113

C.P. Smith*, D.B. Dunger, A.M. Taylor*, A.J.K. Williams*, E.A.M. Gale*, M.A. Preece, M.O. Savage St. Bartholomew's Hosp. and Institute of Child Health, London, UK.

RELATIONSHIP BETWEEN BASAL AND STIMULATED INSULIN RESPONSES AND INSULIN-LIKE GROWTH FACTOR 1 (IGF-1) IN NORMAL SUBJECTS AGED 5 TO 50 YEARS

Insulin and IGF-1 are structurally very similar and there are many functional links between the two hormone systems. However normal relationships between insulin and IGF-1 have never been defined. We performed intravenous glucose tolerance tests (0.5g/kg, maximum 25g) on 59 islet-cell antibody negative siblings of diabetic children and on 43 adults (aged 5.6-50 years). Puberty was staged (Tanner) and subjects divided into 4 groups: I - stage 1 (n=22), II - stages 2 & 3 (n=17), III - stages 4 & 5 (n=20), IV - adults >17 years (n=43). The pattern of fasting IGF-1 concentrations, fasting insulin and incremental 0-60 minute insulin areas (following IV glucose) in Groups I to IV was markedly similar; levels rose significantly throughout puberty ($p<0.001$ for all parameters) and declined to prepubertal levels by the third decade. IGF-1 concentrations: I - 0.85±0.44, II - 1.72±0.81, III - 2.35±0.83, IV - 1.11±0.51 U/ml. Fasting insulin concentrations: I - 7.5±3.2, II - 13.6±5.0, III - 13.8±3.3, IV - 7.6±2.9 mU/l. Incremental 0-60 minute areas: I - 1163±433, II - 2047±668, III - 2441±675, IV - 1117±485 mU/l/min. There was a strong positive correlation between logged insulin and logged IGF-1 levels; fasting insulin versus IGF-1 concentrations $r=0.625$, $p<0.001$, incremental 0-60 min areas versus IGF-1 concentrations $r=0.572$, $p<0.001$. This relationship, constant from 5 to 50 years, suggests that insulin may have an important influence on growth during childhood.

114

Z. Zadik, Y. Altman, M. Chen, H. Landau, E. Liberman, A. Kowarski.
Kaplan Hosp., Rehovot; Hadassah Hosp., Jerusalem; Soroka Hosp., Beer-Sheba Israel. Univ. Maryland, Baltimore, USA.

GROWTH HORMONE (GH) INDUCED IGF-I PRODUCTION IN CLASSICAL GH DEFICIENCY (CGHD) AND IN NEUROSECRETORY- DYSFUNCTION (NSD).

Radioimmuno assay (RIA) IGF-I determinations using incstar (INC) extracted plasma and Nichols (NI) - whole plasma determinations were performed in plasma samples of 19 GHD and 21 NSD prior to initiation of somatotropin (recombinant GH, BioTechnology General (Israel) Ltd.) and 1,4,6,16,24,32,40 and 52 weeks post therapy.

IGF-I RESULTS (u/ml means + SD) are presented in table:

			INCSTAR		NICHOLS	
GROUP		NO		1 year		1 year
CGHD	PP*	15	0.12±0.17	1.22±0.4	0.21±0.11	1.06±1.53
CGHD	PUB**	4	0.45±0.23	1.68±0.84	1.09±0.95	1.51±0.98
NSD	PP*	15	0.41±0.16	1.58±0.68	0.56±0.28	1.93±1.26
NSD	PUB**	6	0.6 ±0.14	2.75±0.4	1.24±1.18	2.04±1.55
Controls	PP*	15	0.66±0.13	-	1.12±0.91	-
Controls	PUB**	15	1.2 ±0.50	-	1.8 ±1.2	-

*PP=prepubertal **PUB=pubertal

INC RIA had a lower coefficient of variation, and a lower overlap between CGHD and controls, and smaller fluctuation in IGF-I levels. NSD group has an intermediate IGF-I levels between CGHD and controls IGF-I levels correlated better with pubertal stage than with growth response. HG effect on IGF-I was greater in CGHD than in NSD.

115

A. Cicognani, M.G. Pascucci*, M. Tacconi*, L. Ravagli*, R. Conti*, S. Tonioli*, I. Paletta*, E. Cacciari.
Department of Pediatrics, S. Orsola - Malpighi Hospital, University of Bologna, Italy.

EFFECT OF GONADECTOMY ON GROWTH FACTORS IN TESTICULAR FEMINIZED CHILDREN.

Sm-C increase during puberty or sex hormones treatment. Whether this increase is mediated by GH is still unclear. Children with testicular feminization submitted to gonadectomy provide a good model to assess the role of sex steroids on GH secretion. We evaluated Sm-C, T and E2 in 9 testicular feminized girls (mean age 11.6±1 yrs) immediately before and after gonadectomy. In 3 subjects GH release was evaluated by means of a sleep test. Mean Sm-C before surgery (2.85 UI ± 1.23) was significantly higher than that after gonadectomy (1.39±0.9, $p<0.025$) and than that of normal controls (n 83) (1.68±1.04, $p<0.025$). In all 3 patients the sleep test showed GH values higher before surgery by 1 SD over the mean value of control subjects and a GH decrease after gonadectomy (see table).

	case 1		case 2		case 3		controls (8)
	before	after	before	after	before	after	
$\bar{X}$-GH (ng/ml)	9.2	6.9	7.3	5.1	6.4	1.9	5.3±1.1
$\bar{X}$-GH area	217.6	158.0	173.2	119.6	153.2	46.9	125.9±25.7
$\bar{X}$-GH pulses area	103.9	43.2	83.3	35.1	67.7	3.4	39.8±15.9

Though the number of subjects studied is small, the fact that all showed the same GH behaviour allows us to hypothesize that the higher Sm-C values before surgery, in spite of androgen insensitivity, are the expression of the high testosterone (or estradiol) levels of these subjects and the Sm-C increase seems mediated through enhanced GH secretion.

116

S. Salardi*, L.F Orsini*, F. Righetti*, S. Donati*, S. Zucchini*, M. Mandini*, P. Tassoni*, A. Cassio*, L. Bovicelli*, E. Cacciari.
Departments of Pediatrics and Obstetrics, Prenatal Pathophysiology Unit, S. Orsola - Malpighi Hospital, University of Bologna, Italy.

GROWTH FACTORS IN HUMAN FOETAL PLASMA DURING THE SECOND TRIMESTER OF GESTATION: "IN UTERO" STUDY

The role of growth factors in fetal development is not clear. Fetal blood was obtained from 61 fetuses aged 19-25 weeks during the course of funicolocentesis performed for: suspected thalassaemia, fetal malformations, chromosomal abnormalities, suspected fetal infections. Plasma samples were assayed for growth hormone (GH), somatomedin-C (Sm-C), prolactin (hPRL), insulin and C-peptide concentrations by radioimmunoassay. GH levels were 53.3±30.8 ng/ml (13.3 - 194), Sm-C levels were all unmeasurable (<0.10 UI/ml), hPRL levels were 15.8 ± 22.1 ng/ml (1 - 118); insulin levels were 6.0 ± 2.4 μU/ml (1.4 - 16.3); and C-peptide levels were 0.56 ± 0.35 ng/ml (0.20 - 2.50). GH was positively correlated with gestational age ($p<0.01$) and with GH levels of the mothers ($p<0.05$). These findings suggest that: at this stage of pregnancy, GH increases and other hormones remain stationary. Low Sm-C levels suggest an autocrine, paracrine role of this peptide growth factor. The wide GH range might indicate differences in the characteristics of the fetuses or in the start of somatostatin secretion. Continuing this investigation in the last trimester of pregnancy will enable us to arrive at a greater understanding of the role of these hormones.

117

Julia S.Johansen*, A.Giwercman*, D.Hartwell*, C.Thøger Nielsen*, C.Christiansen*, N.E.Skakkebæk.
University Department of Clinical Chemistry, Glostrup Hospital and University Department of Pediatrics, Hvidovre Hospital, Copenhagen, Denmark.

SERUM BONE GLA-PROTEIN (BGP) AS A MARKER OF BONE GROWTH IN CHILDREN AND ADOLESCENTS.

BGP (osteocalcin) is a bone-specific protein. It is synthesized by the osteoblast and incorporated into the bone matrix. A fraction, however, is also released into the circulation where it can be detected by radio-immuno-assay.

We measured serum BGP in 450 normal children and adolescents (229 girls and 221 boys), aged 6-19 years. BGP concentrations changed in relation to age and sex with a pattern that resembles the height velocity curves. From 6 to 9 years the mean BGP concentration was 29.0 ± 1.1 ng/ml (mean ± 1SEM) in both sexes. Serum BGP in girls began to rise at about age 10 years, peaked 2 years later (49.2 ± 5.6 ng/ml), and then showed a progressive decline towards the adult levels (range 3-15 ng/ml) at age 17 to 19 years. Serum BGP in boys began to rise at about 11 years, peaked at 14 years with a higher level than in girls (64.0 ± 6.3 ng/ml) and declined towards the adult range somewhat later. Multiple regression analysis including partiel correlation showed that BGP in girls (aged 9-12) and in boys (aged 10-14) were significantly related to height and serum IGF-1, whereas age in itself had minor effect.

We conclude that BGP is a sensitive marker of bone growth. Repeated measurements may provide useful information in the diagnosis and follow-up treatment of children with disturbances in bone turnover.

118

F. Schaefer*, R. Stanhope, H. Scheil*, D. Schönberg, M.A. Preece, K. Schärer*.
University Children's Hospital, Heidelberg, F.R.G.and Institute of Child Health, London, U.K.

PULSATILE GONADOTROPHIN SECRETION IN PUBERTAL CHILDREN WITH CHRONIC RENAL FAILURE (CRF).

Pubertal development is frequently delayed and disturbed in patients with CRF. Renal transplantation may be followed by rapid sexual maturation. Studies in adult uremic patients have demonstrated a loss of pulsatile gonadotrophin secretion, suggesting a hypothalamic lesion. We hypothesized that a similar defect might be responsible for the disorders of puberty observed in CRF. We examined the physiological nocturnal gonadotrophin secretion in 6 male and 2 female patients aged 11.6-19.6 yrs with end-stage CRF (5 treated by dialysis, 3 transplanted). Appearance of pubertal signs was delayed in all but one patient. Blood was drawn every 15-20 min for a period of 8-12 hrs. In none of the dialysed patients a nocturnal rise of serum LH was observed, and pulsatility was reduced to a mean of 1.4 pulses/study, whereas the transplanted patients demonstrated a normal rise and pulsatility of LH (mean: 4.3 pulses/study). No pulsatile FSH secretion was observed in any profile. We conclude that pulsatile GnRH secretion is disturbed in children with end-stage CRF which may be the major cause for the delay of pubertal development. Gonadotrophin pulsatility seems to be restored by successful renal transplantation.