M.Gourmelen, Y.Le Bouc*, L.Perin*, M.Binoux, F.Girard.
Lab. d'explorations fonctionnelles, INSERM U 142,
Hôpital Trousseau, 75012 - Paris - France.

107 IGF I,IGF II SERUM LEVELS IN BECKWITH-WIEDEMANN SYNDROME (BW).

Duplication of the 11p15 region has been described in some patients with BW, also called Exomphalos-Macroglossia Gigantism syndrome. IGF II gene is localized at the 11p15 region. A markedly increased expression of IGF II gene was reported in Wilm's tumour, the incidence of which is increased in BW. These findings had led us to speculate for a possible overproduction of IGF II protein in this disorder. Using a specific binding assay (JCEM 1986) and a RIA for comparative determination of IGF I,we have measured the serum levels of 11 unrelated children (aged from 1 month to 7 years) with BW. 4 had successive investigations. In 4 infants out of 8 before 1 year, IGF I was more elevated than controls. An overgrowth was present in 3. In the older children from one to seven years IGF I did not differ from normals. IGF II levels were similar to the controls whatever the age. Moreover, in three children having developed a tumour (ganglioneuroma n = 2, nephroblastoma n = 1) IGF II levels measured before surgery were not elevated. These patients had normal karyotypes. Quantification of IGF II mRNA in the tumour is under investigation.

K.Mohnike(*),R.Hildebrandt(*),I.Starke(*),
N.Bannert..(Introd. by P.Rochiccioli)
Dept.of Ped.,Med.Acad.of Magdeburg and Centre

108 of Diab. Metab.Disorders,Berlin,GDR.
DECREASED INSULIN DEGRADATION AFTER GROWTH HORMONE(GH) AS ONE REGULATORY FACTOR FOR IMPROVEMENT OF INSULIN IRI IN GH DEFICIENT CHILDREN.

Studies have shown the beneficial effect of normo- and hyperinsulinemia on growth rate of GHD children due to craniopharyngioma (BUCHER et al.). Furthermore others showed that insulinotropic drugs improve growth parameters in experimental and clinical situations. To test whether increased insulin secretion or decreased degradation is responsible for improvement of insulinemic status c-peptide (c-p.),insulin (IRI) and glucose responses to 1.75 g/kg b.w. glucose p.o. as well as insulin binding of erythrocytes were measured simultaneously. After informed consent 10 (GHD) children were tested during GH therapy (phase 1) and after more than 6 weeks (phase 2) withdrawal. Glycemic response was normal in both situations, max.IRI and c-p. were reduced as compared to age-matched normal values in both phases. IRI levels were significantly higher in phase 1 than 2, but c-p. showed only a slight insignificant increase in the older age group. Insulin binding (7.5%+-0.8 vs.5.5 +- 0.6 S.D.) and affinity were reduced in phase 2. Comparable results of binding studies were obtained after 7 days of GH-withdrawal. Our results showed down-regulated receptors in phase 1 as evidence of permanently increased insulin levels. We conclude decreased hepatic degradation under GH.

A.B. Kurtz*, P. Hindmarsh, L. Di Silvio*, P.J. Pringle*,
C.G.D. Brook
The Middlesex Hospital, London W1, U.K.

109 CHANGES IN SERUM INSULIN CONCENTRATION DURING PUBERTY - A POSSIBLE ROLE FOR GROWTH HORMONE (GH)

We have measured the insulin response to oral glucose loading (1.75 g/kg) in 17 prepubertal and 20 pubertal children of varying stature. All pubertal children were studied during the pubertal growth spurt. Mean (SEM) fasting concentrations were, before puberty, glucose 4.3 (0.1) mmol/l insulin 4.5 (0.8) mU/l, and during puberty, glucose 4.8 (0.1) mmol/l, insulin 13.0 (1.7) mU/l ($p<0.001$). The increase in fasting insulin concentration during puberty was accompanied by a 100% increase in the incremental insulin response after glucose. The role of growth hormone (GH) in inducing these changes was studied in 16 tall children (4 pre-pubertal, 12 pubertal) who underwent 24 hour GH profiles. The increase in GH secretion associated with stage 2/3 breast development was accompanied by a rise in fasting insulin. Before puberty the summed GH pulse amplitude was 68 (8.2) mU/l/day with a mean fasting insulin concentration of 6.2 (2.2) mU/l; at breast stage 2/3 the pulse amplitude was 205 (35.5) mU/l/day and insulin 15.9 (6.5) mU/l. In 14 children receiving GH treatment the mean fasting insulin concentration rose at one year of therapy: pre-treatment 4.8 (1.0) mU/l, 1 year 15.4 (2.3) mU/l; $p<0.001$). Tall children had higher mean nocturnal insulin concentrations than short children irrespective of pubertal stage.

There is a physiological increase in serum insulin concentration during puberty which is probably secondary to the rise in serum GH concentration. This has important implications both for the modulation of response to GH and for the management of adolescent diabetics.

M-L.Käär*, P.Tapanainen*, M.Knip, L.Risteli*, J.Risteli*
(Introd.by J.Mäenpää)
Departments of Pediatrics and Collagen Research Unit, University

110 of Oulu, Oulu, Finland
THE USE OF SERUM AMINOTERMINAL PROPEPTIDE OF TYPE III PROCOLLAGEN (PIIINP) CONCENTRATION IN PREDICTING THE RESPONSE TO GROWTH HORMONE (GH) THERAPY IN SHORT CHILDREN

Until recently, due to the limited GH supply, GH therapy has been used only in GH deficiency (GHD). It has been shown that also other short children may benefit from GH therapy. But there has been no other means except trial to predict the response. It has been shown earlier that there is a rise in serum PIIINP concentration during GH therapy. To evaluate the validity of PIIINP determination in the prediction of the response to GH therapy, we followed changes in PIIINP for 6 months after the onset of GH treatment. The study comprised 12 children, 5 boys and 7 girls,with the mean age of 8.3±3.8(2.6-16.8) and bone age 5.6±3.7 (1.2-13) years. In all the relative height was below -2.5SD. Nine were diagnosed GHD (peak GH<7ug/l). The children were treated with biosynthetic GH (provided by Eli Lilly S.A.),given at bed-time,s.c.,0.1U/kg/x3/wk. Blood samples for PIIINP were taken at dg and at 1 wk, 5 wks, 3 and 6 months during the therapy.
Results:After 6 months 5 children were considered non-responders(NR) on the basis of no or insufficient growth velocity acceleration. Therapy was discontinued in them and continued in 7 responders(R). Before the onset of therapy there were no differences in the clinical data between R and NR, but the mean PIIINP was higher in NR than in R (7.6±2.4 vs 5.4±1.0 ug/l,$p<0.025$). There were no differences between R and NR in the mean values of PIIINP during therapy, but there was a difference in the rise of PIIINP after 5 weeks. The rise was higher in R (3.7±1.2 vs 1.3±0.9 ug/l,$p<0.005$). Only in one child whose all PIIINP values were higher than any other values in NR group, the rise of PIIINP fell into the range of R. The more pronounced rise in PIIINP after 5 weeks on GH therapy in responders may help in determing those children who will benefit from long-term GH therapy.

Th. Danne*, A. Grüters*, K. Schnabel*, N. Quandas*,
D. l'Allemand*, J. Waldschmidt*, and B. Weber
Department of Pediatrics and Pediatric Surgery, Free

111 *University Berlin, F.R.G.*
MONITORING GROWTH AND GROWTH HORMONE THERAPY BY SERUM DETERMINATION OF ANTIGENS RELATED TO THE AMINO-TERMINAL TYPE III PROCOLLAGEN PROPEPTIDE (P-III-NP)

Serum P-III-NP reflects fibrillogenesis. To study whether P-III-NP can be used to monitor growth, it was determined by two different radioimmunoassays. One recognizes predominantly the intact triple-stranded propeptide showing a lesser affinity to the smaller monomeric peptide (RIAgnost), while the other detects both forms equally (FAB). In healthy children (n=375, aged 0 to 16 years) P-III-NP determined with either assay followed closely growth velocity. Patients with Turner's-Syndrome (n=11: 17±4/90±22 (RIAgnost/FAB in ng/ml respectively)), constitutional short stature (n=16: 19±5/105±27) and growth hormone deficiency (GHD) (n=23: 16±8/82±29) had low levels, while those with tall stature (n=11: 56±45/174±38) had high levels, which declined during estradiol-therapy in girls (n=3: 23±4/125±22). In GHD during recombinant growth hormone therapy (n=20) P-III-NP values increased after only 3 injections ($p<0.01$) and stayed elevated above baseline for 6 months (ms). Results were compared to growth (median 5.6 cm (0.4 to 13.9) in 6 ms) and to established methods of growth monitoring (somatomedin C, alkaline phosphatase). P-III-NP (FAB) values correlated with the individual growth rates during the first ($r=0.40$; $p<0.05$) and the second 3 ms ($r=0.66$; $p<0.001$) and the total 6 ms periods ($r=0.46$ $p<0.05$). All other parameters showed some association to growth only during one or two treatment periods. Thus, P-III-NP can be used for growth monitoring.

A. Grüters*, K.Schnabel*, D.Schnabel*, D.l'Allemand*,
Th. Danne*, W.Burger*, I.Enders*, B. Weber, H. Helge
Dept. of Pediatrics, Free University Berlin, F.R.G.

112 GHRH-TEST AND SOMATOMEDIN C (SMC) GIVE ADDITIONAL INFORMATION IN THE DIAGNOSTIC PROCEDURE OF SHORT STATURE IN CHILDREN.

GH-tests in 55 children with short stature were compared: 24 hour (q2hr), sleep induced (6hr, q 30 min), Arginin(A)- (0.5 g/kg BW), Insulin(I)- (0.05 µ/kg BW) and GHRH- (1 µg/kg BW GHRH 1-44) stimulated GH-secretion and baseline SMC (U/ml). 20 patients had been diagnosed as growth hormone deficient (GHD; 10 off treatment > 1 year, 10 newly diagnosed) and 35 classified as Non GHD (NGHD) according to a normal spontaneous GH-secretion.Clinically, both groups were similar (CA, BA, growth velocity), GH-levels differed significantly ($p < 0.01$).

group	n	ng·min·ml^{-1} GH 6 h	GH ng/ml median (range) max.24 h	max.A/I	max.GHRH	SMC U/ml
GHD	20	350	1.5	0.85	7.1	0.3
		(180-1120)	(0.5-5.6)	(0.5-6.4)	(0.5-29.5)	(0.1-0.6)
NGHD	35	2240	18.7	10.7	44.49	1.7
		(1170-5120)	(9.6.-50)	(1.7-32.2)	(8.9-110.0)	(0.4-4.0)

In GHD all tests correlated significantly ($p<0.001$), in NGHD no correlation was detected. 28 NGHD-patients were verified as constitutional delay (CD) (normal Arg/Ins, normal GHRH and SMC). In 7 NGHD-patients formerly included among CD, additional information was gained by GHRH and SMC results. 3 had pituitary dysfunction (low Arg/Ins and GHRH, normal SMC), 3 had partial GHRH deficiency (low SMC and GHRH, normal Arg/Ins) and 1 had SMC resistance (high Arg/Ins, high SMC and high GHRH).