119 DOES EARLY DIETARY REGIMEN INFLUENCE CHOLESTEROL METABOLISM IN ADULT LIFE? A STUDY IN MONGOLIAN GERBILS

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Effects of neonatal dietary and medicamental manipulations of steroid metabolism lasting into adult life have been demonstrated in rats and guinea pigs (e.g. Reiser, 1972, J Nutr 102:1009; Li, 1980, J Clin Invest 65:1060). We tried to confirm these data in an other species that shows a distinct effect of diet on cholesterol metabolism. In our study a more physiological approach was chosen.

Mongolian gerbils were put on 6 different diets during 3 generations. Three groups got a basic diet with soy-oil(S), or pal-kernel-oil(P) amounting to 8.75%(w/w) of each oil, or the basic diet only(B). In three other groups 0.05% (w/w) cholesterol(C) was added to the same diets (SC, PC and BC). At the age of 6 months of the 3d generation the diets were replaced by B till 12 months. At that age the gerbils were challenged with C during 2.5 weeks.

Maternal diets profoundly influenced serum and carcass-C of 2-week-old sucklings. At 12 months only serum-C showed differences: BC, 3.01±0.77 vs. B, 2.31±0.42 and S, 2.33±0.24, $p<0.05$. However, after additional challenge with C, the differences were not significant any more.

These data obtained in gerbils, do not support the theory that early dietary manipulations prevent hypercholesterolemia in adult life.

120 High concentrations of glutathione peroxidase (GP) and superoxide dismutase (SOD) in Lesch - Nyhan patients.

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Lesch-Nyhan patients have high concentrations of hypoxanthine in their tissues and body fluids. Since hypoxanthine is a potential oxygen radical generator these patients might be susceptible to a higher oxidative stress than healthy controls. To test this hypothesis we have measured the concentrations of different oxygen radical scavengers in five patients with the Lesch - Nyhan syndrome.

	erythrocyte GP ukat/g Hgb	plasma CuZn-SOD U/ml	plasma Mn-SOD U/ml	plasma EC-SOD U/ml	erythrocyte CuZn-SOD U/mg Hgb
patients	1.68	5.9	8.0	20.1	56.9
n = 5	(.36)	(.6)	(4.6)	(4.3)	(4.7)
controls	.92	2.8	5.4	19.6	57.6
n = 21	(.17)	(.9)	(.5)	(3.0)	(4.1)
p <	.001	.001	.05	NS	NS

These data indicate that Lesch-Nyhan patients are exposed to a higher oxidative load than healthy controls. It is suggested that abundant oxygen radicals are formed through the hypoxanthine - xanthine oxidase system in these patients and it is speculated whether these findings can explain some of the clinical features in Lesch - Nyhan patients.

121 TISSUE LYSYL OXIDASE ACTIVITY IS DECREASED IN MENKES' DISEASE.

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The X-linked recessively inherited disorder, Menkes' disease, is characterised by progressive cerebral degeneration and connective tissue abnormalities. Although the basic defect remains unknown, it appears to render copper unavailable to copper-dependent enzymes. The connective tissue defects are thus explicable on the basis of reduced activity of lysyl oxidase, which initiates the crosslinking of collagen and elastin. Since tissue levels of this enzyme have not previously been determined in Menkes' disease, we have measured its activity in extracts of skin and aorta from a patient who died at 11 months of age with unusually marked connective tissue involvement, i.e. osteoporosis, Wormian bones, pathological fractures, cutis laxa, bladder diverticula and tortuosity of arteries. We found it, indeed, to be only 10-15% of that in extracts from age-matched controls. Despite this, the ratio of β to α components of pepsin-extracted type I collagen from these two tissues appeared to be normal, and it may be that low levels of lysyl oxidase affect the crosslinking of elastin to a greater extent than that of collagen.

122 SORBITOL DEHYDROGENASE IN HUMAN LENS: STUDY OF THE ENZYME IN VARIOUS HUMAN TISSUES.

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Several patients with congenital cataracts were described to have a deficient sorbitol dehydrogenase activity in erythrocytes (Human Genet. 61:338, 1982; J.Inher.Metab.Dis. 7 Suppl.2:151,1984). Since there were obscure findings concerning the erythrocyte enzyme activity and the inheritance, we have studied the enzyme in lens and compared its property with that in other tissues such as liver and blood. The specific activity of sorbitol dehydrogenase in lens was higher than in liver (4.9-5.4 nmol/min/mg protein vs. 2.9-4.2 n=8 each). The Michaelis constant for sorbitol was low in lens compared to that in other tissues (0.9 nmol/L in lens, 2.6 mmol/L in liver). Polyacrylamide gel isoelectrofocusing of the enzyme in lens showed multiple bands between pH 4.4-8.1, while in liver 2-4 bands at pH 7.0-8.6 and in erythrocytes 3-4 bands at pH 7.6-8.4. Xylitol inhibited the enzyme in all samples studied by 30-50 %, whereas xylulose activated the enzyme by 200% in liver, in lens and erythrocytes by 40-60 %. These results indicate that sorbitol dehydrogenase in lens is unique compared with that in liver or erythrocytes.

123 TYPE I HEREDITARY TYROSINEMIA: CHARACTERIZATION OF HUMAN cDNA CLONES ENCODING PEPTIDES IMMUNE-REACTING WITH ANTIBODIES AGAINST FUMARYLACETOACETASE FROM BEEF-LIVER.

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Patients suffering from type I hereditary tyrosinemia exhibit a profound deficiency of fumarylacetoacetase activity in liver, kidney and white blood cells. We have shown previously by the use of antibodies raised against fumarylacetoacetase from beef-liver that cross-reacting material is absent in cells and tissues from patients. In order to characterize the mutations causing type I hereditary tyrosinemia we set out to screen a human cDNA library from liver with antibodies against the beef-enzyme. Four unique clones encoding peptides cross-reacting with the antibodies have been identified. It was shown by cross-hybridization that these clones overlapped with each other. All four cloned fragments were complementary to the same region of human chromosomal DNA. The total length of cDNA encompassed by the four fragments is appr.1800 base pairs. We will present the nucleotide sequence of this DNA and the results of investigations on the expression of the normal vs the mutant gene.

124 EMBRYONIC CELL-POLYMERASES: SEPARATION FROM REVERSE TRANSCRIPTASE IN EMBRYOS OF THE JAPANESE QUAIL

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Retrovirus-like particles have been assumed to play a physiological role in embryogenesis. They have been found in embryos of all investigated species including the japanese quail and man (1), which were previously thought to be virus free. Their final identification as particle-bound reverse transcriptase (RT) (RNA-dependent DNA-poymerase) requires a precise characterization against DNA-dependent DNA-polymerase which are co-purified with these particles from embryonic tissues. After further purification by ion-exchange and affinity chromatography 2 distinct non-mitochondrial cell-polymerases were characterized by elution profile from DEAE-cellulose (0.09 vs 0.24M KCl for RT), substrate preference (incorporation of ^{3}H-labeled nucleosid-3P: DNA/RNA ratio 50 vs 0.34), inhibitor studies and molecular weight ($4 \cdot 10^4$; $1.4 \cdot 10^5$ D vs $1.1 \cdot 10^5$ D).

Our study reveals distinct difference between reverse transcriptase from retrovirus-like particles and embryonic cell-polymerases which are co-purified with these particles. This provides evidence for a separate identitiy of a retrovirus related polymerase in embryonic tissue.

(1) Mondal H, Hofschneider PH: Int J Cancer 30:281, 1982.