73 BILIARY BILE ACID COMPOSITION IN THE HUMAN FETUS.

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Using adequate analytical techniques,which included capillary column gas-liquid chromatography and mass-spectrometry,detailed bile acid (BA) profiles were obtained from 23 fetal bile samples,collected after legal aborption performed between the 14th to 20th week of gestation.Qualitatively,all fetal bile samples were similar:the predominant BA were chenodeoxycholic (CDCA)and cholic (CA) acids.The presence of variable amounts of deoxycholic and lithocholic acids suggested placental transfer of these BA from the maternal circulation;3ß-hydroxy-5-cholenoic acid was bearly detectable.A conspicous feature of the profiles was the presence of BA with hydroxyl groups in position C_1,C_2,C_6, indicating fetal hepatic synthesis via pathways different from those normally seen in adults. Quantitatively,total biliary BA concentrations were extremely low(less than 0.1mM/L) before week 17 of gestation,but thereafter concentrations rapidly increased (greater than 10 fold),reflecting a surge in BA synthesis.However the ratio of CDCA to CA remained relatively constant over this period (mean 1.5) and different from normal adult (0.9).
These data indicate an immaturity in hepatic 12-α-hydroxylation of BA during development and that other synthetic pathways are active at this stage of life.It is of interest that BA metabolism in the adult with severe cholestatic liver disease shows striking similarities to that seen in this study on the fetus.

74 A SIMPLE METHOD FOR THE DETERMINATION OF BILE ACID POOL COMPOSITION IN MAN.

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A method has been developed for easy determination of duodenal bile acids. For this purpose Entero-Test(R)was used, an encapsulated nylon thread originally used for diagnosis of enteral parasites. The capsule is swallowed in a fasting state and one end of the thread is taped at a corner of the mouth. Four hours after swallowing the thread, it is withdrawn and bile acids are eluted with phosphate buffer. The solution is applied to a Sep-Pak C18 cartridge to extract bile acids, which are subsequently analysed by capillary gas chromatography and liquid chromatography.
In vitro analyses showed that there was no preferential binding to the thread of any bile acid and that binding was pH independent. A high correlation (r=0.98) was found between direct analyses of bile and analyses by Entero-Test after in vitro incubation. The values obtained by the Entero-Test were similar to those of duodenal bile simultaneously collected with the normal intubation technique (r=0.99). Duodenal bile acid composition showed a variation measured over weeks. In 11 healthy volunteers the following bile acid composition of unstimulated duodenal juice was found (mean ± SD;%) cholate: 44±12 (glycine/taurine ratio 1.8), chenodeoxycholate: 29±6 (G/T ratio 2.3), deoxycholate: 25±11 (G/T ratio 5.7), lithocholate: 1,ursodeoxycholate: < 1.
The described technique enables longitudinal studies concerning the effects of nutrients on the bile acid pool composition and its relevance to various diseases.

75 ABNORMAL THERMOGENESIS IN DIABETIC CHILDREN RECEIVING CONTINUOUS SUBCUTANEOUS INSULIN INFUSION THERAPY

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The normalization of metabolism with continuous subcutaneous insulin infusion /CSII/ is still questionable and rapid metabolic decompensation due to mechanical failure is reportedly the most frequent complication. In spite of normal blood glucose /BG/,metabolites and normal resting metabolic rate /RMR/,food-induced thermogenesis /FIT/ measured by indirect calorimetry after a standardized meal was abnormally high /4.7±0.6 kJ/kg lean body weight /LBW//3 hr/ in 12 diabetic children /DC/ as compared to 9 controls /2.9±0.4 kJ/kg LBW/3 hr/ /p<0.02/. In order to simulate pump-failure and to further study thermogenesis,measurements were repeated on Day 2 except that no insulin was given for 2 to 5 hours. Short-term insulin insufficiency /51±15 vs 272±61 pmol/l,Day 2 vs Day 1,p<0.01/ resulting in hyperglycaemia /BG:16.2±1.6 vs 5.1±0.5 mmol/l,p<0.01/ and mild ketosis /beta-hydroxybutyrate:595±185 vs 50±12 nmol/l,p<0.01/ were associated with rising RMR /5.6±0.3 to 6.4±0.4 kJ/kg LBW/1hr, p<0.005/ and with a markedly reduced FIT /4.7±0.6 vs 3.3±0.4 kJ/kg LBW/3 hr,p<0.01/. In conclusion,in spite of normoglycaemia and normal RMR,FIT was high in DC receiving CSII. During acute insulin-lack RMR rose and FIT was reduced but not abolished.

76 IMPAIRED CHOLESTEROL SIDE CHAIN CLEAVAGE IN PATIENTS WITHOUT PEROXISOMES (ZELLWEGER SYNDROME).

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Di- and trihydroxycoprostanoic acid (D-, THCA), normal intermediates of bile acid synthesis in man, are usually undetectable in normal serum. Very high levels however are found in the serum of patients with Zellweger Syndrome (ZS), an entity in which the absence of morphologically distinquishable peroxisomes can be considered as the most conspicous finding. To explain the accumulation of D- and THCA,C27-bile acids with an incompletely oxidized side chain, we studied the side chain cleavage activity from cholesterol to primary bile acids in liver homogenates from controls and ZS-patients. The results presented indicate a strongly reduced cholesterol side chain cleavage activity in the liver from ZS patients (n=3) ranging from 9-14% of the activity in normal controls.
The findings that in experimental animals clofibrate stimulates both bile acid formation and fatty acid ß-oxidation, together with the reported deficiency of all fatty acid ß-oxidation enzymes in ZS and the impaired chain shortening of fatty- and bile acids suggest that the same set of enzymes is involved in the ß-oxidation of longchain fatty acids and C27-bile acids. These findings in ZS patients lacking peroxisomes not only provide an explanation for the D- and THCA accumulation in the serum, but it also suggests that peroxisomes are involved in bile acid metabolism in man and especially in the side chain cleavage process. This conclusion is supported by recent findings in the rat.

77 SPECIES DEPENDENCE OF THE HYPERCHOLESTEROLEMIC EFFECT OF DIETARY CASEIN

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We have hypothesized that casein, a phosphorylated protein, binds to an intestinal calcium-phosphate (CaP_i) sediment and thus inhibits the efflux of bile acids from the enterohepatic cycle (EHC); consequently serum cholesterol may increase. This hypothesis has been supported by in vitro studies, which showed that unconjugated and glycine-conjugated bile acids bind to insoluble CaP_i. This binding is inhibited by casein but not by dephosphorylated casein. In vivo studies with rabbits showed that dietary casein immediately inhibited the fecal output of bile acids. This inhibition preceded casein-induced hypercholesterolemia, indicating a cause-and-effect relationship. When rabbits were fed dephosphorylated casein, none of these casein-specific effects was observed. This indicates that the hypercholesterolemic effect of casein is due to its phosphorylation state. In species (like rat and man) with a high activity of intestinal phosphatase and a significant taurine conjugation of bile acids, casein neither affects the EHC of bile acids nor the serum cholesterol concentration. Results indicate that in these species the mucosal enzyme alkaline phosphatase dephosphorylates dietary casein, thus preventing hypercholesterolemia.
In conclusion: the species-dependence of casein-induced hypercholesterolemia seems to be due to species-dependent differences in activity of intestinal phosphatase and in glycine/taurine conjugation of bile acids.

78 GESTATIONAL DIABETES AND CURACAOAN BEANS

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In Curacao gestational diabetes is a great problem (incidence 2.4 /100 deliveries). The assumption that this high incidence is a direct consequence of the change in the feeding pattern over the last decades,is uncertain.
In former days, beans were commonly used in the local diet in Curaçao. Nowadays these beans are mainly replaced by those foods rich in "simple" carbohydrates and fats.
We compared the effect of the consumption of 5 locally grown beans (Bonchi Cora, Bonchi Pela Berde, Bonchi Wandu, Bonchi di Kunuku and Bonchi Wowo Pretu) on the blood glucose response in non-pregnant, healthy pregnant women and gestational diabetes patients. In this study all beans investigated showed a lower relative blood glucose response as compared to a bread meal (with the same carbohydrate content). A lower relative blood glucose response for some of the tested beans was found in pregnant women as compared to non-pregnant women and an even lower response was recorded in the group of mothers with gestational diabetes.
A lower average blood sugar concentration during pregnancy, as induced by the consumption of foods with a low relative blood glucose response, may improve the outcome of the fetus (especially in gestationally induced diabetes) and may thus contribute to the prevention of handicap.