ENDOCRINOLOGY

23

INSULIN RESISTANCE IN 7 YEAR OLD CHILDREN WHO WERE THIN AT BIRTH. Catherine M Law, David J P Barker, C Nicholas Hales, Alistair W Shiell, spn ICS Normand. MRC Environmental Epidemiology Unit, University of Southampton: Department of Clinical Biochemistry, University of Cambridge.

It has been shown recently that men and women who were thin at birth have a high prevalence of impaired glucose tolerance and insulin resistance. These associations may reflect impaired development of skeletal muscle during gestation. To determine whether the relations can be detected in children, we have studied a population sample of 249 British children aged 7 years.

Blood was taken for glucose and insulin in the fasting state and 30 minutes after an oral glucose challenge. Plasma insulin, proinsulin, and 32-33 split proinsulin concentrations were determined by two site immunoreactive assays.

Mean birthweight was 3359 (sd 510) grams. Glucose at 30 minutes was significantly inversely related to thinness at birth, as measured by the ponderal index (weight/height^3). For a given insulin response to the glucose challenge, children who had been thin at birth had high glucose levels at 30 minutes. A high level of 32-33 split proinsulin, a measure of islet cell dysfunction, was related to shortness at birth.

These findings are further evidence that reduced growth in utero is followed by permanent dysfunction of the endocrine pancreas and resistance of peripheral tissues to insulin.

24

THE THRIVE INDEX: A METHOD OF IDENTIFYING AND QUANTIFYING ABNORMAL WEIGHT GAIN IN EARLY CHILDHOOD
Charlotte M Wright, Tony Waterston, Al Aynsley Green
University of Newcastle upon Tyne

Weight gain is a sensitive indicator of health in infancy but there is no recognised point when a fall away becomes abnormal. We collected weights from an annual cohort of 3418 children, aged 18-30 months(m) and, by correlational methods, produced a measure of centile shift, the "Thrive Index"(TI). This is the deficit between a child's actual weight standard deviation score (SDS) and that predicted by their early weight, adjusted for regression to the mean. Only 5% children had a TI value of less than -1.26 SDS in the first 18m and this value can thus be used as a lower threshold of normality in the population.

We report the early findings of a screening programme using this method. 50 children with subnormal TI values have been identified at a median age of 9.6m (2.6-20.4m), and followed up for a median of 9.2m (2.1-17.0m). At medical assessment at a median age of 13.4m, 13/50 had already recovered, but 24/50 now had a TI <-1.75, compared to 17/50 at the time of screen ($p=0.04$ Chi^2). Major organic disease was found in 2 and neglect in 6. Evidence of undernutrition was found in 29 children and advice offered. In the remainder no clear cause was uncovered. At early follow up 19/50 were now recovered and only 15/50 had a TI <-1.75 ($p=0.06$ Chi^2 trend). Bottle feeding, deprivation and undernutrition were significant predictors of non-recovery.

Our findings suggest that the Thrive Index may be useful both to identify a vulnerable group of children and to provide a quantifiable measure of their progress, at an age when other measures of longitudinal growth are impractical.

25

NEURONAL RESCUE AFTER HYPOXIC ISCHEMIC INJURY (HI) USING INSULIN-LIKE GROWTH FACTOR-1. Peter D Gluckman, Christopher E Williams, Erica Bielharz & Jian Guan (spn. by N McIntosh). Research Center for Developmental Medicine & Biology, School of Medicine, Auckland, New Zealand.

Many potential therapies are aimed at mechanisms operative during the HI insult and are likely to be relatively ineffective when administered after the event - the usual therapeutic situation. Using in situ hybridisation we have shown that insulin-like growth factor 1 (IGF-1) is induced in astrocytes in the area of neuronal death within 72 h of unilateral HI in 21 day rats. In contrast IGF-2 is not induced until 10 days. Two of the IGF binding proteins (IGFBPs), IGFBP-2 and IGFBP-3 are also induced within 72 h; IGFBP-4, a potent inhibitor of IGF action, is inhibited. IGF-1 was injected via the lateral ventricle 2 hour after HI. There was a dose dependent reduction ($p<0.01$) in neuronal loss in all damaged areas between 0 and 50 ug IGF-1 ($n=16$/group). The infarction rate was reduced ($p<0.01$) from 87% to 16%. Behavioural testing showed somatosensory function to be protected ($p<0.05$). IGF-2 and insulin did not cause neural protection suggesting a type 1 IGF receptor mediated effect. Des 1-3 IGF-1, which has lower affinity for IGFBPs was not neuroprotective compared to IGF-1 ($p<0.05$) suggesting the role of IGFBP-2 or 3 in the protective effect of IGF-1. Treatment with IGF-1 prior to HI was not neuroprotective suggesting that IGF-1 acts on an active mechanism, possibly apoptosis, initiated by the HI. These data show that endogenous IGF-1 production is a specific response to HI and that post-asphyxial IGF-1 therapy is potently neuroprotective and must be considered as a potential neuronal rescue therapy.

26

NEURAL NETWORK BASED ANALYSIS OF EPISODIC HORMONE SECRETION FOR CLINICAL ROUTINE. Erik Michel, *Reinhard Volmer, Jürgen H. Brämswig (spn. by Gerd Jorch). University Children's Hospital, and *Zentrale wissenschaftl. Einrichtung für Informatik, Fachhochschule, Muenster, FRG.

INTRODUCTION. Artificial neural networks (ANN) may yield incredible results in respect to classification of dithered data where classical statistics fails. We present a ready-to-use computer programme for hormone surge detection based on principles of ANN. METHODS. 15 plasma growth hormone time series (8 to 11 hours, one value every 20 min) of different patients were visually evaluated by an expert endocrinologist (JHB), and 'true' pulses marked *without comment*. Next, *facts* were automatically generated out of those preevaluated data sets of not necessarily equal length using the 'shifting window' technique, and were presented to a PC-based ANN (back-propagation, 2-layer topology, 11 inputs, 7 hidden-, 1 output neuron, language 'C') in random order and repeatedly. The ability to self-organize inherent to the ANN enabled it to associate output (puls/no puls) with general input patterns ('learning'). RESULTS. After a training phase of 400 epochs (20 minutes, 386-AT with coprocessor), the errors F1/F2 had decreased from 175 to 3.4 and 10 to 0.26, respectively. Interpretation of all *facts* was correct. Although the number of *facts* was small, *with independent test data, the satisfying system's capability to generalize could be demonstated.* CONCLUSION. The system enables laboratory staff not specially trained i) to train their local PC-based ANN with preevaluated hormone time series, and thereafter ii) to routinely perform hormone surge detection. The depersonalized expert knowledge becomes consistent and reproducible *without the need to explicitely define pulse criteria.* In summary, due to the neural network's self-organizing and learning properties, the programme is a handy tool to evaluate all kinds of episodic hormone secretion.

27

THE CHARACTERISTICS OF GROWTH HORMONE (GH) PULSATILITY IN NEONATES
Carolyn J Adcock, Andrew R Wilkinson, David B Dunger, Iain C Robinson, John Lewin, Kharen L Clayton, Angela P Watts, David R Matthews. Department of Paediatrics, University of Oxford, John Radcliffe Hospital, Oxford, England.

GH is now recognised to be important in early postnatal growth. High GH levels have been documented but the pulsatility has not been defined because of difficulties in obtaining frequent blood samples. We have developed an automated computerised technique which enables microsamples of blood to be withdrawn through an intravenous (IV) cannula. Blood samples of 40ul were collected in a validated dilution of 1:4 with heparinised saline. GH was measured by immunoradiometric assay. The sensitivity was 0.2mU/l and the intra-assay CV(%) was 9.6, 7.7, and 4.4 at concentrations of 1.0, 5.0 and 25mU/l respectively. GH profiles (10m sampling over 12hr) from 5 normal babies at the end of IV drug therapy were analysed by pulsar and time series analysis.

Gest(wk)	Age(d)	Weight(kg)	Plasma GH($\bar{x}$)(mU/l)	Baseline GH(mU/l)
35	2	2.4	26.6	12.8
36	1	3.0	75.2	33.6
33	13	1.8	47.2	30.6
36	1	2.0	90.2	38.0
34	1	2.0	89.6	40.0

The dominant pulse periodicity (Fourier Transform) in these babies was 90-100 minutes.

We have demonstrated high mean and baseline GH levels and a fast frequency GH pulsatility in newborn babies.

28

GH TREATMENT IN IDIOPATHIC SHORT STATURE: INFLUENCE OF PUBERTY AND SEX ON SKELETAL MATURATION AND GROWTH RESPONSE. R.L. Hintz, K. Attie, A. Johanson, J Baptista, J Frane, A Roche, and the Genentech Study Group. *Department of Pediatrics, Stanford Univ., Stanford, CA, Genentech Inc., South San Francisco, CA, and the Fels Institute, Yellow Springs, OH, USA.*

We treated 121 patients with height below -2 SDS for age and stimulated GH > 10 ng/mL (ISS) with GH for up to 5 years. The majority of these patients achieved improved growth rate, height SDS, and predicted adult height with GH therapy prior to puberty. The age of onset of puberty in these GH-treated ISS patients was not advanced. However, data suggests that GH-treated patients may transit puberty faster and not achieve their predicted gains in adult height. We compared 92 GH-treated ISS patients with 252 untreated normal children followed longitudinally whose height was above -1 SDS (NL $\geq$-1) for age or below -1 SDS (NL <-1) for age. The change in Fels method bone age per year (ΔBA/ΔCA) and the change in Bayley-Pinneau predicted adult height per year (ΔPHt/ΔCA) were compared before puberty (BA $\leq$11yo in ♂, $\leq$9yo in ♀) and during puberty (BA $\geq$ 12yo ♂, $\geq$ 10yo♀):

		PREPUBERTAL		PUBERTAL	
		♂	♀	♂	♀
ΔBA/ΔCA	ISS on GH	0.95	0.88	1.22	0.96
	NL <-1	0.93	0.99	1.04	1.01
	NL $\geq$1	0.98	0.99	1.00	0.98
ΔPHt/ΔCA	ISS on GH	2.65	2.53	-0.02	2.71
(cm/yr)	NL <-1	-0.04	-0.51	0.22	1.14
	NL $\geq$1	0.57	0.29	0.12	1.13

We conclude that GH-treated ISS ♂ progress through puberty faster, and do not continue to increase PHt. Early GH treatment, increased GH dosage, or prolongation of puberty may be needed to achieve target increases of final height in ISS boys.