

**31** HEREDITARY DEFECT IN MEMBRANE TRANSPORT OF CARNITINE  
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Of 3 siblings one boy died unexpectedly at 18 mo,  
one girl is healthy and one girl was admitted at 3 yrs  
9 mo with heart failure and signs of dilated cardiomyopathy. Ana-  
lyses of blood collected for PKU-screening showed low carnitine  
conc in the patient and her brother, but normal in her sister.  
Endocardial fibroelastosis and cardiomyopathy was found at autop-  
sy of the dead boy, and similar changes in endomyocardial biop-  
sies of the patient. Carnitine conc in her plasma was 1.2  $\mu\text{mol/l}$ ,  
in skeletal muscle 0.01  $\mu\text{mol/g}$  non-collagen protein (NCP) and in  
heart muscle 0.05  $\mu\text{mol/g}$  NCP. Skeletal muscle showed lipid accu-  
mulation in type 1 fibres and marked atrophy of type 2 fibres.  
The renal clearance of carnitine was very high (72 ml/min/1.73  
sqm BSA). When labeled carnitine was given i.v., 5% was retained  
after 10 days (in parents 85-90%). Skin fibroblasts grown in a  
medium containing carnitine, had a carnitine conc <5% of controls.  
Treatment with oral L-carnitine resulted in rapid clinical improv-  
ment, normalization of echocardiographic variables and of the myo-  
cardial and skeletal muscle biopsies. Carnitine conc remained low  
in heart and muscle.

In conclusion this family expresses a hereditary defect in  
carnitine transport over different cell membranes.

**32** INTESTINAL ABSORPTION OF PTERIDINES IN CHILDHOOD  
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Oral tetrahydrobiopterin (THB) load has been recommen-  
ded for the recognition of THB deficiency among hyper-  
phenylalaninemic infants. In some patients with dihydropteridine  
reductase (DHPR) deficiency, the test has been reported to be in-  
effective. To explore such a resistance to THB, intestinal absorp-  
tion of pteridines was investigated. In 10 control children the  
maximum biopterin (B) serum value was observed 4 hours after oral  
administration of 5 mg/kg THB. A wide range of B increase  
(14.6-190.5 nmol/l, mean : 73.2 nmol/l) was noted, suggesting a  
great variation in the intestinal absorption of THB. A constant  
rate intestinal perfusion study using a double lumen tube and  
polyethylene glycol 4000 as non absorbable marker was performed  
in 8 control infants and 1 adult. Pteridines were separated after  
acid and alkaline oxydation by ion-exchange HPLC chromatography.  
THB, B, and pterin mean absorption rates were as follows : THB =  
14% (n=9), B=3% (n=3), pterin = 80% (n=3). These results show  
a very low intestinal absorption of THB and B in man, and suggest  
the limiting role of the lateral chain 6-dihydroxypropyl, present  
in THB and B, and absent in pterin. They could explain the resis-  
tance to THB during the oral loading test in DHPR deficient  
patients.

**33** PROTEINASE INHIBITOR CBZ-PHE-ALA-CHN, (CBZ): A DRUG  
FOR TREATMENT OF PATIENTS WITH METACHROMATIC LEUCO-  
DYSTROPHY (MLD)?  
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In cultivated fibroblasts from late onset forms of MLD the de-  
gradation of the mutant enzyme is prevented in the presence of  
CBZ (Proc. Natl. Acad. Sci. USA 80, 6066, 83). - When CBZ  
(inhibitor of cathepsin B) was given i. v., i. p. or p. o. to  
female mice a time and dose dependent inhibition of the enzyme  
was demonstrated in the homogenates of different organs. Using  
2 mg/kg i. v. (solvent: propanediol) the highest inhibition was  
found in the heart muscle (~80%) and the lowest in the brain  
(~20%). After 24 h the residual activity of the enzyme was  
60 and 90% of that of controls, suggesting de novo synthesis.  
Similar results were obtained by i. p. and p. o. administration  
of CBZ when 10 and 100 x higher doses were used (solvents:  
propanediol, DMSO). - Experiments with  $\text{H}^3$ -CBZ revealed no  
correlation between accumulation of radioactivity and inhibition  
of cathepsin B in different organs. - Though CBZ permeates the  
blood-brain barrier it seems to be of no therapeutic benefit  
as it's solubility in organic solvents is low.

**34** LEUKODYSTROPHY ASSOCIATED WITH HYPERLYSINORHACHIA  
AND 2-HYDROXYGLUTARIC ACIDURIA.  
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Two daughters of related Turkish parents were investigated at  
the ages of 11 8/12 and 16 8/12 years for severe neurologic  
disease. This was characterised by pronounced psychomotor retar-  
dation, ataxia, dysmetria, dystonia and choreiform movements.  
Both girls were moderately obese and showed macrocephaly without  
dysmorphism. Laboratory investigation revealed increased protido-  
rhachia (120 and 47 mg/dl), and increased cerebrospinal fluid  
lysine (80 and 50  $\mu\text{M}$ ; nl 10-25) and urinary 2-hydroxyglutaric  
acid (400-500  $\mu\text{M/g}$  creatinine; nl < 1). Plasma and urinary lysine  
as well as cerebrospinal fluid 2-hydroxyglutaric acid were normal  
except for a slightly increased plasma lysine in one patient  
(270  $\mu\text{M}$ ; nl 60-230). Electromyography and nerve conduction  
velocity were normal. Computerised tomography of the brain was  
suggestive of leukodystrophy. Conclusion: this seems to be a  
previously unreported hereditary metabolic disorder. Its basic  
defect remains to be determined.

**35** DIFFERENT TYPES OF MUTATIONS IN CHRONIC AND ACUTE FORMS  
OF TYPE 1 TYROSINEMIA. Ruud Berger<sup>1</sup>, Henk van Faassen<sup>1,3</sup>,  
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This study was undertaken to investigate the molecular basis of  
the two different clinical phenotypes (acute and chronic forms) of  
type 1 tyrosinemia (fumarylacetoacetase deficiency). Fumarylaceto-  
acetase (FAA) was isolated from beef liver and antibodies raised in  
rabbits. Analysis of fibroblasts extracts by immunoblotting showed  
the absence of cross-reacting material in cells from acute patients  
and reduced amounts in cells from chronic patients. Fibroblasts  
from controls and from both acute and chronic patients were pulse-  
labeled with  $^3\text{S}$ -methionine followed by a chase of 1-4 days.  
Radioactively labeled FAA was immunoprecipitated with proteinA-  
coupled antibody, dissociated and subjected to SDS-PAGE followed by  
fluorography. In control fibroblasts after pulse-labeling two bands  
could be visualized, the upper band having a molecular size of  
41.200 daltons, the lower band 0.5-1.0 kilodaltons smaller. These  
bands disappeared after 4 days. In fibroblasts from acute patients  
the M=41.200 band after synthesis disappeared within 1 day while in  
cells from chronic patients the rate of disappearance was in  
between. These results indicate that the acute and chronic forms  
of type 1 tyrosinemia are caused by different types of mutations.

**36** HEREDITARY TYROSINEMIA WITH UNUSUAL PHENOTYPIC EXPRES-  
SION. O.Søvik, Haukeland Hospital, Bergen, E.A.Kvitting-  
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In the chronic form of tyrosinemia renal tubular dysfunc-  
tion with secondary hypophosphatemic rickets usually is  
a major finding. Three patients, two brothers and one girl, had at  
the age of 5, 12 and 15 years no generalized hyperaminoaciduria, nor  
clinical signs of rickets. Untreated the elder brother had only  
slightly elevated serum tyrosine, 141  $\mu\text{mol}$  (normal <80), and low  
excretion of p-OH-phenyllactate. He had pronounced thrombocytopenia  
( $8 \times 10^7 / \text{l}$ ). The brother presented 21 months old with large liver.  
Serum tyrosine was 318  $\mu\text{mol/l}$ , the thrombocyte count  $48 \times 10^7 / \text{l}$ . Succinyl-  
acetone was elevated in urine in both. The third patient was  
investigated for hepatomegaly in infancy, but developed normal-  
ly without treatment until she contracted hepatoma at the age of  
15 years. Her plasma tyrosine level was 600 - 700  $\mu\text{mol/l}$ , she ex-  
creted large amounts of p-OH-phenyllactate and succinylacetone in  
urine was low but elevated, 8 mol creatinine. The fumarylaceto-  
acetase activity in fibroblasts from both brothers and in lympho-  
cytes from the girl was less than 5% of normal level. Lack of  
renal tubular dysfunction in patients with the chronic form of  
tyrosinemia, is unusual. However, absence of this finding should  
not preclude the search for this diagnosis in patients otherwise  
suspected for hereditary tyrosinemia.