11

NEW PERSPECTIVES IN THE MORPHOLOGY OF NEONATAL HEPATITIS (NH). E.Kahn,M.D.;J.Markowitz,M.D.;H.Aiges,M.D.; W.Blanc,M.D.;F.Daum,M.D. North Shore Univ.Hosp. Manhasset, Cornell Univ.Med.College,New York,NY;Babies Hospital and Columbia Univ.Med.College, New York, NY.

The morphology of NH as traditionally defined (Craig & Landing Arch.Pathol.54:321,1952; Witzleben - IAP Monograph 22:347,1981) includes giant cell transformation, disruption of the hepatic plates, cholestasis, extramedullary hematopoiesis and hemosiderin accumulation. During the last 12 mos we have been impressed by the frequency of interlobular bile duct paucity in biopsies from cholestatic neonates at North Shore Univ.Hosp. with morphologic features of NH. Therefore, we reviewed liver biopsies from all 36 neonates with the dx. of NH not associated with extrahepatic biliary obstruction admitted to North Shore Univ.Hosp. or Babies Hosp., NY between 1975-1985. The specimens were examined by one observer (EK) without prior knowledge of the presence or absence of ductal changes. A minimum of 5 portal spaces/biopsy were required for inclusion in this study. By this criteria, 5 pts were excluded. Paucity of interlobular bile ducts, expressed by a ratio of bile ducts to portal spaces < 0.9, was present in 29/31 pts. 83% had a ratio < 0.6. Inflammation was absent in 27/29 spec.

Therefore, we suggest that duct paucity is an integral part of the process designated as "neonatal hepatitis". Emphasis should be directed at the intrahepatic duct insult rather than at the hepatocellular component. The designation of "hepatitis" is unwarranted in biopsies where inflammation is lacking.

12

HLA STATUS IN CHILDREN WITH ALPHA-1 ANTITRYPSIN DEFICIENCY(AATd)(PiZ)& CHRONIC LIVER DISEASE (CLD)
G Mieli-Vergani, DG Doherty, PT Donaldson,AP Mowat DA Hopkinson, D Whitehouse, G Corney
Dept.Child Health,King's Coll.Hospital & MRC Human Genetics Unit, University College, London.

Liver disease of variable severity occurs in only 20% of children with PiZ phenotype. To investigate whether such variability is due to immunogenetic factors we have determined HLA phenotypes of 43 unrelated PiZ children with CLD. 36 classI [A & B] were determined in all patients and 63 controls, and 9 class II(DR) antigens were determined in 33 patients and 47 controls. Haplotypes were obtained by studying family members. Significant differences between patients and controls were limited to B5 which was absent in patients but present in 8 controls [12.6%,p =0.0475] and DR3 which was found more frequently in patients [19 (57.6%) compared with 14 controls (29.8%), $X^2=5.084, p<0.025$, relative risk = 3.20]. Although DR3 is in strong allelic association with A1 & B8 the frequency of these antigens in patients [A1: 11 of 43(25.6%) and B8: 11 of 43(25.6%) were similar to that in the controls.The frequency of haplotypes A1-B8 [5 of 64,7.8%] and B8-DR3[4 of 36,11.1%] in patients were similar to the findings in 8th International HLA Workshop.It is possible that B5 confers protection against liver disease in AATd whereas DR3 increases susceptibility. Thus, an immunoregulatory gene may influence the clinical outcome of AATd.Lack of increase in A1 or B8 despite an increase in DR3 suggests a genetic base different to that usually associated with autoimmunity.

13

BILE ACID (BA) PATTERN AND CONJUGATION IN THE HUMAN FETUS.
C.Colombo,M.Ronchi,KDR Setchell *.
Department of Pediatrics,University of Milan,Italy and * Children's Hospital, Cincinnati,Ohio,USA.

The characterization of BA metabolism during development is essential to understand the clinical problems related to the immaturity of the entero-hepatic circulation of BA in early life.We have previously examined primary BA concentrations in fetal bile during early gestation:these were low prior week 16,but after this time showed a surge in the range of 10-30 fold. We report here the results of qualitative BA analysisof 32 samples of fetal bile (14^{th} - 21^{st} gw)by means of GLC-MS and HPLC.In all the samples,the predominant BA were chenodeoxycholic and cholic acids,while the main secondary BA were present only in small amounts.Several "atypical BA"were found, with hydroxyl groups in unusual positions on the BA steroid nucleus and they constituted around 40% of total BA in each sample;hyocholic acid and a trihydroxy-BA of unknown structure were quantitatively the most important and together these frequently exceeded the amounts of cholic acid. The presence of 3β-Hydroxy-5-cholenoic ac. and 3-oxo-7α-hydroxy-5β-cholanoic acid seems to indicate fetal synthetic pathways in which side chain oxidation preceeds nuclear changes in structure.
HPLC analysis of fetal bile revealed the major proportion of BA (around 80 %) to be taurine conjugated ,while a much lower proportion was in the glycine conjugated fraction;less than 5 % of biliary BA were found to be sulphated.
These unique characteristics of BA metabolism may in part explain the cholestatic tendency during development;these data may also be of help to elucidate the etiology of certain forms of neonatal cholestasis due to abnormalities in BA metabolism.

14

LIVER TRANSPLANTATION - CAMBRIDGE/KING'S SERIES
S Pett,A Pelham, JTizard,N Barnes,G.Mieli-Vergani, AP Mowat$ R Williams$K Rolles,Sir Roy Calne.
Addenbrooke's Hospital,Cambridge & King's College Hosp London*

Between December 1983 and August 1986, 84 children were assessed for possible liver transplant. 18,mainly infants with biliary atresia, were not accepted because of features which made successful trasnplantation unlikely. 4 children were withdrawn from the programme by their parents. 9 died before a donor of suitable size or compatible blood group could be found. 9 await transplantation, 9 have been accepted for liver transplantation but are at present sufficiently well for this to be postponed.35, aged 7mnths-16yrs, had liver grafts. Of these, 17 had biliary atresia, 5 fulminant or subacute hepatic failure, 3 malignant liver tumours and 2 metabolic disease. 15 died, 9 in the first 2 months mainly from primary graft failure or vascular thrombosis, later deaths being due to rejection, infection or dissemination of malignant disease. 2 died of disease in other organs with a normally functioning transplanted liver. 2 of the survivors have had a second liver transplant. 3 have significant hepatobiliary problems which may require retransplantation. The majority of survivors are engaged in normal activities for their age,growing and developing satisfactorily with normal biochemical tests of liver function & complete regression of cirrhosis.Their excellent quality of live is encouraging.Lack of donors,particularly for young infants & prevention of post-operative rejection & infection are continuing problems.

15

ON THE PRIMARY SITE OF CONTROL IN SPONTANEOUS AND IN GLUCOCORTICOID-TRIGGERED PRECOCIOUS DEVELOPMENT OF SMALL-INTESTINAL SUCRASE-ISOMALTASE COMPLEX
G. Sebastio, W. Hunziker*, A. Ballabio, L. Maiuri, S. Auricchio and G. Semenza*
Dept. of Pediatrics, 2nd School of Medicine, University of Naples, Italy, and *Laboratorium für Biochemie, ETH, Zürich, Switzerland.

We have investigated the development of sucrase-isomaltase (SI) activity in rabbit small intestine at the mRNA level. Rabbit SI cDNA was used as a probe (1). Spontaneous development was studied between 1 and 40 days of life. SI mRNA and enzymatic activities appeared simultaneously from day 15 onwards in untreated animals (2), matching one another for over two orders of magnitude. Same results have now been obtained in baby rabbits treated with glucocorticoid. Hormone-triggered precocious development was found at days 4 and 8 after daily injection of the steroid from birth. Our findings strongly suggest that the developmental control of SI complex is located mainly at the transcriptional level. Development of SI is presently being investigated in other systems as well.

1) W. Hunziker, M. Spiess, G. Semenza and H.F. Lodish (1986) Cell 227-234.
2) G. Sebastio, W. Hunziker, A. Ballabio, S. Auricchio and G. Semenza (1986) FEBS Letters 208, 460-464.

16

DEMONSTRATION OF DEFECTIVE JEJUNAL BRUSH BORDER Na^+-COUPLED GLUCOSE TRANSPORT IN CONGENITAL GLUCOSE-GALACTOSE MALABSORPTION
IW Booth, PB Patel, D Sule, GA Brown, K Beyreiss
Institute of Child Health, University of Birmingham and Karl Marx University of Leipzig

Studies in congenital glucose-galactose malabsorption (GGM) have indicated an abnormality in small intestinal glucose and galactose transport but the precise site of the defect has not been defined. We have therefore investigated Na^+-coupled D-glucose uptake, and Na^+/H^+ exchange in a patient with GGM using brush border membrane vesicles (BBMV) prepared from jejunal biopsies using a miniaturised Mg^{++}-precipitation technique. The diagnosis was confirmed by clinical presentation, response to diet and jejunal perfusion studies, which showed markedly defective glucose and galactose absorption ($p < 0.001$) and normal fructose transport.

In contrast to control BBMV, in which an inwardly directed Na^+- gradient (100mmol/l) enhanced 15 sec D-glucose uptake x 5.5 ($p < 0.02$), glucose uptake by BBMV from the patient showed no such enhancement with Na^+ ($p < 0.0025$). Na^+/H^+ exchange was intact, with a 6-fold enhancement of Na^+ uptake by an outwardly directed H^+ gradient (pH in: 6.0; out: 7,4) at 15 sec.

These studies therefore confirm for the first time, that a defect in brush border Na^+-coupled glucose uptake is present in GGM, and suggest that BBMV studies may be the optimal technique for confirmation of the diagnosis.