(FM)) in children with CKD.

METHOD: In a LREC approved study, DXA was used to assess longitudinal changes in 30 children with CKD -15 children(12male,6GHrx) with Chronic Renal Failure(CRF) (median age:11.1yrs,10th,90thcentiles:4.4,15.3) and 15 children (6male,3GHrx) post-renal transplantation(PTX)(median age 11.6yrs,(5.1,14.8)) with a median PTX interval of 3.8yrs(0.8,7.1). TB and LS BMC were expressed as percentage predicted BMC(ppBMC). BC was expressed as LMSDS, FMSDS and percentage predicted truncal adiposity(ppTA). Single assessment of tibia and radius using Quantitative Ultrasound(QUS) and Maximal Isometric Grip Force(MIGF) were also performed in 11 CRF and 8 Tx patients within this cohort and expressed as SDS. All data were corrected for height.

RESULTS: In the CRF group, median time between assessments was 1.5yrs(0.6,2.1). Change(delta)in HtSDS was -0.1(-0.6,0.2). deltaLMSDS was -0.3(-1.2,0.8) whilst deltaFMSDS was 0.3(-0.2,1.5). TB and LS delta-ppBMC were -0.2%(-7.2,7.3) and -2.5%(-8.1,10.9). deltaLMSDS was correlated with deltaTBppBMC(r,-0.5,p<0.05). GH patients had a higher deltaLMSDS and deltaHtSDS (p<0.05). delta-ppTA was 6.1%(-14.4,27.6). Tibial and radial QUS were 0.3SDS(-1.1,2) and 0.4SDS(-1.2,1.9). MIGF was -1.4SDS(-2.4,-0.9) and was correlated with LMSDS(r,0.6,p<0.05). In the Tx group, median time between assessments was 1yr(0.7,2.1). deltaHtSDS was 0.2(-0.5,0.3), deltaLMSDS was 0.1(-0.6,0.8) and deltaFMSDS was 0.2(-0.7,1.1). TB and LS delta-ppBMC were 2.7%(-6.2,13) and 5.7%(-5.8,15.9). delta-ppTA was 1.3%(-26.2,29.4) and inversely correlated with deltaHtSDS. MIGF was -1.3SDS(-2.4,-0.4). Tibial and radial QUS were -1SDS(-2,1.1) and -0.7SDS(-2.5,0.7). deltaLMSDS was associated to deltaTBppBMC and duration PTX(r,-0.7,p<0.05). Radial and tibial QUS correlated with LMSDS(r,0.5,p<0.05) whilst tibial QUS was correlated with TBppBMC(r,0.6,p<0.05).

CONCLUSIONS: BMC and LM are closely associated to each other. In CRF, their reduction may be ameliorated with GH treatment. In PTX, BMC may increase but there is no change in LM. QUS and MIGF may have an additional role in assessing bone health and BC in CKD.

OC11**Increased adiposity, raised C-reactive protein and cardiovascular risk markers in Postpubertal survivors of Leukaemia after Bone Marrow Transplantation**

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*[1] Paediatric Endocrinology and Diabetes, Royal Bristol Children's Hospital, Bristol, UK; [2] Paediatric Oncology and Bone Marrow Transplantation, Royal Bristol Children's Hospital, Bristol, UK.***OBJECTIVE:** To determine if postpubertal survivors of leukaemia have increased cardiovascular risks.**METHODS:** 24 patients fulfilling the criteria of >1year post BMT, >6 months off steroids, postpubertal, age 15years and above, in remission from leukaemia were recruited (Group1, n=16). Controls were siblings or best friends (Group2, n=8). Ethical approval and informed consent was obtained. Height, weight were measured using standard auxological methods. Total percentage fat and lean body mass was measured using the Lunar Prodigy DEXA scan. Fasting insulins, glucose, lipids and high sensitivity C-Reactive protein as a marker of inflammation were measured.**RESULTS:** Mean BMI in the BMT(Group1) was 22.97 vs control(Group2) mean 21.8(NS). Group1 was shorter, mean height SDS -1.26 vs 0.65 in Group2 (P<0.0001) Total percentage fat Group1 was increased mean 36.9 vs 25.6(p=0.05) Total lean body mass was decreased in Group1 mean 34847gm vs 45657gm (p=0.034). There was a trend to decreased mean fat free mass index and increased fat mass index in Group1 vs Group2 (10.47 vs 14.88, 8.3 vs 7.07 respectively) but did not reach significance. Group1 mean percentage truncal fat vs group2 was increased 38.27 vs 25.68(P=0.05). Hs-CRP mean in Group1 was 13.6 vs 6.93milligrammes per litre (p=0.024). 50percent of Group1 (n=8) had increased cholesterol levels >5millimol per litre (max 6.7mmol), 62percent (n=10) of Group1 had increased fasting insulins >7milliinternationalunits per litre. 18.7percent (n=3) had increased triglycerides (>1.7millimol per litre) and 68percent (n=11) had increased LDL Cholesterol >3millimol per litre. 43percent (n=7) had both raised fasting insulins and lipids.**CONCLUSION:** Postpubertal survivors of leukaemia postBone Marrow Transplantation are shorter, have increased truncal adiposity and raised inflammatory markers. Some survivors additionally have raised fasting insulins and deranged lipids predisposing to increased future risk of cardiovascular disease.**OC12****Correlation between clinical and biochemical features on sperm donation and sperm quality in underage minors with cancer**

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The correlation between age, degree of virilisation and endocrine biochemistry and ability to sperm donation in adolescents with cancer is unknown.

AIMS: To determine the correlation between pubertal stage, virilisation, androgen biochemistry, diagnosis and chemotherapy on the likelihood of sperm donation and sperm quality in minors with cancer.**METHODS:** 96 consecutive males aged 12-18 years (median 15.1 yrs) with new or relapsed malignancy between 1.1.1999 and 30.04.2005 presenting at two teenage oncology units at UCLH were identified. Their case notes were retrospectively examined for history, endocrine biochemistry and pubertal status. Semen cryopreservation outcomes were obtained from the local HFEA licensed laboratory. Sperm banking outcomes were classified as 'successful', 'unsuitable': (specimen unsuitable for cryopreservation) and 'unable' (inability to produce a specimen). We compared the above factors in the various outcome groups using the Kruskal-Wallis test and chi-square statistic.**RESULTS:** Sperm banking was offered in 66 (69%) out of 96 patients. 47 patients accepted and attempted banking. The number of patients in the 'successful', 'unsuitable' and 'unable' outcome groups were 25(53%), 12(26%) and 10(21%) respectively. There was no significant variation in the median ages. Unsuitable specimens included azoospermia / low volume (n=9) and necrospermia (n=3). The mean testosterone level of the 'unable' group was lower than the 'successful' group (6.2 vs.11.8 nanomols per litre, p 0.08). Patients in the 'unable' group had a lower median Tanner stage (2.5, p = 0.056) and testicular volume (7.8 mls, p 0.08) compared to the 'successful' and 'unsuitable' groups which were similar. The mean semen volumes in the 'successful' and 'unsuitable' groups were 1.382 and 1.0 mls respectively. There was an overrepresentation of Hodgkins disease in the 'unable' group (5/10).**CONCLUSIONS:** Adolescents with cancer should be warned of a high failure rate at semen cryopreservation particularly if their testosterone levels are low, testicular volume is below 8 mls and their Tanner stage is below 4.**OC13****Fasting and postprandial Peptide YY response in adolescents with obesity**

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*[1] 2Department of Paediatrics, Birmingham Heartlands Hospital; [2] 1Department of Metabolic Medicine, Imperial College London; [3] Department of Paediatrics, University of Warwick Medical School.***BACKGROUND:** The gut hormone peptide YY (PYY) is released postprandially acting as a satiety signal. Obese adults have reduced concentrations of PYY in the fasting and postprandial state. Animal data suggest that lower PYY levels are likely to be a consequence rather than a cause of obesity. We aimed to investigate PYY in the fasting state and after a 420 kcal meal in post pubertal children**METHOD:** Nine normal weight (BMI SDS 0.96 +/- 0.27 (mean +/- SEM)) and six obese (BMI SDS 10.2 +/- 0.74) adolescents received a test meal of 420 kcal. The adolescents were aged 14.1 +/- 0.25 and 14.6 +/- 0.29 years respectively. Venous blood was obtained at 0, 30, 60, 90 and 120 minutes. PYY was measured using an established in-house assay.

RESULTS: PYY concentration reached a peak 60 minutes after the meal in both groups. Fasting and peak PYY concentrations were similar in normal weight (30.2 +/- 2.2 increasing to 43.5 +/- 5.7 pmol/L) and obese (30.2 +/- 3.5 increasing to 40.8 +/- 2.9 pmol/L) adolescents ($p = 0.99$ and $p = 0.73$). There was no difference between the area under the curve in the normal weight (4612 +/- 499 pmol/L/min) and obese (4505 +/- 349 pmol/L/min) groups ($p = 0.88$). Both normal weight and obese adolescents had a significant increment in postprandial PYY concentration compared to baseline. These results are in striking contrast to those of obese adults in whom lower PYY concentrations have been reported for both fasting and postprandial levels.

CONCLUSION: Control of appetite during adolescence is complex and likely to evolve with developmental stage of the child. Differences between children and adults may have implications for pharmacological and dietary interventions for the increasing number of obese children presenting to clinical services. Further work is needed to examine the control of appetite in childhood.

OC14

Mature subcutaneous and visceral adipocyte concentrations of adiponectin are highly correlated in normal-weight children and inversely related to Body Mass Index Standard Deviation Score

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INTRODUCTION: Adiponectin is an adipocyte-specific protein with insulin-sensitising properties. Several studies have examined the expression of adiponectin mRNA or tissue/secreted protein levels in fat obtained from adults but none has assessed tissue levels in childhood.

METHODS: Following ethical approval and written informed consent, paired subcutaneous (Sc) and visceral (V) fat samples were obtained from 12 normal-weight prepubertal children (median age [range] 5.7 [1.1 to 9.9] years; mean [range] BMI SDS 0.55 [-1.64 to 2.13]) undergoing routine surgery. Mature adipocytes were isolated and total adiponectin levels determined by ELISA. Insulin sensitivity and lipid parameters were assessed in fasting blood samples taken at the time of biopsy collection.

RESULTS: A positive correlation was seen between the adiponectin concentration within the Sc and V mature adipocytes derived from each child ($r = 0.924$; $p < 0.001$). Following logarithmic transformation of the Sc and V adiponectin concentrations (Log-Sc and Log-V) to render the data Gaussian, both Log-Sc and Log-V were found to be lower in those children with higher BMI SDS ($r = -0.621$ and $r = -0.357$ respectively), although this only reached statistical significance in the Sc adipocytes ($p = 0.03$). Age was not related to either Log-Sc or Log-V adiponectin levels, although a significant negative association was seen with serum adiponectin ($r = -0.589$; $p = 0.04$). Log-Sc or Log-V did not correlate with serum adiponectin concentrations, markers of insulin sensitivity or circulating lipid levels.

CONCLUSIONS: These data indicate a relationship between total adiponectin levels in different tissue compartments suggesting either some form of interaction or co-regulation by systemic factors, possibly related to body size/fat mass. Although serum concentrations of total adiponectin were inversely related to age they showed no relationship with either tissue levels or BMI SDS suggesting that regulation of serum adiponectin levels is not solely dependent on adipose tissue levels.

OC15

Lower physical activity in childhood diabetes

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BACKGROUND: Activity is promoted for those with diabetes (DM) but there is little available evidence on actual activity undertaken in childhood diabetes. Reduced activity could account for their reported increased weight gain and BMI, and could have implications for diabetes control.

AIMS: To determine activity levels in a cohort of children with DM in comparison with their healthy siblings

METHODS: Activity levels were recorded as daily counts over waking hours during 7 days in 43 children (boys = 21) with DM and 43 siblings (boys = 17) using a Yamax Digiwalker SW-200. This was validated and gives linear results compared to the CSA Actigraph accelerometer. ($r = 0.996$; $p < 0.001$)

RESULTS: Mean age of both groups was 11.5 +/- 2.9 years. Mean BMI SDS and % body fat was greater in those with DM (both $p < 0.05$) compared with their siblings.

Activity levels were similar between families but reduced in those with DM, with only 4 of 43 children with DM having greater activity counts than their siblings. The mean daily pedometer count for the siblings was 11,745 +/- 2473 compared with 8,977 +/- 2041 for those with DM ($p < 0.001$) and this was inversely correlated with BMI SDS in all subjects (DM $r = -0.424$, $p = 0.005$ and Siblings $r = -0.404$, $p = 0.007$).

CONCLUSIONS: A reduction in activity of ~2000 steps/day has been demonstrated in children with DM. In adults 2000 steps equates to walking 1 mile or expending 100kcal (approx 2/3 of a bag of crisps). These results are important given that the metabolic cost of diabetes has been assessed as approx 100-200 kcal from glycosuria and increased hepatic activity. This reduction in activity may be compensatory for the increased metabolic cost of diabetes.

The strong correlation of increasing BMI to reduced activity suggests that BMI might fall if activity was increased. The latter has been shown to improve diabetes control.

OC16**Cognitive Behavioural Therapy for Adolescents with Type 1 Diabetes**

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Diabetes self-care is often compromised during adolescence, but maintaining good glycaemic control is important to delay and minimise the risk of developing complications in the future. We hypothesise that Cognitive Behavioural Therapy (CBT) will be helpful in optimising compliance and promoting self-care in adolescents with diabetes. CBT interventions have been successfully used in a wide range of paediatric psychological and medical conditions and a preliminary study showed group CBT to be effective in improving glycaemic control and well being in adults with diabetes.

MREC approval was obtained for a study in which adolescents (n=87) with type 1 diabetes (aged 11-16 years) attending paediatric out patient clinics at 4 centres in the South West of England participated in a randomized controlled trial of CBT compared with non-directive counselling (control group). Participants attended 6 sessions on a weekly basis followed by 'booster' sessions at 6 and 12 months. Sessions were designed to help participants work on diabetes related goals that were drawn up collaboratively with the therapist.

We present results from a qualitative analysis of case notes and audiotapes from CBT sessions. Data was analysed by a process of data reduction, data display and conclusion drawing and conclusion verification. Analysis revealed variable engagement with therapy, not directly related to gender, age, diabetes duration, or diabetes control. Verbal proficiency and ability to engage in the more sophisticated aspects of CBT were not necessarily required for the participant to achieve change. Adaptations of materials to fit with the individual's learning style were helpful. Serious family problems adversely affected the ability to tackle diabetes related goals.

Further research should target acceptance and commitment, using elements of Dialectical Behavioural Therapy and Acceptance and Commitment Therapy. This would be particularly appropriate for patients who do not readily engage in psycho-educational treatment and who are non compliant.

OC17**Abnormalities of thyroid function at diagnosis of type 1 diabetes mellitus: relationship with diabetic ketoacidosis**

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Assessment of thyroid function (TF) at diagnosis of type 1 diabetes mellitus (T1DM) forms part of the care pathway 'Management of the Hyperglycaemic Child' recently introduced in our hospital. This conforms to the NICE guideline 'Type 1 diabetes: diagnosis and management of type 1 diabetes in children and young people'.

Transient abnormalities of TF are common at diagnosis of T1DM. Previous reports indicate that in this scenario, abnormalities are only observed in patients with diabetic ketoacidosis (DKA). If this is true, it may be appropriate to limit assessment of TF to patients who do not have DKA.

AIM: to describe abnormalities of TF at diagnosis of T1DM and association with DKA.

RESULTS: 81 patients (52 M; 29 F, age (median, range) 10.42 yrs, 1.19 to 15.72) were studied of whom 19 were in DKA. TF was abnormal in 29 subjects (35.7%). 18 (22.1%) had biochemical findings compatible with sick euthyroid syndrome (normal TSH, low T3, fT4, T4), 7 (8.6%) compensated hypothyroidism, 2 (2.4%) hypothyroidism, 1 (1.2%) thyrotoxicosis and 1 (1.2%) thyroid hormone resistance (elevated TSH, T3, fT4, T4). Abnormalities in TF persisted in 3 / 20 subjects who were retested after a median of 12 days (1 to 560 days) and 2 required treatment (1 hypothyroid and 1 thyrotoxic). The other 9 subjects remain clinically euthyroid.

The incidence of DKA was significantly higher in patients with abnormal TF ($p = 0.03$) however most patients (18 / 29 (62%)) with abnormal TF were not acidotic.

CONCLUSIONS: Transient abnormalities of TF are more common patients with DKA but may occur in children who are not acidotic. We suggest that, in the absence of clinical features of hypothyroidism or thyrotoxicosis, assessment of TF is deferred until 1 month following diagnosis of T1DM.

OC18**The practical transfer from injected insulin to oral glibenclamide in permanent neonatal diabetes mellitus due to activating mutations in KCJN11**

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Permanent neonatal diabetes mellitus (PNDM) is a heterogeneous disorder for which activating mutations in the KCJN11 gene, encoding the Kir6.2 subunit of the ATP-sensitive potassium channel in the pancreatic beta cell, have been found to account for 30% of cases. These patients show improved metabolic control on sulphonylureas compared to insulin. We aimed to describe our experience of transferring 2 infants from injected insulin to oral glibenclamide.

Patient 1 (ARS) presented at 7 weeks in acute diabetic ketoacidosis, requiring insulin up to 2u/kg/day initially, then falling to 0.5u/kg/day

by 5 months of age. He had a heterozygous de novo mutation (R201H) in KCJN11. Patient 2 (BC) presented at 5 days with hyperglycaemia. His mother also had PNDM and both carry the R201C mutation. He required 0.75u/kg/day of insulin at 3 months of age.

Both children changed from insulin to glibenclamide at 5 and 3 months of age respectively. They both underwent intravenous glucose tolerance tests (IVGTT) before and 1 week (ARS) and 6 weeks (BC) after commencing glibenclamide 0.1mg/kg 12 hourly.

The IVGTT results demonstrated no insulin secretion (patient 1) before treatment, but insulin secretion after glibenclamide in both (patient 1: fasting insulin <10pmol/L to 34.9pmol/L at 10 min; patient 2: fasting insulin 42.6pmol/L to 111pmol/L at 120 min), with minimal first phase insulin response to intravenous glucose. Both infants stabilised on glibenclamide 0.4mg/kg/day, stopping insulin by day 5. Subsequently, glibenclamide requirements have reduced to 0.3 mg/kg/day (ARS) and 0.2 mg/kg/day (BC). Capillary glucose results have remained between 3.5-10mmol/L. Both infants are developing normally, thriving and without side-effects.

Oral glibenclamide is a safe alternative to injected insulin in PNDM due to KCJN11 mutations. Changeover to glibenclamide should be undertaken with close glucose monitoring for hypoglycaemia. It is unclear why the first phase insulin response is still impaired despite treatment.

OC19

Treatment of precocious puberty with GnRH analogues: an audit of nurses' perceptions of clinical practice

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INTRODUCTION: Following the introduction of a new GnRH analogue for the management of precocious puberty, awareness has been heightened with regards to various issues of current clinical practice. As many Paediatric Endocrine Nurse Specialists are responsible for administering such treatment, it was felt that an audit of current practice would be beneficial.

METHODS: A questionnaire regarding current practice was designed and 52 paediatric endocrine nurse specialists from the UK and Ireland were invited to participate. **RESULTS:** 31/52 (60%) completed questionnaires were returned and 29 nurses were involved in the treatment of children with precocious puberty. Current practice was highly varied between the different centres with regards to: the clinical monitoring of precocious puberty and its therapy, administration of the treatment, i.e. route and site, the product used, the use of shared care protocols and adherence to local and national guidelines. Several nurses (20 %) felt some children experience behavioural problems during and after receiving GnRHa therapy, such as needlephobia, and highlighted the need for psychological support during therapy/long-term. Current lack of age appropriate literature was also emphasised. Many nurses (79 %) reported long term side effects associated with treatment, including: skin scarring, weight gain, behavioural problems and other clinical manifestations (eg: PCOS). **CONCLUSIONS:** This study emphasises the current inter-centre variability of clinical practice in the use of GnRH analogues in the management of precocious puberty. Most nurses were unaware that their practice was different to that of other centres, although they felt that their own practice was appropriate. As a result, we believe that many centres would benefit from the utilisation of standardised clinical practice guidelines. In addition, the long-term follow up of patients in order to explore the possible future complications of GnRH treatment is essential. Further research into the possible psychological problems of children receiving GnRH analogue therapy would also be helpful.

P1**Paediatric Growth Hormone Prescribing in Scotland 1990-2003**

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Data on paediatric growth hormone (GH) prescribing in Scotland have been collated annually since 1990, following recommendations by the Scottish Executive¹. A 10-year audit of this data was published in 2002.

A further audit has now been undertaken in the light of new licensed indications for paediatric GH prescribing, namely chronic renal insufficiency (1997), Prader Willi syndrome (2000) and small-for-gestational age (2003).

The annual total number of children receiving GH has remained relatively stable, at around 350-400 between 1990-1996 and 300-350 from 1997-2003. The decline in numbers during the latter period is largely attributable to a reduction in treatment of normal variant short stature, following completion of clinical trials. In contrast, the number of children treated with panhypopituitarism (idiopathic; septo-optic dysplasia and craniopharyngioma) and other diagnoses, e.g. Crohn's disease, has increased.

The proportion of GH prescribed for licensed indications has risen from 55% in 1990 to 78% in 2003. The 22% unlicensed use of GH in 2003 comprised: normal variant short stature (5%); skeletal dysplasias (5%); dysmorphic syndromes (5.6%); and other diagnoses (6.4%).

In summary, GH is being used relatively conservatively in Scottish paediatric practice, taking into account research experience. While a small degree of ad hoc usage is inevitable, we strongly support participation in national trials wherever possible. The adoption of an open approach with the Scottish Executive regarding GH usage has proved beneficial in alleviating fear of escalating costs and preventing prescribing problems in a country in which 99% of GH is prescribed by general practitioners on the advice of specialist paediatricians.

¹Organisation and Management of Growth Hormone Therapy - a Report by a Working Group set up by the Clinical Resource & Audit Group. HMSO, 1991.

²The boom that never was: results of a 10 year audit of paediatric growth hormone prescribing in Scotland. WF Paterson et al. Health Bulletin 2000; 60: 457-466.

P2**Objective monitoring of compliance to GH therapy**

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To assess compliance to GH therapy we examined prescribing records of 115 GH deficient children (mean age: 12.4y, SD 3.9) from a clinic population from years 2001 and 2003 in a mixed longitudinal and cross-sectional cohort study.

Compliance was objectively assessed in each child by comparing total expected GH usage (mg/day) with the total amount of GH dispensed from all prescriptions during a 12-month period. Height data were taken from growth clinic records.

RESULTS: In cross-sectional analysis, 38% (29/75) missed >4 injections/month, and 21% (16/75) missed >10 injections/month. Decreasing compliance was associated with longer duration on GH therapy ($p<0.005$), lack of choice over GH device ($p<0.005$), and short duration (<4 weeks) of GH prescriptions ($p<0.005$). Poor compliance was also associated with reduced height velocity ($p<0.05$, adjustment for duration of GH therapy).

In longitudinal analysis, improved compliance was associated with increasing duration of GH prescriptions ($p<0.005$), and showed a positive but non-significant association with change in height velocity ($r=0.21$, $p=0.4$, $N=23$). Between 1999 to 2003: more patients had received a choice of GH device, prescription durations increased, rates of poor compliance decreased, and mean height velocity, adjusted for age and years on GH therapy, increased.

CONCLUSION: Monitoring of GH prescription collection in our growth clinic identified avoidable factors related to poor compliance, and informed our interventions to improve compliance and treatment responses.

P3**An analysis of the initial catch-up phase of growth hormone (GH) treatment using the AUXAL non-parametric growth program: is the current regimen maximally effective?**

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INTRODUCTION: Catch-up growth is arguably the most important phase of GH treatment, yet the duration and differential responsiveness to GH during this period has not been described. We therefore used a novel approach employing a novel non-parametric program on GHD patients having previously analysed a large longitudinal UK cohort for reference.

SUBJECTS: Data from 17 boys and 12 girls with IGHD, 4 boys and 4 girls MPHID selected from the Regional KIGS database with complete data and standard GH treatment c.0.6 units/kg/wk.

METHODS: Data for height and age were entered into the AUXAL 3.1 (Bock, 2003) a non-parametric program specifically designed for longitudinal analysis. This produces a kernel-smoothed height velocity curve, which allowed the determination of points of maximum and minimum velocity.

RESULTS: The total duration of catch-up was mean 2.94 SD 1.55 years for males and 2.96 SD 0.6 years for females. The time from the

start of treatment to the peak velocity was 0.74 SD 0.46 years and 0.57 SD 0.25 years respectively. Prepubertal spurts identified subsequent to catch-up were of mean duration 2.07 and 2.59 years respectively.

DISCUSSION: This analysis has for the first time characterised catch-up growth on GH treatment. Although the mean duration is nearly 3 years, intense acceleration occurs in the first 6-9 months only, the remaining period being in relative deceleration. This could suggest an alternative approach to GH dosing in the first 3 years to optimise height gain. Growth subsequent to the catch-up phase shows surprisingly normal dynamics.

P4

The UK Turner Study: Interim Report of Adverse Events in a Randomised, Double-Blind Placebo-Controlled Study of Growth Promoting Treatment in Turner Syndrome

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The UK Turner Study aims to examine the influence on final height (FH) of oxandrolone (Ox) and the introduction of ethinyl oestradiol (E2) therapy at 12 or 14 years in girls with Turner syndrome (TS) receiving a standard dose of growth hormone [10mg/m²/wk in daily injections]. Recruits are randomised to Ox [0.05mg/kg/day; max. daily dose 2.5mg] or placebo from 9 years and further randomised to begin E2 [Year 1: 2 micrograms daily; Year 2: 4 micrograms daily; Year 3: 4 months each of 6/8/10 micrograms daily] or placebo at 12 years, with the placebo group beginning E2 at 14 years.

Patients are reviewed 4-6 monthly for assessment of growth & puberty and treatment adjustment. At each visit, details of any adverse events (AEs) are recorded. These include any illness, injury or surgery, however unrelated to the study medication they appear.

One hundred and two girls with TS aged 7-13 years were recruited at 40 UK hospitals (1999 - 2003). Six patients have withdrawn from the study, leaving 96 currently participating.

To date, a total of 126 AEs have been reported: medical (60) [thyroid (7), other (53)]; surgical (6); ENT (24); injury (10); behavioural (2) [obsessive compulsive (1), attention deficit hyperactivity disorder (1)]; orthopaedic (8); deviations from medication protocol (16).

No serious AEs have been recorded. Unsurprisingly, the largest single category involves ENT problems and surgery (19%). The remaining AEs include the variety of infections, injuries, viral illnesses and routine surgical procedures that would be expected in any paediatric population. Notably, there have been no reports of voice deepening or clitoromegaly, which have been recorded previously with higher doses of Ox.

Families and clinicians can be reassured that no safety concerns have been reported with these doses of Ox, E2 and GH. FH data will be available in the majority by 2007.

P5

Does growth hormone treatment in Turner Syndrome meet patient and family expectations for final height?

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The additional gain in final height following growth hormone treatment in girls with Turner syndrome, outside research studies, is repeatedly reported around 6 cm. Little information is available regarding either patient or family expectations of prospective height gain following treatment or of what that means to them in relation to the height of their normal peers.

A self-administered computer program has been developed which visually morphs a young adult up or down in height at 1cm increments. This is compared with another adult fixed at that individual's projected height and is performed against a background of a room of other normal height adults ranging across the centiles.

Girls (n=37) with Turner Syndrome and their parents (n=35) individually recorded their expectation of height gain on treatment together with the minimal increase they believed would justify such treatment.

Mean expected height gain from patients =8.8cm, from mothers = 8.3cm and fathers = 9.1cm. The minimal height gain deemed acceptable from patients was 3cm (range = -6.5 to 17cm), from mothers 4.8cm and fathers 4.5cm

These visually expressed computer graphic results would support the mean reported height gain in Turner syndrome of around 6cm from various international non research studies as matching the mean parental expectations of treatment and exceeds the minimal height gain they state would justify treatment.

This program could be used with families to assist them in the decision re the initiation of growth hormone treatment with a visual expectation of final height compared with their peers.

P6

Exceptional growth response to GH therapy in a child with IGF-I, IGFBP-3 and ALS deficiencies associated with PTPN11-negative Noonan syndrome

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Growth retardation in Noonan syndrome (NS) with or without mutations in the PTPN11 gene has been associated with subtle abnormalities of the GH-IGF-I axis. PTPN11 mutations may confer more severe IGF-I deficiency and decreased responses to GH therapy.

We report a patient with short stature referred with possible GH insensitivity syndrome (GHIS). The first child of unrelated parents (BWT 3740g), she presented in infancy with failure to thrive. Karyotype and skeletal survey were normal. At 1.9 yrs peak GH was 46.6 mU/L (clonidine), with low IGF-I, IGFBP-3 and absent responses in an IGF-I generation test (GH 0.033 mg/kg/day x 4); IGF-I: 49 to 35 ng/ml [16-215 ng/ml], IGFBP-3: 0.6 to 0.6 mg/L [0.2 - 6.6 mg/L]. A diagnosis of GHIS was considered. At 5.5 yrs height SDS was -5.4. Dysmorphic features were consistent with NS and included hypertelorism, epicanthus inversus, low posteriorly rotated ears, myopia and prominent lumbar lordosis. There was no cardiac abnormality. The IGF-I generation test was repeated and again showed low IGF-I, IGFBP-3 and ALS with poor response in IGF-I: 24 to 46 ng/ml, and no changes in IGFBP-3: 1.7 to 1.5 mg/L and ALS: 4.1 to 3.5 mg/L [12 - 25 mg/L]. Analyses of PTPN11 and GH receptor genes were normal. She was offered GH therapy 0.8 mg/day (0.05 mg/kg/day). Height velocity increased from 5.6 to 9.9 cm/yr during the first 1.53 yrs of therapy (mean 12m HV in NS: 8.5 cm/yr, Cotterill et al. JCEM 1996, 81, 2291-7). IGF-I normalised to 238 ng/ml. At 7.3 yrs, height SDS was -3.7. In summary, NS comprises a heterogeneous group of patients who share certain dysmorphic criteria but have variable genetic and biochemical features. Our patient with PTPN11-negative NS had IGF-I, IGFBP-3 and ALS deficiencies of uncertain cause, but showed excellent clinical and biochemical responses to GH treatment.

P7

The Effects of Recombinant Human Growth Hormone (rhGH) on Linear Growth, Body Composition (BC) and Bone Mineral Content (BMC) in Children with Crohn's Disease (CD) and Severe Growth Retardation

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BACKGROUND: The efficacy of rhGH in growth failure associated with CD is unclear.

METHODS: Retrospective data analysis at 6 months before (T-6), at start (T0) and 6 months after (T+6) of rhGH treatment in 7 CD patients (5 males). BC was assessed using DXA at variable intervals before and after rhGH. All data were corrected for height (Ht). Total body (TB) and lumbar spine (LS) BMC were reported as percentage predicted (ppBMC), fat mass was expressed as % fat SDS (%FSDS) and lean mass (LM) as LMSDS.

RESULTS: Median age and dose of rhGH at T0 was 15.9 years (range, 13.0-17.9) and 0.15 mg/wk (0.02-0.04). Two patients were treated with sex steroids prior to rhGH. Median Tanner stage remained at stage 3 (1,5) at T0 and T+6. Median albumin and CRP were similar at T0 and T+6. One patient had glucocorticoids (GC) before rhGH whilst 2 had GC during rhGH treatment. Median Ht SDS at T-6, T0 and T+6 was -2.2(-3.5,-1.3), -2.2(-3.8,-1.4) and -1.8(-3.0,-1.0), respectively. Median HV at T0 and T+6 was 2.5cm/year(1.5,6.5) and 3.7cm/year (0.8,9.9) respectively (p=0.48). Median HVSDS at T0 and T+6 was -0.7(-3.4,5.0) and 2.4 (1.4,3.4) respectively (p=0.23). Median serum IGF-1 changed from 158mcg/l(30,282) at T0 to 197mcg/l(30,437) at T+6 (p=0.12). HVSDS at T+6 showed a positive correlation with dose of rhGH at T0 (r=0.8, p=0.05). IGF-1 levels at T0 were not associated with HVSDS at T+6 (r=0.2, p=0.66). ppBMCTB before and after rhGH were 68%(60,80) and 66%(60,86). ppBMCLS changed from 75%(49,100) to 77%(58,100). %FSDS and LMSDS before rhGH was -1.3(-2.0,2.0) and -1.8(-6.2,-1.0) and after rhGH was -1.5(-1.9,1.4) and -1.7(-2.0,-1.0), respectively.

CONCLUSION: At the above dose, rhGH may ameliorate growth retardation in CD. A larger prospective trial is needed to investigate the effects of a higher dose of rhGH on growth, BMC and BC.

P8

The case for individualising treatment with growth hormone therapy in children born small for gestational age (SGA) who fail to catch up

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OBJECTIVES: To illustrate clinical issues associated with poor growth in children born SGA. Children born SGA who fail to catch up in growth during childhood have high risk of short final adult height. Growth hormone (GH) improves catch up growth and final height. It appears safe and effective after 13 years' experience and may be associated with beneficial effects on blood pressure, lipid profiles, body composition, IQ and self-perception. International Consensus Group (2001) recommended GH for children born SGA (birth weight (BW) <-2SD and/or length less than or equal to -2SD) with persistent short stature (SS) (height <-2SD), age greater than or equal to 4yrs and height velocity <0SD. In contrast GH is licensed in Europe at height <-2.5SD.

METHODS: 9 patients with SS born SGA or following intrauterine growth retardation (IUGR) are described. Patient 1 received GH late (aged 14 years), with little response (height -2.98SD at 15.5yrs). Patient 2 received GH from age 2.5yrs because of low GH levels and height -4.4SD and is responding well (height -1.52SD at 5.9yrs). Patients 3, 4, 5 have persistent SS (height SD -3.74, -3.59, -3.71) but despite history of IUGR do not fulfil criteria for GH due to BW (-1.35, -1.55, -1.71 SD respectively). Patients 6, 7, 8 do not meet GH licence criteria as height >-2.5SD (-2.27, -2.18, -2.19). Patient 9 is ineligible due to BW (-1.59SD) and height (-2.22SD). GH levels, tested in 6 patients, are normal.

RESULTS: 8 of 9 patients have poor final height prognosis. Although ineligible for GH treatment according to European licence, 3 are eligible according to International Consensus Group.

CONCLUSIONS: Children with poor growth born SGA, who may benefit from GH, could be excluded on the basis of strict recommendations; hence consideration should be given to treat on an individualised basis rather than restricting to those who meet various treatment and licensing criteria.

P9**Insulin Tolerance Tests: A Comparative Re-Audit of Patient Preparation, Safety and Protocol Compliance**

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BACKGROUND: The insulin tolerance test (ITT) is the gold standard for assessing growth hormone (GH) and ACTH reserve but relies on inducing, and reversing a controlled, but potentially dangerous, hypoglycaemia as a 'stress' stimulus.

OBJECTIVES: We aimed to reduce the non-attendance rate for ITT to our adolescent endocrine day unit and improve patient safety, understanding, preparation, arrival time and protocol compliance by raising staff awareness and developing a patient information and consent leaflet.

METHODS: We compared attendance and arrival times, the adequacy of clinical preparation (fasting, priming, hormone medication), and the accuracy of glucometer (BM) readings in 21 consecutively booked adolescents (13-19 years) who received the leaflet (March-June 2005), with similar data from 26 individuals audited before the leaflet was developed (April-June 2004).

RESULTS: Despite an improved patient attendance and preparation rate (86% vs 65%) and earlier (by 8.30h) arrival time (95% vs 89%) between audits, cannula insertion time had deteriorated until after 9.00h (40% vs 15%) or even 10.00h (30% vs 0%) which, in the latter case, should have led to test cancellation; one patient was given breakfast by staff and hence rebooked. There was better protocol compliance with the insulin dose reduction (0.15-0.1 units per kilo) for hypopituitary patients and all, except one, (95%) achieved hypoglycaemia <2.6 millimol per litre (true glucose) by 30 minutes, reversed without complications. One patient in each audit underwent ITT unnecessarily because fasting baseline hypoglycaemia was not detected by glucometer whilst a further patient went home hypoglycaemic for the same reason. Glucometers failed to detect the high 19/21 (94%) prevalence of true hypoglycaemia at 20 minutes in 4/19 (21%) patients (sensitivity 79%, specificity 100%).

CONCLUSION: Information leaflets have improved patient compliance and understanding but staff delays in cannula insertion, protocol deviations and insensitivity of glucometer readings at low values, prejudice patient safety. Test commencement before 9.30h and routine glucose rescue 20 minutes after insulin injection (regardless of BM) would improve the risk-safety profile until essential ward-based fluorimetric glucose assays are made available.

P10**A transatlantic comparison of the dynamics of mid-childhood growth**

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Introduction. An original manual analysis of mid-childhood growth had suggested the occurrence of a regular cyclical pattern of acceleration and deceleration as opposed to a single mid-childhood spurt. This theory of growth spurts was supported by a recent analysis of the U.S.-based Fels longitudinal study using a new analytical program. This study aims to investigate this pattern of growth by using the same parameters and statistical program on a different population.

Subjects and Methods. Data from 89 boys and 67 girls with complete 6-monthly height measurements from the Edinburgh Growth Study were entered into AUXAL 3.1 (Bock, 2003) a non-parametric program specifically designed for longitudinal analysis, of particular advantage as it requires no presuppositions.

Results. The output consisted of kernel-smoothed height-velocity curves, which allowed the identification of points of maximum and minimum velocity. Both boys and girls displayed a range from zero to four prepubertal spurts [number of spurts: percentage male/female. 4: 24/7, 3: 39/30, 2: 29/33, 1: 7/27, 0: 1/3]. The average size and duration of the growth spurts for the Edinburgh data were almost identical to the Fels study.

Discussion. Strong support has been given to the finding of regular pre-pubertal spurts occurring over 2 or 3-year intervals by using the same statistical package and bandwidth setting on two populations separated in time and place and in comparison with the original manual analysis. The AUXAL program seems ideally suited to explore the dynamics of growth in longitudinal cohorts. This observed phenomenon can now be incorporated into the development of the next generation of growth standards.

P11**Growth and weight gain during treatment for juvenile hypothyroidism**

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Patients with juvenile hypothyroidism (JH) are typically found to be short and overweight. Acceleration in growth and improved body composition is anticipated once treatment is initiated, although final adult height may be compromised. It was our impression that BMI seldom fell significantly despite accelerated growth. It was the aim of this study to document changes in height and BMI during treatment and identify factors influencing growth and weight gain.

METHODS: A retrospective case note study. Patients with coexisting pathology were excluded.

RESULTS: Data were available from 79 patients (18M, age 11.2 ± 2.5 yrs, 18M and 25F prepubertal at presentation). Age at most recent assessment was 14.4 ± 2.5 yrs.

Height increased significantly from diagnosis (-0.50 ± 1.56 SD) to most recent assessment (-0.20 ± 1.28 SD, $p = 0.002$). Both measurements correlated strongly with initial T4, TSH ($p < 0.0001$ for each observation) and duration of symptoms ($p = 0.009$ and $p = 0.02$ respectively). Gain in height was unaffected by time to normalisation of TSH or T4.

BMI at diagnosis (0.72 ± 1.36 SD) and most recent BMI (0.64 ± 1.15 SD) were not significantly different. BMI at diagnosis was related to TSH and T4 at diagnosis ($p=0.001$ and $p = 0.006$ respectively) and duration of symptoms ($p<0.001$).

CONCLUSIONS: These data suggest that long term growth is affected by the severity of thyroid hormone deficiency at presentation and may not be fully restored despite prompt normalisation of T4. Although BMI at diagnosis correlated strongly with serum TSH, T4 and duration of symptoms, BMI did not change significantly despite restoration of TSH and T4 to the normal range. This may be because adverse eating behavior and patterns of exercise are established and difficult to reverse. Counseling at diagnosis should therefore include dietary and exercise advice.

P12

Improved growth during etanercept therapy in children with idiopathic juvenile arthritis: preliminary evidence that blockade of TNF augments growth independently of steroid withdrawal and improved nutrition

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Tumour necrosis factor (TNF) is an important inflammatory mediator in juvenile idiopathic arthritis (JIA). In vitro studies demonstrate inhibition of growth hormone signalling by TNF reversible by TNF blockade. We speculated that treatment with etanercept, a TNF antagonist, would accelerate growth in children with JIA, independent of the effects of steroid withdrawal or improved nutrition.

METHODS: Auxological data and details of systemic steroid therapy (SST) were analysed retrospectively 2 years following the introduction of etanercept therapy (ET) (0.4mg/kg twice weekly)

RESULTS: Data were available for 8 children (1M, median age 11.21 yrs, range 7.05 to 14.69) studied for 1.85 yrs (1.19 to 3.03). 2/8 patients were treated with SST at the start of ET, discontinued after 6 months. Height at the start of ET was -0.92 SD (-2.67 to 0.31) and BMI 0.32 SD (-0.70 to 5.76). Catch up growth (CUG) (gain in height greater than 0.5 SD) was observed in 5 / 8 patients (gain in height 0.76 SD, 0.50 to 1.46) and was greatest in children treated with SST (1.17 and 1.46 SD). 2 / 8 children grew steadily during ET (change in height -0.17 and 0.15 SD) and 1 / 8 patients was above average height but grew slowly (initial height 0.30 SD, change in height -0.29 SD). At most recent assessment height was -0.60 SD (-2.15 to 1.07) and BMI 0.04 SD (-0.63 to 3.97 SD).

CONCLUSIONS: CUG was greatest following withdrawal of SST but was also observed in children not treated with SST. The effect of improved nutrition on growth was also considered, however a trend for reduction in BMI SDS was observed, possibly reflecting increased physical activity.

Preliminary data collected from this small cohort of children suggest that TNF blockade may augment growth in children with JIA independent of the effects of SST withdrawal and improved nutrition.

P13

Correlating IGF-1 and IGFBP-3 with chronological age vs bone age in the evaluation of short stature

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AIM: To test the hypothesis that correlating serum IGF-1 and IGFBP-3 with bone age (BA) rather than chronological age (CA) improves their diagnostic value in detecting growth hormone deficiency (GHD).

METHOD: Retrospective casenote analysis of children with short stature attending a single centre who had BA, IGF-1, IGFBP-3 and GH provocation tests (Clonidine or Glucagon) as part of their evaluation. Puberty was assigned as per Tanner staging. BA was assessed using the Greulich and Pyle method. IGF-1 and IGFBP-3 results were classified as low or normal based on reference ranges for age and sex (cutoff -2 SDS). GHD was defined as peak GH level of <20 mU/l.

RESULTS: 64 case notes were analysed in total, age range: 3.3-16.75 years, 46 males:18 females, 44 prepubertal:20 pubertal, 44 not GHD: 20 GHD. There was no significant difference in correlating with CA for IGF-1(sensitivity 75%, specificity 41%) or IGFBP-3 (sensitivity 45%, specificity 73%) or with BA (IGF-1: sensitivity 55%, specificity 68%, IGFBP-3: sensitivity 35%, specificity 82%). The results were similar in both prepubertal and pubertal groups. However, the median age ratio (BA/CA) was significantly lower (i.e. the difference was greater) in the normal GH response group ($p=0.01$). By logistic regression analysis, a model using age corrected IGF-1 and IGFBP-3 and the ratio of BA to CA was a better predictor of GHD with area under Receiver Operating Characteristic (ROC) curve of 0.86 with ideal being 1.0 (complementary area- 0.15)

CONCLUSION: IGF-1 or IGFBP-3 alone or in combination has poor sensitivity and specificity in the evaluation of GHD and correlating these parameters with BA rather than CA does not improve their diagnostic value in both prepubertal and pubertal children. However, a model using age corrected IGF-1, IGFBP-3 and ratio of BA to CA is a better predictor of GH response. Further datasets are required to test this algorithm which can be used as a screening tool.

P14**Specialised & transition paediatric endocrine services in the United Kingdom and Ireland**

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A questionnaire on current specialist paediatric endocrine services (including transition) was sent to all BSPED consultant members. 69 questionnaires were received, of which 53 (20 from historical growth centres (HSHGHC) (Group 1), 8 from other teaching hospitals (Group 2) and 25 from DGHs (Group 3)) were eligible for analysis. 4694 patients are currently receiving GH in the UK: 3740 (80%) in Group 1 and 545 (12%) in Group 2.

58% of units (89% in Groups 1 and 2) provide transfer clinics: transition (N=22), adolescent (10), young adult (10), and adult (3). In 86% the paediatric and adult endocrinologist sit in the same room, and 56% are held in the paediatric unit (69% in Group 1). Clinic entry is based on final height (26%), age (49%), both (23%), and other (2%). Whilst 50% of units transfer all GH-treated patients, 46% do not transfer those non-GHI on retesting. 86% of units retest prior to transfer using ITT (N=27 (including 3 DGHs)), glucagon (22), arginine (4), clonidine (3) and other (5). Few additional tests recommended for GHI patients at follow-up are, however, performed at baseline.

Whilst 25% of units hold specialist clinics for GH-treated patients (45% of Group 1), apart from intersex (13) there are few clinics for non-GH treated patients. Only 3 units (all Group 1) have a specialist TS clinic, and only 10 (7 in Group 1) transfer patients to multidisciplinary adult TS clinics; the remainder are transferred to adult endocrinology (27), gynaecology (14), cardiology (5); none are discharged or referred back to the GP.

This questionnaire has confirmed more patients treated with GH than previous audits, and that many remain within historic growth centres. However, within the UK & Ireland specialist and transition services in paediatric endocrinology, both for GH- and non-GH-treated patients remain patchy, even where consensus guidelines exist.

P15**The impact of stretching and knee visibility on height measurement**

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BACKGROUND: The precise and accurate estimation of stature is an important part of an endocrine assessment. However there are a number of variations in practice. A study was performed to investigate the effects of stretching the child and removing knee-concealing clothing on the measurements obtained.

Design and METHODS: 178 patients attending morning and afternoon clinics were measured twice during their visit, before and after the consultation. The patients had a range of disorders and the mean interval between the two assessments was 42 minutes (SD 20 minutes). Each measurement was made with the patient either stretched or not and with the knees either visible or not. The methods used were determined by randomization according to a design which ensured balance of all combinations of conditions and orders. The statures were all made by the same experienced auxologist using a Harpenden stadiometer calibrated before each clinic. The data were analysed using a multilevel model.

RESULTS: The statures recorded when the patient was stretched were 0.53 cm larger (95% CI 0.43, 0.63). Measurements made with the patient stretched and with the knees not visible were the most precise (error SD = 0.22 cm) and least precise when stretched and knees visible (error SD = 0.41 cm). However, the null hypothesis that the error SD was the same for all conditions of measurement could not be rejected (P=0.13).

CONCLUSIONS: While further work is needed to make some results more precise, the effects of stretching or ensuring that the knees are visible when measuring stature do not appear to be substantial. This has important implication for those measuring children at school entry. However, stretching leads to a substantial bias, so it is essential to ensure a consistent policy if measurements are collected as part of the longitudinal assessment of growth.

P16**Exploring Psychosocial Aspects of Children, Adolescents and Families attending a Diabetes Clinic**

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INTRODUCTION: Diabetes is a chronic illness affecting more than 20,000 children in the UK. Compliance with diabetes regimens is often difficult and psychosocial factors are known to be highly relevant to this. We therefore offered screening to children and families attending the diabetes clinic for behavioural problems, depression, coping strategies and family stress.

METHODS: Children and adolescents attending our clinic aged from 7 to 15 years old and their families were invited to complete standardised questionnaires, stratified according to their age.

RESULTS: A total of 50 questionnaires were handed out. The response rate was 38% in children (aged 7-12) and 67% in adolescents (aged 12-15). Among the children and adolescents, the mean total internalising score, Birlson Depression scale score and Rutter Scales results (which are measures of coping abilities) were within the normal range. Our population also scored high in problem-focused coping. The overall scores achieved by the parents in the family resources and stress scale, however, were high with 'Pessimism' and 'Parent and family problems' sub-scales being the highest scores.

CONCLUSIONS: Both stressors and resources have been the focus of research in relation to how children and families adapt to chronic illness. Results of the screening conducted indicate that the scores of children and young person with diabetes attending this clinic who responded to the questionnaires are within the normal range. However the higher scores on the family resources and stress scale were indicative of greater distress in the parents, despite the children and adolescents apparently coping well.

P17

Survey of screening practices for coeliac disease in children with Type 1 Diabetes Mellitus

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The National Institute of Clinical Excellence (NICE) has recommended screening for coeliac disease (CD) at the time of diagnosis of Type 1 Diabetes Mellitus (T1DM) and three-yearly thereafter.

AIM: To find out the screening practices in the United Kingdom (UK) for CD in children with T1DM in light of these guidelines.

METHODS: Questionnaires were sent by post to all the Paediatric Diabetic Nurses in UK and electronically to all professional members of the British Society of Paediatric Endocrinology and Diabetes.

RESULTS: We sent questionnaires to 210 centres and response rate was 71% (149). Seven centres do not screen for CD (4.7%). The number of centres that screen at diagnosis is 113(79.6%). Ninety seven centres (68.3%) do annual screening, 27(19%) two-yearly, 17(12%) three-yearly and 19(13.4%) if clinically indicated.

Seventy five centres (53%) screen at diagnosis and annually, while 24(17%) screen at diagnosis and 2 yearly, and 15(10.6%) screen at diagnosis and 3 yearly. Three centres screen only two-yearly and 2 only three-yearly.

Out of 19627 children with T1DM, 598 had CD (prevalence 3.0%).

Data on time of diagnosis of CD was available on 432 children from 125 centres (84%). Of these, 17 patients (3.9%) were diagnosed with CD before the onset of T1DM, 57(13%) at diagnosis, 181(42%) were diagnosed within 2 years, 111(26%) between 3 and 5 years and 61(14%) between 6 and 12 years after diagnosis of T1DM.

Coeliac serology was used for screening in 97.2% and confirmation was by intestinal biopsy in 93.7% of the centres.

CONCLUSIONS: A majority of the centres follow the NICE guidelines at the time of diagnosis of T1DM, but the screening practices for CD vary thereafter. Our data shows that most of the CD patients were diagnosed within 2 years of diagnosis of T1DM. For effective coeliac screening, annual or two-yearly intervals could be considered instead of three-yearly interval.

P18

NICE guidelines on screening for hyperlipidaemia in children and young people with type I diabetes: time for a rethink?

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OBJECTIVES: Current NICE guidelines state that screening for hyperlipidaemia in children and young people with type I diabetes is no longer recommended. However, the American Diabetes Association recommends a selective screening programme. Neither guideline is based on robust evidence. Therefore, we present our experience in screening and evaluate the relative merits of our policy.

METHODS: A retrospective observational study of all children and young people with type I diabetes attending our clinics between January 2000 and March 2005. During this time, our policy was that all patients would be screened for hyperlipidaemia beginning two years after the diagnosis of diabetes and thereafter, annually. Abnormal results were repeated earlier.

RESULTS: 147 patients underwent 421 screening blood tests. The mean age at entering the study was 11.2 yrs (range 2.0 to 19.1). The mean duration of follow up was 3.3 yrs. 22 of our patients (15 percent) were identified as having persistent hyperlipidaemia. 21 of these had an HbA1C greater than 8 percent at the time of diagnosis of hyperlipidaemia. 13 of the 22 patients with hyperlipidaemia were considered to have significantly high enough lipids to warrant intervention. 8 had multifactorial hyperlipidaemia, 2 patients had type III hyperlipidaemia, 1 patient had familial hypercholesterolaemia, 1 patient had membranous glomerulonephritis and one patient had her care transferred before diagnosis. Only 2 of our patients required lipid-lowering agents. 17 of the 421 screening tests were required in order to diagnose patients needing intervention (4.04 percent of tests). Hence, 25 (95 percent CI 16, 40) screening tests were required to identify 1 case warranting intervention. At 25.3 pence per lipid test, the basic cost is only 6 pounds and 33 pence (95 percent CI 4.04, 10.12).

CONCLUSIONS: Screening was cost effective and identified clinically significant diagnoses which would have been missed had NICE guidelines been followed.

P19

Pilot study of the diurnal levels of salivary cortisol in pre-pubertal children with type I diabetes mellitus (T1DM)

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Psychological morbidity can cause changes in the HPA axis, which in turn may adversely affect glycaemic control, as chronic hypercortisolaemia may be associated with increased insulin resistance. We hypothesise that children with T1DM may have evidence of HPA axis resetting secondary to chronic stress.

AIM: This pilot study investigated diurnal cortisol levels using salivary cortisol, and psychological morbidity in pre-pubertal children with T1DM (group 1) and a control group (group 2),

METHOD: LREC approval and informed consent were obtained. 31 Pre-pubertal children with T1DM and 34 control children agreed to provide saliva samples (T1 am, T2 lunch, T3 tea, T4 bed) for cortisol analysis over 3 days. Their main carer was asked to complete the Strengths and Difficulties Questionnaire and General Health Questionnaire, which screen for psychological symptoms in the child and carer respectively. Information about frequency of hypoglycaemic episodes, HbA1c, and BMI were recorded at the time of sample collection.

RESULTS: Group 1: N= 18. Mean(SD) age, BMI, duration of diabetes, HbA1c were: 8.6(2.2) years, 18.53(3), 3.67(1.8) years, 8.01(0.7)% respectively. Mean(SD) cortisol: T1 6.4(4.7), T2 1.7(2.6), T3 1.8(3.1), T4 0.3(0.2)nanograms per millilitre. There were no recorded episodes of severe hypoglycaemia.

Group 2: N=22. Mean(SD) age, BMI were 8.9(2.3)years, 16.8(2.2) respectively. Mean(SD) cortisol T1 7.8(5.3), T2 2.3(1.8), T3 1.6(1.6), T4 0.6(0.5)nanograms per millilitre

The incidence of psychological morbidity was similar in both groups.

This pilot study has shown that saliva samples of cortisol are an acceptable, non-invasive procedure but with a 61% return rate. There was no evidence of significant change of cortisol diurnal rhythm. There may have been a recruitment bias in those who took part and returned samples.

Further studies of those with documented psychological symptoms are indicated to fully investigate whether there is any association between psychological morbidity, changes in the HPA axis and poor glycaemic control.

P20

Psychological and fitness characteristics of obese and morbidly obese adolescents

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Introduction. We describe the baseline psychological and fitness characteristics of participants in a randomised controlled study undertaken to evaluate the effects of a supervised exercise therapy intervention upon mental health outcomes in obese adolescents.

METHODS: Eighty-one adolescents aged between 11-16 years participated in the study. They were recruited from Hospital referrals and community advertisement. At entry to the study psychological measurements of self-perceptions, physical self-perceptions, depression & affect were made. Physical activity, fitness and BMI were also measured. The study was approved by the South Sheffield Clinical Ethics Committee.

Results. At entry to the study the mean BMI SDS scores for boys and girls were 3.16 (\pm 0.33) and 3.32 (\pm 0.52) respectively. 96.3% of sample had BMI scores above the 99.6th (+2.6 SDS) percentile. 82.7% were Caucasian. Twenty-five (30.1%) participants had a Children's Depression Inventory (CDI) score \geq 13, consistent with clinically significant depressive symptoms. Furthermore, 26.9% of participant indicated that in the past two weeks they have had 'thoughts of killing themselves but would not do it' or 'wanted to kill themselves'. Boys had significantly higher sport/athletic competence, strength competence and positive affect scores with lower resting heart rate scores and higher aerobic fitness and physical activity scores than girls. Morbidly obese (BMI $>$ 3.5 SDS) participants (n=18) reported significantly lower global self-worth and higher depression scores than obese participants and displayed significantly poorer aerobic fitness than the obese group. There were no differences between hospital referred participants or those recruited by advertisement.

CONCLUSIONS: As obesity rates are rapidly increasing it is important that interventions are designed to address psychological problems and issues relating to exercise rather than concentrating solely on weight loss.

P21

Paediatric Lifestyle Clinic - a multidisciplinary, multi-agency approach to managing teenage obesity

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OBJECTIVES: An audit of the children attending the Paediatric Dietitians in our hospital for weight reducing advice revealed that 80% were falling within the IOTF criteria for obesity. Many of these children also had concurrent social problems, so were having psychology input and some had medical problems directly related to their obesity. Very few undertook any physical activity at all. It was decided to try to streamline their needs in a multidisciplinary 'one-stop' clinic.

METHODS: Ten obese (IOTF criteria) children were invited to attend the 'Paediatric Lifestyle Clinic' programme, six of which ultimately agreed to take part (3 girls and 3 boys, aged 11-15). This consisted of an initial medical assessment, followed by 10 weekly, two-hour sessions held at the local leisure centre. The first hour involved education followed immediately by an hour's exercise session. The participants were reviewed in clinic at 1, 3 and 6 months after the 10 week programme. At each clinic visit, weight, height, waist circumference, body mass index, blood pressure and pubertal status were recorded. Biochemical markers were checked at the beginning and the end of the full programme.

RESULTS: 5/6 children completed the programme. At the start, 1/6 had impaired glucose tolerance, 3/6 had abnormal liver functions and 1/6 had abnormal lipids. These all normalised on repeat testing. 3/6 showed improvements in their BMI, which was sustained at 6 months.

CONCLUSIONS: Empowering morbidly obese children to manage their obesity using a multi-agency approach does appear to have some success, which is sustained longer term.

P22**Orlistat may aid weight management in treatment resistant adolescents**

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AIM: To examine whether the addition of Orlistat to conventional lifestyle modification therapy can improve body mass in obese adolescents proving resistant to simple changes in diet and exercise.

PATIENTS: 18 cases (9 males, age 9 to 18 years), 6 with learning difficulties (LD) +/- syndromic obesity, 12 of normal educational capabilities (2 with Type II diabetes, 1 with MC4R gene mutation). 16/18 gained weight prior to commencing orlistat. All had previously attended the 'Care of Childhood Obesity Clinic' (4-68 months), except one subject with type II diabetes who started therapy at diagnosis. Mean weight of subjects prior to commencing Orlistat was 110.3 kg (range 81.4-149.5kg)

METHOD: All patients received 120 milligrams Orlistat orally, three times a day with meals: (fat soluble vitamin supplementation at bedtime) and instructions to phone MAP helpline before starting medication.

RESULTS: 11 subjects decreased weight; range 0.1kg to 11.6kg (mean 3.34 kg, median 2.1kg) over a follow-up period ranging from 2 to 12 months. Four subjects increased weight after initiating Orlistat during a 2 to 7 month follow-up. 3 subjects were lost to follow up. In the 6 subjects with LD +/- syndromic obesity, 5 lost weight (range 1.2kg to 3.2kg, mean 2.34kg, over a follow-up period of 2 to 7 months). One subject with LD was lost to follow up. Analysis of the mean change in slope before and after orlistat therapy of BMI (corrected for Child Growth Foundation, median of age and sex) was -2.792 (SE 2.253) units per year but this did not reach statistical significance.

CONCLUSION: Orlistat now has a licence for use in adolescents with obesity. We used it as an adjunct to lifestyle modification in patients resistant to standard care. Initial results suggest this may prove useful in some adolescents and may be beneficial in children with LD in whom basic lifestyle modification can prove difficult to implement.

P23**Sex and Ethnic Differences in Glucose Homeostasis and Insulin Resistance in Obese Children**

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AIM: To determine the prevalence of insulin resistance (IR) and glucose intolerance in obese children and to assess sex and ethnic differences.

METHODS: 109 obese children (mean BMI SDS 6); Female: 72 (British white [BW] 58, British Asian [BA] 14); Male: 37 (BW 25, BA 12), median age 13.4 years (3-19) underwent an oral glucose tolerance test with results categorised by WHO criteria: impaired fasting glucose (IFG), impaired glucose tolerance (IGT), Type 2 DM. Fasting hyperinsulinaemia (FH) and 120 minute hyperinsulinaemia (HI) were defined above 26 and 95 mIU/L, respectively (in-house reference range). HOMAIR was calculated ($N < 2.5$) and acanthosis nigricans (AN) recorded.

RESULTS: There were no significant differences in BMI SDS or age, between sex or ethnic groups.

Abnormalities in glucose homeostasis were observed in 23%: IFG 4%, IGT 13%, T2DM 6%.

Insulin resistance was observed in the majority: HOMA IR > 2.5 78%, FH 42%, HI 38% and AN 40%. AN contributed to the variance of fasting insulin (FI, mIU/L), $r^2 = 0.14$, $p = 0.005$.

All subjects with type 2 DM were female. HOMA IR was raised in 86% females compared with 70% males, $p = 0.06$. HI was present in 62% females compared with 38% males, $p = 0.04$. Within the BA group, mean FI was higher in females (42) than males (22), $p = 0.02$.

Obese BA children comprised 23% of this cohort (BA comprise 3% NW UK population). AN was present in 62% BA compared with 34% WB, likelihood ratio 10.1, $p = 0.006$. Mean FI was higher in BA (40) than in BW (28), $p = 0.06$. Within the female group, HOMA was higher in BA than BW, $p = 0.02$.

CONCLUSION: IR and glucose intolerance are significant problems in obese children. Females are more IR than males. BA children are more IR than BW. BA females are the most IR group.

P24**Maturity Onset Diabetes of the Young in UK Asian families**

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Type 2 diabetes (T2DM) has emerged in youth, disproportionately affecting ethnic minorities. Maturity Onset Diabetes of the Young (MODY) has been reported in exclusively white UK children. Correct diagnosis is essential as these conditions differ in prognosis and management. We report the first UK Asian children with MODY, highlighting differences from T2DM.

Child 1 is a slim (BMI SDS -0.14) female of Indian descent without acanthosis nigricans (AN). She presented aged 12 years with polydipsia and polyuria (HbA1c 8.6%). Hypoglycaemia with insulin and sulphonylurea prompted cessation of treatment. The dominant family history of diabetes, and elevated HbA1c suggested the diagnosis of HNF1A- MODY. Testing detected a heterozygous P291fsinsC

mutation co-segregating with diabetes in the family.

Child 2 is a female of Indian descent (BMI SDS +1.6) without AN. She presented aged 8 years with asymptomatic hyperglycaemia. Oral glucose tolerance test (OGTT) showed diabetes (fasting glucose 6.3mmol/l, 2 hour 16.6mmol/l, HbA1c 8.6%). She responded to Gliclazide, with improved glucose results. The dominant family history of diabetes and glycosuria, suggested HNF1A-MODY. Testing detected a heterozygous P291fsinsC mutation co-segregating with diabetes in the family.

Child 3 is a slim (BMI SDS +0.44) male of Pakistani descent without AN. He presented aged 14 years with asymptomatic hyperglycaemia. OGTT showed impaired glucose tolerance (fasting glucose 5.8mmol/l, 2 hour 8.4mmol/l, HbA1c 6.8%). He responded to diet alone. The family history of diabetes, including permanent neonatal diabetes, suggested Glucokinase MODY. Direct sequencing of the GCK gene detected a heterozygous R397L mutation.

MODY is seen in Asian families. Absence of obesity, and absence of acanthosis nigricans, with apparent dominant family history of diabetes, suggest MODY; though family history does not discriminate between MODY and T2DM. Correct diagnosis will alter management as the first pharmacological agents in HNF1A-MODY are sulphonylureas, but in T2DM it is Metformin.

P25

Performance of a Risk Score in Predicting Abnormal Glucose Tolerance in Children

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BACKGROUND: Increased awareness about type 2 diabetes in childhood has resulted in a steady increase in the number of children referred for assessment of glucose tolerance. We have previously developed a risk score for the assessment of children at high and low risk of an abnormal oral glucose tolerance test (OGTT).

AIMS: The objective of this audit was to retrospectively review the performance of the risk score in predicting abnormal glucose tolerance in our population.

METHODS: The audit was undertaken by case-note review and retrospective risk-scoring of all children who had undergone an OGTT during a 19-month period.

RESULTS: Of 53 OGTTs undertaken during the time period, 48 were normal and 5 (9.4%) were abnormal. All 5 children with abnormal results had impaired glucose tolerance and were obese. Two were White UK, 2 Pakistani and 1 African-Caribbean. Three had a family history of diabetes. Two were classified high risk and 3 low risk on the basis of the risk score, giving the score a positive predictive value of only 11% (sensitivity 40%, specificity 67%). Children with positive OGTTs but low risk scores included an obese African-Caribbean female with acanthosis but no family history, an obese white male with a strong family history and an obese white male with suspected metabolic syndrome who was subsequently found to have non-alcoholic steatohepatitis.

CONCLUSIONS: The risk score failed to correctly identify over half of the children with abnormal glucose tolerance. Clinical judgement should be used to determine which children with a low risk score warrant glucose tolerance testing. As the population of children referred for testing becomes more heterogeneous with increased awareness of the other features of metabolic syndrome in childhood, we now plan further modification of the risk score before it can be used as a clinical tool to select children for screening.

P26

Serum leptin levels and severity of obesity in 7 to 11-years-old Children

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INTRODUCTION: Prevalence of childhood obesity is showing a rise in the developing countries. As leptin may have a role in the pathogenesis of childhood obesity, we aimed to determine the levels of serum leptin in association with severity of obesity in a sample of Iranian obese children.

METHODS: 13089 children from all the primary schools of a region of Tehran were screened for obesity. Anthropometric measurements were done and blood samples (for serum leptin levels, lipid profile, insulin, and fasting blood sugar) were collected from 495 enrolled obese children. Participants were divided to obese and over-weight groups based on the International Obesity Task-Force criteria. Multivariate linear regression analysis was used to investigate the impact of different biochemical variables on the severity of obesity. The study was approved by the Ethics Committee of Tehran University of Medical Science.

RESULTS: Serum leptin levels (mean \pm standard deviations 10.93 \pm 8.19, range 0.5 to 50.1 nanogram per millilitr) were higher in obese children than overweight ones ($P < 0.001$). There were significant correlations between body mass index (BMI) and serum leptin levels, child age, triglyceride levels and blood pressure. In multivariate regression analysis, leptin, age, and cholesterol levels were determined as independent variables that could predict 78.1% of variations of BMI. 22 participants had undetectable levels of serum leptin, of whom 18 were in the obese group.

CONCLUSION: Among Iranian obese children, leptin levels are higher in children with more severe obesity. This may affirm a role for this hormone in the severity of childhood obesity.

P27**Thyroidectomy as treatment for Graves' Disease: complications and outcomes**

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Thyroidectomy is the definitive treatment of choice in patients with Graves' Disease (GD) in whom close contact with young children is unavoidable. Surgery is offered for poor compliance, cosmetic reasons or patient preference following relapse.

In this centre, endocrinologists (MD, JCB) work closely with experienced thyroid and paediatric surgeons (AW, MJ) who operate together. Prior to surgery, propranolol and Lugol's Iodide are administered for 2 weeks to ensure beta blockade, inhibit thyroid hormone (TH) secretion and reduce thyroid vascularity. The patient is confirmed euthyroid. Postoperatively, serum calcium is assessed at 6 - 8 hourly intervals. Propranolol is weaned over 48 hours and TH replacement therapy commenced on the 5th postoperative day.

AIM: To assess complications and control of serum TH following thyroidectomy.

METHODS: Retrospective case note review.

RESULTS: 11 / 50 children (3 M, 8F) with GD proceeded to thyroidectomy. Median age of diagnosis was 11.8 yrs (3.6-14.0) and of thyroidectomy 13.7 yrs (10.3-16.2), GD being present for 3.0 yrs (2.0-8.1). 9 / 11 patients had a family history of autoimmune thyroid disease (5 GD) and 4 / 5 relatives with GD had undergone thyroidectomy.

One patient bled postoperatively requiring ligation. Transient hypocalcaemia was documented in 4 / 11 patients. One patient required treatment, continued for 10 days. There were no episodes of permanent hypocalcaemia, transient or permanent recurrent laryngeal nerve damage.

Biochemical evidence of poor compliance (elevated TSH and low / normal fT4/Total T4 on an appropriate dose of T4) was observed in 4 patients at 1 month, and in 3 patients at 6 months. One patient, with undetectable fT4 at 1 month, was lost to follow up.

CONCLUSIONS: To date, our experience suggests surgery is safe and no permanent complications have occurred. However, postoperatively compliance remains problematic.

P28**Management of Childhood Thyrotoxicosis: 'Dose Titration' versus 'Block and Replace' Regimes**

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Childhood thyrotoxicosis (CT) is rare and optimal treatment remains controversial. In this study we report outcomes of 'dose titration' (DT) using thionamies alone and 'block and replace' (BR) regimes using thionamides and thyroxine in combination.

METHODS: Retrospective case note review of 50 patients with CT. 5 patients with coexisting pathology were excluded. Outcome variables were: (1) time to normalisation of thyroid function (TF), (2) prevalence of relapses and (3) changes in height and body mass index (BMI).

RESULTS: 45 patients (9M, age 12.0 ± 3.5 yrs, 5 M and 13 F prepubertal) were followed for 2.9 yrs (0.6 to 9.1). 21 patients were treated by DT and 24 by BR.

Time to normalisation of TF was longer on DT (8.00 ± 7.78 weeks vs 5.10 ± 4.00), though not statistically significant. Prevalence of relapses (9 (37.5%) BR vs 9 (43%) DT) did not differ between treatment regimes.

Height at presentation (0.80 ± 1.17 SD) was greater than most recent height (0.49 ± 1.06 SD, $p < 0.009$) but did not differ between regimes except in patients followed for 3 yrs (DT, $n=7$, BR, $n=12$) when height SDS was significantly greater in patients treated by DT (1.24 ± 0.89 SD vs 0.24 ± 1.01 SD, $p=0.03$).

Weight gain was significant during treatment (BMI at presentation: -0.28 ± 1.11 SD vs most recent BMI: 0.38 ± 0.95 SD, $p < 0.0001$) and was greatest in patients treated by DT (gain in BMI SDS 0.67 ± 0.93 SD vs 0.08 ± 0.91 SD, $p = 0.04$).

CONCLUSIONS: Our data suggest DT enables optimal growth although weight gain may also be greater. Superiority of either regime for control of TF was not demonstrated. The national prospective study currently in progress should enable more definitive conclusions to be drawn.

P29**Clinically euthyroid autoimmune thyroiditis - how frequently should we be monitoring thyroid function?**

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Autoimmune thyroiditis is the commonest cause of paediatric goitre and acquired thyroid dysfunction in the Western World. The clinical features of thyroid disease are well known but may be subtle early in the disease process. There is a paucity of evidence-based recommendations for the frequency with which thyroid function tests (TFTs) should be performed in clinically euthyroid children with positive thyroid antibodies. Several sources suggest 'regular follow up' but none are specific.

We report 3 girls aged 9 to 12 years presenting to our unit clinically euthyroid, with goitres and strongly positive thyroid antibodies. Case 1 presented with fatigue, weight gain and goitre and changed from mild biochemical hyperthyroidism (TSH 0.4 milliunits per litre, fT4 14.3 picomols per litre) to overt hypothyroidism (TSH 82.8, fT4 4.0) in just 2 weeks. She remained hypothyroid on subsequent follow-up and was treated with thyroxine. Case 2 presented with one month's history of unexplained weight loss, goitre and was found to be

biochemically hyperthyroid (TSH 0.02, fT4 35). After 2 weeks her TFTs normalised yet 6 weeks later she developed increasing thyromegaly, clinical and biochemical hypothyroidism (TSH 193, fT4 less than 5.1). She is now on thyroxine. Case 3 presented with goitre but was otherwise asymptomatic. Her TSH was initially elevated (9.3) and fT4 normal. Her TFTs normalised within 2 months. 5 months later she became biochemically hyperthyroid (TSH 0.01, fT4 22.4) but remained clinically euthyroid. 2 months following this she became biochemically hypothyroid (TSH 182, fT4 less than 5.1) but her TFTs returned to normal within 2 months without treatment. In conclusion, autoimmune thyroiditis can result in a variety of rapidly changing serum TFTs. We suggest frequent monitoring of children with positive thyroid antibodies to decide on the correct line of management. The frequency of biochemical monitoring is an area for further research.

P30

The value of the TRH test in pediatric practice - an audit

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OBJECTIVE: Assessing the value of the TRH test in pediatric endocrine practice.

Design: Retrospective analysis of all pituitary function tests performed in the Royal Hospital for Sick Children, Edinburgh (1/7/99 to 28/2/05).

Subjects: 135 subjects (one month -18.8 years) undergoing pituitary function testing between 1/7/99 - 28/2/05 were studied. 92 controls and the 43 patients were evaluated.

Measurements: FT4, baseline TSH, TSH response to TRH at 20 and 60 minutes and peak growth hormone response to insulin/hypoglycaemia or clonidine. Principal diagnosis and treatment data were collected from the case-notes.

RESULTS: The TSH response was not sex related in either group. In the patient group, but not the controls, a significant negative correlation was found between TSH response and age ($p < 0.05$). There was no correlation between TSH response and pubertal stage in either group. Baseline TSH was correlated with FT4 in the patient group, but not in the controls. In the patient group 9.5% had a slow-rising TSH response (TSH 60 > TSH 20) and in the controls 3.5%. All 4 controls with a low FT4 (8-9 picomoles per liter) had a normal TSH response. Baseline TSH and FT4 were sufficient for diagnosis, management and follow up decisions. The TRH test did not give additional information and was sometimes confusing.

CONCLUSION: In this patient group the TRH test did not add any information regarding diagnosis, management and follow up compared to baseline TSH and FT4. A low baseline FT4 is poorly diagnostic of an abnormal TSH response. Dropping the TRH test in pediatric practice will save side-effects, time and costs.

P31

Audit On Initial Management Of Congenital Hypothyroidism In The United Kingdom

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BACKGROUND: Optimal management of Congenital Hypothyroidism (CH), which includes early diagnosis and prompt treatment is crucial for optimal neurodevelopment.

OBJECTIVE: To identify whether the practice of paediatricians in the initial management of CH were in adherence to standards published by the UK Newborn Screening Programme Centre in 2005.

METHODS: A standard questionnaire survey of paediatricians involved in the initial management of CH in the United Kingdom using the British Society for Paediatric Endocrinology and Diabetes as mode of contact.

RESULTS: 41 paediatricians from 34 / 44 Strategic Health Authorities (SHA)/ Health Boards (HB) responded to the questionnaire. 56% were from endocrinologists and 44% from generalists. There was a wide variation of opinion on the level at which a screening blood spot thyroid stimulating hormone (TSH) would stimulate referral to the paediatrician (>5 mu/L to >20 mu/L), the subsequent investigations undertaken and initial starting dose of replacement thyroxine. 80% felt that the time lapse between the screening laboratory's referral to the clinician and commencement of treatment was within 2 working days and 85% of respondents were able to treat infants within 21 days of age. 65% of respondents felt that patients with CH needed shared care with a paediatric endocrinologist.

CONCLUSIONS:

1. There is a wide variation in the criterion used for referral following confirmation of an elevated blood spot TSH, the investigations undertaken to confirm the diagnosis, the initial replacement dose of thyroxine and follow up in the first 6 months after birth
2. 66% of paediatricians would like infants with CH to have shared care with a tertiary endocrinologist and this will need to be addressed in our model of care for CH patients.
3. There is a need for national consensus guidelines for standardisation of both laboratory protocols for CH screening and the care of infants identified with CH.

P32**Combined Ultrasound and Isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning**

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Thyroid imaging in neonates with TSH elevation is helpful in confirming the diagnosis of congenital hypothyroidism, and establishing the aetiology.

OBJECTIVE: To investigate neonates with TSH elevation using ultrasound and isotope scanning, and thus determine the strengths and weaknesses of each.

Design: Parents of babies with raised TSH levels on screening were invited to participate. Sick and extremely premature neonates were excluded. Ultrasonography was performed using an ACUSON 128XP 10 system. Measurements were performed using a linear 7.5 MHz probe and volumes calculated. Isotope scanning was performed with a pinhole collimator after an injection of intravenous pertechnetate. Thyroglobulin was measured on neonatal blood spots (Delfia assay).

RESULTS: Forty children (29 female) underwent dual scanning at a median age of 17days (range 12days-15months). Scans were concordant in 34 infants. However, six had discordant scans with no uptake on isotope scanning but visualisation of thyroid tissue on ultrasound. This was attributed to TSH suppression from thyroxine (n=3); maternal blocking antibodies (n=1); cystic degeneration of the thyroid (n=1). A TSH receptor defect was postulated in the remaining infant. All six had detectable thyroglobulin levels median 25.6 nanograms per millilitre (range 2.1-98). The agreed final diagnosis was agenesis in 11, ectopia in 12, hypoplasia in 8, dysmorphogenesis in 5, transient hyperthyrotropinaemia in 1 and uncertain status with glandin situ in 3 (of which 1 had transient hypothyroidism).

CONCLUSIONS: While isotope scanning was superior in detecting ectopic tissue, ultrasound detected tissue not visualised on isotope scanning. Ultrasound can show abnormalities of volume and morphology, which cannot be fully appreciated on 2-dimensional isotope scans. We would advocate dual scanning as each modality provides different information. A TSH level should be measured on the same day to accurately interpret the scan results. Thyroglobulin is useful to determine the presence of thyroid tissue with discordant scan results.

P33**Presence of an ectopic posterior pituitary gland is associated with a smaller anterior pituitary gland, interrupted pituitary stalk and persisting growth hormone deficiency (GHD) into adulthood**

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AIM: The aim was to compare pituitary morphology and hormonal data at initial assessment (baseline) and at end of growth (retest) in GHD subjects with an ectopic posterior pituitary gland (EPP) versus a normally sited posterior pituitary gland (NPP).

METHOD: 20 patients diagnosed with GHD and an EPP on MRI and 17 patients who were GHD but had a NPP were identified from the Manchester growth clinic database. In these 2 groups data were compared as follows: hormonal data (determined by pituitary stimulation) collected at baseline and at retest, MRI morphology (site and size of pituitary gland and appearance of stalk) and demographic characteristics.

RESULTS: In the EPP v NPP group: age at presentation was lower (4 v 12 years, $p < 0.001$), anterior pituitary height was less (4 v 3mm, $p = 0.08$) and prevalence of an interrupted pituitary stalk was greater (75 v 12%, $p < 0.001$). No difference existed in prevalence of multiple pituitary hormonal deficiencies (MPHD) between the groups (25 v 18%) or in peak stimulated hormone levels at baseline, however 100% were GHD. However at retest compared to baseline: GH levels were higher in both groups but this was less apparent in the EPP group (EPP GH mean difference 3 milli-units per litre [95% CI -0.5 to 7], $p = 0.07$ and NPP GH mean difference 19 milli-units per litre [6 to 32], $p = 0.006$ and comparison by ANCOVA, $p = 0.03$). Thus at retest, prevalence of persisting GHD was greater in the EPP compared to NPP group (89% v 59%, $p = 0.04$). No difference in other hormone levels existed at retest.

CONCLUSIONS: The presence of an EPP is associated with a smaller anterior pituitary gland, interrupted pituitary stalk, and at retest is not invariably associated with abnormal peak stimulated GH levels.

P34**Risk for multiple hormone deficiency in patients with an ectopic posterior pituitary gland is associated with antenatal factors, history of admission to NICU and size of pituitary gland**

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AIM: The aim of this study was to identify risk factors for developing multiple pituitary hormone deficiency (MPHD) compared to isolated growth hormone deficiency (IGHD) in patients with an EPP.

METHOD: Between 1996 and 2004, 65 patients were diagnosed as having an EPP by MRI scan. The site (hypothalamic v stalk) and

surface area ($\text{Pi} \times \text{maximum diameter}/2 \times \text{maximum height}/2$, mm^2) of the EPP was recorded by a radiologist. The relationship between these data and demographic/clinical characteristics were compared in patients with IGHD and MPHD, as determined by pituitary stimulation testing.

RESULTS: In MPHD ($n=27$) compared to IGHD ($n=38$) patients: age at 1st referral was less ($0.8 [0.1-6] \text{ v } 4 [0.1-11]$ years, $p=0.001$), major incidents during pregnancy were increased ($52 \text{ v } 21\%$, $p=0.01$), as were admissions to NICU ($61 \text{ v } 24\%$, $p=0.02$) and history of traumatic delivery ($41 \text{ v } 16\%$, $p=0.02$). Prevalence of MPHD was greater in subjects with a hypothalamic compared to stalk located EPP ($48 \text{ v } 9\%$, $p=0.03$). EPP surface area was reduced in the MPHD group ($15 \text{ v } 24\text{mm}^2$, $p=0.03$ adjusted for age). For the lowest tertile of EPP area compared to the other tertiles, the prevalence of hypothalamic compared to stalk site was greater ($41 \text{ v } 0\%$, $\text{chi}^2=11.4$ $p=0.003$) and a history of admission to neonatal intensive care (NICU) was non-significantly increased ($45 \text{ v } 24\%$, $\text{chi}^2=2.8$ $p=0.1$).

CONCLUSION: These data suggest that pre-natal factors may be relevant to the pathogenesis of ectopic posterior pituitary gland and aid identification of subjects at high risk of multiple pituitary hormone deficiency.

P35

The impact of endocrinopathies on length of gestation

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INTRODUCTION: The timing of parturition in many species is linked to a late gestational increase in corticosteroid production from the foetal adrenal gland. We hypothesised that gestational age would therefore be extended in our patients with congenital adrenal hyperplasia.

METHODS: Information on gestational age was collected on patients attending our regional unit. We analysed gestational age in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (born 1978-2004, $n=42$), patients with secondary hypoadrenalism (born 1981-2004, $n=31$), patients with congenital hypothyroidism (born 1982-2003, $n=42$) and a control group of short children without a recognised endocrinopathy (born 1973-2003, $n=288$). Each group was compared with national (2002-3) and regional (2003-4) data (Hospital Episode Statistics). Term delivery was defined as delivery between 37 and 41 completed weeks. Data was analysed using chi-squared.

RESULTS: National statistics over several years demonstrate a frequency of 5% for deliveries beyond 41 weeks. In our region (2003-4) the frequency was 6.6% (NS). In the CAH group the frequency of deliveries beyond 41 weeks was 19% ($p<0.001$) and in patients with secondary hypoadrenalism the figure was 10% ($p=0.02$ compared with regional data). 14.5% of patients with congenital hypothyroidism were born post-term ($p=0.002$). The proportion of short children without a recognised endocrinopathy born post-term was comparable to National and Regional data at 5.9% ($p=0.2$).

CONCLUSIONS: Impaired cortisol production in CAH appears to prolong gestation. Patients with secondary hypoadrenalism are also more likely to be born post-term although this may be linked to other hormone deficiencies or CNS dysfunction.

P36

DAX-1 gene mutations - uncertainties resolved

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Mutations in the DAX-1 gene are well described in patients with adrenal hypoplasia congenita (AHC) and hypogonadotropic hypogonadism but can be a useful tool in the elucidation of unusual or difficult cases of adrenal insufficiency. As the clinical presentation of congenital adrenal hyperplasia and AHC can be clinically identical, diagnosis in the neonate often depends on the levels of 17-hydroxyprogesterone (17-OHP). If these are unavailable or non-diagnostic, gene analysis can be important. We present three patients from two unrelated families in whom genetic evaluation both corrected misdiagnoses and also significantly altered long-term clinical management and genetic counselling.

In the first family, a male infant presented with a salt-losing crisis at 3 weeks of age and was erroneously diagnosed with 21-hydroxylase (21-OH) deficiency. DNA analysis of the 21-OH gene was normal, but DAX-1 mutation analysis revealed a single base pair G deletion in codon 183 resulting in a premature stop codon at codon 263. They have subsequently had a second son without the mutation.

In the second family, DAX-1 mutation analysis was carried out on a mother who had lost two sons in infancy with adrenal crises of undetermined aetiology thirty years previously. Her daughter was considering starting a family so the cases were revisited. Inspection of the boys' medical records revealed post-mortem confirmation of adrenal hypoplasia in one and aplasia in another. Analysis of the mother's DNA revealed a C to G nucleotide substitution at position 458 causing a stop codon at codon 153.

These 2 families illustrate the need for clinicians to be aware of the possibilities of DAX-1 gene mutations in male patients presenting with hypoadrenalism both in the neonatal period and beyond. It is important to make the diagnosis not only for the patient, but also in order to assess accurately the risks to other family members.

P37**Flattened Salivary Cortisol circadian rhythm in Survivors of Leukaemia Bone Marrow Transplantation (BMT)**

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AIM: To investigate the hypothalamic-pituitary-adrenal (HPA) axis in prepubertal survivors of leukaemia as chronic stress in adults causes HPA axis resetting with evening hyper-cortisolemia.

METHODS: 88 subjects fulfilling the criteria of >1year post treatment for leukaemia, >6 months off steroids, prepubertal, age 5-12years were recruited. Group1 BMT(n= 26), Group2 Chemotherapy(n=30) and Group3 Controls(n= 32). Ethical approval and informed consent were obtained. Salivary cortisol levels were obtained for 3 consecutive days from awakening (T1), 30 minutes post-awakening (T2), before lunch (T3), tea (T4) and bedtime (T5). HPA axis feedback was assessed by overnight dexamethasone suppression test with salivary cortisol the morning before (T6) and after 0.5mg oral dexamethasone on awakening (T7) and before tea (T8). Statistical analysis was by non-parametric tests.

RESULTS: 72 percentage of salivary samples were returned. Median(range) cortisol levels in nanogrammes per millilitre were: Group1 T1 2.34(0.58-18.63), T2 5.615(0.52-21.34), T3 1.07(0.1-21.07), T4 0.9(0.12-5.7) and T5 0.24(0.12-0.87), Group2 T1 5.07(0.84-17.9), T2 7.21(0.97-15.9), T3 1.59(0.2-8), T4 1.07(0.2-4.94), T5 0.29(0.1-3.6); group3 T1 3.81(1.03-13.4), T2 6.47(0.54-23.7), T3 1.81(0.2-6.56), T4 1.34(0.2-6.9), T5 0.38(0.15-2.4). Cortisol levels were therefore lower overall, with reduced awakening rise (T1-T2) in Group1 vs Group2 and 3 (0.25 vs 2.19 and 2.5) although this did not reach statistical significance. Difference in the fall between T1 and T5 was also smaller in Group1 vs Group2 and 3 (1.72 vs 4.63 and 3.03), due to a lower awakening (T1) value. More patients in Group1 and Group2 were suppressed at T6 post-dexamethasone (73 and 75 vs 59percent) and had longer suppression at T8 than group3 (56 and 59 vs 35percent). **CONCLUSION:** The BMT group show a clear trend to lower salivary cortisol levels, reduced awakening response and overall lack of variability. However this did not reach statistical significance due to insufficient numbers in this study, but warrants further investigation to identify its clinical relevance.

P38**Factors contributing to successful semen cryopreservation process in minors with cancer: A re-audit**

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OBJECTIVES: We sought to optimise the process of informed consent and successful semen cryopreservation in adolescent minors by re-auditing factors which had compromised success in a previous audit of practice.

METHODS: We compared offer of sperm banking, puberty and Gillick assessments, endocrine biochemistry, disease, gonadotoxicity risks and uptake/ outcome of sperm banking between two cohorts of adolescent males (12-18 years) presenting with new or relapsed cancer in two periods between January 1999 and December 2002 (Audit 1) and January 2003 to April 2005 (Audit 2). The proportions of patients in the two audits were compared by the chi square statistic.

RESULTS: 61 (median age 15.1 years) and 35 (median age 14.8 years) patients were studied in audits 1 and 2 respectively. Sperm banking was offered in a significantly larger proportion of patients in audit 2 (86 vs 60%; p 0.012). Uptake was similar in both audits (73 and 69%) suggesting ethical implementation of an informed consent process. There was improvement in the documentation of endocrine biochemistry (88 vs 67%; p 0.057). The overall rates of pubertal and Gillick competence assessment were similar in the two audits. In audit 2 puberty assessment by the endocrinology team was requested in only 31% of all cases but in 8/9 (89%) of those under 16. Where puberty was assessed this was more likely to be done by an endocrinology (75%) professional. There was a tendency to avoid the younger and less virilised children as in the previous audit. A larger proportion of patients failed to provide a suitable sample in audit 2 (54 vs 32%, p 0.38), possibly due to higher proportion of patients in a higher gonadotoxic risk category (Hodgkins) rather than age.

CONCLUSIONS: Despite improved opportunity, prioritisation of high risk groups and better endocrine biochemistry assessment the rates of acceptance, puberty assessments and competency assessments were similar. Younger patients should be prioritised for pubertal assessment, age appropriate and risk-based counselling by dedicated endocrine professionals.

P39**McCune Albright Syndrome - A case of early and severe polyendocrinopathy**

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McCune-Albright syndrome in its classic form consists of at least 2 features of the triad of polyostotic fibrous dysplasia, cafe au lait skin pigmentation, and autonomous endocrine hyperfunction. The most common form of autonomous endocrine hyperfunction is gonadotropin independent precocious puberty, but affected individuals also may have hyperthyroidism, hypercortisolism, and pituitary gigantism. We describe a young and extreme case of McCune Albright Syndrome. By 8 months of age this girl had already developed intrahepatic biliary hypoplasia, cafe au lait skin pigmentation, peripheral pulmonary artery stenosis, adrenal autonomy (micronodular adrenals with Cushing's syndrome with associated severe metabolic bone disease and nephrocalcinosis), ovarian autonomy with cystic ovaries (oestradiol was 13,500 picomols/litre), breast and pubic hair development and intermittent menses with severe growth retardation. She underwent bilateral adrenalectomy and ovarian cystectomy at 8 months. Blood analysis for mutations of the alpha subunit of the stimulatory G protein (Gsa) was negative. By 14 months she had developed widespread polyostotic fibrous dysplasia and multiple pathological fractures with leg length discrepancy. She received Pamidronate therapy and left femoral osteotomy at 2 years of age. She subsequently developed hypophosphataemia requiring phosphate replacement. She was commenced on Anastrozole at 21 months following further pubertal advance, but plasma oestradiol remained moderately elevated. Pubertal advance continued to be a problem, attaining grade 4 puberty by 2.5 years, and a TW3 bone age of 8 by 3 years. However, she had persistent growth and global developmental delay. She was subsequently changed to Letrozole and her oestradiol level settled. By 3 years, she developed thyrotoxicosis. At 3.3 years of age she developed a transient marked raise in prolactin. Her ongoing problems include short stature, marked femoral bowing with disability, scoliosis and markedly advanced puberty. Few patients with such early severe multiple endocrinopathies in McCune Albright syndrome have been described.

P40**Mucopolidosis II partially mimicking Neonatal Severe Hyperparathyroidism**

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This report illustrates the diagnostic challenge of metabolic bone disease in neonates. This case presented with some bony and biochemical abnormalities suggestive of hyperparathyroidism.

Mother was a 29 year old G3P1 in a consanguineous marriage. Both parents were of Indian origin. Antenatal scans identified polyhydramnios, poor growth, multiple bony abnormalities, including short bowed femurs, suggestive of arthrogyposis and echogenic abdominal changes.

Infant delivered by Caesarean section at 39 weeks for breech presentation and poor fetal trace, and required intubation and ventilation. Examination showed growth retardation (weight 1620g, <0.4th centile), joint contractures, small thorax, short bowed femurs, bilateral

talipes, mild hepatomegaly. Skeletal survey showed severe generalised osteopaenia, widened long bone epiphyses, periosteal new bone formation, metaphyseal fraying and fractures of humerus and femurs.

Day 2 bone profile showed normocalcaemia (2.42 millimols per litre), hypophosphataemia (0.76 millimols per litre), elevated ALP (554 IU per litre), low 25OHD level (11.6 nanograms per ml), markedly elevated PTH (164 picomols per litre). Day 9: hypocalcaemia (1.75). Phosphate, calcium and vitamin D supplements were commenced. Serum calcium and phosphate improved to normal levels over the next few weeks but elevated ALP (1351 IU per litre) day 19 and elevated PTH (125 picomols per litre) day 15 persisted.

Diagnoses discounted included: infantile hypophosphatasia (ALP not low), osteogenesis imperfecta (abnormal biochemistry), primary renal tubular abnormality (antenatal fractures), hyperparathyroidism (no hypercalcaemia). Co-existing primary bone disease with maternal vitamin D deficiency was considered.

Chest deformity continued ventilator dependency. Day 19, Mucopolipidosis II was confirmed by white cell enzyme assay. The infant died shortly after palliative care had been instituted with agreement of both parents. This condition generally presents later with Hurler phenotype. A smaller group present as neonates with bony abnormalities and secondary hyperparathyroidism, as lysosomal storage is thought to impair placental calcium transfer which leads to secondary hyperparathyroidism.

P41

Thyroid dysmorphogenesis presenting as Hyperinsulinemia and persistent Neonatal Hypoglycaemia

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Neonatal hypoglycaemia is a common occurrence in NICU setting. We would like to report a case on thyroid dysmorphogenesis presenting as hyperinsulinism and persisting neonatal hypoglycaemia.

Case: A 35 weeker male child first of twin with a birthweight was 2.13 kilograms below the 0.4th centile was noted to hypoglycaemic. Despite increasing volume of feeds, child continued to be profoundly hypoglycaemic (true blood glucose 1.0 millimoles/litre). Every dextrose bolus normalized the blood sugar initially, but later became profoundly hypoglycaemic. He eventually required initiation of IV dextrose therapy (10 milligram/kilogram/minute). Bloods done at time of hypoglycaemia showed higher insulin/glucose ratio of more than 5 (normal range (NR) less than 5); normal cortisol, normal free fatty acid levels.

Thyroid function (TFT) was abnormal on neonatal screening and repeat TFT showed TSH 128 milli international units (NR: 1.3 to 6), T4: 7 picomoles/litre (NR: 10.6 to 19.3). A radioisotope thyroid scan showed a normal bilobed gland with normal uptake suggesting thyroid dysmorphogenesis. Thyroid receptor blocking antibodies were not present in the baby and mother's TFT were normal. The child was commenced on 25 microgram of thyroxine and there were no further hypoglycaemic episodes. The TFT'S normalised within one week and repeat insulin levels were normal within 2 weeks of starting thyroxine.

Transient hyperinsulinemia has been reported in hypothyroidism due to impaired insulin clearance and the other speculated mechanism is increased sensitivity to insulin action. Our case suggests impaired insulin clearance may have been a factor as with bolus of dextrose child became hypoglycaemic. We speculate insulin secretion may have stimulated with dextrose bolus and these high levels of insulin may have been cleared slowly leading to hypoglycaemia especially in a baby with low glycogen stores due to intra uterine growth retardation.

P42

Hypercalciuria and nephrocalcinosis in indomethacin-treated pseudohypoaldosteronism

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BACKGROUND: Hypercalciuria and nephrocalcinosis as complications of pseudohypoaldosteronism (PHA) have been reported once previously. We report two cases of PHA developing hypercalciuria and nephrocalcinosis during treatment with indomethacin, a previously unreported association.

Case reports: Female and male infants were born preterm (32 weeks, 30 weeks) into two consanguineous families. Both pregnancies were complicated by antenatal polyhydramnios. PHA was diagnosed following severe hyponatraemia (sodium requirements up to 60 millimoles/kilogram/day), hyperkalaemia, metabolic acidosis and polyuria (fluid requirements up to 300 millilitres/kilogram/day) from less than 24 hours age. Indomethacin was commenced at the ages of 6 weeks and 5 weeks due to persistent polyuria, poor weight gain and high sodium requirements. Both infants responded well to indomethacin. Attempts at withdrawing indomethacin at 4 years age resulted in recurrence of initial clinical picture and so was continued.

Renal ultrasound following severe urinary tract infection in the female patient at age 5 years demonstrated medullary nephrocalcinosis. Further investigations revealed hypercalciuria with urinary calcium creatinine ratio 3.5 millimoles/millimoles creatinine (0-0.59), raised serum parathyroid hormone 27 picomoles/Litre (1.3-7.6) and 1,25-dihydroxy vitamin D 390 picomoles/Litre (20-120) with normal serum calcium, phosphate and 25-hydroxy vitamin D levels suggestive of secondary hyperparathyroidism.

Similar investigations were undertaken in the male patient showing identical biochemical and radiological profiles.

9 months later, both continue on indomethacin therapy, thriving well and continue to have hypercalciuria.

CONCLUSION: In PHA and other tubulopathies, it is important to look for abnormalities of calcium balance. The mechanism for development of hypercalciuria and nephrocalcinosis is unclear but tubular pH and renal prostaglandin may play important roles. Experimental and human studies have demonstrated benefits of indomethacin, a potent prostaglandin synthesis inhibitor, in reducing/normalising hypercalciuria. In our cases, developing hypercalciuria and nephrocalcinosis during indomethacin treatment suggests a prostaglandin-independent tubular mechanism. Long term outcome and appropriate treatment in PHA remains uncertain.

P43**Cullen's sign: a further manifestation of long-standing primary hypothyroidism with a normal FSHR**

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BACKGROUND: Manifestations of longstanding hypothyroidism include pseudo-precocious puberty, SCFE and pituitary 'tumour' formation. Here we report a new manifestation - Cullen's sign. Furthermore, 2 pregnant women were recently reported with ovarian hyperstimulation. They were heterozygous for a mutation in the FSHR resulting in enhanced affinity for HCG. In view of the severity of the clinical picture in our patient we hypothesised that she might have an abnormal FSHR.

CASE REPORT: A 12 year old girl was referred because of vomiting and periumbilical pain. Her abdomen was distended with periumbilical bruising (Cullen's sign) and a palpable mass. Imaging demonstrated a cystic structure in her pelvis. At laparoscopy her ovaries were massively enlarged with haemorrhagic fluid in the peritoneal cavity. She was subsequently noted to be short (- 2.4 SD), Tanner stage B2 with a history of vaginal bleeding. TFT's revealed a TSH of 1310 milliunits per litre and Free Thyroxine of 2 picomols per litre. She was commenced on thyroxine and her hypothyroid phenotype and ovarian enlargement resolved.

METHODS: Following informed consent genomic DNA was extracted from peripheral blood mononuclear cells and was used as a template in the PCR amplifications. Primers were designed in the introns flanking the first 9 exons of the FSHR gene. Exons 7 and 8 were amplified as a single product and exon 10 was amplified as 3 overlapping products. DNA sequence analysis was performed on both strands by Semi-Automated Cycle Sequencing.

RESULTS: The sequencing results were compared to the known FSHR sequence and a healthy control using Sequencher. No differences in DNA sequence in the 10 exons were observed between wild type FSHR gene and our patient.

CONCLUSION: Cullen's sign is usually associated with acute pancreatitis. However, any process causing haemoperitoneum can result in this physical sign. This includes the ovarian enlargement seen in long-standing primary hypothyroidism.

P44**Reversal of central precocious puberty and hyperprolactinaemia in two boys with end-stage renal failure following live-related renal transplantation**

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This is the first report of two boys who were maintained on efficient haemodialysis for end-stage renal failure (ESRF) and developed central precocious puberty (CPP) and hyperprolactinaemia. Their pituitary-thyroid and pituitary-adrenal function was normal. In both cases successful live-related renal transplantation (LRD) resulted in regression of puberty.

CASE 1: A 9 year old boy with congenital nephrotic syndrome developed ESRF aged 2 years and commenced haemodialysis. At 6 years of age he developed testicular enlargement (8 millilitres) and pubic hair growth. His FSH (2.2 international units per litre), LH (2.9 international units per litre), testosterone (4.1 nanomoles per litre) and prolactin (3319 milliunits per litre) were raised. Height velocity was 7.5 centimetres per year. Bone age was 4 years advanced. Cranial MRI was normal. GnRH analogue therapy was started but this failed to completely suppress either his testosterone production or gonadotropin response to GnRH. He received a successful LRD aged 8 years and within 3 months became clinically and biochemically prepubertal with a normal prolactin level.

CASE 2: A 7 year old boy with bilateral cystic dysplasia developed ESRF aged 6 months. At 5 years of age he developed testicular enlargement and pubic hair growth. His peak FSH (3.1 international units per litre), peak LH (32.9 international units per litre), testosterone (20 nanomoles per litre) and prolactin (3928 milliunits per litre) were raised. Bone age was 1 year advanced. He did not wait long for transplantation and consequently did not receive GnRH analogue therapy. He received a successful LRD aged 8 years and within 3 months became clinically and biochemically prepubertal with a normal prolactin level.

The mechanism of CPP in association with ESRF is unknown. The failure of GnRH analogue to completely suppress FSH/LH in Case 1 may suggest a direct effect of chronic renal failure on pituitary-testicular regulation.

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