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3-KETOTHIOLASE DEFICIENCY: BIOCHEMICAL INVESTIGATION OF 15 CASES

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3-ketothiolase deficiency is an inherited disorder of isoleucine degradation, characterized by excretion of 2-methyl-3-hydroxybutyric acid and tiglylglycine. The clinical findings vary widely, from life-threatening acidosis a few days after birth, to single episodes of acidosis in late childhood.
We have investigated the biochemical basis of this clinical heterogeneity. The pathway of isoleucine degradation was studied in cultured fibroblasts by measuring the incorporation of 14-C from 2-methylbutyric acid into protein (Iden et al. Soc Study Inborn Errors Metab, 24th Ann Symp, Amersfoort 1986, Abstr 25). Fibroblasts from 18 verified or suspected cases of 3-ketothiolase deficiency were studied. Three cell lines showed normal incorporation, whereas in 15 cases the incorporation varied from 2% to 79% of controls, low incorporation correlating with clinically severe disease.

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Glucose metabolism in patients with glycogenosis type III.

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In patients with glycogen storage disease due to the deficiency of debranching enzyme glycogen is only a limited source of glucose. It is unknown to what extent these patients produce glucose endogenously. We have measured the turnover and endogenous production of glucose in patients after fasting by isotope-dilution with 6.6-$^2H_2$-glucose. 7 Patients between 1 and 16 yr of age were studied. During the measurement the average glucose concentration in blood was 2.6±0.3mM. The glucose turnover decreased from 6.7±0.5mg/kg min at 1 yr of age to 2.2±0.1 mg/kg min at 16 yr of age. The turnover was 0.73± 0.13 of normal. The endogenous production of glucose decreased from 4.9± 0.6 mg/kg min at 1 yr of age to 1.6± 0.1 at 16 yr of age. In our patients the endogenous glucose production was 0.72±0.07 of the turnover. These data indicate that these patients have a nearly normal glucose turnover and a glucose production too low for the demand.

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POLYMORPHONUCLEAR LEUCOCYTES (PML) AS A MODEL TO ASSESS INTRACELLULAR METABOLISM IN DIALYSED PATIENTS

The optimal dialysis procedure for treatment of end-stage renal disease in children is still controversial. By using the PML model we have studied the different influences of regular hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) on cell metabolism. We determined protein synthesis (PS, by ^{3}H-LEU incorporation), intracellular amino acids (AA, by reverse phase HPLC), glycolytic enzymes (PK, PFK) and energy rich adenine nucleotides in PML of 26 patients aged 2-22 yrs either on HD (n= 8) or on CAPD (n=18) compared to controls (C, n=20). PS was more reduced on HD (m±SEM: 699±220 pmoles/h/mg DNA, $p < 0.02$) than on CAPD (1184±173 vs 1649±217 in C, NS). Profound alterations were observed in intracellular AA in both CAPD and HD. Activities of PK (means: HD 12678*/CAPD 8457/C 6314 u/mg DNA) and PK (134*/179*/ 104 u/mg DNA) were significantly* increased in patients. Energy change derived from adenine nucleotide levels was significantly increased on CAPD (0.918 vs 0.896 in C). These results suggest improved PS by CAPD compared to HD.

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Role of red blood cells (RBC) in amino acid (AA) interorgan transport in vivo in man : a stable isotope study.

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RBC contain most AA at concentrations as high or higher than plasma. Yet their role in AA interorgan transport is controversial, since AA uptake by RBC is very slow in vitro. We therefore used 4-hr primed, continuous intravenous infusions of L-[^{13}C]leucine, [^{15}N]glycine, and L-[^{15}N]alanine to assess AA exchange between plasma and RBC in vivo. Stable isotope enrichments and AA levels were measured by gas chromatography-mass spectrometry in both plasma and whole blood, and calculated (using hematocrit) for RBC. Results were as follows (mean of 5 subjects ± S.D.) :

	Amino acid levels (μM)		Steady state Tracer enrichment
	Plasma	RBC	RBC/Plasma
Leucine	176 ± 44	141 ± 52	1.08 ± 0.15
Glycine	155 ± 35	552 ± 268	0.23 ± 0.04
Alanine	192 ± 94	216 ± 97	0.59 ± 0.09

We conclude that the exchange of leucine between plasma and RBC in vivo is much faster than that of alanine and glycine. These data suggest that the role of RBC in AA interorgan transport differs widely from one class of AA to the other.

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5 years follow-up of a male patient homozygous for familial hypercholesterolemia treated with repeated plasma exchanges.

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A boy suffering from multiple tendinous xanthomas has been diagnosed as being affected by the homozygous form of familial hypercholesterolemia (FH) at the age of 16 years. Both parents had hypercholesterolemia, the patient had total cholesterol 650, LDL-chol. 570 and LDL-Apo B of 253 mg/dl prior to treatment. Coronary angiography showed complete stenosis of LAD, the patients fibroblasts were LDL-receptor negative. Dietary and drug regimen did not show any significant cholesterol lowering; repeated plasma exchanges have been performed in order to remove the atherogenic LDL particles. In total, within 5 years 55 exchanges have been performed without any problems. During these procedures approx. 110 l plasma has been removed, containing about 300 g pure cholesterol. Repeated coronary angiography after 4 years did not reveal any signs of a progression of the atherosclerotic process. It is concluded from the long-term observation that continuous plasma exchange is to be considered as an effective treatment of the homozygous form of FH and definitively inhibits the progression of atherogenesis.

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Lipids and lipoproteins in children of male patients who had a myocardial infarction

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There are recent contradictory reports, whether lipids, lipoproteins and apoproteins are slightly different in the children of fathers who had suffered from a myocardial infarction compared to control subjects. Therefore we studied lipids, lipoproteins and apolipoproteins (A I, A II and B) in 56 children and adolescents and their fathers (n=40, mean age 44.6±7 years) who had a myocardial infarction within the last 6 months.
Results:

mg/dl	n	Chol.	TG	LDL-C	HDL-C
Fathers	40	242±54	151±79	185±53	38.3±10
children 14 yrs.	20	166±26	66±27	103±24	51±20
children 14-20yrs.	20	168±45	65±24	116±38	46±11
adolescents>20yrs.	16	177±35	87±54	124±34	47±10

Using the percentiles of lipoproteinslipids of the Lipid Research Clinics Study, 16 of the 56 (=28,5 %) children had had values higher than the 90th (Chol., TG, LDL-C) or lower than the 10th percentile (HDL-C). Mean apolipoprotein concentrations however, did not differ significantly from those of control subjects. This fact emphasizes the importance of screening procedures for lipoprotein abnormalities in affected family members.