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R.Rappeport, R.Brauner*, C.Prévot*, M.P.Roy*, E.Mugnier*.
Department of Pediatric Endocrinology and Diabetes and INSERM U.30,Hôpital des Enfants-Malades,75015 Paris,FRANCE.

EVIDENCE FOR A DIRECT AND A GH-SmC MEDIATED EFFECT OF SEX STEROIDS ON GROWTH IN PRECOCIOUS PUBERTY (PP).

During puberty, growth and circulating SmC increase require normal GH secretion but the respective role of GH and sex steroids is still unsettled.This question was adressed by comparing children with low or normal GH secretion during PP. 28 children, with PP and similar gonadal activity, were classified into 2 groups according to their GH peak response to AITT : Group I > 10 ng/ml, Group II < 5 ng/ml. They were compared to prepubertal hypopituitary cases (Group III). Plasma SmC/$IGF_I$ was measured by RIA (m ± sem).

| Group | n | CA (yr) | BA (yr) | cm/yr | GH peak (ng/ml) | SmC (U/ml) |
|---|---|---|---|---|---|---|
| I | 20 | 7.1 ± 0.5 | 9.8 ± 0.6 | 9 ± 0.6 | 24 ± 2.5 | 2.01 ± 0.17 |
| II | 8 | 8.2 ± 1.1 | 9.5 ± 1.3 | 6.8 ± 0.6 | 3 ± 0.5 | 0.71 ± 0.14 |
| III | 7 | 11.3 ± 1.1 | 6.9 ± 0.9 | 1.9 ± 0.5 | 1 ± 0.3 | 0.07 ± 0.01 |

By comparison of II/I it appears that GH deficiency decreased the mean SmC level ($p<0.001$) and growth rate ($p<0.05$), but both of these values were superior ($p<0.001$) to values observed in group III indicating a possible role of sex steroids.In addition a 6 yr old girl (in Group II) with PP and GH (AITT/sleep) <3ng/ml, SmC <0.2 U/ml grew 9.5 cm/yr.

In conclusion these data show that in PP beside the GH effect, growth and possibly circulating SmC may be directly stimulated by other factors as sex steroids.

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P.F. Bougnères, P. Brambilla*, J.L. Chaussain, J.V. Santiago*
Service d'Endocrinologie Pédiatrique, Hôp. St Vincent de Paul, Paris et Department of Pediatrics,Washington University, St Louis.

**GLUCOSE COUNTERREGULATION (CR) IN PRESCHOOL AGE DIABETIC CHILDREN WITH RECURRENT HYPOGLYCEMIA DURING CONVENTIONAL TREATMENT (CT)**

To determine wheter immature or defective glucose CR was responsible of the severe recurrent hypoglycemia (3,6 per patient per yr) observed during **CT** in 6 preschool diabetic children, we investigated their metabolic and hormonal responses to **iv insulin infusion** (40 mU $kg^{-1}$ $hr^{-1}$). **CR** was considered adequate since no patient experienced symptoms requiring discontinuation of the test, and (BG) nadirs averaged 42 ± 5 mg/dl. **Glucose production** decreased from 4.2 ± 0.2 to 2.6 ± 0.6 mg $kg^{-1}$ $min^{-1}$. Blood 3-hydroxybutyrate levels were high (~ 3 mM) and did not change during the test. The responses of **epinephrine** (from 137 ± 37 to 393 ± 143 pg/ml), **norepinephrine** (from 145 ± 33 to 347 ± 152 pg/ml) and **GH** (from 6.0 ± 1.5 to 20.3 ± 5.1 ng/ml) were normal. As observed in diabetic adults, **glucagon** response was deficient (from 117 ± 30 to 114 ± 18 pg/ml).

The 6 children were subsequently treated with insulin pumps (**CSII**), which resulted in a 20 fold decrease of severe hypoglycemia. During this therapy, a significant inverse correlation appeared between the individual frequence of BG values below 40 mg/dl and BG nadir during the insulin infusion test ($r=-0.94, p<0.001$)

We conclude that the glucose CR status evaluated by a simple standardized insulin infusion test reliably predicts the risk of developing hypoglycemia during CSII in young diabetic children.

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J.Karjalainen[1*], M.Knip[1*], A.Mustonen[1*],H.K.Åkerblom[2]
1)Department of Pediatrics, University of Oulu, Oulu, Finland
2)The Children's Hospital, II Department of Pediatrics, University of Helsinki, Helsinki, Finland

THE CLINICAL SIGNIFICANCE OF INSULIN AUTOANTIBODIES (IAA) IN INSULIN-DEPENDENT DIABETES MELLITUS (IDDM)

Recently, insulin autoantibodies (IAA) have been detected in 16-38% of newly diagnosed IDDM-patients. In our study of 60 IDDM-patients IAA were detected by a modification of the method described by Palmer et al. and islet-cell antibodies (ICA) by conventional (IF-ICA)- and complement-fixation(CF-ICA)-tests. Together with clinical parameters analyses were performed at diagnosis and every three months for a year.

At diagnosis 28.3% had an insulin-binding exceeding that(2.8%) of 68 age-matched controls. 45 of them were positive in IF-ICA- and 38 in CF-ICA-study. 12 IAA-positive subjects had IF-ICA and CF-ICA in their serum. However, no association could be observed between IAA and ICA, particularly CF-ICA, suggesting that IAA are not involved in the beta-cell destructive process mediated by autoimmune mechanisms. A negative correlation ($p<0.001$) between IAA and the age of the patient found at diagnosis suggests generally increased immune response in young children. IAA-levels got higher during the follow-up both in the initially negative and positive groups, but the difference was significant ($p<0.05$) only for first three months. IAA had association neither to C-peptide concentrations, hemoglobin-$A_1$-values, duration of remission phase and insulin dose nor ICA. IAA were poor predictors of antibody response to exogenous insulin. As a conclusion:IAA have no influence on the clinical course of IDDM and their predictive value of the antibody response to exogenous insulin is insignificant.

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C.L.Marchal*, P.Czernichow.
Department of Pediatric Endocrinology and Diabetes, and INSERM U.30, Hôpital des Enfants-Malades,149 rue de Sèvres, Paris 15ème, FRANCE.

DOSE RELATIONSHIP EFFECT OF CICLOSPORINE A(CsA) IN CHILDREN AT THE ONSET OF IDDM.

CsA induced prolonged remissions in adults with IDDM. We report on our experience in children treated with 2 different CsA dosages. CsA was given orally, for 6 mth targetting a CsA trough plasma level either of 100 ng/ml (group I - n=14) or 200 ng/ml (group II - n=14). Both groups were compared to 12 "control" cases of comparable glycemic control receiving no CsA. Results were evaluated on insulin requirement and glucagon stimulated C-peptide. In group I, no major side effects were observed. In group II, blood pressure was elevated in 6. Creatinine levels increased (82 ± 12 at 6 mth, vs 62 ± 10 µmol/l-ns-). All the side effects have been reversible.In group I, 5 cases underwent a total insulin remission for 1-4 mth, 3 cases no remission at all, and 6 a partial remission. In group II so far (n=7) at 6 mth, 4 cases underwent a total remission for 2-9 mth and 3 a partial remission. Stimulated C-peptide was higher in group II, compared to group I (273 ± 1.4 vs 1.84 ± 1.3 ng /ml respectively at 6 mth). In group II, both basal and stimulated C-peptide were higher in non insulin treated cases from the 3rd mth on.

In conclusion : In this open trial, CsA has a positive effect on the remission period. A dose effect relationship was demonstrated. Benefits of a high CsA dosage,inducing a sustained remission, might be balanced by noticeable side effects.

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G. Faiman*, Z. Flexer*, P. Fainmesser*, Y. Albag*
M. Rapaport*[,†], M. Karp, Z. Laron.
Inst. Ped. & Adoles. Endocrinol., Beilinson Med. Ctr. Petah Tikva, Sackler Med. Sch., Tel Aviv Univ. & MLL[†] Software & Computers Ind. Ltd., Tel Aviv, Israel

A MICROCOMPUTER PROGRAM AS AN AID IN NUTRITIONAL COUNSELLING AND FOLLOW-UP IN DIABETES AND OBESITY

An integral part of the DIACON (Diabetes Control System) is the nutritional analysis. Data are entered into the computer at each visit. Medical data are entered with the help of the nurse. The dietician together with the patient enter data on daily food intake and the time of consumption using a code relating to different foods. The program calculates calories, CHO, fat and protein in grams and percentage and their distribution among the daily meals. The data are printed out as tables and histograms. These data can be related to the daily blood glucose (BG) levels obtained by SBGM, daily insulin dose, HbA1, exercise, etc.

This system was tried for 2 yrs in 24 newly diagnosed diabetic children and for 6 mos in 10 recently diagnosed diabetics and 10 matched controls and 6 obese children. The system was readily accepted by the patients who encountered no difficulty in using it routinely. Its use increased the patient's involvement in the analysis and interpretation of dietary habits and BG fluctuations. The diabetic patients using DIACON were more compliant, performed a greater number of SBGM tests than others (2.4±0.8 vs 1.67+0.8 BG tests/day)and had lower daily BG levels (140+23 vs 153+25 mg/dl), lower HbA1 (9.05 vs 10.3%). The patients using DIACON had a better understanding of nutritional needs. It is concluded that the DIACON system is a useful new tool in the management of diabetes and probably of obesity as well.

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Th. Erb*, J. Girard, A.N. Eberle*, J.B. Baumann*, U. Zumsteg*, U. Zuppinger
Children's Hospitals, and Dept. of Research, University of Basel and Bern, Switzerland

GROWTH HORMONE IN URINE. DEVELOPMENT OF AN ULTRASENSITIVE RADIOMETRIC ASSAY APPLICABLE TO NEAT PLASMA AND URINE

The assay of growth hormone (GH) in urine has been hampered by lack of sensitivity/specificity of methods. Calculated from a renal clearance of .01%, 9-60 ng of GH can be expected in a 24 h urine. A radiometric assay was developed with a goat anti-GH-antiserum, covalently coupled to polyacrylamid. After immunextraction by shaking for 15 h at 4°C, the immunosorbent was washed and bound GH quantitated by $I^{125}$-labelled monoclonal anti-GH-$\gamma$-globulin. The assay is insensitive to plasma protein, NaCl (.25-1 M), urea (.1-.4 M), pH 6-8. Its specificity is shown by the fact that neat and spiked (50 pg/ml) urine samples gave a 90-110% recovery before and 0% after immunextraction. A volume of up to 10 ml of unknown (urine, plasma) can be used for immunextraction, resulting in an overall sensitivity of 300 fg/ml of neat urine. First morning or spot samples from 31 patients (2 weeks - 17 yrs) contained 1.5-100 pg GH/ml urine (highest values in neonates and prematures). In timed urine samples of 6 hypopit. patients, GH was undetectable: a) day off treatment: a.m. 6/6, p.m. 5/6, sleep 3/6, b) treatment day: a.m. 4/6, p.m. 1/6, sleep 2/6. Timed urine samples during a prolonged period from children at different age groups are currently under investigation for 24 h secretion, monitoring effect of stimulating/suppressive therapy and hypoglycemic reactions.