65 EFFECTS OF TAURINE (T) AND URSODEOXYCHOLIC ACID (UDCA) ON LIVER FUNCTION TESTS IN PATIENTS WITH CYSTIC FIBROSIS

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Patients with Cystic Fibrosis (CF) often develop liver disease and although the mechanism leading to the pathognomonic lesion (focal biliary cirrhosis) is still unknown, quantitative/qualitative alterations in bile secretion may of of major importance. Correction of the complex abnormalities of bile acid (BA) metabolism described in these patients, (BA malabsorption with predominance of relatively more hydrophobic glycine-conjugated BA), may thus slow the progress of liver involvement associated to CF. Recently, a shift of the BA pool composition towards more hydrophilic-less hepatotoxic components, induced by UDCA and, in one report, by T administration, has been shown to be beneficial in adults with Primary Biliary Cirrhosis and Chronic Hepatitis. In 6 CF patients (aged 8-12 years) with clinical and biochemical signs of liver involvement but no portal hypertension, T (30 mg/Kg/die) was administered one month before and during the successive treatment with UDCA (10-15 mg/Kg/die). Liver functin tests were determined before and during each period of treatment, fecal fat and BA (GLC) exretion and biliary BA composition (HPLC) before and after long term administration of UDCA and T. Before treatment, both mean coefficient of fat absorption n enzymatic therapy (83.7 ± 10%) and fecal BA excretion (12.3± 5.9 mg/Kg/die) were abnormal. Chenodeoxycholic acid was predominant among biliary BA (44.1 ± 9.1%) and the glycine to taurine conjugate ratio was 2.7 ± 2.0. T administration produced only inconsistent changes of lvier function tests from basal abnormal values, whereas in patients treated fo two months with T + UDCA a substantial improvement was observed: AST -28%, ALT -40%, GT -33%, Alkaline Phosphatase -19%. The effects of longer periods of treatment are currently investigated, with purpose of establishing their relationship with changes in the BA pool composition.

66 ROLE OF IMMUNOGLOBULIN IN GASTROINTESTINAL TRACT GROWTH OF CHOLESTEROL FED PIGLETS.

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The gastrointestinal tract of a newborn piglet undergoes a remarkable increase in weight, length, protein, and DNA content when the piglet is suckled during the first day of life (Widdowson 1976). We have confirmed this observation and have observed that the increases are dependent upon the feeding of pig colostrum or colostral whey. When the piglet is given cow's milk formula or mature pig milk, gastrointestinal growth does not occur. The rate of intestinal growth is most evidence by 6 and 12 h of life. Histologic examination revals no increase in mitosis during this period, although protein is stored in the "lysosomes" of villar enterocytes of the suckled piglet. Because IgG is abundant in pig colostrum (up to 80% of why protein) we examined the function of IgG in mucosal growth and lysosomal storage observed histologically. Pig colostral whey was depleted of IgG by thiophilic column chromatography. When we fed the IgG-depleted colostral whey, we found reduced intestinal growth and no evidence for IgG transport or "lysosomal" storage. We conclude that IgG "lysosomal" storage accounts for a major proportion of the previously reported intestinal growth in the suckled piglet.

67 EFFECT OF FEEDING ON SUCRASE PROCESSING IN VIVO

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Brush border sucrase (S) is derived from precursor sucrase-isomaltase (SI) by post-translational glycosylation and proteolysis. We have examined the effect of feeding on the rate at which the conrvsion proceeds in vivo. Fasted)n = 9) and fed (n = 8) rats received a constant infusion of ^{3}H-leucine for 1 to 6 h. Triton extracts of mucosal membranes were treated with purified anti-sucrase monoclonal antibody bound to sepharose. SI and S were separated by SDS-PACE, and the specific radioactivity (SR) of leucine in SI and S and mucosal free amino acids (F) was measured after isolation by ion-exchange chromatography. Leucine in SI attained an isotopic steady state by 1 hour and at plateau the ratio SR of SI/SR of F was 2.6 ± 0.3 (fasted) and 1.7 ± 0.1 (fed). Preliminary results suggest that the half-life of the SI to S conversion was 6.7 ° 0.6 h (fasted) and 5.6 ± 0.5 h (fed). We conclude that the regulation of the rate of SI processing may be of importance to the nutritional regulatio of the steady state concentration of sucrase. As such it provides a control step that is superimposed on the regulation of the transcription of the SI gene.

68 LATE ONSET LACTASE DEFICIENCY: EVIDENCE OF ALTERATIONS IN THE POST-TRANSLATIONAL PROCESSING OF LACTASE.

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Twenty volunteers with late-onset clinical lactose-intolerance have been investigated. Mean lactase activity measured in small intestinal biopsy homogenates was 8.55 IU/g protein vs 27.4 IU/g protein in controls (31/2%), mean sucrase activity was 74.6 IU/g protein vs 46.1 IU/g protein in controls (161.8%). Maltase and Isomaltase activities were not significantly different. The ratio of total lactase-protein to aminopeptidase N-protein was reduced to 14.7% as assessed by analysis of iodinated and immunoprecipitated protein on SDS-PAGE. Biosynthesis of lactase, sucrase and aminopeptidase N was studied in organ culture of small intestinal biopsies, followed by analysis of immunoisolated enzymes on SDS-PAGE In biopsies from individuals with reduced lactase activity biosynthesis of lactase was reduced to (10%, while biosynthesis of sucrase was increased to 223%.) In addition, proteolytic processing of Pro-lactase to the mature enzyme was found to be occurring at a much lower rate. After 4 h of culture, 82% of total lactase was still present in the form of Pro-lactase in tissue from lactase-deficient individuals whereas in control tissue this was only 41%. Immuno-electron-microscopy wit protein A-gold-labelling revealed an accumulation of immuno-reactive staining in the Golgi region of enterocytes from lactase-deficient tissue with almost absent staining in the microvillus membrane.
Conclusion: In late-onset lactase-deficiency, biosynthesis of lactase is reduced at the transcriptional or translational level, and in addition post-translational proteolytic processing is slowed down leading to an intracellular accumulation of lactase and probably to its subsequent intracellular degradation, thus preventing the synthesised molecules from reaching the microvillus membrane. An unexpected finding was the increased level of sucrase in tissue from lactase-deficient individuals. Possibily, this is an attempt by the enterocytes to compensate for the inability to hydrolyse lactose.

69 GENETIC DIFFERENCE IN HLA-DR PHENOTYPES BETWEEN CHILDREN WITH COELIAC DISEASE AND 'TRANSIENT' COELIAC DISEASE

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Aims: The reason why some of the patients with initially diagnosed coeliac disease (CD) according to the first 3 criteria of ESPGAN do not react with mucosal damage after gluten challenge remains unclear. We investigated whether genetic variances on their HLA-DR phenotypes could account for the different course of the disease.
Methods: 61 children with CD were typed for their HLA-DR phenotypes according to standard techniques. 45 of the CD patients were true coeliacs according to the 4 criteria of ESPGAN. In contract 16 showed no mucosal relapse after prospective gluten ghallenge. 76 normal subjects from the area served as controls. Statistical analysis with two tailed p-value was calculated using Fisher's chi-square test after Yates correction.
Results:

HLA-DR	Controls (n= 76) %	True CD (n=45) %	Transient CD (n=16) %
DR3	0	4.4	12.5
DR5	1.3	0	0
DR7	25	6.7	12.5
DR5/Dr7	5.2	26.7*	0
DR3/Dr7	11	24.4	12.5

*= p (0.01

Conclusion:
HLA-DR phenotypes in hildren with 'true' CD show significantly higher proportions of DR 5/DR 7 or DR3/DR 7 than those with 'transient' CD. We speculate that mucosal reactions to gluten by later challenges might depend upon the HLA-DR phenotype of the host. Thus HLA-typing might even be of predictive value in CD.

70 POSSIBLE TRANSCRIPTIONAL REGULATION OF SUCRASE-ISOMALTASE (SI) EXPRESSION IN A NEW PHENOTYPE OF CONGENITAL SI-DEFICIENCY (CSID) IN HUMANS.

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Aims: In a recent paper (Naim et al.,J.Clin.Invest.,82:667,1988) three phenoptypes of CSID have been characterized in which different mutations in the SI gene lead to the synthesis of transport-incompetent or functionally altered enzyme. In this communication three biopsies from patients with CSID were investigated.
Methods: Biopsies were studied in organ culture by labelling newly synthesised proteins with ^{35}S-methionine for 6 hours continuous pulse. They were further processed by immunoprecipitation with monoclonal natibodies (Mab's) against SI and analysed by SDS-PAGE. Sucrase and isomaltase activities were measured in parallel.
Results: The synthesis of SI was completely abolished in two biopsy samples, since no SI molecules were immunoprecipitated with a mixture of four epitope-specific Mab's against SI. In one biopsy sample very little precursor and mature form of SI were detected. In contrast the biosynthesis and processing of the control brush border glyco-proteins aminopeptidase N and lactase-phlorizin hydrolase in the biopsies form these patients were similar to those found in normal controls. Sucrase and isomaltase activities were absent or drastically reduced.
Conclusion: We conclude that in this novel phenotype of CSID the expression of SI is affected already at the transcriptional level resulting in the failure to generate (or if any, very few) mRNA coding for CSID. We describe herewith a fourth phenotype of CSID in addition to those published previously.