● **PHENPROCOUMON FOR PREVENTION OF EARLY SHUNT OCCLUSION AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT SHUNT (TIPS): RESULTS OF A RANDOMIZED TRIAL.** P. Sauer, L. Theilmann, G. Richter, T. Roeren, W. Stremmel and A. Stiehl. Depts. of Gastroenterology and Radiology, University of Heidelberg, FRG.

INTRODUCTION: Stenosis and occlusion are one of the major problems of TIPS. Stenosis has been observed in 50 - 70% of patients within the first year, most frequently in the first 3 -4 months. Stent stenosis seems to depend on Child-Pugh classification and prothrombine time. Therefore we conducted a randomized trial to evaluate the effect of phenprocoumon on stenosis and/or occlusion within the first three months after TIPS placement. **METHODS:** Patients were randomized 3 days after TIPS placement into a group receiving phenprocoumon to maintain prothrombin time between 2.1 and 1.7 (INR) or into a control group. Both groups were comparable with respect to age, sex, etiology of liver cirrhosis and Child classification. Patients with Child class C were excluded. TIPS were placed in standard technique using the Palmaz stent with a diameter of 8 to 12 mm to reduce the portosystemic pressure gradient to 10-15 mmHg. Patients were reevaluated after 3 months and underwent endoscopy, ultrasound and angiography. Reintervention was performed, if portosystemic gradient was > 17mmHg and/or lumen of the stent showed obliteration >50%. So far, 22 patient in the treatment group and 21 patients in the placebo group have finished the 3 months study period. **RESULTS:** In the treatment group stent stenosis occured in 11/22 patients (50%), in the control group in 11/21 (52%). 5/11 patients in the control group with increased portosystemic gradient showed complete occlusion, whereas in the treatment group no occlusion was observed (p=0.021). No deaths occured in both groups. In 2/21 patients in the control group rebleeding was observed (1 rebleeding of varices, 1 bleeding ulcer), in the treatment group one episode of rebleeding due to varices occured. New onset or worsening of HE developed in 3/21 of controls and in 4/22 of the treatment group. Complications in the treatment group were stent dislocation (2), intraabdominal bleeding (1), in the control group worsening of ascites due to stent occlusion, rebleeding and liver failure with need of OLT due to stent occlusion, intraabdominal bleeding (1) and stent dislocation (1). **CONCLUSION:** In the first 3 months after TIPS placement phenprocoumon significantly reduced stent occlusion, whereas rate of stenosis was not altered. We conclude that stent occlusion may be prevented by phenprocoumon treatment.

● **THE KINETICS OF PRIMARY BILE ACIDS IN PATIENTS AFTER ORTHOTOPIC LIVER TRANSPLANTATION ON CICLOSPORIN A.** P. Sauer, G. Rudolph, W. Stremmel, R. Endele*, M. Senn* and A. Stiehl. Dept. of Gastroenterology, University of Heidelberg and Dept.of Analytical Biochemistry, Boehringer Mannheim*, FRG.

INTRODUCTION: Ciclosporin A (CsA) is widely used for immunosuppression after orthotopic liver transplantation (OLT). Among others, CsA may induce cholestasis. In animal experiments CsA has been shown to impair hepatocellular uptake, transport, secretion and intestinal absorption of bile acids. To test whether CsA affects pool sizes, synthesis-, or turnover rates in man, we determined kinetics of primary bile acids in patients after OLT. **METHODS:** 2 male and 4 female patients were studied 6 to 20 months after OLT. The patients had no ouvert signs of cholestasis, graft dysfunction or rejection. Pool sizes, synthesis and turnover rates of cholic acid (CA) and chenodeoxycholic acid (CDCA) were simultaneously determined after oral administration of ^{13}C CA and ^{13}C CDCA on the basis of isotope dilution in a single pool of bile acids. 7 healthy volunteers served as controls. **RESULTS:** In patients after OLT pool size of CA was (Mean ± SD) 27.2 ± 12.2 µmol/kg, fractional turnover rate was 0.3 ± 0.1/day and synthesis rate was 8.4 ± 4,8 µmol/kg x day. In healthy controls pool size of CA was 37.1 ± 1.9 µmol/kg, fractional turnover rate was 0.29 ± 0.06/day and synthesis rate was 10.7 ± 2.2 µmol/kg x day. In patients pool size of CDCA was 20.7 ± 8.6 µmol/kg, fractional turnoverrate was 0,24 ± 0.05/day and synthesis rate was 5.23 ± 2.7 µmol/kg x day. In controls pool size of CDCA was 30.5 ± 3.0 µmol/kg, fractional turnover rate was 0.21 ± 0.03/day and synthesis rate was 5.9 ± 0.12 µmol/kg x day. **CONCLUSION:** In patients after orthotopic liver transplantation and chronic treatment with CsA, pool sizes, synthesis- and turnover rates of bile acids are normal. In spite of the interference of CsA on hepatocellular uptake, transport, secretion and intestinal absorption, treatment with CsA does not disturb the kinetics of bile acids in man.

● CLINICAL FEATURES OF AUTOIMMUNE CHOLANGIOPATHY. GD Schapiro, RA Rubin, SJ Munoz. Dept. of Medicine, Jefferson Medical College, Philadelphia, PA.

Autoimmune cholangiopathy (AIC) is a chronic cholestatic disorder which shares clinical features with primary biliary cirrhosis (PBC). Patients with AIC, however, have positive antinuclear (ANA) and negative anti-mitochondrial (AMA) antibodies. Whether AIC is a distinct entity is controversial.
METHODS: 50 consecutive patients with biliary cirrhosis (BC) were evaluated between 1/90-12/94; their clinical data were reviewed to identify patients with AIC. Criteria included chronic cholestatic liver disease in the absence of intra- or extrahepatic ductal dilatation without drug-induced cholestasis; patients also had negative AMA (< 1:80) and strongly positive (≥ 1:640) ANA.
RESULTS: 42 of 50 patients had PBC (including 9 with positive ANA and 1 whose AMA was initially negative), 1 had BC secondary to obstruction, and 7 (14.0%) had AIC. All AIC patients were female; 6 Caucasian; mean age 52 yr (range, 32-71); histologic stage I (1), III (3), IV (2) and not biopsied (1); mean follow-up 5.8 yr (0.5-14). Fatigue and pruritus were prominent in 4 and 1 patients, respectively. The ANA pattern was speckled in 6/7 cases. Anti-smooth muscle and anti-thyroid antibodies were found in 3 and 2 cases, respectively. No patient had hepatitis C antibodies. In 3 patients (1 with active portal inflammation) prednisone therapy led to minimal response in symptoms or laboratory tests; one of these received liver transplantation. Ursodiol (UD) therapy [for mean 13 mo (1-48)] was associated with improved pruritus in 1 and marked decreases in transaminases and alkaline phosphatase in 3/6 patients; two of these (both non-responders) received concurrent methotrexate. Progressive bile duct loss and portal hypertension (variceal bleeding) developed in 2 patients treated with UD despite improved biochemical tests. An intracranial bleed occurred in 1 patient who was thrombocytopenic when UD was started. Pulmonary fibrosis developed in one patient treated with methotrexate.
CONCLUSIONS: AIC is more prevalent than previously recognized. AIC defines serologically unique patients whose clinical picture resembles PBC. AIC can be resistant to immunosuppressives. Disease progression may occur on UD despite symptom and laboratory improvement. Patients with AIC should be identified to clarify the natural history and response to therapy of this entity.

● ALPHA 1-ANTICHYMOTRYPSIN DEFICIENCY IS ASSOCIATED WITH CHRONIC HEPATITIS C AND CIRRHOSIS OF VARYING ETIOLOGIES. T.D. Schiano, F. Kueppers, S.V. Bellary, R. Thomas, R. Shayiq and M. Black. Temple University School of Medicine, Depts. of Gastroenterology, Pulmonary and Pathology.

Alpha 1-antichymotrypsin (AIAC) is a protease inhibitor normally present in human serum. Genetically determined deficiencies of alpha 1-antitrypsin (AIAT) and AIAC are known to predispose to chronic liver disease. The purpose of this study was to examine any association between AIAC deficiency and chronic hepatitis C (CHC) or biopsy proven cirrhosis of varying etiologies. Methods: The AIAC and AIAT levels were determined in serum samples (frozen and fresh) that were obtained from 175 unselected patients (pts) with CHC (HCV-RNA (+) by PCR) and cirrhosis of varying etiologies by using radial immunodiffusion. AIAT genotyping was performed using isoelectric focusing. The normal serum levels have been established as 0.316±.07 mg/ml for AIAC and 1.34±0.24 mg/ml for AIAT. Patients with serum levels of ≤ 0.17 mg/ml for AIAC and ≤ 0.96 for AIAT were considered to be heterozygous deficient for AIAC and AIAT, respectively. Results: Of the 175 patients, 31 (18%) had AIAC levels in the heterozygous deficient range (mean 0.152±0.021 mg/ml) of which 27 (15%) had isolated AIAC deficiency with normal AIAT levels and 4 (2.3%) had combined AIAC and AIAT deficiencies. Both of these were significantly greater ($p < 0.001$) than the expected prevalence in the general population of 1% for AIAC deficiency and of < 0.03% for combined AIAC and AIAT deficiencies. Of the 94 patients (56m, 38f) with cirrhosis (mean age 51.3±12.2; range 20-71 yrs), 47 pts (50%) had cirrhosis due to HCV and 47 (50%) had non-HCV related cirrhosis (alcohol, cyyptogenic, autoimmune, PBC, PSC). Eighty-one pts (64m, 17f) with a mean age of 44.3±1.3 yrs (range 23-82) had CHC without cirrhosis. The AIAC levels were low in 9/81 (11%) pts with CHC as compared to 15/47 (32%) pts with cirrhosis due to HCV which was statistically significant ($p = < 0.01$). The AIAC levels were low in 7/47 (15%) pts with non-HCV related cirrhosis as compared to 15/47 (32%) pts with HCV related cirrhosis which was not statistically significant. Immunohistochemistry of liver biopsy samples for AIAC and AIAT inclusion bodies in 15 pts (6 HCV+, 9 non-HCV) with cirrhosis was non-contributory. Conclusions: AIAC deficiency is associated with chronic hepatitis C and cirrhosis of various etiologies. AIAC deficiency is associated with progression of chronic hepatitis C to cirrhosis. These associations appear to be independent of AIAT deficiency. Combined AIAT and AIAC deficiency is associated with cirrhosis.