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BEHAVIORAL PROBLEMS IN VERY LOW BIRTHWEIGHT AND NORMAL BIRTHWEIGHT CONTROLS. P.Zelkowitz, A. Papageorgiou. McGill University and The SMBD-Jewish General Hospital Perinatal Center, Montreal, Canada.

Prematurity and perinatal complications are considered risk factors in the development of behavioral problems in children. We have examined behavioral adjustment in a sample of 100 children (52 age 6y and 48 age 9y) with birthweight < 1500 g. and compared to a normal birthweight control group, matched for age, sex and socio-economic status (SES).Multivariate analysis of covarience with B.W. and age as independent variables and IQ as a covariate was performed on dependent variables consisting of parental ratings of behavioral problems and teachers' ratings of social and academic competence. At age 6, VLBW children were rated as more considerate ($p<.05$) and less aggressive ($p<.01$) than controls. At age 9, the following patterns emerges:

	VLBW age 9y	Control age 9y	P value
PARENT RATINGS	(n=48)	(n=48)	
Conduct problems	3.9 (3.2)	2.8 (2.8)	ns
Learning problems	4.3 (2.8)	1.8 (1.9)	.01
Psychosomatic	0.9 (1.5)	1.3 (1.7)	ns
Impulsivity/ hyperactivity	5.0 (2.9)	3.8 (2.6)	.05
Anxiety	3.7 (2.5)	2.6 (1.8)	.05
TEACHER RATINGS			
Extroversion	27.3 (5.9)	30.8 (6.4)	.05
Aggression	1.6 (2.4)	1.2 (1.6)	ns
Withdrawal	3.0 (2.1)	1.2 (2.0)	.001
Likability	3.0 (1.6)	3.9 (1.3)	.10

The data suggest that VLBW children with learning problems need special attention as school difficulties may develop into social withdrawal, anxiety and isolation.

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A STUDY ON THE EFFICIENCY OF COMMUNITY TO HOSPITAL REFERRAL SYSTEM IN THE CATCHMENT AREA OF DODOMA HOSPITAL, TANZANIA. Filiberto Donzelli, Paola Facchin, Paolo Allegri. Dept of Paediatrics, Padova University, Padova, Italy. Gabriel L. Upunda, Dausein Kimaro.Regional Hospital of Dodoma, Tanzania. Marzia Franzetti, Anna M. Dal Lago, Mauro Anselmi. CUAMM International College for Health Cooperation in Developing Countries, Dodoma and Padova.

Unnecessary or delayed hospital admissions are prevented by an efficient referral system.

Objectives of the study: Community Health Services (CHS) coverage, accessibility, efficiency, and interaction with the hospital. Method: from March to June 1991 four Dodoma hospital paediatricians, using two structured questionnaires, studied 1,154 consecutive case of children (< 5 yrs) examined at the Outpatients Dept and 796 admitted to the Paediatric Ward.

Preliminary results: 1) Outpatients Dept: 84,5% of the children bypassed the CHS. Of them, 73% could have been treated in the CHS without needing to go directly to hospital. 2) Paediatric Ward: 66% of the children bypassed the CHS; 48% of these unreferred patients were admitted to the hospital with delay as compared to only 17% of the previously referred children. This delayed admission was followed by a high mortality rate within 48 hours (12,5%).

Conclusion: there is a need to study the factors which influence the flow of patients from the Community to the CHS and ultimately to the Hospital.

GENETICS

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DEVELOPMENTAL REGULATION OF HOX GENE EXPRESSION IN FETAL MOUSE LUNG. Barbara A. Shephard, Brent H. Cochran, Heber C. Nielsen. Boston Perinatal Center, Department of Pediatrics, New England Medical Center, and Department of Biology, Massachusetts Institute of Technology, Boston, Massachusetts, USA.

Homeotic genes regulate structure specific development in Drosophila. They contain the homeobox region, a highly conserved DNA sequence which is also conserved in the mammalian genome. Mammalian homeotic genes are proposed to regulate [mammalian] fetal development. Mouse homeobox genes are called "hox" genes; specific hox genes are known to be expressed in fetal mouse lungs. We hypothesize that hox gene expression in fetal lung is developmentally regulated in a lung specific fashion. RNA was isolated from fetal mouse lungs and liver at 16, 17, and 18 days gestation, transferred to Northern blot, then probed with 32P labelled cDNA probes for hox 1.3, hox 1.5, and hox 2.1. Expression was analysed by autoradiography [and computer phosphorimagery.] Specific expression of hox 1.3 was seen in lung but not liver of males and females on days 16, 17, and 18. Expression of hox 1.5 was seen in both lung and liver of males and females on days 16, 17, and 18. Expression of hox 2.1 was not seen on these days, but has been previously described in day 12.5 and 14.5 fetal mouse lungs. These findings support our hypothesis of developmental regulation of hox gene expression. We speculate that hox genes regulate pattern specific development in the mouse similar to homeobox genes in Drosophila.

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Direct Transfer of Human Dystrophin Genes into Striated Muscles of MDX Mice

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Plasmid DNA constructs containing either a human full length dystrophin cDNA (G. Dickson, London, UK) or a deleted, Becker type, dystrophin cDNA (K.E.Davies, D.R. Love, Oxford, UK.) were injected into hearts and quadriceps of dystrophin deficient MDX mice. Seven days later, analysis of immunohistochemical staining for dystrophin showed expression of dystrophin proteins in ~1 % of quadriceps muscle cells localized mostly in the sarcolemma. 10-15 dystrophin positive cardiocyte were also seen in sections of injected hearts. Western-blot of quadriceps muscles has also identified the dystrophin expressions. Peripherally localized nuclei of muscle cells were shown in about 50 percent of dystrophin positive myofibers compared with 20 percent of dystrophin negativ myofibers suggesting the the functional effect of expressed human dystrophin protein. This direct gene transfer method has an alternative application for genetherapy of inherited myopathies but the efficiency must be increased.

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PEROXISOMAL DYSFUNCTION IN A HETEROGENEOUS GROUP OF CHONDRODYSPLASIA PUNCTATA (CP) SYNDROMES. Ruud B.H. Schutgens, Ronald J.A. Wanders, Joseph M. Tager* and Judith C. Heikoop*. Department of Pediatrics and *Laboratory of Biochemistry, University of Amsterdam, Amsterdam, The Netherlands.

Peroxisomal dysfunction is found in a growing number of bone dysplasias in which CP is one of the characteristics. This includes (1) the rhizomelic type of CP (RCDP) that is characterised clinically by dwarfing, congenital cataracts, skeletal malformations and psychomotor retardation (2); the recently recognised dihydroxyacetone-phosphate acyl-transferase (DHAPAT) deficiency that is clinically identical to RCDP and (3) a new type of CP (NTCP) (Poll-Thé et al, J Inher Met Dis 14, 1991, 361) with bilateral cataracts but normal psychomotor development and normal skeletal radiography except for CP.

Sofar we identified 34 RCDP patients, 2 patients with DHAP-AT deficiency and 1 NTCP patient. Moreover, in 11 pregnancies at risk for RCDP, 6 affected fetuses were identified prenatally by the finding of an impaired plasmalogen metabolism in cultured chorionic villous cells. In RCDP and NTCP patients biochemical abnormalities include a deficiency of the peroxisomal enzymes DHAP-AT and alkyl-DHAP-synthase and of phytanic acid oxidase and abnormal (precursor) peroxisomal thiolase enzyme protein. In DHAP-AT deficiency only an isolated deficiency of DHAP-AT is found. Genetic heterogeneity between classical RCDP and DHAPAT deficiency was observed in complementation studies. These findings are important for the understanding of the pathogenesis in these disorders.

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METHYLATION AND MUTATION PATTERNS IN THE FRAGILE X SYNDROME. Helena Malmgren, Marie-Louise Steen-Bondesson, Karl-Henrik Gustavson, Eva Seemanova, Gösta Holmgren, Isabelle Oberlé, Jean Louis Mandel, Ulf Pettersson and Niklas Dahl. Department of Medical Genetics and Department of Pediatrics and Clinical Genetics, Uppsala University, Uppsala, Sweden.

Chromosomes carrying the mutation causing the fragile X [fra(X)] syndrome have been shown to have an unstable DNA sequence close to or within the fragile site. The length variation is located within a DNA fragment containing a CGG trinucleotide repeat which is unstable in both mitosis and meiosis.

We have used the probe StB12.3 from the Xq27.3 region to analyze the mutations and the methylation patterns by Southern blot analysis in 21 families segregating for the fra(X) syndrome

Results: Among 40 fra(X) males all showed an abnormal pattern. Six out of 33 fra(X) negative females at risk were diagnosed as carriers using DNA analysis. Mentally impaired females showed a high degree of methylated, inactive X as compared to healthy carriers.

Conclusion: The probe StB 12.3 provides a sensitive and specific test for the presence of the fra(X) mutation. Carriers without cytogenetic expression of fra(X) can be detected. The prediction of mental impairment in female carriers can be made by the estimation of the degree of methylation of the normal chromosome.