141 PRL, PLASMA RENIN ACTIVITY AND ALDOSTERONE RESPONSE TO DOMPERIDONE IN IDDM CHILDREN.

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A Prolactin (PRL) hyper-response to TRH was described in IDDM children suggesting an alterated dopaminergic control. No changes in plasma renin activity (PRA) and aldosterone (A) plasma levels after Domperidone (DMP), a dopamine antagonist, were reported in adult healthy subjects. PRL, PRA and A levels were measured before and after i.v. DMP injection (10 mg/1.73 m^2) in 10 IDDM insulin treated, normotensive, 2 hrs-recumbent, well controlled outpatients (10 to 19 years old).

The IDDM patients showed higher PRL responses than 11 control subjects of corresponding age (peak values: 112.7 ± 27.0 vs 45.4 ± 15.0 ng/ml; $p < 0.02$). The mean PRA values rose significantly (from 1.78 to 2.72 ng/ml/hr; $p < 0.05$) in 2/3 of the patients. The levels of A increased in all patients but not significantly.

The PRL hyper-responses to DMP in IDDM patients fit well with the hypothesis of abnormalities in dopaminergic tonus. Similar impairments seem to cause the unexpected PRA and A responses. The pathogenesis remains unknown.

142 SUPERFICIAL CHRONIC GASTRITIS IN IDDM CHILDREN.

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Hypergastrinemia (↑ G), hypopepsinogenemia (↓ PG1) and gastric parietal cells autoantibodies (PCA) are considered as markers of atrophic gastritis which is a common complication in diabetic adults.

We investigated 32 insulin treated, non ketotic IDDM children (5 to 18 yrs old), without any gastro-intestinal symptom, with diabetes lasting from 2 to 130 mos. ↑ G, ↓ PG1 and PCA have been found (single or in association) in 7/32 subjects (21,8%; 4 F-3 M).

In 5 of them a multiple perendoscopic gastric biopsy showed the histological pattern of a chronic superficial gastritis of antral and fundic mucosa in 2 females without correlation with a duration of diabetes.

In conclusion:

- A chronic superficial gastritis may be present, in single cases of IDDM. yet in the pediatric age. It may be clinically silent but ↑ G ↓ PG1 and PCA seem to be useful indicators.
- The pathogenesis and the possible relationship with the atrophic gastritis of diabetic adult are still to be clarified.

143 B-EP RESPONSE TO TRH/LHRH IN DIABETIC CHILDREN (IDDM).

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Opiate receptors seem to play a role in the maintenance of glucose homeostasis. Both B-endorphin (B-EP) and opiate antagonist drugs may modulate the endocrine pancreas secretions. Considering the changes of circulating B-EP through puberty, we studied B-EP plasma levels in IDDM patients. Since IDDM children are characterized by LH/FSH aspecific rises after TRH injection, we also evaluated the B-EP pattern after TRH and LHRH administration. In 46 IDDM patients (7-18 years),under insulin treatment, blood sample was collected in basal condition and in 16 of them TRH (200 mcg, i.v.) and LHRH (50 mcg, i.v.) tests were performed. B-EP levels were measured after silicic acid extraction and Sephadex G-75 column cromatography, by RIA utilizing material provided by C.H. Li (San Francisco). Basal B-EP levels in IDDM children were similar to age-matched controls; no correlation was found with the duration and the metabolic control of the disease. LHRH stimulated B-EP release between 60' and 120' ($p < 0.05$) (from 5.8±1.2 fmol/ml to 13±1.8 M±SD) in about 30% of the patients, namely those at more enhanced stage of puberty. Similary TRH induced B-EP increase between 90' and 120' ($p < 0.01$) in the 45% of the patients (from 5.5±1.2 to 13.5±1.4). No B-EP changes was observed in healthy controls under similar experimental conditions. These data suggest: 1)IDDM does not seem to influence plasma B-EP levels, at least in well controlled subjects; 2) the aspecific pituitary responses to hypothalamic releasing-hormones previously described in IDDM patients, involve also B-EP release.

144 ALTERED DRUG METABOLISM IN POORLY CONTROLLED INSULIN DEPENDENT DIABETES MELLITUS (IDDM).

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Animal experiments have documented alterations in hepatic drug metabolism in diabetic rats. In addition to abnormalities in glycosylation of hemoglobin other heme proteins such as cytochrome P-450 might also be expected to be altered. We report here changes in cytochrome P-450 dependent drug metabolizing activity in children with IDDM. We have studied antipyrine (AP) kinetics in 8 children (age 10-22 yr) with IDDM of at least 3 months duration who were all in poor control as defined by Hgb A1 levels. Liver function tests and renal function were normal. Insulin dose ranged between 0.5-1 U/kg. AP (test dose 16 mg/kg p.o.) is widely used as a measure of hepatic drug metabolism in man. Its elimination from plasma is largely determined by hepatic oxidizing enzyme activity. AP kinetics were compared to age matched controls (mean±1 SD) AVD: volume of distribution.

	AP $t_{1/2}$ (hrs)	AP Clearance (ml/min/kg)	AP AVD (L/kg)	Hgb A1 (%)	
Diab.	4.6±0.4*	1.22±0.2**	0.55±0.2	13±2.4	* $p<.01$
Control	8.1±1	0.80±0.19	0.6 ±0.21	<8	** $p<.05$

In three IDDM patients with near nl Hgb A1 levels (6.8,7.1,8%) AP $t_{1/2}$ was nl when compared to age matched controls (8.1,9.2,8hr) as was AP clearance.

Conclusion: In poorly controlled IDDM hepatic drug metabolism may be altered: AP clearance is increased, AP $t_{1/2}$ is shortened. In well controlled IDDM antipyrine drug metabolism appears to be nl. These findings provide another cogent argument for tight metabolic control in youngsters with IDDM.

145 GROWTH HORMONE RECEPTORS AND THE ONSET OF HYPERINSULINEMIA IN THE OBESE ZUCKER RAT.

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Growth hormone (GH) release, hepatic GH and insulin receptors have been studied in the genetically obese male Zucker (fa/fa) rat. In chronically cannulated 14 week-old rats, the pulsatile GH secretion is suppressed in obese rats and the GH pituitary content is 2 times lower in fa/fa than in lean animals. At 2, 3 and 5 weeks of age, no difference in the pituitary GH content is found in the two groups. At 23 days of age, fa/fa rats have a two-fold increase in their plasma insulin level ; the specific binding of ^{125}I-hGH to liver membranes of obese male rats as compared to lean littermates is increased, 2.8 times in plasma membranes, 1.4 times in Golgi fractions. At 5, 11 and 14 weeks of age, plasma insulin is markedly elevated in obese rats and the level of GH receptors is higher in all liver subfractions of obese rats as compared to lean rats. After the 11th week, hyperinsulinemia is associated with a decrease binding of insulin to plasma membranes and to microsomal fractions of obese rats. Before the increase in plasma insulin appears, at 16 days of age, no difference in the level of GH receptors exists in plasma membranes and Golgi fractions of fa/fa rats and of their lean littermates. The increase in GH binding observed in obese male rats is simultaneous with the onset of hyperinsulinemia.

146 IMMUNOGENETIC STUDIES OF SPONTANEOUS DIABETES MELLITUS IN THE RAT.

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The major histocompatibility complex (MHC) of the rat, RT1, codes for class I(RT1.A) and class II (RT1.B and RT1.D) products. The presence of at least 1 u haplotype derived from a BB diabetic rat (RT1.AuBuDu) is necessary for the development of diabetes (DM). We now report that the Class II gene products (coded by the RT1.B and RT1.D loci) of the BB strain and the DM strains derived from them do not differ from the Class II products found in the non-DM inbred Wistar Furth rat (RT1.AuBuDu). A cross between the homozygous u/u DM rat and rats of the inbred PVG.R8(RT1.AaBuDu) strain results in F2 DM animals typing u/u,u/a, and a/a at the RT1.A locus. Since all animals in these crosses are homozygous u/u at the RT1.B and D loci, the results suggest that (1) Class I MHC gene products are not necessary for DM and (2) RT1 B and D genes(or genes closely linked to them) from non-diabetic inbred strains bearing the u haplotype can, in conjunction with other genetic or environemntal factors, confer susceptibility to DM. In such susceptible rats increased numbers of peripheral blood lymphocytes capable of binding a mouse ascites protein provide a marker of conA unresponsiveness and are a more reliable predictor of DM susceptibility than enumerations of lymphocyte subsets by monoclonal antibody staining.