In 48 patients with negative histology, UBT results matched in 39 patients, while 9 had a positive UBT test. When subsequent re-gastrosopies were performed in these 9 patients and multiple antral biopsies were taken, all of them showed positive histology results. Thus, discontinuous H. P colonization as correctly diagnosed by UBT was responsible for all false negative histology results in the first gastroscopy. In 10 H. P positive and 10 H. P negative patients, non-fasting conditions were tested and were found to compromise the UBT result. Food intake induced 2 false positive and 1 false negative UBT result.

Conclusion: The 13C-Curea breath test is the gold standard in H. P diagnosis. It correlates with the H. P colonization density. Specificity is 100% and sensitivity 97.8%. False negative results were due to a very low H. P colonization during spontaneous elimination of H. P or to pyloric obstruction. Strict fasting conditions are necessary for a reliable test result.

**1073 Inducible Nitric Oxide Synthase is a Local Defence Mechanism in H. pylori-associated Gastritis**

G. Rieder, R.A. Hatz, M. Stolzel, E. Enders. Dept. of Surgery, Germany; Institute for Surgical Research, LMU Munich, Germany; Institute of Pathology, Klinikum Bayreuth, Germany.

Infection of human gastric mucosa with H. pylori results in a local immune response leading to an increase in mucosal production of iG2 and IgA antibodies. Beyond this, a characteristic feature of inflammation is the marked infiltration with neutrophils. These cells produce and release defensins as a further defence against bacterial infection. The aim of our study was to confirm the above defence mechanisms against H. pylori and to investigate further inflammatory mechanisms such as the expression of the inducible nitric oxide synthase (iNOS).

Methods: Antral biopsies were taken endoscopically from H. pylori-associated gastritis and non-gastritis patients. Defensins were analysed immunohistochemically and RNA was extracted from homogenized biopsies by means of a silica-based membrane technique. PCR was performed on synthesized cDNA using specific primers for iNOS and the housekeeping gene superoxide dismutase (Cu-Zn-SOD).

Results: An equal concentration of cDNA was assayed by the amplification of Cu-Zn-SOD. iNOS mRNA amplification was only obtained in gastritis patients but not in negative control individuals. The amount of mRNA coding for the enzyme iNOS was strictly correlated with the degree of gastritis. Furthermore, we could show a local increase of defensins in submucosal gastritis tissues.

Conclusions: NO, a cytoxic substance, is produced by the enzyme NOS. The increased amount of mRNA for iNOS in tissues of active gastritis might reveal a further local defence mechanism against H. pylori infection. Furthermore, it is assumed that NO and other oxygen radicals produced by chronic inflammatory processes may initiate or enhance carcinogenesis in humans like gastric cancer due to chronic H. pylori infection.

**1076 Autoantibodies in Porphyria Cutanea Tarda in Germany**


Recently, a high frequency of autoantibodies and hepatitis C infection were reported as main pathogenetic factors in Italian patients with PCT. Therefore, we investigated these markers in 100 German patients with PCT.

Results:

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Italy* (n = 23)</th>
<th>Germany (n = 100)</th>
<th>p-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA ≥ 1 : 40</td>
<td>17%</td>
<td>16%</td>
<td>NS</td>
</tr>
<tr>
<td>SMA ≥ 1 : 40</td>
<td>72%</td>
<td>20%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>PCA ≥ 1 : 40</td>
<td>ND</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Anti-LKM</td>
<td>4%</td>
<td>0</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Anti-LSA</td>
<td>ND</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AMA</td>
<td>ND</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Anti-GOR</td>
<td>53%</td>
<td>4%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>91%</td>
<td>8%</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

*Data from Italy reported by Ferri et al. 1993; ND, not determined

In our patients only 8% tested positive for anti-HCV and the frequency of autoantibodies was low. In Italy the high frequency of SMA, Anti-LKM and Anti-GOR may be the result of the high frequency of associated HCV infection. These results indicate that these autoantibodies can not be considered to be linked to the pathogenesis of PCT in Germany.

**1077 Serum Ferritin in Chloroquine-Treated Patients with Porphyria Cutanea Tarda**


Because iron overload is common in PCT and chloroquine-treatment has been found to remove iron deposited in the liver comparable to venesection, we investigated serum-ferritin in 46 patients with different clinical stages of PCT.

Results:

<table>
<thead>
<tr>
<th>Serum-ferritin</th>
<th>PCT overt</th>
<th>PCT in remission*</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>676 ± 526</td>
<td>312 ± 259</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Normal value: ferritin < 440 μg/l; *remission after "chloroquine" treatment (125-250 mg twice weekly)

These results indicate that ferritin serum levels as markers of hepatic iron deposition were normalised in chloroquine-treated patients with PCT in remission. Moreover, diminished levels of ALT/AST and urinary porphyrins were observed that correlated with serum-ferritin. Therefore, the potential of chloroquine to remove iron in the liver, merits further studies.

**1079 Serum Markers of Collagen Synthesis and Breakdown Suggest an Antifibrotic Effect of Ursodeoxycholic Acid in Patients with PBC Stage I-IV**


Aims: The question if ursodeoxycholic acid (URS) has an anti-fibrotic effect in patients with PBC remains controversial. Therefore, we used a presumed serum marker of collagen synthesis (PIIPN) and a recently established serum marker of collagen breakdown (collagen VI, CVI) to follow the course of 23 patients with PBC (12 stage I-III, 9 stage IV) treated over 2-4 years with oral URSO at 10-15 mg/kg b.w.

Methods: Each patient underwent initial liver biopsy, and serum levels of PIIPN (RIAgnost) and CVI (inhibiton-ELISA) were determined at regular intervals. The means of year 1 (2-5 values, group II) and year 2 (4-6 values, group III) after initiation of URSO-treatment were compared to each other and to pretreatment levels (group I) by using linear regression analysis and the Mann-Whitney U-test.

Results: In all patients both PIIPN and CVI in groups II-III were higher than in controls (p < 0.01 or p < 0.05). There was no correlation to conventional laboratory markers except for ALP vs. PIIPN (p < 0.05). Whereas PIIPN remained unchanged in I vs. II vs. III, CVI increased from a mean of 128 ± 51 (1 SD) μg/l (group I) to 156 ± 57 μg/l (II) to 212 ± 101 μg/l (III) (p < 0.01 for I vs. III, p < 0.05 for II vs. III). Subgroup analysis showed a significant decrease of PIIPN for PBC stage III-IV (1.47 ± 0.31 U/l) (II, 1.20 ± 0.47 U/l (I), 1.11 ± 0.28 U/l (III) (p < 0.05 for III vs. I). Accompanied by a significant increase over time for CVI, both in PBC stage I-III (p < 0.05). The ratio of CVI over PIIPN supposedly reflecting the balance of collagen breakdown over collagen synthesis in the liver, further improved the discrimination between groups. However, individual patients (3 each stage I-II and III-IV) displayed an unfavourable evolution of these markers.

Conclusion: Serum markers of fibrogenesis and fibrosis suggest an antifibrotic effect of URSO in most but not all patients with PBC.

**1080 Autonomous Neuropathy in Achalasia: Postprandial Decrease of Pulsatility Index (PI) is Augmented and Increase of Peak Flow Velocity is Impaired in Superior Mesenteric Artery**


It has been suggested that achalasia is associated with extrasphegeal sympathetic and parasympathetic dysfunction. Methods: In a prospective study, we investigated basal and postprandial gallbladder volume and peak systolic
velocity of superior mesenteric artery and portal vein in 9 patients with achalasia (5 men) and 10 healthy controls (4 men). Gall bladder volume was measured by ultrasound and peak systolic velocity and peak systolic Doppler-sonography (Toshiba duplex Doppler ultrasound machine with a 3.75 MHz transducer). In each measurement, flow velocity was corrected by evaluation of the doppler angle, PI was calculated as (v max – v min)/v mean. Decrease of PI is a parameter of decreased in the distal portal vascular resistance. Triple measurements were obtained at basal state, 15, 30, 60 and 90 minutes postprandially. The meal consisted of 300 ml liquid formula diet (Fresubin, 300 kcal, 11.4 g protein, 10.2 g lipid, 41.1 g carbohydrate). Results: At basal state, gallbladder volume, peak systolic velocity and PI were not significantly different between both groups. Gall bladder volumes significantly decreased (p < 0.05, students t-test) and peak systolic velocity in portal vein significantly increased 15, 30, 60, and 90 minutes postprandially in achalasia and controls. However, no significant differences occurred between both groups. In contrast, significant differences between both groups (PI: 15° and 30° peak systolic velocity: 15°, 30° and 60°) were found according to postprandial decrease of PI and increase of peak systolic velocity in superior mesenteric artery (p = 0.01 and p < 0.05).

Postprandial decrease of PI compared to basal state was 24% (15°), 19% (30°), 15% (60°) and 10% (90°) in controls and 49% (15°), 48% (30°), 31% (60°) and 25% (90°) in achalasia. Increase of postprandial peak systolic velocity was 61% (15°), 44% (30°), 28% (60°) and 18% (90°) in controls and 25% (15°), 19% (30°), 1% (60°) and 5% (90°) in achalasia. Conclusion: These data suggest altered autonomous regulation of superior mesenteric artery in patients with achalasia. The study provides further evidence of generalized autonomous neuropathy in achalasia that extents beyond the esophagus.

1082 Inhibition of PAF-Synthesis by Salicylates
M. Stuffer, F. v. Bruchhausen. Dept. of Gastroenterology, Klinikum Benjamin Franklin, Germany; Institut für Pharmakologie, Freie Universität Berlin, Germany

Platelet activating factor (PAF) is a mediator of inflammation with considerable importance in inflammatory bowel disease. We investigated the inhibitory effect of Salazosulfapyridine (SASP), 5-Aminosalicylic-acid (5-ASA) and 4-Aminosalicylic-acid (4-ASA) on PAF-synthesis in a subcellular (microsomal) and cellular (polymorphonuclear leukocytes (PMN)) model.

Methods: 1. The microsomal preparation was gained by homogenization of sheep intestinal lymphocytes and subsequent ultracentrifugation. Incubation was performed in the presence of acetylated-CoA (0.2 mM), 1.5 µM 3H-Acetyl-CoA and Lyso-PAF (0.16 mM). 2. PMN were isolated from buffy coats and incubated (107 cells/ml) in the presence of Ca++ (1.5 mM) and Ca++-ionophor A23187 (4 µM). PAF synthesis was measured by incorporation of 3H-Acetil. 3. Lipids were extracted (Bligh and Dyer) and PAF was isolated on TLC. Characterization of PAF was performed by 1H-Cerotonin release biosay.

Results: PAF-synthesis (by Lyso-PAF-transacylatase EC 2.3.1.67) is dose-dependent inhibited by the above aminosalicylates, SASP having the lowest IC50-value (Table).

<table>
<thead>
<tr>
<th>IC50</th>
<th>SASP</th>
<th>5-ASA</th>
<th>4-ASA</th>
<th>PMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>microsomal</td>
<td>0.5</td>
<td>2.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>cellular</td>
<td>0.5</td>
<td>2.0</td>
<td>10.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Discussion: The concentrations to inhibit PAF-synthesis halfmaximally are high. Nevertheless, these concentrations are evident in the intestinal contents if therapy with appropriate doses of aminosalicylates is performed. Thus, inhibition of PAF-synthesis may be an important aspect of therapeutical efficacy of aminosalicylates.

1083 Surgical Therapy of Refractory Ascites with the Peritoneovenous Shunt — 18 Years of Experience

The pathogenesis of ascites is multifactorial. Possible causes are advanced liver diseases, malignant tumors, lesions of the thoracic duct and peritoneal or intra-abdominal disorders.

When the large quantities of free intra-abdominal fluid cannot be mobilized under maximal conservative therapy, implantation of a peritoneovenous shunt is indicated in order to permanently drain the ascites, deliver waste and electrolytes to the central venous system and restore the psychic and physical stability of the patient.

From June 1976 to May 1984, we implanted 141 shunt systems in 132 patients. The Diagnosis system was implanted in more than half the cases, particularly in the last eight years. Among the patients were two children, age five and seven. The mean age of the other patients was 53.9 with a sex distribution of 75 men and 57 women. In 112 patients, the ascites was caused by liver cirrhosis (hepatitis, alcoholic); 10 had a malignant ascites. The other causes were: a hepatoportal syndrome, a portal thrombosis and, in one case, a chylous ascites after hemicolectomy.

Thirty complications were 21%. The implanted systems had a mean functional rate of 27.5 months. Early postoperative complications were often technically determined in the initial phase of establishing this new system. These included faulty implantation, system kinking and ascites leakage. Disease-related complications such as thrombopathy, cachexia and hepatic and renal insufficiency determine the long-term survival rate.

1088 Splitproducts of Extracellular Matrix Proteins: Relevance in Diagnosis and Follow-up of Pediatric Liver Fibrosis

Introduction: The determination of splitproducts of synthesis and degradation of extracellular matrix (ECM) proteins in serum is a new approach for diagnostic and follow-up of patients with fibrotic liver disease. These parameters are rarely investigated in infancy and childhood and their diagnostic relevance is not clear. The aim of the present study was to prove the significance of aminoterminal procollagen-III-peptide (PIIINP), laminin P1 and type VI collagen in children with hepatic fibrosis.

Material and Methods: PIIINP, laminin P1 and type VI collagen concentrations in serum have been evaluated in 54 children between 2 and 18 years with different years of follow-up of liver fibrosis and after LTX. Determination of PIIINP and laminin P1 in serum has been performed by RIA (Behring Werke Marburg, Germany), type VI collagen by inhibition-ELISA.

Results: Elevation of PIIINP levels in serum has been found in children with chronic liver disease but also in children during catchup growing after LTX. Laminin P1 serum concentrations were elevated in patients with hepatic induced portal hypertension (mean ± SD: 3.9 ± 1.3 E/ml), in contrast they were in a norm range in patients with extrasaphic induced portal hypertension (mean ± SD: 1.35 ± 0.22 E/ml). All patients with fibrotic liver disease have shown significantly increased type VI collagen serum concentrations (mean ± SD: 50.3 ± 12 ng/ml; p < 0.001). High levels were also found after LTX in late organ rejection.

Discussion: Because of the dependency on growth, concentrations of PIIINP in serum has poor diagnostic significance in children. The determination of laminin P1 levels in serum is useful to distinguish hepatic from extrasaphic induced portal hypertension. Type VI collagen seems to be a helpful marker for diagnosis and follow-up of fibrotic liver disease in children.

1090 Cystic Neoplasms of the Pancreas
J. Zanow, T. Benhajdej, K. Geller. Department of Surgery, Charité, Berlin, Germany

From 1984 to 1994, 27 patients with cystic neoplasms of the pancreas were treated at the Surgical Clinic of the Charité, including 7 serous adenomas, 6 mucinous adenomas, 11 mucinous cyst-adenocarcinomas, 1 cystic acinar cell carcinoma, and 2 cases of cystic neuroendocrine tumors.

The patients ranged from 31 to 77 years in age. The main symptoms were mild to moderate abdominal pain, weight loss, intolerance to alcohol and a
presenting palpable mass. The duration of anamnesis ranged from 2 weeks to 10 years. Between 4 and 49 months previously five patients had undergone cyst drainage procedures. Mean tumor size was 7.9 cm (3 to 17.5 cm). Only in 56% the diagnosis was obtained by US, CT, ERCP or an endoprothesis. One patient with cyst-adenocarcinoma died prior to operation. The tumor was resected by distal pancreactectomy in 15 cases and proximal duodenopancreatectomy in 3 cases, without any operative deaths. In 3 cases of cystadenocarcinoma the tumor was unresectable. The cystic tumor was malignant in 14 cases. Whereas in all cases of serous or mucinous adenomas the patients are well without evident recurrence, 8 patients with malignant cystic tumors died 4 to 21 months after the operation. Only 5 patients are alive at 3 months to 9 years.

It is concluded that the complete excision of cystic pancreatic tumors, whenever possible, is the procedure of choice. A carefully histological examination of every removed or drained cystic tumor of the pancreas is required.

**1091 Gastric Functional Disorders in Gastro-esophageal Reflux Disease**

K. H. Fuchs, M. Fein, S. M. Freys, J. Heimbucher, A. Thiede. Chirurgische Universitätsklinik Würzburg, Germany

100 patients with GERD and 20 volunteers underwent functional evaluation of the foregut with 24 h esophageal and gastric pH monitoring, manometry of the esophagus, and gastric emptying studies. The aim of the study was the description of the prevalence of gastric functional disorders as cause of GERD. 1. persistent gastric acidity (PGA), 2. pathologic duodenogastric reflux (DGR) and 3. delayed gastric emptying (DGE). The pH probes were placed 5 cm above and 5 cm below the lower esophageal sphincter. The pH data were analysed by calculating the percent time the gastric luminal pH was at whole number pH intervals, i.e. 0–1, 1–2, 2–3 etc., the number of pH movements into these intervals, and the incidence the pH remained continuously in an interval for five minutes or longer.

The results show that in 36% of patients with GERD, gastric functional defects can objectively be quantified and documented by 24 hour gastric pH monitoring. 29% of the patients proved to have PGA on 24 hour gastric pH monitoring criteria. 4% had isolated PGA with no other esophageal functional defect. 12% of the patients had a pathologic DGR score. The incidence of PGA did not correlate with the severity of esophagitis. However, 8 out of 9 Barrett patients had a pathologic PGA and 5 out of 9 had a pathologic DGR score, which represents a significantly higher incidence of concomitant gastric pathology (p < 0.01). Delayed gastric emptying was documented in 16% of the patients, while in 28% of the patients clinical signs and delayed decline in postprandial gastric pH were suggestive of delayed emptying. Conclusions: In GERD, complete functional evaluation of esophagus and stomach should be performed in combination with esophageal and gastric pH monitoring. This allows for qualitative evaluation of gastric functional defects responsible for the disease which has important therapeutic consequences. Preferably combined monitoring should be used.

**1093 Mechanical Effect of Different Anti-reflux Procedures — An Experimental Study**

S. M. Freys, K. H. Fuchs, J. Heimbucher, M. Fein, A. Thiede. Chirurgische Universitätsklinik Würzburg, Germany

Objective: The diversity of different pathophysiologic components and their individual combinations in gastroesophageal reflux disease (GERD) reflect the large number of different operative anti-reflux procedures. However, modern diagnostic investigations allow for an exact differentiation of functional defects in the individual patient. In GERD patients an isolated incompetence of the lower esophageal sphincter (LES) is found in 56% and, in combination with other functional defects, in 88%. These findings represent the basis for an experimental study investigating the mechanical effect of different anti-reflux procedures.

**Material and Methods:** 28 minipigs in 4 groups of 7 animals underwent 4 laparoscopic anti-reflux procedures with different degrees of wrap formation (Nissen-Rossetti, Nissen-DeMeester. Toupet, Anter Hemifunduplicaion). Standardized pre- and post-op. manometric evaluations were performed according to the DeMeester criteria.

**Results:** Median increase of manometric LES parameters pre- vs. post-op:

<table>
<thead>
<tr>
<th>LES tot. length</th>
<th>LES intrastr. length</th>
<th>LES pressure</th>
<th>LES vector vol. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nissen-Rossetti 67</td>
<td>100</td>
<td>50</td>
<td>79</td>
</tr>
<tr>
<td>Nissen-DeMeester 22</td>
<td>100</td>
<td>75</td>
<td>480</td>
</tr>
<tr>
<td>Toupet 50</td>
<td>0</td>
<td>75</td>
<td>216</td>
</tr>
<tr>
<td>Ant. Hemifund. I 25</td>
<td>0</td>
<td>67</td>
<td>156</td>
</tr>
</tbody>
</table>

**Conclusions:** Standardized anti-reflux procedures with different degrees of wrap formation at the GE-junction lead to different degrees of LES-augmentation, thus allowing for a calculated calibration of the LES according to the individual sphincter defect.

**1096 Release of GLP-1 [7-36 Amide] After Oral Glucose in Patients with Upper and Lower Gut-resections**

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Purpose of the study: Glucagon-like Peptide 1 (GLP-1 [7-36 amide]) is an incretin hormone primarily synthesized in the lower gut (ileum, colon/rectum). Nevertheless, there is an early increment in plasma GLP-1 immediately after ingesting glucose or mixed meals, before nutrients have entered GLP-1-rich intestinal regions. The responsible signaling pathway between the upper and lower gut is not clear. It was the aim of this study to see, whether removal of GLP-1-rich or GLP-1-poor parts of the gut change GLP-1 [7-36 amide] release after oral glucose.

Methods: In 7 healthy controls, in 7 patients with inactive Crohn’s disease (no surgery), in 9 patients each after primarily jejunal or ileal small intestinal resections, and in 6 protocolecotomized patients not different in age (p > 0.10), body-mass-index (p = 0.24) and waist-hp-ratio (p = 0.43), vitamin B12 (p = 0.23), β-carotin (p = 0.48) and HbA1c (p = 0.22), oral glucose tolerance tests (75 g oral glucose) were performed in the fasting state. GLP-1 [7-36 Amide], Insulin, C-peptide, GIP and glucagon (specific RIAs) were measured over 240 min. Statistics: Repeated measures ANOVA, t-tests (significance: p < 0.05).

**Results:** A dear and early (peak: 15–30 min) GLP-1 [7-36 amide] response was observed in all subjects, without any significant difference between gut-resected and control groups (p = 0.95). There were no significant differences in oral glucose tolerance (p = 0.21) or in the suppression of pancreatic glucagon (p = 0.36). Colonectomized patients had a higher insulin response (p = 0.011), with a similar trend also for C-peptide (p = 0.25, interaction of group assignment and time significant) in comparison to all other groups. GIP responses also were higher in the colonectomized group (p = 0.01), whereas glucagon responses did not differ significantly.

**Conclusions:** Inactive Crohn’s disease and resections of the small intestine as well as proctocolectomy do not change overall GLP-1 [7-36 amide] response and especially not the early increment after oral glucose. This may indicate release of GLP-1 [7-36 amide] after oral glucose from the small number of GLP-1 [7-36 amide] producing L-cells in the upper gut rather than from the main source in the ileum, colon and rectum. Colonectomized patients were characterized by insulin hypersecretion, in combination with their normal oral glucose tolerance possibly indicating a reduced insulin sensitivity in this patient group. GI/G may play a role in mediating insulin hypersecretion in these patients.

**1097 Photodynamic Therapy Using 5-Aminolevulinic Acid in Esophageal Dysplasia and Carcinoma In Situ**

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Conventional photosensitizers like hematoporphyrin lead to a clinically significant skin photosensitization that persists for about 4 weeks. 5-aminolevulinic acid (ALA), a precursor of hem in the hem biosynthesis which induces photoporphyrin IX (Pp IX) as an endogenous photosensitizer, is a promising agent for PDT as it can be applied orally and only causes skin photosensitivity for about 36 hours due to a rapid clearance from the skin. ALA mainly localizes in the epithelial layer of the esophagus, and therefore, might be a suitable treatment modality for severe dysplasia and carcinoma in situ. We report on the first therapeutic use of ALA in severe dysplasia or carcinoma in situ of Barrett’s esophagus in Germany for the treatment of dysplasia and carcinoma in situ. After oral administration of ALA in the animal model a light dose of 150 J/cm² was delivered with a dye laser (800 KTP/YAG, Lasercscope, San Jose, CA) with an output of 100 mW/cm². The ablated mucosa of patients with BE was kept in low acid environment using antacid therapy with 20 mg famotidin.

**Results:** Endoscopy and biopsies taken 2–3 days after PDT showed a fibrinous necrosis of the epithelial layer. 9 patients with severe dysplasia or carcinoma in situ had a complete response and are being proven dysplasia/tumor-free for 1–9 months after ALA-PDT. In three patients with carcinoma in situ (2 SCC and 1 BE) a reduction of the tumor length was observed, but the lesions were not completely eradicated. No major side effects occurred. 8 patients had a mild increase in blood pressure and/or serum enzymes, but the values normalized within 3–4 days. 3 patients had local pain during light therapy, none of the patients showed cutaneous photosensitivity after 2 weeks.

**Conclusions:** Although the follow-up is still very short, ALA-PDT seems to be effective for the destruction of severe epithelial dysplasia and carcinoma in situ. The role of ALA-PDT as a minimally invasive treatment modality of BE and alternative to esophagectomy has yet to be established.
1098 Therapeutic Routes of Long-term Enteral Nutrition by Percutaneous Endoscopic Gastrostomy (PEG) — A Meta Analysis of 1214 Patients
L. Gossner, J. Keymling, S. Jazzy, H.J. König, E.G. Hahn, C. Ell. Institute of Medicine, University of Erlangen, Nuremberg, Krankenhausstr. 12, D-91054 Erlangen, FRG

Since percutaneous endoscopic gastrostomy (PEG) was first described in 1980 by Gauderer it has gained wide acceptance and is now the preferred method for providing long-term enteral nutrition. However, most published studies describe only short-term follow-ups in limited numbers of patients.

Methods: We report the long-term outcome and complication rate after PEG insertion at the University Hospital of Erlangen between August 1984 and January 1994. 1214 patients (310 female and 904 male patients; mean age 57.1 ± 12.5 years) whose mean length of PEG feeding was 243 days (range 2–1031). Data were collected retrospectively by an integrated home enteral nutrition team that uses a standard recording system to manage and follow up patients on PEG feeding.

Results: The procedure related mortality of PEG insertion was 0.3%. The average daily enteral nutrition over the tube was 1710 ± 710 kcal. A significant increase in body weight (>2 kg) was induced in 70% of the patients even during radiological therapy. In 204 patients the PEG tube was removed when normal food intake was regained possible after radiological therapy (n = 128) or were fed orally with a liquid formula diet (n = 55) or due to the lack of complications.

There were 9 severe complications within 30 days of PEG insertion, including three cases of peritonitis, 1 perforation, 1 leakage, 1 puncture of the liver (0.7%). Three deaths occurred in patients who developed generalized sepsis (0.2%). Perforated peritonitis were found in 9 patients (8.2%). Minor complications like pain at the insertion site, diarrhea and constipation were seen in 53% of the patients.

Conclusions: Long-term enteral feeding by PEG is safe, effective, and has an acceptable low complication rate. Our patients were managed by a specialist nutrition team, a policy which may reduce the complication rate and hospital visits for patients being fed at home and allow early discharge of dysphagic patients, thereby reducing costs.

1099 Inhibition of Gastric Emptying by GLP-1 [7–36 Amide] and GLP-2: Effects on Postprandial Glycemia and Insulin Secretion

Purpose of the study: Glucagon-like Peptide 1 (GLP-1) has been shown to profoundly inhibit gastric emptying of liquid meals in Type 2 diabetic patients. It was the aim of the present study to compare the action of physiological and pharmacological doses of intravenous GLP-1 [7–36 amide] and [7–37] on gastric emptying in normal volunteers.

Methods: 9 male subjects participated (26 ± 3 y, BMI 22.9 ± 1.0 kg/m2, HbA1c 5.9 ± 0.2%). A total of 6 experiments were performed. A nasogastric tube was positioned for the determination of gastric volume using a dye-dilution technique (phenol red). GLP-1 [7–37] (0.4, 0.8, or 1.2 pmol/kg.min) or GLP-1 [7–37] (1.2 pmol/kg.min) or placebo were infused from −30 to 240 min. Mean glucose (50 g saccharose in 440 ml) was administered at 0 min. Glucose, insulin (IMX, Abbott) and C-peptide (ELISA, DRG) were measured up to 240 min. Statistics: Repeated-measures ANOVA.

Results: Gastric emptying was dose-dependently slowed by GLP-1 [7–36 amide] [volume at 120 min: 54 ± 18, 160 ± 28, 250 ± 27, 350 ± 44 ml for placebo, 0.4, 0.8 and 1.2 pmol/kg/min GLP-1 [7–36 amide]; p = 0.0001]. Effects of GLP-1 [7–37] were virtually identical. GLP-1 dose-dependently stimulated insulin secretion (∼30 to 0 min) and reduced glucose concentrations. After the meal, integrated incremental glucose (p = 0.0001) and insulin (p = 0.031) were reduced (dose-dependently) rather than enhanced.

Conclusions: (1) GLP-1 [7–36 amide] or [7–37] inhibit gastric emptying in normal as in Type 2 diabetic subjects. (2) Almost physiological doses (0.4 pmol/kg.min) still have a significant effect. (3) Despite the known insulinoctopic actions of GLP-1 [7–36 amide] and [7–37], the net effect of administering GLP-1 with a meal in normal subjects is a reduction in insulin responses. These findings have to be considered when attempting to treat Type 2 diabetic patients with GLP-1 or analogues.

1101 p16 Expression in Pancreatic Carcinoma Cells Shows an Inverse Correlation to Retinoblastoma Protein and Cell Cycle Progression
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Cell-cycle is regulated by a group of cell-cycle-inhibitors controlling cellular growth. The natural targets of some of these inhibitors are represented by cyclin-dependent kinases, which phosphorylate the tumor-suppressor retinoblastoma protein (pRb), enabling cells to arrest, the G1-inhibitor p16 interacts with the G1/cyclin-complexes and blocks Rb phosphorylation. The purpose of our study is, to evaluate the dysregulations in pancreatic tumor cells concerning G1-phase cell-cycle-factors. Expression of cell-cycle-factors was investigated either in cyclomycin-resistant or with cell extracts by Western blotting, and the subcellular localization was studied by immunofluorescence.

We observed in pancreatic carcinoma cell lines (n = 18) an inverse correlation of p16 to Rb and cyclin D expression. Most of the cell lines, which showed no p16 expression (8/18) did not express cyclin D (7/8) as well. Expression of cyclin D in asynchronously grown pancreatic carcinoma cells is generally weak, whereas breast carcinoma cells and NIH3T3 fibroblasts exhibit normal levels of cyclin D1. Surprisingly, the absence of cyclin D1 expression in pancreatic carcinoma cells is accompanied with strong cdk4 expression and exclusive cytoplasmic localization of cdk4.

We conclude from these data, that changes in cellular expression either in the cyclin D1-negative, Rb-positive pancreatic carcinoma cell lines or in normal pancreatic duct cells, that the expression of cdk4 in the absence of cyclin D and its cytoplasmic localization in pancreatic carcinoma cell lines points to a cellular dysregulation of this kinase.
In 53% of the patients the main pancreatic duct was totally free of stones (41%) or contained only minimal fragments (12%) after the treatment (I: 52/15%, II: 53/33%, III: 24/9%). 74% of the patients reported on pain relief after the last therapeutic intervention (I = 85%, II = 73%, III = 64%).

Conclusions: Interventional techniques are most effective in patients with localized stones and/or strictures in the pancreatic head. In contrast to the low technical success rate in the majority of the patients with advanced CP even a remarkable pain reduction was achieved. Therefore, interventional measures seem to be justified in all patients with CP independent of extent and localization of stones and strictures.

1108 Pharmacokinetics and -Dynamics After Application of Budesonide Ph-modified-release-capsules in Patients with Chronic Disease as Compared to Healthy Volunteers
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The use of steroids for the treatment of inflammatory bowel diseases is often limited by adverse reactions. Topically acting steroids like budesonide (BUD) in pH-modified-release-capsules are a new approach for treating inflammatory Crohn’s disease (CD). The rationale is to achieve a high local concentration of the drug and to avoid systemic side effects. BUD has been shown to be effective in acute CD as compared to 6-mercaptopurine or prednisolone. However, there are no data about the pharmacological properties of BUD in patients with CD after multiple oral dosing of BUD under steady state conditions. Patients and methods: In 2 patients with CD in remission (66.5, M age: 31.8 ± 11.7 yrs; CDAI: 101.2 ± 22.9) pharmacokinetics and -dynamics of BUD were studied under steady-state conditions after pretreatment (3 weeks) with a 3 mg dose, followed by a 3 mg, 6, 12, and 18 mg daily oral BUD-phmodified-release-capsules (BUDENOFALK). 18 blood samples were taken within 24 hours. BUD plasma concentrations were analyzed by radioimmunoassay and HPLC. Pharmacodynamic effects were monitored by peripheral granulocytes and lymphocytes.

Results: Under steady state conditions no cumulation of BUD could be observed. Peak plasma concentrations (HPLC-RIA) were detected 4.3, 5.0 and 7.7 hours after each application (tmaxl = 4.3 hrs.; tmax2 = 13.0 hrs.; tmax3 = 23.7 hrs.). A marked time lag of 2-4 hours was observed in each patient. AUC∞ was found to be 30.08 ng/ml*hrs and 13.98 ng/ml*hrs by HPLC-RIA. With respect to the kinetics of peripheral lymphocytes and granulocytes the pharmacodynamic effects were lower as compared to 6-mercaptopurine in equivalent doses. Discussion: The data confirm the low bioavailability of budesonide and the beneficial application in pH-modified-capsules. Multiple application does not lead to cumulation. AUC∞ levels and pharmacodynamic effects were similar to those from healthy volunteers but showed a larger variability. Conclusion: With respect to these pharmacological data and clinical trials BUD represents a progress in the treatment of inflammatory disease. Further clinical studies are required to evaluate the optimal dosage and to identify those subgroups of patients which will respond best to topically acting steroids.

1111 Randomized Prospective Comparison of High- and Low-compliance Balloon Dilatations in Patients with Achalasia
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Pneumatic dilation is the most effective nonsurgical treatment of achalasia. Esophageal perforation is the most serious complication of this procedure occurring in about 5% of cases. We compared a high-compliance latex balloon (HCB) mounted on an endoscope (Pentax FG-29K, 40 mm max. distention diameter, 6 psi inflation pressure) with a low-compliance balloon (LCB) (Microvasive Rigiflex ABD, 35 mm, 20 psi) which is said to be safer, since it increases esophageal wall tension in the stenotic zone only.

Methods: We studied the complications in 25 patients after dilation and a controls group of 6 months up to 3 years after dilation. A symptom score for dysphagia, regurgitation and chest pain was calculated by multiplying the frequency of a symptom (0-5) by the severity (0-4). Complications were graded for severity from none to perforation (0-3). All dilations were performed for 3 minutes under direct endoscopic control. Patients were assigned to the two different balloon types by random. The obtained data were analysed by using Wilcoxon rank-sum test.

Results: The perforation was seen in the CB-group, which reached not statistical significance. Superficial mucosal tears appeared in 42% of all dilata-

<table>
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<th>Intervventional techniques</th>
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<th>AUC∞</th>
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<tr>
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<td></td>
<td>II (15)</td>
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<td>III (33)</td>
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<tr>
<th>Symptom score</th>
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<td>3.0</td>
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<tr>
<td>LCB</td>
<td>16.7</td>
<td>5.9</td>
<td>4.6</td>
<td>6.8</td>
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Three patients required repeated dilations during the observation period. They were treated with the competitive balloon system and showed no difference compared with the initial post-treatment symptom score.

Conclusion: No significant difference concerning the complication rate and the clinical outcome could be seen between the HCB- and LCB-system. In consequence both systems appear equally effective, even if the scope-mounted system (HCB) can be handled easier.

1114 Endoscopic Sphincterotomy in Chronic Pancreatitis: Indications, Techniques, Results and Complications
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Aims and Methods: Aim of this study was to analyze the different pharmacokinetics-techniques and their success, including complications and mortality in patients with chronic pancreatitis (CP) for the period 1989 to 1993. Results: 1. Frequency and techniques of sphincterotomy: From January 1989 to December 1993 in 111 pts. with CP cutting techniques were used for diagnoStic and therapeutic purposes. In 53/111 (47.8%) pts. pancreatic sphincterotomy with the standard sphincterotomy (PST) and in 21/111 (19.8%) pts. only a needle-knife incision of the pancreatic duct (PD-PRE) were performed. In 30/111 pts. (27.0%) needle-knife incision of the papilla (BD-PRE) or hiliary sphincterotomy (EST) were done without PST. In 7/111 (6.3%) the minor papilla was cut by means of the needle-knife because of CP and pancreatic divisum. 2. Technical success: Depending on the different indications the overall success rate was 96% (107/111). In 3 cases ERP could not be achieved in spite of BD-PRE (2 pts.) or EST (1 pt.). In 1 patient PST was not successful even after PD-PRE. 3. Complications and mortality: The complication rate was 3.5% (1 bleeding, 3 acute pancreatitis). No complication lead to death, but one patient died in hospital 4 days after sphincterotomy because of heart infarction. Conclusion: Endoscopic sphincterotomy techniques are effective for the therapeutic and diagnostic approach to CP. They do not show a higher risk for complication than conventional sphincterotomy for biliary diseases.

1116 Role of Nucleolar Organiser Regions (AgNORs) in Cytological Diagnosis of Brush Cytology
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The cytological evaluation of cellular material prepared from brushings by Endoscopic Retrograde Choledochopancreatography (ERC/P) is often difficult because of distinguishing neoplastic adenocarcinoma cells from those of non-specific inflammatory tissue. To evaluate the diagnostic importance of the possibility to differentiate malignant cells on the basis of their higher number of interphase silver-binding nuclei-organiser regions (AgNORs) the study was performed.

In 41 patients with suspicious space-occupying or cystic lesions of the pancreas or biliary tract, subsequently ERC/P examination was performed. Cellular material from brushings was obtained and stained with hematoxylin eosin and parallel AgNORs were analysed using the silver-colloid method. In all cases, the diagnosis was confirmed histologically (21 cases: 16 malignant, 5 benign) or by following the clinical course (20 cases; including CT scans or ultrasound examinations: 5 malignant, 15 benign diseases).

The range of the mean number of AgNOR dots per nucleus was 1.6 to 6.5. Cells on specimens with severe atypia or cancer had a significant higher number of mean AgNOR dots (4.5-6.5) than inflammatory or non-neoplastic cells (1.0-3.8). Atypical cells were characterised by a large number of AgNORs which were small in size and showed a scattered distribution. Cells from normal pancreatic or biliary duct epithelium or mesothelial origin had not only a smaller number of AgNOR but also large sized and clustered dots. These results indicate that the visualization of AgNORs helps to distinguish between malignant and benign cells not only in terms of their number, but also in regard to their spatial distribution inside the nucleus and their size. The simple and rapid AgNOR technique seems to be a useful adjunct in the diagnosis of cytological cells in brush cytology.

1117 Preliminary Experience with Balloon-expandable Stent™ Stents in Chronic Pancreatitis
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Chronic pancreatitis is characterized by the development of stenosis of the pancreatic duct, pretectonic dilatation of the duct, intraductal concrements, pancreatic pseudocysts and recurrent inflammatory attacks which are painful for the patient. For this reason, the main target of an interventional endo-
scop treatment, also in combination with EWW, should be the facilitation of free duct drainage by means of endoscopic papillotomy or transient prosthesis implantation. We are reporting on initial experience concerning implantation of balloon-expandable Streeker™ stents in the pancreatic duct in patients suffering from more severe chronic pancreatitis.

From September 1993 until September 1994 6 patients (1 female, 5 male, age 47 [32-58] years) with histologically confirmed benign stenosis of the papillary duct or chronic pancreatitis, 1x acutely stenosing pancreatitis) were provided with balloon-expandable metal stents (Streeker™ Stent, Microvasive®, Boston Scientific; Ø 21F, 40, 60 or 80 mm length) and observed over a mean period of 2 months (2.5-14 months). After implementing the patients with chronic pancreatitis exhibited attacks on average once a week up to every three months for a period of 2 to 11 years. In all cases implantation uneventfully proved to be a success and was conducted without complications by an additional laparotomic approach. In one patient the stent was again removed endoscopically after 2.5 months. During this endoscopy a pronounced epithelialization of the stent was found. The histological investigation of which revealed the presence of a pancreatic carcinoma which in spite of initial negative histology was responsible for the acutely stenosing pancreatitis. Like another patient in whom the stent was removed due to persistent attacks of pain after 5 months this patient was provided with surgical treatment. Two patients suffered an attack after 3 and 5 months, respectively, but were symptom-free during further follow-up examinations (11 and 17 months). Two other patients have been symptom free since implantation (5 and 15 months).

These initial results possibly indicate a new endoscopic interventional therapeutic approach of more severe chronic pancreatitis and justify further investigations, even prospective randomized ones.

**1118 NM23-H1 Immunoreactivity in Colorectal Carcinomas and their Corresponding Metastases**

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**Aim:** Reduced expression of the metastasis suppressor gene nm23-H1 has heretofore been correlated with high tumor metastatic potential and fatal clinical outcome in human tumors (lung, breast). For colorectal carcinomas, we have recently reported, that the expression of nm23-H1 correlated with the stage of disease at time of primary surgery. To evaluate, if the nm23-H1 expression pattern of the primary colorectal carcinoma comparable with those of corresponding lymph node metastases and also with liver metastases from the same patient, this immunohistochemical study was performed.

**Methods:** Routinely fixed paraffin-embedded tissue from 45 colorectal carcinomas (UICC-Stage III) and their corresponding metastatic lymph nodes were stained using monoclonal antibody against nm23-H1. The degree of nm23-H1 positivity was classified into three categories by semiquantitative estimation of the proportion of positive staining tumor cells on the entire slide (absent or weak: less than 30% of positive tumor cells, moderate: 30-60% of positive tumor cells, strong: more than 60% positive minor cells).

**Results:** The nm23-H1 immunoreactivity in the metastatic lymphnodes were equal to those of the primary tumor in 13 and lesser intensive in 32 cases. During follow up of these 45 patients, metastatic hepatic metastases were diagnosed in 8 cases. The comparison of the immunostaining pattern revealed, that the metastatic neoplastic epithelium was completely negative for nm23-H1 in six patients. From these, the primary tumor was moderate positive in four cases and, weak in two cases. The corresponding metastatic lymph nodes exhibited: a weaker staining pattern than the primary also. In case of two patients, the nm23-H1 immunoreactivity of the liver metastases was weak, the corresponding primary was strong, and the lymph nodes were graded as weak positive also.

**Conclusions:** These results indicated, that the nm23-H1 immunoreactivity is weaker or even absent in lymph node or liver metastases as compared with the corresponding primary colorectal cancer. Further studies are required to evaluate if this decrease of nm23-H1 has biological significance in terms of mediating enhanced metastatic potential.

**1120 Acceleration of Wound Healing in Gastric Ulcers by Local Injection of Neutrophil-Anti (NA) to Transforming Growth Factor β1**

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Application of neutralising antibodies (NA) to TGFβ1 improves wound healing in experimental glomerulonephritis and dermal incision wounds. TGFβ1 has been detected in the stomach, but the defect in this cytokine plays a cental role in wound healing no information is available at present whether modification of the TGFβ1-profile influences the healing of gastric ulcers. Here we examine gastric ulcer healing in the rat after local injection of NA to TGFβ1.

**Method:** Chronic gastric ulcers were induced in Wistar rats by the application of 100% acetic acid to the serosal surface of the stomach. Immediately after ulcer induction and on day 2 neutralising antibodies (NA) to transforming growth factor β1 (50 µg), TGFβ1 (50 ng), saline or control antibodies (IgG; 50 µg) were locally injected into the subserosa. Gastric blood flow was determined at a constant pressure of 60 mmHg, enabling steady flow over day 11. Animals were sacrificed on day 11, the ulcer area was measured planimetrically, sections were embedded in paraffin and stained with trichrome or H&E. Depth of residual ulcer was assessed by a scale of 0-3, the percentage of collagen was determined by the method of Miettinen and Miettinen. The number of mitoses and macrophages in the ulcer bed were assessed also. Results: The application of NA to TGFβ1 lead to a significant acceleration of gastric ulcer healing (0.6 [SD 0.8] vs 3.7 [SD 2.6] mm²)1, a reduction in macrophages (23.7 [SD 22.6] vs. 38 [SD 26] per 40x power field) and granulocytes (8.5 [SD 5.6] vs. 20 [10] per 40x power field), fewer histological residual ulcers (mean 1 [SD 0.8] versus 2 [1.1]), a reduced matrix score and a regenerative healing pattern. Gastric blood flow at the ulcer margin was significantly higher than at the ulcer crater but no significant difference was found in this flow between studied groups. TGFβ1 treated animals did show smaller ulcers (1.7 [SD 1.6] mm²)1 than the controls (3.7 [SD 2.6]mm²) but excessive scarbing was observed. Conclusion: Further treatment of gastric ulcers may induce a new treatment modality by local injection of NA to TGFβ1 in an attempt to accelerate and improve ulcer healing.

**1121 Higher Concentrations of Procollagen III Peptide in Bile in Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis**

G. Silleisen, F. Erster, W. Domschke, 1 Department of Medicine B, University of Muenster, Muenster, Germany

In primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) fibrosis is found next to the bile ducts. Consequently, it was tempting to investigate concentrations of procollagen III peptide (P-III-P) in bile.

We analyzed bile samples from 5 patients with PBC and 5 patients suffering from PSC and controls. The bile was obtained free of contrast medium during ERC examination. P-III-P concentrations were measured with a commercially available radioimmuno assay (Behring, Marburg, Germany).

P-III-P concentration measured in the bile fluid of controls was 0.17 ±2SD (±2SD = 0.11). All 10 patients suffering from PBC or PSC had significantly (p < 0.05) higher concentrations of P-III-P averaging 0.48 ±2SD (±2SD = 0.28).

In the bile patients of primary biliary cirrhosis or primary sclerosing cholangitis procollagen-III-peptide is found in significantly higher concentrations than in normal controls indicating the possible role of this marker for the assessment of the fibrotic activity in these diseases.

**1122 Expression of bFGF, EGF, TGF-α, and their Receptors During Healing of Chronic Gastric Ulcerations in Rats**

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Wound healing involves the synthesis of extracellular matrix components combined with cellular proliferation, migration and differentiation. Growth factors appear to play a key role in this process. This study was designed to analyze the distribution of major growth factors during healing of chronic gastric ulcers.

**Material and Methods:** Chronic gastric ulcers were induced in 50 Wistar rats by the application of 100% acetic acid on the serosal surface of the stomach. The animals were then sacrificed at 0, 2, 4, 6 and 8 days after ulcer induction. The stomachs were removed, the ulcer area measured and the sections were immunostained with antibodies against TGFα (GF 10, Oncogene), EGF (GF01, Oncogene), EGF-R (Sigma), PCNA (PC 10, Oncogene), bFGF (GF 22, Oncogene), PDGF (PC 21, Oncogene) and PDGFR-Receptor (Sigma P-7679). Results: A gradual decrease in ulcer size was observed from day 2 (20 mm²) to day 8 (4 mm²). Immediately after ulcer induction (day 0), a marked vascular congestion in submucosa and necrosis of superficial mucosa were observed. Under the necrotic mucosal cells in the area of vascular damage there was increased staining for bFGF and bFGF, and weak staining for EGF, TGF-α and their receptors. Day 2 strong staining for EGF, TGF-α and their receptors in the epithelial cells at the ulcer margin and for bFGF in endothelial cells and fibroblasts of the granulation tissue were noticed. Expression of EGF, TGF-α and bFGF and their receptors peaked at day 4 and remained unchanged thereafter but PDGF staining was negligible. Also an increased number of PCNA-positive cells at the ulcer margin and in granulation beds were seen.

Conclusion: Healing of chronic gastric ulcer involves spatial and sequenced distribution of growth factors and their receptors and these factors are significant for the stimulation of reepithelialization of the wound and in granulation tissue to reconstruct the microvascular network of grossly healed ulcer. The quality of these mucosal reconstruction processes controlled by growth factors may play important role in future ulcer relapse.
Background: The mechanism of stress-induced gastric ulceration and mucosal healing is not entirely clear. Transforming growth factor α (TGF-α) and epidermal growth factor (EGF) stimulate mucosal growth and cell proliferation and protect the gastric mucosa against injury via action on their common receptor (EGFR). The aim of this study was to assess the expression of TGF-α, EGF, and EGRF in the gastric mucosa after single exposure to stress.

Material and Methods: 25 rats were exposed to water restraint stress for 3.5 h and then sacrificed at 0, 2, 4, 6, 8, and 12 h. Each group included at least 5 rats. The number of stress lesions were counted and sections obtained from the stomach were stained immunohistochemically for proliferating cell nuclear antigen (PCNA), TGF-α, EGF, and EGF receptor (all antibodies from Oncogene). At least 300 consecutive cells were counted in each section to determine the number of positive cells per 1,000 cells counted. The intensity of cytoplasmic staining for TGF-α and EGF were graded (0, 1, 2) by examination of 30 consecutive cells per section. In addition, we evaluated the number of EGF receptor-positive cells. All semiquantitative data were assessed according to different regions of the gastric gland (top, neck, and base). DNA synthesis was measured in the mucosal scraping by in vitro incorporation of ³H-thymidine into DNA.

Results: The number of ulcerations at 0 h was about 15 ± 3 and then gradually decreased to about 2 at 12 h after stress. Labeling index for PCNA showed a significant increase at 2 h after stress and reached its highest level at 6 h after exposure to stress. There was almost no staining for EGF immediately (0 h) after stress compared to the control (staining index, x = 0.26). Staining intensity for EGF, then increased reaching its peak at 6 h after stress (x = 0.93), and then declined at 8 h and 12 h after stress. EGF expression increased from 0 h, reaching peak at 4 h and then gradually declining from 6 h to 12 h. In contrast, immunostaining for TGF-α increased gradually from 0 h to 12 h with predominant staining of superficial epithelial cells. At 0 h, h DNA synthesis fell by about 35% compared to intact gastric mucosa and then started to rise after 12 h after stress.

Conclusions: This study provides evidence that there is a time-dependent increase in TGF-α, EGF, and EGF receptor expression in the gastric mucosa after single exposure to stress and this is accompanied by increased mucosal cell proliferation and DNA synthesis. These findings suggest an important role of growth factors in the mucosal repair by cell proliferation and DNA synthesis after exposure to stress.

**Extracellular Matrix (ECM) Proteins in the Gastric Ulcer Healing Process**

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The extracellular matrix (ECM) in the submucosa of healing gastric ulcers plays an important role for the quality of the resulting scar. To obtain more information about the distribution of collagen types I, III, fibronectin and tenascin during different stages of the healing process we used the model of acetic acid induced gastric ulcers in rats.

Gastric ulcers were induced in 100 male Wistar rats by application of a 1% acetic acid solution on the stomach, once a day for 30 seconds during laparotomy in anesthetized rats. Each group of 100 animals was laparotomised as controls without induction of an ulcer. On days 3, 5, 7, 9, 12, 15, 16, 20, and 30 after ulcer induction 10 animals of each group were sacrificed and the stomach was removed for histological and immunohistochemical analysis.

All ECM proteins were investigated in the mucosal submucosa of the control animals as well as in the mucosa contralateral to the ulcers without any changes during healing process. Collagen types I and III were detectable in the submucosa of the ulcer ground and at the ulcer edge in increasing amounts during the healing process. Fibronectin and tenascin were found in the same localization as the fibbrial collagens and their expression was mainly enhanced during the early healing phase at days 3–12 and returned to normal levels after 20 days of healing.

Our results show the different expression of fibbrial collagen types I and III, fibronectin and tenascin during all stages of gastric ulcer healing process indicating their importance for the rebulding of submucosal connective tissue in this context.

**Metabolism of Isoursodeoxycholic Acid in Man**


Purpose: UDCA, commonly used for symptomatic treatment of various cholestatic liver diseases, is isomerized at C3 forming isoUDCA. N-Acetylgalactosamines (GlcNAc) are the major urinary metabolites of UDCA and isoUDCA. The selective formation of β-glucuronidase may be one mechanism of action of UDCA. Since isoUDCA is an even better substrate for hepatic UDP-GlcNAc-transferase the metabolism of isoUDCA was studied in humans.

Methods: isoUDCA was synthesized with >99% purity as estimated by TLC, GCMS, and FABMS. This acid was orally administered to 6 healthy male volunteers (33–54 years of age) at a daily dose of 3 × 250 mg for 7 days. A comprehensive analysis of bile acids considering all known groups of conjugates was performed by reverse phase, endoskopically sampled bile, and 24 h urine from the day before and day 7 of this study.

Results: isoUDCA was tolerated without any side effect. Liver function tests remained unchanged, however, both bile lithogenic and cholesterol saturation indices were further increased. The relative amounts of isoUDCA, UDCA, and 3-dehydro-UDCA (C3-intermediate of isomerization) were in bile: 0.8 ± 0.1% (mean ± SEM), 27.8 ± 8.7% (before: ± 0.9%), and 2.6 ± 2.0% (in serum: 15.2 ± 5.3%, 22.6 ± 9.1%, and 13.5 ± 10.5% in urine: 80 ± 27.7%, 3.3 ± 1.4%, and 4.7 ± 1.5%, respectively. GlcNAc-conjugates of biliary and urinary isoUDCA consisted 76.8% and 94.5%, respectively. Urinary isoUDCA excretion rate was approximately 25% higher than the previously estimated urinary excretion rate of UDCA after 2 × 350 mgid of UDCA.

Conclusion: Orally administered isoUDCA is partly isomerized to UDCA which in turn is enriched in bile. The major part of isoUDCA, however, is not secreted into bile but excreted in urine as GlcNAc. isoUDCA may be a safe and well-resorbed drug. A pilot-study in patients with cholestasis comparing isoUDCA with UDCA is planned.

**Hepatoprotection and Acute Phase Proteins Induced by Isoursodeoxycholic Acid in Vitro**


Purpose: Isoursodeoxycholic acid (UDCA) has been shown to improve clinical and biochemical parameters in patients with cholestatic liver diseases. UDCA is partly isomerized to C3 and both acids are conjugated at C7 with N-acetylgalactosamine (GlcNAc) with isoUDCA being an even better substrate for hepatic UDP-GlcNAc-transferase than UDCA. Formation of GlcNAc conjugates might interfere with the biosynthesis of glycoproteins. The aim of this study was to compare the cytoprotective effects of UDCA and isoUDCA and the possible induction of acute phase proteins in vitro.

Methods: isoUDCA was synthesized from UDCA to >99% purity, in order to assess cytoprotective properties human hepatoma cells (HepG2) were incubated for 24 h with and without 80 mM ethanol and various bile acids (isoUDCA, UDCA, CA, DCA, or CDCA), each at 100 μM. Ethanol toxicity was tested by trypan blue staining, induction of acute phase proteins (α-macroglobulin, fibrinogen, and haptoglobin) was measured by Northern Blot analysis.

Results: UDCA and isoUDCA were significantly less (p < 0.01) cytotoxic than other bile acid tested. Ethanol cytotoxicity was prevented better (16%, p < 0.05) by isoUDCA than by UDCA. Induction of acute phase proteins by isoUDCA or UDCA was negligible as compared with interleukin-6 (IL-6).

Conclusion: These results suggest that isoUDCA is not cytotoxic and may exert an even better cytoprotective effect than UDCA. Both bile acids do not induce acute phase proteins.

**First Administration to Man of the New Acid Pump Antagonist BY841: Tolerability, Safety and pH-metry**


Introduction: BY841 is a reversible H⁺-K⁺-ATPase inhibitor, a so-called acid pump antagonist (APA), newly developed by Byk Gulden Pharmaceuticals, Germany. The aim of this first study in man was to investigate safety, tolerability and effect on intragastric pH of single oral doses.

Methods: 18 healthy male volunteers were integrated into 3 groups of 6 each. Each group was given 2 single oral doses of BY841 in increasing order with interposed placebo (pl): group I: pl, 10, 20 mg; group II: pl, 50; group III: pl, 200, 400 mg. Safety parameters, pepsinogen, HCC, clinical signs, laboratory and adverse events. Intragastric 24 h pH was measured in groups II and III only.

Results: BY841 did not influence ECG, vital signs, laboratory nor were there relevant adverse events. The pH-profiles of group III are shown.
1131 The Role of Endogenous Nitric Oxide (NO) in the Regulation of Gastric Motor Activity in Humans

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Nitric oxide (NO) is an unstable neurotransmitter formed from L-arginine (L-arg) and released by nonadrenergic-noncholinergic (NANC) nerves in the gastrointestinal tract, but its role in the control of gastric motility in man is unknown.

We have studied the possible involvement of NO in the control of gastric motor and electrical activity. Five male volunteers (age 21–24 years) were involved on three separate occasions in this placebo controlled study on the effects of Nω-monomethyl-L-arginine (L-NMMA, 4.0 μmol/ml i.v.) and L-arg (1 mM/ml) on the gastric emptying of 600 ml standard liquid meal (Fresubin®, Fresenius, Germany). The gastric emptying rate was determined using 13C-acetate breath test. Simultaneously, the antral motor activity was determined manually using a 3-channel Kingsberg catheter (Kingsberg, Pasaden, USA) and Microdigitrapper (Synectics, Stockholm, Sweden). The gastric myoelectrical activity was measured before and during the gastric emptying period using cutaneous EGG system (Synectics, Stockholm, Sweden). The motility patterns were analyzed using specially developed software (Gastrosoft, Irving, USA). Statistical analysis was performed using Statpac III software (Gastrosoft, Irving, USA). significance was accepted with p values less than 0.05; L-NMMA caused significant (p < 0.01) reduction of the gastric emptying rate averaging 9.7 ± 2.5 min, when compared to placebo (19.3 ± 3.6 min) and this increased gastric emptying rate was nearly completely reversed (21.7 ± 4.4 min) after addition of L-arg to L-NMMA infusion. The postprandial antral motor activity calculated as motility index (number of contractions × mm/hr/ml) significantly increased in tests with L-NMMA from 298.5 ± 104 (6.0% NaCl) to 489.6 ± 132.6 and this increase was not observed when L-NMMA was given in the combination with L-arg (322.1 ± 96.9 min). The gastric myoelectrical activity during the postprandial period remained unchanged in all tests showing mainly regular rhythms of 2.8 ± 0.3/min. We conclude that: 1. endogenous NO affects the gastric emptying of liquid meal. 2. The increase of the gastric emptying rate after blockade of endogenous NO is presumably due to the suppression of receptive relaxation of the proximal stomach.

1132 Repeated Oral Administration of the Acid Pump Antagonist BY841


BY841 is a reversible inhibitor of the gastric H+/K+-ATPase, newly developed by Byk Gulden Pharmaceuticals. It is the first representative of the so-called class of the acid pump antagonists (APA). The aim of this study in man was to investigate safety, tolerability and influence on intragastric pH following repeated oral doses.

Eight healthy male volunteers were given 100 mg bid and 200 mg bid for 7 days each in a randomized two-period crossover. Two placebo days preceded the active treatment in each period. 24 hour intragastric pH was recorded on the first placebo day, and on the first and seventh treatment day with BY841. Blood was taken for pharmacokinetic analysis on days 1 and 7.

Both treatments were well tolerated without clinically relevant changes in vital signs or clinical laboratory. No relevant adverse events occurred. The results of the pH-metries on day 7 are shown below.

Median pH (range) pH > 3 and pH ≤ 4

<table>
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<tr>
<th>pH value</th>
<th>Median (range)</th>
<th>Median (range)</th>
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<tr>
<td>&lt; 3</td>
<td>41.5 (28, 50.8)</td>
<td>58.4 (42, 75.6)</td>
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<tr>
<td>≥ 4</td>
<td>31.9 (18.6, 44.9)</td>
<td>48.1 (32.6, 62.1)</td>
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As to the increase in intragastric pH, 100 mg bid were more effective than 200 mg bid, in particular during the night. A slight increase in inhibition of intragastric acidity was observed during repeated dosing; this effect was more pronounced with 100 mg bid.

In conclusion, BY841 was shown to be safe and well tolerated during repeated dosing. Bid dosing was more effective than sid administration.

1133 Pantoprazole Lacks Pharmacokinetic and Pharmacodynamic Interaction with Phenprocoumon in Man

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Pantoprazole is a proton pump inhibitor with a low potential to interact with the cytochrome P450 enzyme system in man. In particular, no interaction was found with warfarin. However, due to the clinical importance of therapeutic failure or bleeding during anticoagulant therapy, an additional interaction study with phenprocoumon was performed.

16 healthy male volunteers were given individually adjusted doses of phenprocoumon over 15 days. Quick and 50% Quick values were decreased to about 30–40%, and the phenprocoumon doses were then kept constant until day 15. From day 11 to 15, additionally 40 mg pantoprazole were administered. Quick values from days 14 and 15 (Test) were compared to those of days 9 and 10 (Reference). Pharmacokinetics of R- and S-phenprocoumon were investigated on day 10 (Reference) and day 15 (Test). Lack of interaction was concluded if the point estimate and 90% confidence interval in man is unknown. We have investigated the possible involvement of NO in the control of exocrine and endocrine pancreatic secretion. Six healthy volunteers (20–24 years old) were studied and basal and stimulated pancreatic secretion was examined after i.v. infusion of secretin (5) at 80 pmol/kg/h and carbenul (C) at 50 pmol/kg/h. Aspiration by double lumen duodenal tube and nonabsorbable marker (PEG 4000) were used. The procedure was repeated but S and C were infused together with gradually increasing doses of NGω-monomethyl-L-arginine (L-NMMA, 1–8 μmol/min i.v.) and/or L-arg (1 mg/min i.v.). The pancreatic juice volume and/or concentration of HCO3, protein and enzymes (amylase, lipase, trypsin) were determined. Plasma samples were taken for RIA of pancreatic hormones. In addition, intact pancreatic tissue samples were taken during surgery on pancreas from 5 patients to prepare dispersed pancreatic acini using collagenase digestion. Infusion of L-NMMA did not influence basal pancreatic secretion but reduced dose-dependently S + C-stimulated protein enzymes reaching 40–70% at a dose of 8 μmol/min L-NMMA. Addition of L-arg reversed in part L-NMMA-induced reduction. S + C caused significant increments in plasma insulin, (by ≈ 5 μU/ml) and PP (by ≈ 50 pmol/l) without alteration in plasma glucagon or somatostatin. Addition of L-NMMA reduced significantly by about 30% plasma insulin and PP and increased plasma somatostatin by by 4 pmol/l. L-arg alone caused significant rise in plasma insulin (by ≈ 8 μU/ml), glucagon (by ≈ 20 pmol/l) and PP (by ≈ 64 pmol/l) while decreasing somatostatin (by ≈ 4 pmol/l). L-arg combined with L-NMMA reversed the changes in plasma hormone levels. Studies in vitro on dispersed acini revealed that L-arg or L-arg + L-NMMA (10−5 M) failed to affect basal or stimulated (C at 10−2 – 10−3 M) amylase release. We conclude that endogenous NO affects hormone stimulated exocrine pancreas, presumably by alteration of its circulation, and endocrine secretion but has no direct action on acinar cells.

1135 A Novel Nucleotide Receptor of the Hepatocyte Plasma Membrane

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Pharmacological and functional studies suggest that the hepatocyte plasma membrane is equipped with purinergic receptors of the P2Y type with ATP being the major physiological agonist. Several other studies, however, presented evidence that UTP is equipotent to ATP in evoking cellular responses in hep-
Cretoliculin, a Target for Circulating Autoantibodies in Inflammatory Bowel Disease?

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Cretoliculin (CRT) is a multifunctional protein, involved e.g. in Gα2 isoform storage, protein-protein interactions and autocrine/paracrine factors. Extensive sequence homology exists with one of the known Ro/SS-a autoantigens. T lymphocyte activation sharply increases the expression of CRT and the protein is released from activated neutrophils and binds to C1q. CRT is highly conserved and homologues have been described as major antigens in oncocrinacs and schizophrenia. CRT is covalently modified by reactive metheoxides of nucleotides.

Since the pathogenesis of Crohn's disease is still obscure, we started to test a potential role of CRT: Results: CRT was purified from human small intestine mucosa and liver as described elsewhere. The identity and purity of the protein was confirmed by N-terminal amino acid sequencing, SDS-PAGE and immunoreactivity to a specific anti-CRT antibody. Sera of fifty healthy volunteers and of patients with Crohn's disease of different activity were tested for autoantibodies to CRT by immuno-dot blot or ELISA. Anti-Ro/SS-A positive sera from patients with Crohn's syndrome and systemic lupus erythematoses (SLE) were taken for positive control. All of the anti-Ro/SS-A positive sera exhibited high anti-CRT titres. Among 50 sera of patients with Crohn's disease 40 sera (80%) revealed significant anti-CRT immunoreactivity (dot blot) of varying intensity that could only be detected from 50 controls. Anti-CRT activity in sera could be detected by ELISA (serum dilution 1:1000) or immuno-dot blot with purified native CRT but not by Western blotting of the denatured protein. Summary and Conclusion: Circulating autoantibodies directed to CRT could be detected in a high proportion of sera of patients with Crohn's disease. This is unclear at present whether these autoantibodies could be involved in the pathogenesis of Crohn's disease or represent an epiphenomenon. Anti-CRT autoantibodies were detected only with native antigen, suggesting major importance of the preserved immunoreactive conformational epitopes of CRT.

Cretoliculin (CRT) belongs to the KDEL family of endoplasmic reticulum resident proteins. The multitude of suggested functions implies e.g. binding to Ca, Zn, Fe, protein-protein interactions and autocrine/paracrine factors. The primary structure of CRT is very similar to those of e.g. calnexin, the human collectin receptor (C1q-R), and the dominant antigens in oncoinarcacs and schizophrenia. Considerable anti-CRT activity has been detected in sera from patients with SLE and Sjogren's Syndrome. Here we tested the sera of patients with autoimmune liver diseases for autoantibodies to calreticulin as a first approach to evaluate a potential pathogenic significance of CRT autoimmunity. Methods: CRT was purified from human liver and described (BBRC 1993) 611–616 and used as antigen. Sera of 67 healthy volunteers (control), 31 patients with autoimmune hepatitis (AIH), 6 with primary sclerosing cholangitis (PSC), 75 with primary biliary cirrhosis (PBC), and 11 with other than autoimmune liver diseases were analysed for autoantibodies to CRT by ELISA at serum dilutions up to 1:1000. Only titers exceeding a twofold SD of the mean control values at a serum dilution of 1:1000 were taken as positive. Results: Among the 31 AIH sera 28 sera (80%) were positive and revealed by far the highest anti-CRT titres of all the sera tested. 45 (65%) of 75 PBC sera, 3 (50%) of 6 PSC sera, and 4 (36%) of 11 sera of patients with non-autoimmune liver diseases had positive anti-CRT titers, but of considerably lower activity. Summary and Conclusions: Autoantibodies against calreticulin could be detected in a high proportion of sera of patients with autoimmune hepatitis. Whether these autoantibodies could be involved in the pathogenesis of the disease or represent an epiphenomenon is unclear at present and merits further investigation.

The analysis of circulating autoantibodies to calreticulin may provide a novel diagnostic tool for autoimmune hepatitis.
Among the multitude of suggested functions are e.g.: binding and storage of Ca, Zn, Fe (mobiliser), chaperone function, autoregioncy, modulation of signal transduction, and gene expression.

Results: The intestinal CRT was purified to homogeneity and had a molecular mass of 60,000 in SDS-PAGE. The protein was concentrated in the ER; it was hydrophilic, acidic (pI 4.7), stained blue with ‘Stains All’, and glycans were weakly detected when stained with colloidal Coomassie. The N-glycosylation and acidic sequences (EPAVYF-K-EQ-F) was almost identical to that of CRTs of other sources. A specific anti-CRT antibody reacted with the purified protein and detected a single 60 kDa-protein in homogenates of intestinal mucosa (Western blot). Western immunoblotting of mucosal samples from human stomach, duodenum, jejunum, ileum and various segments of the colon suggest rather uniform distribution of CRT along the intestinal tract. In a radioligand overlay assay the protein bound Ca**2+** and Mg**2+** at distinct sites. CRT was phosphorylated by both Ca**2+**-dependent protein kinase and casein kinase II. Phosphorylation seems to modulate Ca binding to CRT.

Summary and Conclusions: Calreticulin was purified from human small intestine and liver, and from the intestine of other species. The protein is expressed in various cell types in rather uniform concentrations along the intestinal tract, where it may bind and store Ca and Zn within the ER, and regulate their intracellular activity. Phosphorylation by Ca**2+**-dependent protein kinase and casein kinase II provides a possible mechanism for regulation of CRT’s functions.

## 1141 Correlation Between Hepatitis C Virus (HCV) Genotypes and Graft Hepatitis Outcome in Patients with Orthotopic Liver Transplantation (OLT)


Patients chronically infected with HCV prior to OLT will suffer graft reinfec- tion in nearly all cases. Despite reinfection, graft hepatitis will occur in only about 50% and is histologically mild in most cases. HCV genotyping becomes increasingly important as prognostic marker for the responsiveness of interferon-alpha treatment in patients with chronic hepatitis C. Furthermore, HCV genotype 1 infection might be correlated to a more aggressive form of chronic hepatitis C and probably a more severe form of transplant hepatitis in patients after OLT. We investigated the distribution of HCV genotypes in patients undergoing OLT and the influence of the HCV-genotype on the development and outcome of graft hepatitis.

Patients and Methods: Between Sept. 1988 and Sept. 1994 534 liver trans- plantations were performed in our hospital. We investigated 64 patients (w/m = 36/28, age range: 36-63 years, weight range: 56-105 kg) who were infected with HCV after OLT for anti-HCV antibodies and HCV-RNA (nested PCR with primers from the 5' non-coding region). Determination of HCV genotypes (according to Simmonds’ classification) was performed using a restriction fragment length polymorphism (RFLP) analysis of the PCR products. Results: Before OLT 53 patients (83%) were infected with HCV genotype 1, six with genotype 2 (9%), and five with genotype 3 (8%). After OLT we observed in four patients a change of the HCV genotype: 2 patients with genotype 3 changed to type 1 and two patients with genotype 2 changed to type 1 and 3, respectively. In 3 of these patients (6%) [3 type 1 and type 2] became HCV-RNA (PCR) negative in a mean of 8 months after OLT. In the overall follow-up (mean 18 months, 1-60) 31 of 64 patients (48%) developed graft hepatitis: H1 in 17 (27%), H1 and H2 in 16 (25%); H2 in 6 (9%); 4 type 1, 1 type 2, 1 type 3, 2 type 3/4 (3%) and 4 type 3 (1%). HCV genotype 1, therefore, might be one factor for an unfavourable course after OLT.

## 1142 Hepatitis B, C and E Virus in Fulminant Non-A Non-B Hepatitis


The cause of fulminant non-A, non-B hepatitis is still unclear. To evaluate the role of hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis E virus (HEV) in this disease, we measured the viral DNA/RNA in serum and liver biopsy specimens of these patients using a nested polymerase chain reaction.

Patient and Method: Between Sept. 88 and Sept 49 534 orthotopic liver transplantation (OLT) were performed in our hospital. We studied 17 patients who were referred for transplantation with non-A, non-B fulminant hepatitis (NANB-FH). Diagnosis of NANB-FH was made according to three criteria: (i) negative tests for IgM and IgG antibodies to HBV, (ii) HBV surface antigen, IgM to HBV core antigen, anti-HCV antibody, anti-HEV antibodies, anti-nuclear antibody, anti-actin antibody and liver kinase microsome antibody. Serum and liver biopsy specimens were obtained in each patient before OLT, shortly after OLT (mean 3 months) and after the OLT (mean 9 months) respectively. In these patients nested PCR was performed with published primer sets for HBV (core and surface region), HCV (5' non-coding region) and HEV. Specific DNA fragments were visualized by ethidiumbromide stain- ing after agarose gel electrophoresis. All assays were performed with appropriate positive and negative controls. Results: Before OLT, HBV DNA was detected in 4 of 17 patients (23%) with NANB-FH (one in both, serum and liver tissue, two in serum and one in liver tissue); two of these four patients remained HBV-PCR positive shortly after OLT (mean two months), but all patients became HBV-PCR negative in the long-term follow-up (mean 26 months). All four patients were completely negative for serological HBV markers. In addition, one anti-HBs positive and HBV-PCR negative patient before OLT, became HBV-PCR positive two days after OLT, but cleared HBV one month later. HCV and HEV-RNA was not found in any of the 17 patients. Histological examinations gave evidence of reinfertion hepatitis only in two of the 17 patients (in the HBV positive group). Conclusion: Our results con- firm that some cases of NANB-FH in Europe are associated with HBV, HCV and HEV do not seem to play a substantial role in causing NANB-FH.

## 1143 Action of Glucagon-like-Peptide (7-36) Amide (GLP-1) on Cytosolic Calcium in Insulin-secreting Cells

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INS-1, a well differentiated rat insulinoma cell line, serves as a model for en- docrine pancreatic beta cells. We used this cell line to investigate the signal transduction of the incretin hormone GLP-1 underlying its stimulatory role in insulin secretion. Here, we examine the effects of GLP-1 on the cytosolic free calcium concentration ([Ca**2+**]**i**).

Cytosolic calcium was measured fluorimetrically in Fura-2 loaded cells, ei- ther with slurred cell suspensions in a fluorometer, or examining single, adherent cells with digital imaging fluorescence microscopy.

GLP-1 (10**–10**-10** M) raised cytosolic calcium in a concentration-dependent manner. This effect was prevented by the hyperpolarizing agent diazoxid (200 μM) and attenuated by the L-type calcium channel blocker verapamil (20 μM), showing that GLP-1 acts by inducing depolarization-dependent calcium influx. The [Ca**2+**]**i** rise by GLP-1 was also attenuated by prior depleation of intracellular calcium stores, indicating a secondary involvement of store release. The effect of GLP-1 was dependent on the ambient glucose concentration, being most pronounced at intermediate glucose levels (10 mM) but absent with- out glucose. Single cells measurements confirmed this glucose dependency. At low glucose (1-2 mM), without GLP-1, [Ca**2+**]**i** remained constantly at a low level in most cells, also not affected by subsequent addition of GLP-1. In contrast, at intermediate glucose, an intermediate spontaneous [Ca**2+**]**i** elevations, and GLP-1 augmented amplitude and frequency of these elevations. GLP-1 then also elevated calcium in cells without prior spontaneous [Ca**2+**]**i** elevations. This dependency on ambient glucose is in accordance with the concept of glucose competence induction in the beta cell by GLP-1.

Conclusively, our results demonstrate the high value of INS-1 cells in the characterization of GLP-1-mediated signal transduction and argue for a major role of calcium in this process.

## 1144 Accuracy of the Fecal Elastase Test (FET) for the Diagnosis of Chronic Pancreatitis (CP)


Pancreatic elastase is highly stable during the intestinal transit. Therefore fe- cal elastase concentrations accurately reflect pancreatic secretion. Aim of the present study was to evaluate the accuracy of a human specific FET for the diagnosis of CP, and to compare it with two other indirect tests (serum elastase assay -ELTA- and fecal chymotrypsin -FCT-).

Material and Methods: 80 patients (48 males, 32 females, age range 17–76 years) submitted for exploration of pancreatic function were studied. The final diagnosis was CP in 31 patients (based on ERCP in 26 months, 12-48 patients) and chronic pancreatic diseases in the remainder 39 patients. Two samples of faeces were collected from each patient for twice determination of FET (ELSA) and FET (activity). A modified serum PLT was then thereafter performed as previously described (Am J Gastroenterol 1985; 80: 1237). Sensitivity (S) and specificity (Sp) for the diagnosis of CP were calculated.

Results: FET and PLT but not FCT significantly decreased in patients with moderate (n = 10) and severe (n = 13) CP (as assessed by ERCP) compared to patients with exocrine pancreatic disorders (S = 100%) and FET and PLT.

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*Gut: first published as 10.1136/gut.37.Suppl_2.A121 on 1 January 1995. Downloaded from http://gut.bmj.com/ on September 15, 2023 by guest. Protected by copyright.*
4th UEGW Berlin 1995

A131

Characterization of the Golgi-apparatus and Cytoskeletal Transport Tracks of Rat Liver Myofibroblasts

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Although myofibroblasts (MFb) are the main producers of extracellular matrix during liver fibrosis, only little is known about the Golgi-apparatus (CA) and the intracellular transport. In order to analyze the role of the cytoskeleton for the morphology of the GA and the secretion of extracellular matrix components we performed immunofluorescence and transport analysis in the presence of cytoskeletal disrupting agents. Methods: Myofibroblasts (MFb) were obtained by culturing fresh isolated FSC in DMEM supplemented with 10% fetal calf serum (FCS). Two times passaged MFb were transfected with pSV2-neo and pSV2-GFP and used as fully transfomed MFb. For immunofluorescence analysis the β-COP specific antibody E5A3 and the comitin specific antibody 190-68-1 were used according standard protocols. Results: Immunofluorescence analysis using β-COP and comitin specific antibodies showed a clear Golgi apparatus in the perinuclear region. It consists of interconnected tubular structures and is recognized by both antibodies. A direct interaction of Golgi-membranes with actin-filaments (AF) and microtubules (MT) could be shown by colchicine (5 mM) or cytochalasin D (20 μM) induced depolymerization of the filaments. In both cases we observed a condensation of the GA-membranes near the nucleus. Only after simultaneous disruption of both filament types, a partial fragmentation of the GA occurred. Thus, we could show that both MT and AF are involved in the maintenance of the GA-architecture and ii) serve as transport tracks for secretory transport vesicles in rat liver MFb.

A1152

Characterization of TGF-β1 Overexpressing Rat Hepatoma Cells

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The transforming growth factor-β1 (TGF-β1) plays a central role within the development of liver fibrosis. It is involved in the transformation of hepatocyte stellate cells into myofibroblasts and induction of hepatocyte apoptosis. Although gene expression of TGF-β1 and 2 is detectable in isolated rat liver hepatocytes only little is known about the protein expression and the resulting functional consequences for this cell type. Therefore we decided to overexpress TGF-β1 in rat hepatoma cells (FAD) and start to analyze the resulting effects. Methods: FAO rat hepatoma cells were transfected with an episomal expression vector harboring the complete human TGF-β1 coding sequence under the control of a CMV-promoter. A stable TGF-β1 overproducing cell line was obtained after hygromycin B selection. As a control untransfected and mock transfected cells were used. Overexpression of TGF-β1 was determined by RT-PCR, ELISA and Mv-Lu-cell bioassay using the standard protocols. The transfectants were analysed by RT-PCR and immunofluorescence analysis. The proliferation rate was determined by measuring the bromodeoxyuridine incorporation into the DNA (BrdU-ELISA). Results: Gene expression analysis of the generated TGF-β1 overproducing cell line showed that the transfected TGF-β1 gene is efficiently transcribed. The transfected cells expressed large amounts of TGF-β1 mRNA, whereas the message was only barely detectable in untransfected cells. The generated TGF-β1 mRNA is transcribed and the protein released from the cells into the culture medium. The culture medium of the transfected cells contained only nonactivated, latent TGF-β1 at concentrations of about 300 pg/ml (controls: 0 to 5 pg/ml). The recombinant TGF-β1 was functionally active after acidification as determined by Mv-Lu-cell bioassay. The TGF-β1 overproducing cells had no obvious morphological alterations but exhibit a reduced growth rate as compared with control cells. A characteristic feature of the TGF-β1 overproducing cell line was their altered aggregation behaviour, because the transfected cells had a strong tendency to aggregate which was not observed in control cells. Conclusion: We could show that TGF-β1 overproduction i) is possible in rat hepatoma cells and ii) that the cell line has an altered growth and aggregation behaviour.

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Recent studies with transgenic mice suggest a role of gastrin during intestinal cell differentiation. The underlying molecular mechanisms are poorly understood. We previously demonstrated sodium butyrate (NaB) induced cell differentiation and concomitant transient gastrin increase in insulinoma cells. The present study was designed to confirm the effect of NaB on cell differentiation of RINm5F cells on gastrin promoter activity. Methods: Cells were cultured for 0, 12, 24, 48 and 72 hours in presence or absence of 0.5 mM NaB. Gastrin mRNA was determined by Northern blot analysis. A CAT reporter gene containing 1.3 kb gastrin 5′-flanking sequence was transfected into RINm5F cells prior to NaB treatment and CAT assay. Results: RINm5F cells revealed

A1149

Effects of Silibinin and Silibinin Derivatives on Hepatic Stellate Cells and Myofibroblasts

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The activation of hepatic stellate cells (HSC) plays the key role in the pathogenesis of liver fibrosis. This process is defined by proliferation and transmigration of the HSC into myofibroblasts (MFb). In order to analyze the known hepatoprotective mechanisms of the flavonoid Silibinin, we studied the effects of Silibinin and its derivative NH4O-HCl on freshly isolated HSC and MFb. Methods: HSC were prepared by the pronase/collagenase reperfusion and cultured in DMEM with 10% fetal calf serum. One time passaged HSC (≤14 days after isolation) were defined as MFb. The cells were treated with various concentrations of Silibinin and NH4O-HCl (each in culture medium) for 24 h. 48 h and 72 h. The cell viability was determined using the microflament system. In the case of MFb both drugs were toxic at concentrations of about 10-3 M but only Silibinin at 10-4 M. There was no significant effect of the proliferation of MFb under non toxic conditions. Conclusion: The growth inhibitory effect of Silibinin on freshly isolated HSC underlines the therapeutic potential of the flavonoid.

Identification and Partial Characterization of the Gene Expression of Cytokine-binding Membrane Proteins in Normal and Liver Cirrhotic Patients

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Cytokines like TGF-β are involved in many aspects of liver fibrogenesis like transformation of hepatic stellate cells (HSC) into myofibroblasts (MFb) or hepatocyte apoptosis. After elucidating the role of soluble factors produced by keratinocytes (KC), hepatocytes (PC) and MFb we focused our attention on the role of cytokine-corceptors and within this group particularly on the membrane bound heparan sulfate proteoglycans (HSPG) syndecan-1, 2, 3, and 4 and betaglycan. In order to identify and characterize their gene expression in isolated HSC, Fibroblasts (FB), MFb and KC we performed Northern-blot and RT-PCR analysis. Methods: The rat liver cells were isolated by using the collagenase or pronase/collagenase reperfusion method. To obtain MFb, freshly isolated FSC were cultured in DMEM supplemented with 10% fetal calf serum (FCS) for 16 days. Damaged PC were obtained by cultivating the cells initially with 10%, later on with 0.2% FCS for 1 to 4 days in culture flasks. Total RNA isolation, Northern blot analysis, cDNA synthesis and RT-PCR were performed according to standard protocols. Results: Freshly isolated FSC express syndecan-1, 2, 3, 4 and betaglycan. During transformation of FSC towards MFb the steady state levels of syndecan-1, 2, 3, 4 and betaglycan remain constant whereas the amount of syndecan-2 mRNA increased about three fold and betaglycan decreased. Isolated KC express syndecan-3 and 4 and very low amounts of syndecan-2. Syndecan-3 and -4 mRNA are detectable in untransfected cells. The generated mRNA of both filament types by about 90%. Conclusion: We could show that both MT and AF are involved in the maintaince of the GA-architecture and ii) serve as transport tracks for secretory transport vesicles in rat liver MFb.

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Effect of Sodium Butyrate and Cell Differentiation on Gastrin Promoter Activity in Islet Cells

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Recent studies with transgenic mice suggest a role of gastrin during intestinal cell differentiation. The underlying molecular mechanisms are poorly understood. We previously demonstrated sodium butyrate (NaB) induced cell differentiation and concomitant transient gastrin increase in insulinoma cells. The present study was designed to confirm the effect of NaB on cell differentiation of RINm5F cells on gastrin promoter activity. Methods: Cells were cultured for 0, 12, 24, 48 and 72 hours in presence or absence of 0.5 mM NaB. Gastrin mRNA was determined by Northern blot analysis. A CAT reporter gene containing 1.3 kb gastrin 5′-flanking sequence was transfected into RINm5F cells prior to NaB treatment and CAT assay. Results: RINm5F cells revealed
at 12 h in presence of NaB a 50% and at 48 h a maximal 10fold increase in gastrin mRNA. We examined the cells after a 48h increase at 12 h, continuously decreasing throughout the experiment. Transient transfection of the gastrin reporter gene revealed at 12 h in NaB treated cells a 20fold induction, while gastrin promoter activity declined again after 24 h maintaining basal activity. In contrast, untreated cells revealed a continuous decrease of promoter activity. Conclusion: The experiments suggest that increased gastrin expression during NaB induced cell differentiation is due to activation of the gastrin promoter. This could be a consequence of NaB effect on the cell cycle or direct induction of the gastrin promoter. Further deletion analyses might identify potential NaB responsive elements in the gastrin promoter.

**1155 Transcriptional Regulation of the Tumor-Associated Antigen 17-1A in Colon Carcinoma Cells**

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The 17-1A (EGP40) antigen is a target for immunotherapy in colon cancer. As the patients immune system co-operates with the monoclonal antibody (MAb) for destruction and/or growth control of the tumor cells, simultaneous application of cytokines were suggested to activate the immune system. However, addition of cytokines to MAb 17-1A drug treatment could also effect 17-1A expression on tumor cells. We investigated the effect of Interferons (IFN) on 17-1A expression and transcriptional activity. Methods: We previously reported cloning the 17-1A cDNA. This sequence was used to isolate the gene including promoter sequence. The structure was established by sequence analysis. Transcription start sites were determined by RNase protection. 17-1A 5' flanking DNA was cloned into pcCAT basic reporter gene, transduced into the colon cancer cell line HT29 and CAT activity analysed. HT29 cells were cultured in presence or absence of 50, 250 and 1000 U/ml IFN-γ or IFN-α for 12, 48 and 72 hours (h). 17-1A antigen expression was revealed by cell-surface IgM antibodies and northern blot analysis. Results: 17-1A mRNA was maximally repressed after 72 h of IFNγ treatment, while antigen expression was reduced to 66%, 50 U/ml IFN-γ revealed complete repression of 17-1A promoter activity. IFN had no effect on 17-1A expression nor transcription. Conclusion: 17-1A is transcriptionally repressed by IFN. This suggests that co-stimulatory molecules also modulate 17-1A target expression. This is the first tumor-associated gene repressed by IFN. It will be of interest to identify the negative signalling pathway.

**1157 Proton Pump Inhibitor (PPI) Pretreatment Affects Helicobacter pylori — Sensitivity to Antibiotics**

department of Internal Medicine, University of Bonn, Germany.

Aim of the study was the investigation of time-and concentration-dependent effects of antibiotics in vitro on growth, viability and morphology of H. pylori (HP) after pretreatment with non-lethal doses of the proton pump inhibitors (PPI) omeprazole and lansoprazole.

Methods: 3 HP-strains were incubated with culture media containing 8 μg/ml (omeprazole) and 2 μg/ml (lansoprazole) of PPI for 24 hours. After washing bacteria were incubated for further 24 hours with culture media (pH 7.4) containing 0.2, 2, 16, 64, 128 and 256 μg/ml of antibiotics (amoxicillin, clarithromycin, roxithromycin). Optical density of the cultures was measured at 0, 4, 8, 12, 16 and 24 hours after preincubation. Viability of bacteria was tested after 24 hours by plating on Wilkins-Chalgren Agar. Gram stain was used to assess the morphological changes of HP from helical to coccoid like forms (CLF). In addition intra- and extracellular ATP-concentration as indicators for bacteriolyis and cell metabolism was measured with a bioluminescence assay.

Results: After preincubation of HP with sublethal doses of PPI no change in MIC is observed. However striking effects on H. pylori morphology were observed. CLF formation by antibodies was extremely influenced after PPI-pretreatment (Table). Bacteriolyis due to roxithromycin and clarithromycin but not amoxicillin was determined by extracellular ATP-concentration which was inhibited by preincubation with PPI (p < 0.05).

Table: Induction of CLF by antibiotics

<table>
<thead>
<tr>
<th>Substance</th>
<th>PPI</th>
<th>PPI</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>CLF</td>
<td>98.9%</td>
<td>2%</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>CLF</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>CLF</td>
<td>21%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Conclusion: Preincubation of HP with sublethal doses of PPI reduces the transformation of helical forms to CLF caused by macrolide antibiotics but not with amoxicillin. Bacteriolyis also decreases with macrolides but the bactericidal effect of all used antibiotics is maintained. The mechanisms of this phenomenon are unclear.

**1160 Enteric Coating of Aspirin Substantially Reduces Gastric Mucosal Damage**


Aspirin in low dose cardiovascular prophylaxis may still increase melena risk (US Physicians Study). Enteric coating may protect the stomach against topical damage. We therefore studied the effects of plain or enteric-coated aspirin in a dose of 100 mg on acute endoscopic injuries.

Methods: 40 volunteers received in this double blind (double dummy) parallel group design 7 days treatment in random order of enteric coated aspirin 100 mg (EC-ASA) or plain aspirin 100 mg (plain ASA). Acute gastric fundus, body and antrum injury was assessed endoscopically (Lance score) on day 1 and 7 of treatment.

Results:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total gastric score (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 7</td>
</tr>
<tr>
<td>EC-ASA</td>
<td>1.43 ± 1.91</td>
</tr>
<tr>
<td>Plain ASA</td>
<td>3.68 ± 3.38</td>
</tr>
<tr>
<td>2.00 ± 2.02</td>
<td>6.35 ± 4.1*</td>
</tr>
</tbody>
</table>

*p = 0.0004 (U-test corrected for ties)

In all three gastric areas — fundus, body, antrum — a significantly higher lesion score was found after 7 days of treatment with plain ASA (p < 0.05). Adverse events were reported in 8 cases: EC-ASA: 4 of 21, plain ASA: 4 of 20. Most frequently abdominal discomfort was documented (EC-ASA: 2, plain ASA 1).

Conclusion: Plain ASA produces significantly more gastric lesions than EC-ASA.

**1161 Progression of Colonic Involvement in Crohn’s Disease and the Risk of Surgery — A Ten Year Follow-up Study**


More than two thirds of patients with Crohn’s disease will eventually develop colitis. Unlike ulcerative colitis, disease extent and progression of Crohn’s colitis influencing medical and surgical management have not been defined. We therefore evaluated the anatomical pattern of colitis and its progression during the course of the disease in a large number of patients. In addition, the impact of colonic disease pattern on the subsequent risk of colonic surgery and colectomy was assessed.

Methods: The charts of 323 patients with Crohn’s colitis (mean follow-up 9.8 years) were analyzed. Patients were followed regularly (5700 documented examinations) with standardized clinical, radiological and endoscopical assessment of disease. Extent of colitis was evaluated by radiological, endoscopical, histological and intraoperative findings. It was classified as total colitis (TC), left-sided (LC) or right-sided (RC) colitis. Segmental colitis (SC) was defined as disease in segments of right and left colon. The progression of colonic extent and the probabilities of respective colonic surgery and colectomy were analyzed using actuarial methods (log-rank test for statistical differentiation).

Results: The pattern of colitis at initial diagnosis (ID), the frequency of rectal disease, the probability of progress to TC and the risk of surgery and total colectomy are given (table).

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Frequency</th>
<th>Risk to progress</th>
<th>Risk to surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td>Disease</td>
<td>TC</td>
<td>Colectomy</td>
</tr>
<tr>
<td>ID</td>
<td>5 y</td>
<td>10 y</td>
<td></td>
</tr>
<tr>
<td>RC</td>
<td>25%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>LC</td>
<td>17%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>SC</td>
<td>9%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>TC</td>
<td>49%</td>
<td>16%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*p < 0.05 compared to LC. SC and TC. +p < 0.05 compared to LC and TC

The overall high progress to TC was not seen in patients with RC. In LC, SC and TC the risk of surgery was relatively low compared to RC. This may be due to the high concomitant incidence of ileal disease in RC (93% versus 60% in other groups). The overall risk of a permanent stoma was 7% and 12% after 10 and 15 years respectively.

Conclusion: Most patients with Crohn’s colitis will eventually have extensive disease, and surgery is necessary in more than half of the patients within 10 years. However, the risk of total colectomy or a permanent stoma is low. Segmental resections with preservation of colonic length can be performed even in more than half of the patients with total colitis if surgery becomes necessary because of complications of the disease.

**1162 The Antisecretory Activity of Ranitidine 300 MG and Cimetidine 800 MG OM Meal Stimulated Gastric Acid Secretion**


The aim of this double blind two-fold cross-over study was to assess the...
comparative efficacy of Ranitidine (R) and Cimetidine (C) on meal-stimulated acid secretion.

Methods: 12 healthy volunteers (6 male, 6 female) received R 300 mg and C 800 mg respectively for three consecutive days. Meal-stimulated acid secretion was measured two and seven hours after administration of the third dose (0700 h). The pH of a standardized test meal (600 ml) was adjusted to 5 and the meal was infused into the stomach within 5 min. Thereafter the meal was aspirated continuously over 2 hours (0900-1100 h and 1400-1600), titrated with 0.1 n NaOH to pHS and then reinjected into the stomach.

At least 4 days prior to the application of the study medication baseline meal-stimulated acid secretion values were established.

Results: Acid secretion (mmol H+ h⁻¹) is summarized in the following table:

<table>
<thead>
<tr>
<th>Time of measurements</th>
<th>Baseline</th>
<th>R</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0900-1000 h</td>
<td>7.0 ± 4.5</td>
<td>5.0 ± 1.2</td>
<td>1.5 ± 3.6</td>
</tr>
<tr>
<td>1000-1100 h</td>
<td>13.5 ± 5.3</td>
<td>1.5 ± 3.4</td>
<td>4.14 ± 4.6P</td>
</tr>
<tr>
<td>1400-1500 h</td>
<td>6.5 ± 4.0</td>
<td>2.6 ± 2.5</td>
<td>7.5 ± 7.5*</td>
</tr>
<tr>
<td>1500-1600 h</td>
<td>14.2 ± 5.7</td>
<td>7.4 ± 6.6</td>
<td>15.3 ± 6.6**</td>
</tr>
</tbody>
</table>

*p < 0.05, *p < 0.01.

Conclusion: During the second morning hour (1000-1100 h) and the afternoon hours (1400-1600) R was significantly more potent than C in inhibiting meal-stimulated gastric acid secretion.

1163 The Gastrointestinal mucosal Damage Effect of Tenoxicam and Diclofenac in Healthy Volunteers

H.G. Dammann, F. Burkhardt, N. Wolf, Th. A. Walter. Institute for Clinical Research, Hamburg

In this double blind parallel group design study we investigated the effects of tenoxicam and diclofenac on acute esophageal gastroduodenal injury.

Methods: 60 volunteers received 21 days treatment in random order of tenoxicam 20 mg od (n = 40) or diclofenac 50 mg tid (n = 20). Acute gastroduodenal injury was assessed endoscopically (Lanza score) on day 21 of treatment.

Results:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gastric score</th>
<th>Duodenal score</th>
<th>Total gastroduodenal score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenoxicam</td>
<td>3.0 ± 3.2</td>
<td>0.9 ± 1.7</td>
<td>3.9 ± 4.0</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>4.5 ± 4.2</td>
<td>2.0 ± 2.5</td>
<td>6.5 ± 5.2</td>
</tr>
<tr>
<td>20 mlvalues</td>
<td>0.16</td>
<td>0.06*</td>
<td>0.046*</td>
</tr>
</tbody>
</table>


In the tenoxicam and diclofenac treatment groups 26 of 40 and 18 of 20 developed gastroduodenal mucosal lesions (p = 0.062, Fisher's exact test) respectively.

Conclusion: In the dosages applied diclofenac produces substantially more gastroduodenal lesions than tenoxicam. However, these differences reached no statistical significance.

1164 Clinical Course of Perianal Fistulas in Crohn’s Disease

F. Makowiec, E. C. Jehle, M. Starlinger. Department of Surgery, University of Tübingen, Germany

In contrast to intestinal disease factors influencing perianal Crohn's disease and the frequency of symptoms related to perianal disease have not been evaluated in prospective studies.

Methods: The clinical course of perianal fistulas and associated abscesses was evaluated prospectively in 90 patients with Crohn's disease. Fistula type, rectal disease, faecal diversion and immunosuppression were examined as prognostic indicators for fistula healing and recurrence. Median follow up was 22 months. Surgical therapy consisted in drainage of pus collections. The outcome was evaluated with life table analysis. Prognostic factors were analyzed by multiple regression analysis.

Results: Inactivation was achieved in all patients. The risk of recurrent fistula activity was 48% (1 year) and 59% (2 years). Fistulas were healed in 51% after 2 years but reopened in 44% within 18 months after healing. Faecal diversion and absence of rectal disease decreased recurrence rates (p = 0.019/0.04) and increased healing rates (p = 0.005/0.17). The outcome in patients with transspinchiatric fistulas was better than with ischiorectal but worse than with subcutaneous fistulas (p = 0.015 for healing; p = 0.007 for recurrent fistula activity). Following initial therapy about 20% of the patients were symptomatic and about 10% had painful events per 6 month period. Incontinence was rare and did not increase during the study period.

Conclusion: Perianal fistulas and associated abscesses can be controlled safely by simple drainage. Frequent refection and reopening after healing of fistulas characterize their recurrent nature. Fistula type, rectal disease and stool contamination influence the clinical course. However, only a minority of patients have continuous symptoms from perianal fistulas.

1165 Frequency of Silent Coeliac Disease in Paediatric Risk Groups

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Subclinical (“silent”) coeliac disease (CD) is known to occur in siblings of index patients and patients with other associated disorders. We have investigated the frequency of silent coeliac disease in several risk groups.

Sera were examined for IgA- and IgG antigliadin antibodies by ELISA and for IgA-antidomainsantibodies by indirect immunofluorescence. 402 children with the following diagnosis were studied: siblings of CD patients (n = 45), children with short stature (n = 210), diabetes mellitus (n = 103) and rheumatic diseases (n = 44). Total serum IgA was measured to exclude selective IgA-deficiency. Small intestinal biopsy was proposed if either IgA antigliadin- or antidomainsantibodies were positive. If a flat mucosa was found, a gluten-free diet was started.

IgA antidiomainsantibodies were found in 13 of 402 patients — 4 siblings (9.6%); 5 with short stature (2.4%) and 4 with diabetes (3.9%). 5 of them also had high IgG antigliadin antibody levels. Increased IgG antigliadin antibody levels were measured in 40 of 420. None of them had selective IgA-deficiency. 4 of 5 children with short stature (1.9%) and positive endomysium antibodies underwent an intestinal biopsy until now, showing villous atrophy indicative of CD. The other individuals with serological findings suggestive for CD still await definitive classification by biopsy. 2 of 4 children with short stature and villous atrophy have been controlled after one year of treatment with gluten-free diet, both revealing catch-up growth.

In conclusion, frequency of CD in our children with short stature was at least 1.9%. IgA-antidomainsantibodies should be included in their primary diagnostic evaluation.

1166 The CCK-R Receptor in Kidney: Evidence of Receptor Expression in Tubular and Mesangial Cell Lines

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The gastrintestinal hormone gastrin mediates various actions in the gastrointestinal tract such as gastric acid secretion, smooth muscle contraction, mucosal growth and proliferation. We have recently demonstrated expression of the CCK-R receptor (CCKR) in the kidney of the guinea pig (GP) as well as 125I-gastrin 17-1 binding to tubular structures within this organ. Aim: This study was performed 1) to identify the cDNA sequence of the CCK-R in GP kidney and 2) to identify the exact target renal cell that expresses this peptide receptor by using a system of murine renal cell lines. Methods: GP kidney mRNA and mRNA from murine renal cell lines was isolated using established methods. Each mRNA (10 µg) was evaluated by Northern blot hybridisation using a 32P labelled full length CCK-R probe (GP). RT-PCR using GP CCK-R
cDNA homologous primers was performed according to standard protocols, products were confirmed by Southern hybridisation. DNA analysis was performed using the cycle sequencing technique.

Results:

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Origin</th>
<th>Northern</th>
<th>RT-PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Kidney</td>
<td>whole organ GP</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>TFB</td>
<td>fibroblast mouse</td>
<td>neg.</td>
<td>neg.</td>
</tr>
<tr>
<td>LLC-PK</td>
<td>prox. tubulus pig</td>
<td>neg.</td>
<td>neg.</td>
</tr>
<tr>
<td>C2</td>
<td>prox. tubulus mouse</td>
<td>neg.</td>
<td>neg.</td>
</tr>
<tr>
<td>MMC</td>
<td>mesangium mouse</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>mTL</td>
<td>asc. loop mouse</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>MCT</td>
<td>prox. tubulus mouse</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

The DNA sequence of the guinea pig kidney CCK-R is identical to the recently identified sequences of the GP gallbladder and pancreas CCK-R. Conclusion: CCK-R receptors are expressed in GP kidney. These receptors can be found on tubular and mesangial cell lines. In agreement with studies demonstrating a proliferative effect of gastrin on nephroblastoma cells, these studies provide evidence that the kidney is an important target for gastrin.

1167 Generation of Recombinant Hepatotropic Retro-Viral Pseudotypes for Usage in Liver-Restricted In Vivo Gene Therapy

M. Spiegel, M. Gregor; U. Lauer. Dept. Internal Medicine I, University Clinic, Tübingen, Germany

Liver gene therapy treatment of extended patient populations requires the generation of hepatitis delta virus core gene-derived pseudotypes. In current studies MoMLV amphotropic retroviral vectors are widely used in ex vivo gene therapy protocols. However, possibilities for their in vivo application are still limited — mainly due to safety problems raised by the broad tissue spectrum inherent in amphotropic retroviral transduction. In this context, generation of recombinant hepatotropic retroviral pseudotypes via substitution of the amphotropic env-protein with surface proteins of hepatotropic viruses might open up a perspective for future liver-restricted in vivo gene therapy treatment.
As a promising candidate, we focused on Sendai Virus (SV) temperature-sensitive mutations (SVTS171), known to specifically interact with its host glycoprotein with the hepatitis-C-specific asialo-glycoprotein receptor (ASGP-R). Initially, it was necessary to determine whether stable MoMLV(SVTS) pseudotypes could be generated.

Amphotropic retroviruses were produced by transfecting packaging cell line PA317 with retroviral vector pXLSN. 24 hrs later pXLSN-transfected PA317 cells were infected with SV wild-type. The produced supernatant was then tested on BHK cells which cannot be infected by amphotropic retroviruses but by SV. In this assay, we have shown that BHK cells transfected by neo encoding pseudotype retroviruses survived G418 selection, whereas control cultures either infected with SV wild-type or transfected with amphotropic retrovirus did not. For the generation of recombinant MoMLV(SVTS) pseudotypes, the SV-F-CNA was inserted downstream of the 5′-LTR in pXLSN. Transfection of ectopic cell line PES01 with this vector yielded recombinant MoMLV(SVTS) pseudotypes which are being tested further.

In summary, these experiments show, for the first time, that stable MoMLV(SVTS) pseudotypes can be generated, thereby opening up new possibilities for future liver-restricted in vivo gene therapy treatment.

1168 Regional Differences of G Protein α-subunit mRNA Expression in the Gastrointestinal System

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Many gastrointestinal hormones and transmitters stimulate or inhibit adenyl cyclase activity by coupling to guanine-nucleotide-binding proteins (G proteins), which function as a common switch for multiple receptors. However, there is limited information about the physiological distribution of G proteins in the gastrointestinal system. The spatial pattern of G protein α-subunit mRNA expression within the gastrointestinal system of guinea pigs was determined by northern blot analysis (ISH). Cryo sections (7–10 µm) of esophageus, stomach, small and large intestine were hybridized with single stranded digoxigenin labeled cRNA probes complementary to rat Gαs, Gαq and Gαo. Specificity was controlled by using Northern blots, simultaneous hybridization of rat brain sections, and hybridization with sense cRNAs. Results: (1) the relative abundance of mRNAs was Gαs > Gαq > Gαo. (2) Strong perinuclear signals of Gαq and Gαo were seen in the basal epithelium of the distal esophagus, at the base of gastric glands, and tubular glands of small and large intestine. (3) Levels of Gαq and Gαo mRNA were enhanced in neuronal structures within the muscularis. (4) Gαo mRNA is only detected in isolated cells within the mucosa of the small intestine. These results demonstrate that G proteins are regionally specialized in their expression. The cell type specific pattern of Gαs and Gαq mRNA may reflect the abundance of a large number of different G protein coupled receptors, which either stimulate or inhibit adenyl cyclase activity.

1172 Does Split Liver Transplantation Put Right Graft Recipients at an Increased Risk?

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Split liver transplantation is becoming more and more important to overcome the increasing organ shortage. It has, however, not gained wide acceptance yet. This may not only be related to the complexity of the procedure but also to the worse results reported on the right side graft.

In the period from 1.1994 to 31.12.1994 sixteen out of sixty-six patients receiving cadaveric organs (24.2%) were served with a split liver transplantation. Ten of these patients (including one patient who was transplanted with a shipped organ at another center) received right grafts. These grafts were achieved by splitting the liver either the classical way (n = 6) or by applying two new techniques of splitting (n = 5). Using the in-situ technique the liver is divided in the heart-beating cadaveric donor using the technique of living related liver procurement. This avoids compromising the hilar structures of the right graft and long benching times with the risk of warming up the graft. It allows judgement of perfusion during the procedure and achieve perfect hemostasis. The modified ex-situ technique is derived from the in-situ technique allowing to avoid dissection of the bifurcation of the bile duct and to minimize manipulations of the hilar structures of the right lobe.

Within the ‘classical’ group one patient (UNOS 4, acute hepatic failure due to Budd-Chiari Syndrome) died 11 days postoperatively due to sepsis after splenic necrosis because of a nonfunctioning ileostomy. Another patient (UNOS 3, alcoholic cirrhosis) died 13 days post transplantation multiorgan failure after small bowel perforation. A third patient (UNOS 4, acute hepatic failure due to Budd-Chiari Syndrome) had to be retransplanted because of bile duct necrosis without arteral thromosis. Within the ‘new technique’ group one patient (UNOS 3, hepatitis tumor) died due multigorgan failure following primary poor liver function. The other four patients had uneventful postoperative courses and are alive and active at home.

We came to the conclusion that using the classical technique of splitting the right graft recipient is at risk. Using the new techniques introduced by us the manipulations to the right graft can be minimized and excellent results can be achieved.

1173 Interferon α 2 b Therapy in Chronic Hepatitis C

H. Port, J. Lohmann. III. Medical Clinic Hospital Clinic Dresden, Friedrichstadt, Germany

Introduction: Of a group of patients observed over a period of 15 years (state after iatrogenic postnatal hepatitis-C-infection with contaminated anti-D-globulin) we chose patients suited for interferontherapy.

Subject: 17 patients (women) average age 38.03 ± 5.1 years were treated. All patients, infected with identical virus (HCV I) got 3 x 3 mio units interferon α 2 b (Intron b) weekly over a period of 6 months. Secondary diseases as well a nutritive hepatic damages can be regarded as out of question.

Results:

<table>
<thead>
<tr>
<th>Alat (mmol/l)</th>
<th>Aaste (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>3 months</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>6 months</td>
<td>0.6 ± 0.6</td>
</tr>
</tbody>
</table>

Conclusion: It is remarkable that after such a long course of disease the interferon therapy was rather effective and a lot better than the results in common literature conclusion. According in our results, patients with a long chronological course of hepatitis C benefited from interferontherapy.

1174 Differential Regulation of Cytoskeletal Protein Expression During Interferon Treatment of Squamous Carcinoma Cells In Vitro

M. Steffen, B. Everding, T. Heinig, F. Hötzle, H. Greten. Department of Internal Medicine, University Hospital Eppendorf, Hamburg, FRG; 1Department of Physiological Chemistry, University Hospital Eppendorf, Hamburg, FRG

The growth-inhibitory effect of IFN-gamma was investigated in vitro using a panel of human tumor cell lines derived from squamous cell carcinomas. Cells of three lines were growth-arrested in combination with morphological alterations by INF-gamma. The effects of IFN-gamma on proliferation and morphology were reversible after withdrawal of the cytokine. Aim of the study is the analysis of cytoskeletal alterations during growth-arrest. Cells of one line (KNS-82) were examined in more detail. During treatment with INF-gamma, the KNS-82 micro-tubule structure assumed a higher degree of aggregation as demonstrated immunocytochemically. Northern Blot analyses revealed differential expression of tubulin mRNA during various modes of growth arrest. While the level of tubulin-specific mRNA increased, western blot analysis showed a decrease of the amount of tubulin protein after IFN-treatment. In the same experiments, beta-actin mRNA decreased, but the actin protein amount remained unchanged. Our data show that the expression of cytoskeletal proteins is differentially regulated during IFN-gamma treatment.

1175 Modulation of the Proinflammatory Cytokine Expression in Patients with Inflammatory Bowel Disease (IBD) by Substance P and TGF-β

T.D. Heinig, A. Raedler, S. Mirau, M. Steffen. University of Hamburg, Medical Department, Germany

Introduction: Proinflammatory cytokines such as TNF-α and IL-1β are known to play an important role in IBD. Nevertheless, the causative trigger mechanisms leading to the self-destructive, cytokine-mediated inflammation are still unknown. Elevated cytokine levels in IBD may be due to either increased upregulating or decreased downregulating mechanisms.

Methods: We studied the regulatory influence of Substance P (SP) and TGF-β on the cytokine response of peripheral blood monocytes (PBM) in vitro. PBM from IBD patients and normal controls (NC) were isolated by density centrifugation and plastic adherence. Cytokine mRNA levels were measured by a competitive RT-PCR assay.

Results: In general PBM from IBD patients show an enhanced expression of the pro-inflammatory cytokines TNF-α and IL-1β in comparison with normal controls. In PBM from patients with Crohn's disease (CD) was a further upregulation of the cytokine response mediated by SP while there was only a slight increase in ulcerative colitis (UC) and normal control PBM. We also measured elevated TNF-α and IL-1β mRNA levels under the influence of TGF-β in Crohn's disease monocytes. In contrast there was a downregulation in PBM from ulcerative colitis and normal controls.
1176 Comparative Analysis of the Cost-Effectiveness of Pantoprazole, a Novel Proton Pump Inhibitor

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Pepitic ulcer disease (PUD) affects approximately 5% females and 10% of males in the developed Western world. In Germany, PUD alone causes 42,000 hospitalizations, 10,000 deaths per year. Reflux esophagitis (RE) occurs in another 5–10% of the Western population. With the introduction of H2-receptor blockers (H2RA, e.g., cimetidine, ranitidine) and, more recently, the proton pump inhibitors (PPIs, e.g., omeprazole, pantoprazole), effective treatment of acid-related diseases has become available, making surgery a rare necessity for patients affected. Therefore, acid controlling treatment has been widely adopted, creating a market value exceeding DM 700 million per year. H2RA + PPIs in Germany, H2RA are still the mainstay of ulcer therapy, accounting for 65% of prescriptions and a similar market share by value.

To assess the economic impact of treatment of PUD and RE with the novel PPI pantoprazole, a cost-benefit and cost-effectiveness analysis was performed. A decision-tree analysis, based on data on direct cost derived from 10 randomized double-blind clinical trials versus the H2-receptor antagonists and the PPI omeprazole, respectively.

Treatment for duodenal ulcer (DU) with pantoprazole are more cost-effective than with ranitidine (30%) and with omeprazole (20 mg/d, 3%). Pantoprazole is about 40% more cost-effective than ranitidine and 6% more cost-effective than omeprazole (20 mg/d) for the treatment of gastric ulcers (GU). Costs for treating RE with pantoprazole are about 35% lower compared to ranitidine. Compared to 40 mg omeprazole which is often used in practice, pantoprazole is clearly more cost-effective for the above areas.

Potential savings for the German healthcare system could be demonstrated to amount to at least DM 235 million per year in direct cost if, hypothetically, ranitidine and omeprazole for PUD and RE were replaced by pantoprazole.

1177 Pantoprazole — Which Cytochrome P450 Isozymes Are Involved in Its Biotransformation?

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The benzimidazole sulphoxides (gastric proton pump inhibitors, PPIs) are substrates, inhibitors and inducers of cytochrome P450 (CYP) in the liver. Biotransformation of these sulphoxides to sulphones is a common feature of all PPIs. Pantoprazole (PANTO) is mainly demethylated at the 4-methoxy-phenyl position with subsequent 4-sulphate conjugation. The only detectable phase 1 metabolite of PANTO in human plasma is the sulphone. Since the demethylation of PANTO is not detectable due to its extreme chemical instability the metabolite formation of PANTO cannot be examined. Instead, four different experiments were performed using human microsomes: (a) Biotransformation of PANTO using well characterized microsomes with highflow activity for debrisoquine (CYP2D6); for midazolam (CYP3A4) and of poor and extensive metabolizers of mephentoin (CYP2C19). (b) Disappearance of PANTO in presence of inhibitors for CYP2C8-10 (rosuxil, CYP2D6) and (c) 5-azauracil (ketoconazole). (d) Formaldehyde formation during demethylation. Use of pantoprazole sulphone as substrate. Analysis by HPLC; formaldehyde was detected after incubation with aminro cótic acid methylster by fluorescence (374–466 nm).

Results suggest that PANTO is metabolized by CYP3A4 (ulphoxone formation) and by CYP2C19 (demethylation). Km value > 100 μM for PANTO demethylation might be the reason why it readily leaves the CYP mediated phase 1 biotransformation and gets immediately conjugated in phase 2. The differences in Kms for demethylation of PANTO (> 100 μM) and hydroxylation of omeprazole (3–16 μM, T. Anderson et al., Br J Clin Pharm, 1993) both catalyzed by CYP2C19 may explain the lack of CYP inhibition by PANTO, in contrast to omeprazole, on concomitant administration with diazepam or another substrate for CYP2C19.

Conclusions: Our data show a constitutively elevated expression of pro-inflammatory cytokines in IBD monocytes, but a different responsiveness to mediators such as SP and TGF-β in CD and UC. This may be a clue to different mechanisms in the onset and perpetuation of inflammation in Crohn’s disease and ulcerative colitis.
Patients and methods: 64 patients with cirrhosis of different Child Pugh stages were investigated with respect to the plasma concentration of cGMP and cAMP. Twelve patients were treated with sulindac, which was administered either intravenously (hepatic sorbitol extraction, galactose elimination capacity, indocyanine green elimination). Results: ANP was inversely correlated with total systemic resistance (r = -0.653; p < 0.02; n = 14) and cGMP from right atrium was correlated with heart index (r = 0.84; p < 0.01; n = 14). There was no correlation between renal function, quantitative liver function and plasma concentration of ANP and cGMP. Highest concentrations of ANP and cGMP were measured in right atrium, right ventricle and pulmonary artery.

Conclusions: Because ANP was significantly associated with total systemic resistance we conclude that ANP is involved in vasodilatation in cirrhosis. Blood pressure in right atrium as most important stimulus for ANP secretion was not elevated and is not correlated with plasma ANP.

**1186 Regression of Small Duodenal Polyps After Sulindac Treatment in Patients with FAP**


Duodenal cancer is the leading cause of death in patients with familial adenomatous polyposis (FAP) already treated by colectomy. The purpose of this study was to assess the effect of the non-steroidal anti-inflammatory drug sulindac on periampullary, duodenal polyps in patients with FAP.

Twenty-three patients with advanced duodenal polyposis were randomly allocated to receive a 6-months treatment of either 200 mg sulindac [sulindac group (SG), n = 12] or placebo [placebo group (PG), n = 12] twice a day. Duodenoscopy before sulindac treatment and after 6 months was performed on videocassettes and dimension and number of polyps in the periampullary region were assessed by a blinded observer. The size of polyps was estimated by comparison with an opened biopsy forceps.

Both groups were comparable with regard to age and sex, previous laparotomies, disease duration, quality-of-life, education, occupation impairments, inflammatory bowel diseases (IBD) regression, smoking habits or occupational status. The mean number of duodenal polyps was 0.2 ± 0.5 (PG) and 0.3 ± 1.2 (SG). After six months, more patients in the PG than in the SG have developed new polyps (5 vs. 2; p = 0.05). Polyps with less than 2 mm in size decreased or disappeared in 44.8% (SG) and 25.4% (PG) (p = 0.05). Polyps with more than 4 mm in size were not significantly changed in both groups.

Our findings suggest that sulindac induces regression of small duodenal polyps. Further studies will reveal if FAP patients with early stage of duodenal disease could benefit from sulindac therapy.

**1187 HDL-retroendocytosis in Cultured Intestinal CaCo-2 Cells Does Not Require Intracellular Calcium Release for HDL-mediated Cholesterol Eflux**

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Binding of apo AI-containing particles results in endocytosis of the HDL-receptor complex in CaCo-2 cells. Endocytosed HDL particles contact lipid droplets, pick up cholesterol and are removed from the cells at the basolateral membrane by endocytosis. In human skin fibroblasts (HSF) HDL3 is bound to the surface without internalization, activates Protein Kinase C and releases calcium from intracellular stores in cultured human fibroblasts. This leads to a translocation of intracellular cholesterol to the plasma membrane. The purpose of the present study was to test if intracellular calcium release is also involved in HDL-retroendocytosis.

Methods: CaCo-2 cells and HSF were cultured under standard conditions. HDL3 was prepared by ultracentrifugation (d = 1.125-1.210). Apo E containing particles were removed by heparin-Sepharose affinity chromatography. Intracellular calcium release was measured using the fura-2 method. Cellular HFL3-processing was visualized by electron microscopy using a post embedding immunocytochemistry method with an apo A1 antibody.

Results: In HSF intracellular calcium was released at a minimal effective HDL3-concentration of 0.8 μg/ml. The effect was not dose dependent. In contrast CaCo-2 cells did not increase intracellular calcium levels after addition of HDL3 in concentrations up to 80 μg/ml. However ionomycin, phorbol esters and ATP increased intracellular calcium in a similar fashion as in fibroblasts.

Concluding remarks: Intracellular calcium release is not required for HDL3-mediated cholesterol efflux in cultured intestinal CaCo-2 cells.

**1188 Prognostic Factors in Orthotopic Liver Transplantation**

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Purpose. The purpose of this study was to assess pre- and postoperative risk factors in orthotopic liver transplantation (OLT).

Methods: 200 patients with cirrhosis transplanted at our clinic were included in this retrospective analysis. In 47 patients all required data were available. Laboratory, clinical and intraoperative data as well as Child and Thuer classification were evaluated with regard to patient survival, graft survival and occurrence of acute rejection. Statistical methods: Fisher’s exact test, Kaplan-Meier, Cox-model, linear and loglinear regression.

Results: 1. Two-year patient and graft survival was 66% and 58%, respectively. 2. The evaluated laboratory parameters, age, sex, previous laparotomies, ascites, encephalopathy, variceal bleeding, cardiorespiratory function, catabolism, duration of cold graft ischism, preservation solution and portal hypertension did not have any influence on survival. 3. Infections prior to OLT, amount of intraoperative substitution of red blood cells and plasma and graft quality (as expressed by time zero biopsy) had a high impact on both graft and patient survival (p = 0.0008; 0.013; 0.007; 0.0001, respectively). 4. There was a tendency towards improved survival in younger patients without infection and with Thuer-index > 27.

Conclusion: Graft quality, units of red blood cells and plasma required during surgery and pre-existing infections were the only variables with influence on patient survival in OLT.

**1189 The Latency Period in the Diagnosis of Coeliac Disease Is Still Too Long**

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The aim of this study was to determine the diagnostic interval between the beginning of symptoms and the date of diagnosis of coeliac disease (total interval), and both the intervals between beginning of symptoms and first visit to the general practitioner (interval-1) and first visit to the general practitioner and date of diagnosis (interval-2).

Patients. Questionnaires completed for 408 patients. 15 years and older, who were diagnosed for coeliac disease, were placed at our disposal from the Deutsche Zoellekake-Gesellschaft and evaluated.

Results. During the periods <1974, 1975-1979, 1980-1984, 1985-1989, 1990-1992 and 1993-1994, the total interval decreased from 16.1 ± 7.9 (x ± SD) to 9.0 ± 11.1 years (p = 0.12, not significant). Interval-1 decreased from 3.6 ± 11.7 to 2.4 ± 6.0 (p = 0.02, not significant), interval-2 from 12.6 ± 15.5 to 7.0 ± 9.8 years (p = 0.03, significant). General practitioners needed significantly more time for making the diagnosis (interval 2) than patients needed from the onset of symptoms and first visit to their general practitioner (interval-1; p < 0.001). There were no significant differences between male and female patients in respect to all intervals.

Conclusion. Although the intervals between onset of symptoms and the date of diagnosing coeliac disease have shortened over the years, patients and practitioners have to be better informed about the indications of the disease.

**1190 M. Crohn and Ulcerative Colitis — A Basic Research**

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Introduction: Because of the far-reaching consequences regarding personal, social and occupational impairments, inflammatory bowel diseases (IBD) require great efforts in the investigation of this aspect of disease and their integration in therapy-concepts. In Germany this aspects have been investigated only cursory in highly-selected patient-samples (FEUERLE 1988). This questions became increasing consideration in different european countries and the USA (BINDER 1988), but the results can not be transferred to Germany because of the different social and health-system. Aim of our investigation was to get basic information about medico-social aspects and aspects of Public Health.

Method: After randomization we send away 1490 questionnaires with 61 questions and about 300 items to 10 members of the DCCV e.V. in all parts of Germany. The questionnaire gives information about basic personal data, disease, therapy, medical care, general condition, diseased state, mode of living with the disease, discomfort, quality-of-life, education, profession, situation at place of work and special problems with a stoma at work.

Extract of results: Return-rate 62.1%, age 40.2 ± 17.2 years; ratio Crohn/Colitis 1:4, 7.8% of the interviewee are classified as ill; 90.5% takes drugs regularly; 53.6% are accepted as severely disabled; 11.0% are unemployed; the mean duration of staying away from work because of the disease was 7.3 weeks/year over the last 5 years. 54.9% feel stressed because of working hours, 45.2% due to overtime work and 61.2% to due to expenditure of work. The date of our investigation allows objective statements to the upper mentioned aspects of IBD in Germany.
Neither Age nor Aetiology are Decisive for the Prognosis of Acute Pancreatitis
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There is a long-standing controversy about whether age and aetiology are risk factors for the prognosis of acute pancreatitis. The aim of this investigation was to clarify these points in a retrospective large-scale study.

Aetiology. The study comprised 237 patients with acute pancreatitis followed-up in the University of Göttingen Hospital from 1980 to 1993 and in the Municipal Hospital of Lüneburg from 1986 to 1993. Aetiology was biliary tract disease in 227 (38%) patients, alcohol abuse in 177 (29%), and unknown in 12 (3%). In the remaining 86 (11%) patients, other aetiologies had led to acute pancreatitis.

Results. Mortality rates of patients according to aetiology were as follows: biliary tract disease 6%, alcohol abuse 7%, other 5%, unknown 6% (differences not significant).

Mortality rate according to age groups did not differ significantly: 21–30 years 5%, 31–40 years 5%, 41–50 years 3%, 51–60 years 7%, 61–70 years 6%, >70 years 10%. Differences were also not significant when the ages of 50, 60, and 70 years were taken as cut-off points.

Conclusion. Neither age nor aetiology are negative prognostic factors for acute pancreatitis.

Effect of Exercise Testing on Esophageal Motility and Gastroesophageal Reflux in Patients with Non-cardiac Chest Pain (NCP)
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The aim of this study was to evaluate the influence of exercise testing on esophageal motility and gastroesophageal reflux in NCP patients. Methods: Six patients (3 M 3 F; 39–72 yrs) with NCP were included. In all patients coronary artery disease had been excluded by a cardiologist. All patients underwent a combined 24-h-manometry and pH-monitoring of the esophagus. During the long-term recording a standardized exercise testing (treadmill) was performed with continuous ECG monitoring. Intravesophageal pressure was measured using 3 microtransducers with a sampling rate of 100 Hz, data were recorded on a datalogger and analysed with a dedicated software package (Polygram, Synetics). Intravesophageal pH monitoring was performed by an antimony electrode placed 5 cm above the lower esophageal sphincter. Statistical analysis: Wilcoxon test. Results: Data are given as median ± SEM. The number of patients reporting typical chest pain during 24 h-recording. During pain episodes simultaneous and retrograde contractions were significantly reduced compared to the symptom-free recording time (5.9±4.8% vs. 21.5±6.9%, p = 0.028; 0.3±0.03% vs. 1.7±0.6%, p = 0.028). Pain episodes were not accompanied by exercise testing the total number of propulsive contractions diminished from 45.8±8.6% to 22.7±6.4% (p = 0.048) compared to the total upright recording as did the number of retrograde contractions (1.1±0.5% vs. 0%, p = 0.067). Simultaneous contractions were not influenced by exercise testing. Duration of the contractions decreased from 2.5±1.1 sec to 2±0.1 sec, p = 0.07, but the amplitudes remained unchanged. Exertional gastroesophageal reflux test resembled that of the upright test. Exercise period (3±2.6 sec vs. 4.5±2.1% of recorded time, p = 0.25). No patient reported pain nor showed ST depression in ECG during exercise testing. Conclusions: (1) Exercise testing modifies motility patterns in NCP patients only marginally. (2) Exercise testing does not increase gastroesophageal reflux in NCP patients.

Electrophysiology in Achalasia: Evidence of a General Motility Disorder?
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Previous studies have shown gastrointestinal motility disturbances to occur in patients with achalasia. Recently electrogastrography (EGG) has received attention as a possible diagnostic tool in motility disorders. Aim: To look for gastric dysrhythmias in patients with achalasia. Methods: 10 patients with achalasia (3 M 7 F; 17–75 yrs) of different grades (G) (G1: G = 0 esophageal dilatation; 4 patients: G2: moderate dilatation; 3 patients: G3 = mega-esophagus) and 10 healthy control subjects (5 M 5 F; 19–74 yrs) were examined. Diagnosis was confirmed by manometry and esophagoscopy. Gastric electrical activity was recorded via abdominal surface electrodes for 6 hr and sampled by a portable 96 kbyte data logger (EGG Digitar, Syndicus, Sweden). During each 6 hr period two typical German meals (breakfast (500 Cal) and lunch (800 Cal) were served. Electrically recorded EGG was analysed off-line by an expert. Results: Data are given as mean ± SEM. Differences were considered significant at p < 0.05. Duration of the contractions began from 0.5 to 20 (mean 6.2) years. During manometry and esophagoscopy (mean ± SEM) was 2 ± 0.2. Dysrhythmies occurred more often in achalasia than in controls (31 ± 5% vs. 21 ± 4% p < 0.08) (TG: 30 ± 6% vs. 37 ± 7%: BH: 6 ± 2% vs. 4 ± 2%; DR: 26 ± 5% vs. 3 ± 0.3%). In achalasia, DR were significantly increased (p = 0.0008), preprandially 15 ± 3% of time vs. 0.2 ± 0.2% (p = 0.0005) and postprandially 15 ± 3% of time vs. 0.1 ± 0.1% (p = 0.0003). BH and TG showed a similar reduction. There was a positive correlation between duration of achalasia and the presence of BH (r = 0.86, p < 0.005). Grade of achalasia correlated positively with DR (r = 0.64, p < 0.05), tendentially with BH (r = 0.49, p < 0.1) and inversely with TP (r = −0.73, p < 0.01). Conclusions: In achalasia gastric dysrhythmies are significantly increased. This supports the hypothesis of a general motility disorder. Duration and grading of illness may play an important role.

Percutaneous Endoscopic Gastrostomy in 1000 Consecutive Patients — An Effective Nutritional Procedure with a Low Complication Rate

Percutaneous endoscopic gastrostomy (PEG) is increasingly used for long-term enteral nutrition in patients with impaired swallowing or obstruction in the upper gastrointestinal tract. This invasive procedure is potentially of patients' greatest benefit.

Methods: From Feb. 1987 to Jan. 1994 1000 consecutive patients in only one endoscopy unit underwent PEG because of sustained swallowing problems risky. We therefore set out to study its effectiveness and risks in a large group of upper gastrointestinal obstruction mainly due to ENT and esophageal tumors and neurologic disease. A special PEG set (Fleka-PEG, unsupported) was used in these patients. The results of 1000 consecutive PEGs were analyzed with regard to success rate and complications.
Fresenius, Germany) was used according to the pull-through technique of Ponsky and Gauderer (1980). We evaluated the success rate of the procedure, minor and major complications and any mortality related to it.

Results: In 100% of liver transplants the procedure was successfully done. In 6 patients diaphanoscopy was not achieved due to tumor growth, thick scarring or post-surgical situations. During the implantation no patient died, 3 patients (18%) died post-operatively due to b) postoperative arrhythmia and heart fibrillation, 2 upper GI bleedings and aspirations. Other major complications were peritonitis requiring surgery (3 pat.), airway obstruction necessitating intubation (3) and septic reactions managed medically (1). In 59 patients minor complications occurred: 6 wound infections and 53 broken tubes needing a replacement by a new PEG set.

Conclusions: PEG is a useful method in achieving long-term enteral nutrition in selected patients. In experienced hands the method is very safe with a risk of lethal complications of <0.5% and major complications of about 1%.

1199 Sinusoidal Endothelial Cells and Kupffer Cells are Similarly Effective Accessory and Antigen Presenting Cells

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The liver is the site of many acute and chronic inflammatory diseases in which local LNCs and Kupffer cells are postulated to play an immunological role. Effective antigen-presentation in situ must be postulated. It was thought that Kupffer cells (KC) are the cells responsible for presenting antigens to T-lymphocytes in the liver, as Kupffer cells derive from the macrophage lineage. In the context of a study of CD14+ monocytes and Kupffer cells as putative targets for the polyamine derivative HOE-140, we have determined the degree of CD14+ monocytes and Kupffer cells in the liver of rats and dogs. 3H-putrescine uptake was significantly increased, but still short of the desired high uptake in CD14+ monocytes and not tabulated to Kupffer cells as expected biologically. The inhibitory effects of the reversible SAM-DC inhibitor CGP-48664 were much less pronounced.

Conclusions: Essentially MDL-73811 caused a highly potent and long-lasting inhibition of pancreatic SAM-DC in vivo with consequent accumulation of putrescine, counterregulatory increase in ODC and — for the first time — a nearly complete intracellular depletion of a polyamine derivative (putrescine). The present data support the general belief in the importance of spermine for maintenance of pancreatic growth, since in contrast to spermine, highly potent intracellular inhibition of spermidine de novo synthesis is counterregulated by compensatory uptake from extracellular sources. In parallel to the failure of long-lasting inhibition of intracellular spermidine accumulation the inhibitory effect of the SAM-DC inhibitors on pancreatic growth was low and transient as well. (DFG Lo 458/1-10)

1201 Genotyping and Quantification and of HCV-RNA in Chronic Hepatitis C During Interferon Treatment


Purpose: Quantification of serum HCV-RNA and HCV genotyping was studied in pts. with chronic hepatitis C undergoing interferon treatment.

Methods: Patients with chronic hepatitis C were treated with interferon alpha-2b 5 MIU i.m. three times a week. Baseline and interferon treatment serum HCV-RNA levels were quantified using competitive RT-PCR (J. Hepatol. 21: 1994: 678-682) and compared to a quantitative RT-PCR assay based on coamplification of HCV-RNA with synthetic RNA standard (Amplisor Monitor Kit. Roche, Basel). HCV genotyping was performed using a line probe reverse hybridisation assay (LIPA, Innohealth, Belgium) or direct solid phase sequencing.

Results: 176 pts. showed complete response to interferon treatment. Pretreatment viral titers were between 1 x 10^5 and 6 x 10^6 HCV genome/ml serum. In non-responders (20/27) the amount of HCV-RNA ranged between 1.5 x 10^5 to 1.5 x 10^6 HCV genome/ml serum. Comparative evaluation of both reverse transcriptase results showed concordant results. However, quantitative RT-PCR was baseless using less consuming 1 log less sensitive than competitive RT-PCR assay. In 7 complete responders 3 pts. showed genotype 1b, 3a and 1a. In 20 non-responders 16 pts. genotype 1b, 1a, 2a and 1 mixed genotypes 1a and 1b. 16/19 pts. with genotype 1b and 2a/3 pts. with genotype 1a were non-responders whereas 3/4 pts. with genotype 3a showed complete response to interferon. Conclusions: 1) RT-PCR based on coamplification was highly concordant to in-house competitive RT-PCR assay. 2) Low pretreatment HCV-RNA titer less than 6 x 10^5 genome equivalents/ml serum did correlate with a complete sustained response to e-interferon in chronic hepatitis C. 3) In our study, genotype 1b was predominantly associated with a high non-responder rate.

1202 Recovery from Experimental Edematous Versus Hemorrhagic-necrotizing Pancreatitis

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While complete recovery is expected to follow clinically edematous pancreatitis it is uncertain whether cellular or functional defects persist after a single episode of hemorrhagic and necrotizing pancreatitis in man. We have addressed this question in an animal model of the disease.

Edematous pancreatitis was induced in male Wistar rats by i.p. injection of caerulein (10 mcg/kg i. at 0 and 3). Necrotising (25% of tissue) and hemorrhagic pancreatitis was induced by s.c. co-administration of a bradykinin antagonist (HOE-140, 0.1 mg/kg at ~30 min and 3 h). Animals were sacrificed at time intervals up to 80 days. Serum ws was determined for amylase, protein, lipase, albumin, ceruloplasmin, tryptase, fibrinogen, cholesterol, triglycerides, and protein, blood, and urine glucose.

Serum amylase activity rose sharply to 4x normal in both groups and normalized after 3 days. Higher activities were found in the edema group. After the first day serum glucose remained within the normal range in all animals. Stool chymotrypsin activity plus Cg was measured to the same extent in both groups and recovered to normal by day 5 in the edema group but only by day 5 in the necrosis group. The necrosis group was affected by a deeper and longer (21d) decrease in pancreatic amylase and protein content, as well as a higher (250%) and longer (21d) decrease in hydrolytic activity. The normal pancreatic ultrastructure by 60d regardless of whether edematous or necrotizing pancreatitis had been induced.

We conclude that despite the differences in the development of morphological, biochemical and functional alterations between edematous and necrotizing experimental pancreatitis complete recovery results within 3 months after a single episode.
Specific Interaction of Sendai Virus and Asialoglycoprotein-Receptor: A New Approach for Liver-Directed Gene Therapy

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For liver gene therapy the development of highly tissue specific in vivo gene delivery systems is required. In this context, Sendai Virus (SV) — a negative-stranded RNA virus — offers many interesting features: persistent infections in eucaryotic cells; replication restricted exclusively to the cytoplasm; the possibility to generate recombinant tissue-specific SV vectors via modification of both SV envelope proteins, HN and F.

When grown at 39°C (non-permissive temperature), SV temperature-sensitive mutant 2771 (SV 2771) no longer binds to conventional SV host cells due to a loss in expression of functional SV HN envelope proteins. However, a new interaction between remaining SV F envelope proteins and hepatocyte-specific asialoglycoprotein-receptors (ASGP-R) is set up which results in a hepatocyte-restriction of SV 2771 infections. As a basis for the generation of recombinant hepatotropic SV vectors, we are currently characterizing the features defining the hepatropism of SV 2271 based on its specific interaction with the ASGP-R.

SV 2271 was propagated in embryotared chicken eggs and in cell culture systems. At 39°C SV ts271 displayed a dramatically reduced HN envelope uptake (<5%) in comparison both to the permissive temperature (30°C) and to standard wildtype SV conditions (37°C). Incubation of SV ts271 (38°C) supernatants with ASGP-R positive human hepatoma cell lines (HepG2, Huh-7) led to infection and subsequent replication as demonstrated by immunoblot and hemadsorption. Furthermore, we are currently transducing the ASGP-R CDNA into ASGP-R-negative cell line NCTC 2071, which is known to be non-permissive for SV infection. Thus we were able to clearly demonstrate ASGP-R-restriction of SV ts2271 uptake as the main basis for SV ts2271 hepatotropism in this mid-term, generation of recombinant liver-restricted SV vectors opens up a perspective for the application of somatic in vivo liver gene therapy as a routine method for treatment of in born genetic errors, chronic hepatitis as well as hepatocellular carcinoma.

Cisapride in Functional Dyspepsia


This multicentre trial was initiated to investigate the efficacy and tolerability of the prokinetic drug cisapride in patients with functional dyspepsia under conditions of daily practice.

The efficacy was evaluated by the assessment of the clinical symptoms epigastric discomfort, fullness, regurgitation, heartburn and bloating under cisapride treatment (4weeks).

After a drug-free-interval (6weeks) the development of symptoms were investigated again to verify a potential sustaining effect of cisapride. Further the influence of the cisapride treatment on sick-leave days was evaluated.

2291 Patients were investigated and statistically analysed.

The symptoms improved clearly in most of the patients and disappeared totally. Also the drug-free-interval showed a further improvement of the symptoms. The mean symptom score of epigastric discomfort improved from 2.1 in the beginning over 0.7 after the treatment to 0.6 after the drug-free-interval. The symptom fullness improved in the mean symptom score from 2.3 over 0.7 to 0.6. The mean symptom score of regurgitation improved from 1.9 over 0.5 to 0.4. The mean symptom score from heartburn improved from 1.8 to 0.4 and remained after the drug-free-interval on the same level.

The symptom score of bloating improved from 2.0 to 0.6 and remained also on this level after the drug-free-interval. 1.4% of the patients reported adverse events, mostly unimportant diarrhoea and headache. Cisapride is an effective and well tolerated drug in functional dyspepsia. After drug treatment with cisapride the six weeks follow-up period showed a sustaining absence of symptoms in most of the patients. The sick leave days could be reduced with the treatment of cisapride and this effect continued in the drug-free-follow up period.

Lack of Nephropathy of 5-Aminosalicylic Acid and Sulphasalazine in Chronic Inflammatory Bowel Disease

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Introduction: Elevated urine enzymes indicating tubular damage in IBD patients may reflect renal involvement as an extraintestinal manifestation of IBD or tubulotoxicity of therapy.

Methods: In 104 patients with Crohn’s disease (CD) and 43 patients with ulcerative colitis (UC) we measured activity of dipeptidyl-peptidase 4 (DPP4), β-N-acetyl-D-glucosaminidase (β-NAG), and alanine-aminopeptidase (AAP) in the urine as markers of tubular toxicity.

Enzyme activities are expressed as U/lg creatinine in the urine (mean±SD). *significant difference to control. Blood creatinine and urea creatinine excretion in the urine were normal in all patients. Active CD: CDAI > 150. Active UC: CAl > 6.

β-NAG is elevated in active and inactive CD or UC. DPP4 is elevated only in active UC. There is no correlation between enzyme activity and activity indices, however. (2) There is no statistically significant difference between treated patients (only 5-ASA: n = 27; only SASP: n = 8; 5-ASA + steroids: n = 17; SASP + steroids: n = 12; only steroids: n = 25) and patients receiving no treatment during the past two years. (3) The cumulative doses of 5ASA (12–2660 g) or SASP (120–8400 g) do not correlate with enzyme activities.

Conclusion: Tubular damage in IBD may be an extraintestinal manifestation of the disease rather than a toxic effect of therapy.

Endothelin-1 Modulates Ion Transport in Human Intestine: Different Mechanisms of Action in Jejunal and Colonic Mucosa

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The presence of immunoreactivity and abundant binding sites for endothelin-1 (ET-1) in the human enteric nervous system suggests a role for this peptide as a neuromodulator in the regulation of intestinal functions. In the present study we investigated the secretory effect of ET-1 on human intestinal mucosa. Methods: Changes in short-circuit current (Isc), release of prostaglandin E2 (PGE2) and intracellular cAMP and cGMP contents in response to ET-1 were measured in muscle-stripped segments of both small and large intestinal specimens mounted in Ussing chambers. Results: In colonic mucosa, serosal added ET-1 increased Isc in a concentration-dependent manner (at 0.1 μM ET-1, ΔIsc = 88 ± 4 μA/cm2). Bumetanide inhibited Isc responses indicating that ET-1 stimulates electrogenic Cl− secretion. In jejunal mucosa, ET-1 exhibited a concentration-dependent dual action. At low concentrations (0.1–10 nM) it stimulated rapid increases in Isc which were inhibited by bumetanide. At a higher concentration (0.1 μM), ET-1 provoked a drastic and progressive decrease in Isc below the baseline value (ΔIsc = −67 ± 13 μA/cm2). The decrease in Isc evoked by ET-1 in the jejunum was insensitively to the potassium channel blocker, barium, but was significantly prevented by the omission of glucose in the Krebs-Ringer solution at the luminal side of the mucosa (at 0.1 μM ET-1, ΔIsc = −13 ± 4 μA/cm2; p < 0.05), suggesting that ET-1 inhibits the glucose-coupled electrogenic Na+ absorption. In both intestinal segments, tetrodotoxin (TTX, 1.2 μM) inhibited the ET-1 induced increases in Isc by about 60%. The decrease of Isc evoked by ET-1 in the human jejunum, however, was not affected by TTX. Pretreatment with 1 μM indomethacin did not significantly alter the effects of ET-1. Also, no changes in the release of PGE2 could be detected up to 60 min after the addition of ET-1. In the presence of the phosphodiesterase inhibitor, IBMX (1 mM), ET-1 caused significant increases in intracellular cAMP; cGMP levels were not affected. Conclusions. ET-1 decreases electrogenic Cl− secretion across human intestinal mucosa in vitro. This effect is mediated in part by the activation of enteric nerves, possibly via the release of a cAMP-increasing neurotransmitter. Responses of the human jejunal mucosa to ET-1 exhibit a second component, namely the inhibition of electrogenic Na+ absorption. This effect is independent from neural mediators. We conclude that ET-1 is an important modulator of water and electrolyte transport in human intestine.

Long Term Outcome of Liver Transplantation for HCV-Related Liver Disease


The long term outcome in 61 patients transplanted for Hepatitis C Virus (HCV) induced liver disease and 10 patients who acquired Hepatitis C infection during liver transplantation was studied. Patients were followed for up to 10 years. Of the 71 patients included in the study 19 died within 1 year after liver transplantation. The causes of death were unrelated to the HCV infection (sepsis = 9; respiratory failure = 5; pulmonary embolism = 1; peritonitis = 1; myocardial infarction = 2; acute rejection = 1). In the later course 4 patients died of them of recurrence of hepatocellular carcinoma.

Only one patient transplanted for HCV-induced cirrhosis was permanently negative for HCV-RNA after transplantation, all others were reinfected immediately. Significant inflammatory activity was present in less than 60% of the patients. Even in these, transaminase elevation was only moderate (GPT
max ≤ 120 U/l in 90%). 1 patient developed HCV-induced cirrhosis within 2 years after OLT, 1 patient developed chronic active hepatitis with severely impaired liver function tests. 7 Patients had graft dysfunction unrelated to the HCV-infection; 29 patients had an uncomplicated long term course. Of the 10 patients who acquired HCV infection at transplantation, two developed active hepatitis, the others had normal values throughout. We conclude that Hepatitis C Virus infection may lead to active hepatitis after liver transplantation, but in the majority of cases it is associated with only minor abnormalities of liver function.

**1211 Fecal Elastase 1: An Easy, Inexpensive and Highly Sensitive and Specific Tubeless Routine Test in Pancreatic Insufficiency**

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Human specific pancreatic elastase 1 is stable during intestinal passage. The present study was designed to determine fecal elastase 1 concentrations in 34 patients with mild (I°, n = 8), moderate (II°, n = 9) and severe (III°, n = 17) exocrine pancreatic insufficiency according to the results of the secretin-cerulein test (SCT). In 21 patients with various non-pancreatic gastrointestinal diseases (GI) and 35 healthy controls. As "gold standard" the SCT was performed in all patients to define or exclude pancreatic insufficiency and fecal chymotrypsin (FTC) was calculated in parallel. Furthermore, elastase 1 was measured in pancreatic juice during lipase, amylase, trypsin, volume and bicarbonate as well as fecal elastase and chymotrypsin were evaluated. Furthermore, correlation studies to morphological parameters (ERUS, CT) were performed as well. Elastase was determined immunologically (ELISA).

**Elastase 1 and Chymotrypsin**

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Fecal Elastase 1 (µg/g)</th>
<th>Chymotrypsin (µg/g)</th>
<th>Controls</th>
<th>596 ± 45</th>
<th>184 ± 18</th>
<th>CP I°</th>
<th>208 ± 89</th>
<th>9.3 ± 4.4</th>
<th>CP II°</th>
<th>35 ± 11*</th>
<th>3.7 ± 0.9*</th>
<th>CP III°</th>
<th>14 ± 4.0*</th>
<th>G</th>
<th>648 ± 89</th>
<th>11.0 ± 1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>0.92%</td>
<td>98%</td>
<td>88%</td>
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*p < 0.01 *p < 0.001

Duodenal elastase concentrations significantly (p < 0.001) correlate with duodenal lipase (r = 0.733), amylase (r = 0.643) and trypsin (r = 0.681) in patients and controls. Furthermore, significant correlations were found for duodenal elastase and fecal elastase (r = 0.588; p < 0.001), and for fecal elastase and FTC (r = 0.562; p < 0.001). Daily measurements over 10 days showed very low variations of fecal elastase in individual patients.

**Conclusions:** Pancreatic elastase 1 shows highly similar secretion pattern compared to lipase, amylase, and trypsin. Elastase is human specific, stable during GI-transit and not affected by pancreatic enzyme replacement therapy. The evaluation of the reaction to the "gold standard" SCT proved that fecal elastase determination is a highly sensitive and specific tubeless test for easy, rapid and inexpensive routine application in patients with suggested exocrine pancreatic insufficiency.

**1212 Liver Transplantation Corrects Hypermetabolism in Patients with Liver Cirrhosis**

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Patients with liver cirrhosis show various metabolic alterations. In a substantial proportion of the patients who role body resting energy expenditure (REE) is elevated. This is often associated with a decrease of body cell mass (BCM). We examined the effect of liver transplantation (OLT) on metabolic activity and body composition in patients with liver cirrhosis.

**Methods:** Thirty-six patients with advanced liver cirrhosis were examined before and 63–187 days after OLT. Whole body resting energy expenditure was examined using indirect calorimetry (DeltaTrac Metabolic Monitor, Datex Instr.) and 24 h urinary urea excretion. Body composition was determined by bioelectrical impedance analysis (BIA 101, RJL Systems).

**Results:** Body weight remained essentially stable in the patients before and after OLT (70.8 ± 70.1 kg), there was an increase in BCM after OLT (26.8 ± 28.0 kg). The ratio between extracellular mass and body cell mass decreased significantly (1.1 ± 0.9, p = 0.007). Whole body oxygen consumption decreased (250 ± 235 ml/min), as did REE (1685 ± 1800 kcal/day). As a measure of metabolic activity REE/BCM also decreased significantly (68.5 ± 60.2 kcal/kg BCM, p = 0.04). The examination of the substrate oxidation rates showed a change from predominant fatty oxidation to carbohydrate oxidation after OLT. These changes were associated with normalization of catecholamine, insulin and glucagon levels.

**Conclusions:** After liver transplantation the hypermetabolic state of liver cirrhosis is normalized in nearly all patients. The patients gain body cell mass although body weight did not increase in most of the patients.

**1214 Prevalence of H. pylori Antibodies in Children and Young Adults Living in the Southeast of Turkey**

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In a former study young Turks growing up in Germany we found an increasing rate of infection of H. pylori from 12.9% in infancy up to 66.6% in adolescence (Amer J Gastroenterol 1994, 89:1303). In the present study the prevalence of positivity of this ethnic group was investigated in their native country. **Methods:** H. pylori IgG-antibodies levels were estimated by an ELISA (Elias Inc., Freiburg, Germany) in 509 Turkish infants, children of all age groups as well as in young adults living in Diyarbakir, Anatolia, Southeast of Turkey. The samples were recruited from nongastroenterologic pediatric patients in infancy, from an orphan asylum, from a junior high school and from young healthy adults. Levels ≥ 10 U/l were defined as positive. Results are shown in the following table (A = Turks in Anatolia, n = 509: G = Turks in Germany, n = 95, for statistical evaluation: p = 0.05).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1-5</th>
<th>6-10</th>
<th>11-15</th>
<th>16-20</th>
<th>20-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>A positive/ investigated</td>
<td>23/1</td>
<td>37/1</td>
<td>111/1</td>
<td>55/1</td>
<td>109/1</td>
</tr>
<tr>
<td>A positive %</td>
<td>28.4</td>
<td>44.0</td>
<td>69.4</td>
<td>67.9</td>
<td>71.7</td>
</tr>
<tr>
<td>G positive/ investigated</td>
<td>4/51</td>
<td>6/16</td>
<td>6/12</td>
<td>4/6</td>
<td>9/14</td>
</tr>
<tr>
<td>G positive %</td>
<td>12.9</td>
<td>35.0</td>
<td>50.0</td>
<td>66.6</td>
<td>64.3</td>
</tr>
</tbody>
</table>

There was a rising H. pylori positivity during the first 15 years of life of Turks in Anatolia. After that age a constant rate of infection at the level of about 65–70% could be observed. Compared with the Turks living in Germany the time course of H. pylori positivity in Anatolia showed a similar pattern but started at a higher level. Therefore the plateau was reached at an earlier age. **Conclusions:** The significant increase of the rate of infection in Turks in infancy and childhood may be due to an increasing chance of infection by contact with already positive elderly family members bearing H pylori subtypes of low virulence. Another explanation may be a cohort effect reflecting a change in life conditions or a change in H. pylori virulence.

**1215 Multicentre Pilot Study of Quality Assurance in Snare-decotomy of Colorectal Polyps**

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**Introduction:** The aim of the study was, for the first time in Germany, to establish quality assurance measures in the field of internal medicine. The "tracer diagnosis" is polypectomy with the diathermy snare. The development of a questionnaire was intended to provide a basis for the uniform assessment of proper endoscopic polypectomy of the histological findings. Quality standards are defined as a starting point for generally accepted guidelines.

**Method:** The medical and pathological departments of 10 Hospitals in Baden-Württemberg recorded in a questionnaire all consecutive polypectomies done over a period of 6 months. The results (anonymous) of each hospital and the overall profile of all hospitals were analysed by the participants. In a 2nd phase (11 months) the suggestions made were evaluated for their ability to improve quality.

**Results:** Phase I involved 334 patients with a total of 540 polyps, phase II 368 patients with 535 polyps. Among the hospitals differences were found, sometimes significant, in terms of premedication frequency (10.8% to 95%), localising fluoroscopy (90.2% to 96.2%), polyp recovery (78% to 100%), removal with a margin of clearance (29.4% to 64.6%), non-assessability (5.3% to 70.6%) and complication rate (0% to 8.8%). In 30% of cases, further polyps were found proximal to the snare-ectomized polyps in the rectum or sigmoid, thus impressively supporting the contention that total colonoscopy is the gold standard for primary diagnosis and treatment of polyps.

**Discussion:** Improvement of the quality of endoscopic polypectomy is possible.

**1217 Adjustment of the 13C Urea Breath Test to Body Weight of Children with Helicobacter pylori Gastritis or Ulor**

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The 13C urea breath test (UBT) is the most important noninvasive test for Helicobacter pylori (H. pylori) infection. It has important advantages over other noninvasive methods. In a recent multicentre study we confirmed following a 14-day proton pump inhibition of H. pylori in most adult and paediatric patients 75 mg 13C urea (or 2 mg/kg b.w.) is given.
Aim: We prospectively evaluated the UBT with 1 mg/kg and 2 mg/kg b.w. (max. 75 mg) of 13C-urea in the follow up of children with abdominal pain for more than 4 weeks and nocturnal awakened.

Material and Methods: Now 8 patients (mean age: 10.8, range: 4.5–18 years, 5 of turkish origin, 3 girls) with a mean body weight of 37 kg (range: 15–50) had an upper endoscopy after sedation with midazolam (Olympus videocapsule GIF 100). 1 normal, 1 duodenal ulcer and 6 antral nodularity children were found. The last 7 patients had a positive CLO-test (1 h), a positive histology with a positive silver stain, and a positive UBT with 75 mg 13C-urea (isotope ratio mass spectrometry — IRMS). All H. p. + patients were treated with amoxicillin and omeprazole and had a follow-up time of 4 weeks after the end of treatment using UBT (75 mg 13C urea; IRMS) and 1 mg/kg b.w. 13C urea (Cedex® method on the EKAP 6870 analyzer). 0.1 N citric acid was used as test "meal”.

Results: Description of symptoms UBT and endoscopy revealed unchanged results: All 7 H. p. + patients retained their antral nodularity, the ulcer had disappeared. UBT were positive regardless if 75 mg or 1 mg/kg 13C-urea was used. UBT remained negative in patient 8.

Conclusions: UBT may be performed safely and cheaper in children with a significantly reduced dose adjusted to 1 mg/kg b.w. 0.1 N citric acid may be very important in that respect. Eradication of H. p. appears to be difficult in paediatric age.

1219 Detection of Secretory Immunoglobulin a (s-IgA) on Colonic Mucosa Using a New Endoscopic Tool
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Background: The aim of this study was to develop a method to obtain pure colonic secretion for the analysis of secretory IgA (s-IgA). The proposed role of this immunoglobulin is to prevent the mucosal penetration of infective agents, viruses, and toxins.

Methods: Probes were obtained by routine colonoscopy from patients (ulcerative colitis [UC], n = 11) and normal controls (n = 23). 13C-labeled s-IgA (200 μg) was applied to a cap-closed catheter was developed for this purpose and was brought to the colon mucosa through the endoscope. The catheter was opened under visual control and the paper wiped over the surface. After fluid acquisition the catheter was wiped over the cell surface. It was demonstrated that the concentration of s-IgA in the area of the colon transversum (median 212.2 μg/ml) and the lowest in the coecum area (median 133.3 μg/ml). S-IgA concentration did not differ in various age categories. But in 4 of 6 colon areas there were higher antibody concentrations in males than in females (p < 0.05).

Unaffected mucosa or on mucosa after infection, s-IgA was only in districts or circumcised areas different from normal values. We found lower s-IgA concentrations in areas of progressive inflammation.

Conclusions: With this new technique it was possible to measure the s-IgA concentration on the surface of mucosa in the colon. The low s-IgA content in UC could be explained as consequence of the switch from IgG to IgG production in the infiltrated lymphocytes in UC. This may reflect an additional pathogenic factor since the invasion of bacteria and endotoxins is facilitated.

1220 Secretion Patterns of Prolinflammatory Cytokines and their Modulation In Vitro Inflammatory Bowel Diseases
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Background and Aim: In Crohn’s disease (CD) and in ulcerative colitis (UC) an imbalance between immunoglobulin isotypes and sub-classes lead to disorders in the mucosal barrier. This study was carried out to investigate the secretion patterns of the proinflammatory cytokines IL-1β, IL-6, IFN-γ, and TNF-α. In addition the IgG-subclass-production by isolated lamina propria mononuclear cells (LP-MNC) from patients with inflammatory bowel diseases (IBD). Methods: 14 patients with CD, 35 with UC, and 49 controls were included. Intestinal biopsies were obtained from patients undergoing colonoscopy. The LP-MNC were isolated using an EDTA-collagenase technique. The cells were cultured with or without pokeweed mitogen (PWM) and with or without specific monoclonal antibodies Anti-IL-6 and Anti-TNF. The concentration of IL-6, IL-1β, TNF-α and IgG subclasses in the supernatants was measured with ELISA. Results: We found increased levels of IL-6 in the unstimulated culture supernatants of CD and UC patients. In controls after PWM-Stimulation we found the IL-6 production increased 2.61 fold, in unstimulated CD 2.67 fold. In IL-1β further increase was detected. Increased levels of IL-1313 in UC were measured whereas CD patients and controls produce only small amounts of IL-1313. No significant differences between the three groups could be shown for the production of TNF-α. We also demonstrated a possible in vitro inhibition of IL-6 and TNF-α production. We also found decreased amounts of IgG1 and IgG2 after incubating the cell cultures with anti-IL-6 in all three groups. Conclusions: These disorders in the secretion pattern of cytokines may reflect the high state of activation in mucosal immune cells. The regulatory function of IL-6 regarding the production of immunoglobulins was demonstrated in vitro. The results shown suggest that T cells, in particular, may be involved in the disorders in the local immunity.

Supported by DFG Se 621/1-1

1221 Coagulation Disturbances in Patients with Pancreatic Carcinoma: The Role of Tissue Factor
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Background and Aim: patients with pancreatic adenocarcinoma tend to have hemostasis disturbances ranging from activated coagulation to frank thrombosis (Trousseau’s syndrome). We studied a coagulation cofactor, tissue factor, which is the initial factor in the blood coagulation cascade.

Methods: Coagulation factor assays were carried out in the course of an additional TAT investigation for TAT (Vila) and parameters of activated coagulation in patients with pancreatic adenocarcinoma. Methods: 30 patients with pancreatic adenocarcinoma (PCa), III with chronic pancreatitis (CP), 6 with cholangiocarcinoma including the papilla Vateri (CC), 4 with colonic carcinoma (CoCa), and 30 controls (n) were investigated. The occurrence of thrombotic or embolic disease was monitored. The plasma was investigated for TAT and PT 1:2. TF activity in plasma was measured by a modified clotting time and/or ELISA. Tissue factor expression was investigated by indirect immunofluorescence using a monoclonal antibody (SG9) in 19 of the 32 patients with pancreatic carcinoma, 5/13 patients with chronic pancreatitis, and 3/5 patients with cholangiocarcinoma. Results: TF expression of the pancreatic duct cells was negative in all controls and weakly positive in chronic pancreatitis. 17/19 PCa and 1/3 CCC stained positive. TAT [μg/l] was 4.04 ± 3.5 (n), 109 ± 40 (PCa), 136 ± 45 (CP), 10 ± 10 (CCC), and 3.3 ± 4.5 (CoCa). Three patients showed TF activity in the plasma. Four of the 19 patients with PCa had anemia, and 1/3 additional cases showed laboratory signs of DIC. Conclusions: Most of the native pancreatic carcinoma express significant amounts of TF on the tumor cell surface. In the plasma of these patients, coagulation disturbances and elevated TF can be detected. In some patients, this is associated with overt thrombosis. It may be speculated that the TF expression of the tumor is responsible for the activated coagulation and clotting disturbances.

1222 Reduction of Bile Secretion After Induction of Experimental TNB-Colitis in Rats
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Inflammatory bowel diseases are often associated with cholesterol. The underlying mechanisms are still not completely understood. The present study was undertaken to analyse bile acid secretion in experimental colitis. Methods: In Wistar rats, colitis was induced by single intrarectal application of the hapten, trimethoxybenzene sulfonic acid (TNS) in 50% ethanol. In animals beta-interferon represents a therapy that is quick and effective with relatively slight, reversible side effects. The effect of beta-interferon should be established in a randomized double-blind study.

14th EUGC Berlin 1995

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1, 2, 7 and 14 days after induction of TNB-colitis and controls, bile flow and acid secretion were analysed. Myeloperoxidase detection and histological examination of the colon and liver tissue were used as parameters for neutrophil infiltration in the colonic mucosa and venous blood, endotoxin and 6-keto-prostaglandin F1a, a stable metabolite of prostaglandin I2, were measured. Results: 1 day after induction of colitis, bile flow was significantly decreased (1.15 ± 0.07 vs 0.89 ± 0.06 ml/h, P<0.05) and acid levels after 14 days significantly increased (227 ± 33 mmol/l). Bile flow and acid secretion was diminished after 1 day (0.8 ± 0.06 to 0.3 ± 0.12 mmol/l/min), but back to normal after 2 days and significantly increased after 7 days (1.3 ± 0.2 mmol/l/min) presumably due to an enhancement of endogenous bile acid synthesis. In portal vein blood, endotoxin was not detectable at any time point. However, the levels of 6-keto-prostaglandin F1a increased, whereas bile flow data decreased, inversely, suggesting a role of prostaglandins mediating cholestasis. The myeloperoxidase measurement and the histological data reflect a high leukocyte infiltration of the colonic mucosa, and in contrast myeloperoxidase was not detectable in the liver and histology was negative for leucocyte infiltration over the whole observation period. Conclusions: Experimental TNB-colitis is associated with a decrease in bile secretion and acid output. The present data favour a role of prosta glandins synthesised by the colon rather than an inflammatory reaction of the liver responsible for this effect.

1224 Gene Transfer Into the Esophagus Wall Mediated by DNA-Liposomes in an Animal Model
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The possibility to transfer and express genetic material in mammalian cells represents a major breakthrough to the treatment of genetic diseases. We use in vitro techniques to introduce foreign DNA into cultured cells, followed by reintroduction of these genetically altered cells into living organisms. The present study have designed to explore the feasibility of liposome mediated in vivo gene transfer into the esophageal wall. Specifically we wanted to determine 1. histological changes after gene transfer, 2. the cell types transfected in vivo, 3. how gene expression is altered by varying the amount of DNA, 4. the time course and persistence of gene expression in the esophagus wall, 5. cell type specific expression using tissue specific promoters.

Methods: As a marker for gene transfer efficiency eukaryotic expression vec tors were used, pRSV-LacZ, pCMV-LacZ, or control DNA. The keratin K5 promotor was used for tissue specific expression. Removed were used for histochemistry, X-gal staining (β-galactosidase activity), DNA PCR and RT-PCR. Results: After transfection, the recombinant reporter gene, LacZ was expressed in several cell types including epithelial cells, fibrobasts and endothelial cells of the esophagus wall. Recombinant gene expression was not detected in other organs or when control DNA was transfected, 10 μg of pRSV-LacZ or pCMV-LacZ yielded in a strong β-galactosidase expression, which was only marginally increased using 100 μg of DNA. X-gal staining was positive for at least 100 days. The presence of the plasmid encoding LacZ and specific LacZ mRNA was detected in the esophagus using DNA-PCR and RT-PCR. Specific expression in epithelial cells was achieved using tissue specific promotors. No acute toxicity or pathologic changes were observed in the animals subjected to this treatment. Conclusion: Specific gene expression in the esophagus wall can be achieved by direct gene transfer of non viral vectors in vivo. The expression lasts for a long time. This approach to the transfer of genetic information may open new avenues for the study of gastrointestinal biology and possibly result in treatment options for esophageal disease.

1226 Inhibition of Postprandial Gallbladder Contraction and CCK-response by Omeprazole or Ranitidine Treatment
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It has been recently reported that pretreatment with omeprazole inhibits gallbladder contraction and gastric emptying. This study was designed in order to clarify whether (1) the effect on the gallbladder is drug specific and (2) altered secretion of regulatory peptides may be involved.

Methods: Ten male volunteers were treated in a randomized cross over design for 7 days with either 150 mg ranitidine twice daily or (after a 7 day wash-out period) with 20 mg omeprazole once daily. Before and after each period the gallbladder volume was monitored by ultrasound scanning and plasma levels of secretin and cyclic nucleotides were measured by specific RIA's after a mixed standard meal (550 kcal).

Results: Pretreatment with ranitidine or omeprazole significantly inhibited postprandial gallbladder contraction, increased serum gastrin levels and decreased acetylcholine (see table) while the plasma responses of pancreatic polypeptide, gastrin, insulin and C-peptide were unchanged.

1227 Long-term Follow-up of HBs Antibody Level After Immunization with Hepatitis B Vaccine and Booster Immunization
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Introduction: The purpose of this study is to compare HBs antibody seroconversion rate in various types of HB vaccine and to determine the need for booster immunization.

Materials and Methods: From 1986 to 1994, five types of HB vaccine were injected in 2283 medical staffs (999 men and 1284 women). The mean age was 26.5 years in men and 22.3 years in women. Five types of HB vaccine were plasmid-derived vaccine (pCMV-LacZ) and yeast-derived recombinant vaccines (r-HB vaccine) with subtype adw, ayw and adw with preS2 amino (preS2). A 20-fold protection of HBs antibody was defined as more than 10 mIU/ml. One month after vaccine, HBs antibody were detected in 3 groups by HBs antibody level: high responder with more than 1000 mIU/ml, middle responder with 100-1000 mIU/ml and low responder with 10-100 mIU/ml.

Results: The serum conversion rate was higher in r-HB vaccine (88% in men and 98% in women) than plasmid vaccine (77% in men and 88% in women). The rate of high responder was higher in r-HBVaccine (46% in men and 74% in women) than p-HB vaccine (21% in men and 42% in women). The serum conversion rates in adw, ayw and preS2 were 95%, 91%, 79% 76%, respectively, in men. The immunogenicity of adw was superior to that of ayw and preS2 (p<0.01). In p-HB vaccine, the rates of subjects with protective HBs antibody level after 3.5 and 7 years were 93%, 76% and 56%, respectively, and in -HB vaccine, were 90%, 72% and 48%, respectively. On the contrary, protective HBs antibody level persisted for only 2-3 years in 50-70% of middle or low responder. And booster dose was given, when the antibody level decreased less than 10 mIU/ml.

Conclusions: Immunization with HB vaccine is a comprehensive strategy to eliminate HBV and HBs antibody must be assessed after immunization to determine the need for a booster dose.

1229 Multidisciplinary Therapy with Hyperthermia, Systemic Chemotherapy, and Transcatheter Arterial Embolization for Unresectable Hepatocellular Carcinoma
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Introduction: Multidisciplinary therapy with hyperthermia, systemic chemotherapy, and transcatheter arterial embo lization (TAE) for unresectable hepatocellular carcinoma (HCC) was performed, and the therapeutic effects were evaluated.

Materials and methods: Twenty eight patients (21 male, 7 female) with unresectable HCC were treated. The hyperthermia was applied for 40 minutes once a week, using the equipment of radio frequency of 13.56 MHz and during, systemic chemotherapy such as MMC, ADM was injected simultaneously. For one shot chemotherapy and TAE, catheterization of the hepatic artery supplying the HCC was performed selectively and emulsion with ADM and Lipiodol injected. Furthermore, we placed it with gelofix and or cubes with ADM. The therapeutic effects of multidisciplinary therapy were evaluated by imaging modalities such as angiography, CT and US.

Results: Four patients of 28 revealed partial response (PR) in tumor size. 12 cases no change, 12 cases were progressive. Patients with PR were all massive HCC. A patients showed PR was performed hepatic resection after 8 months of therapy and has survived with no sign of recurrence. Survival rate of 6 months and 12 months were 40% and 28%.

Conclusion: The multidisciplinary therapy may be useful as a part of the cases with massive type HCC.

1230 Expression of Src-family Kinases in Human Pancreatic Carcinoma Cell Lines: Inhibition of Kinase Activities by a Novel Convolutin A Correlates with Growth Characteristics
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Tyrosine kinases of the Src family are thought to play important roles in cell-
lar growth control. 5 of the 9 family members are present solely in hemopoietic cells, whereas Src, Lyn, Fyn and Yes have been detected in other tissues. As shown by us before, the prototype of this kinase family — p85Src — is present in 11/12 human pancreatic carcinoma cell lines, and highly active in 10/12. Furthermore, Src is activated in human pancreatic tumor tissue ex- points as compared to the normal pancreas. To date, activities of other mem- bers of this kinase family, as well as their potential role for growth control in pancreatic carcinoma have not been examined. Therefore, expression of Src, Lyn, Fyn and Yes was determined by west- ern blotting. In addition, kinase activities were measured in detergent extracts from human pancreatic carcinoma cell lines after immunoprecipitation of the kinase proteins. To examine the importance of Src family kinases for growth of pancreatic tumor cell lines, cells were preincubated with the Src-kinase specific tyrosine kinase inhibitor Herbimycin A. Growth was measured using the MTT assay according to counting cell number.

Out of the 12 pancreatic carcinoma cell lines examined, significant amounts of Lyn protein levels and kinase activities were detected in 11 and in 10, of Fyn in 9 and in 6, and of Yes in 7 and in 6 of the cell lines respectively. There was no parallel activation of all four kinases in individual cell lines. Add- ition of Herbimycin A inhibited kinase activities in vitro with IC50s between 50 and 200 ng/ml. Cell growth was inhibited by 60% to 78% in 4/4 cell lines tested. In three of the cell lines half-maximal inhibition correlated well with the IC50 of the cell lines. In the fourth cell line kinase activities were barely detectable and the IC50 for cell growth was 500 ng/ml. No change in the fraction of non-viable cells was observed.

In summary, Src as well as other members of this kinase family are expressed and active in most pancreatic carcinoma cell lines. Since we could not observe consistent activation patterns of different kinases in individual cell lines, there does not seem to be a common mechanism of activation. Growth inhibition by Herbimycin A may indicate a potential role for these kinases in pancreatic tumor cell growth. Further studies using different experimental approaches will have to confirm this observation.

1232 P53 Protein Overexpression as a Prognostic Factor in Leiomysarcoma of Alimentary Tract
Leiomysarcoma of alimentary tract is rare entity. Prognostic factors that can identify high-risk groups for recurrences after surgery and poor survival have not been elucidated.

We evaluated a correlation between p53 protein overexpression in tumors and recurrences after surgery in 17 patients. None of the patients had metastatic disease. All the seven patients who had recurrences after surgery had p53 protein overexpression. Of four tumors with mitotic rates <10 per 10 high-power fields at 400× magnification, three had abnormally high levels of p53 protein.

In conclusion, p53 protein overexpression in tumors is significantly asso- ciated with recurrences after surgery and poor survival of the patients.

1237 The Pathogenesis of Antral Metaplastic Gastritis: Effects of Helicobacter pylori Reflux and Cigarette Smoking
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Recent reports have suggested that Helicobacter pylori (HP) infection might be a major cause of atrophic gastritis. However, duodenal ulcerogenic reflux (DGR) may have long been suggested to play a role in the pathogenesis of atrophic gas- tritis. The Aim of this study is to investigate the relationship between the reflux of duodenal contents into the stomach (DGR) and intestinal metaplasia (IM), patients with severe IM were compared with control subjects, in this study.

The study subjects consisted of the IM group (42 patients, 24 males, mean age 65 yr), all of whom had findings of IM by endoscopic and histological exam- inations, and the control group (28 patients, 16 males, mean age 64 yr) had no IM.

Methods: The following factors were measured and examined: pH total bile acid (BA) and NH3 in the gastric juice, the presence of HP anti- IgG body in Hp, fasting serum gastrin (G), pepsinogen (P) and II, gastric emptying time (GET) using the scintigraphic method, the contraction rate of the gallbladder, histologic findings, and food, drinking and smoking habits. Results are presented as a mean ± SGM. Results: In the IM group, pH and total bile acid were statistically higher (p = 0.2 ± 4.1 vs. 4.9 ± 4.0, BA; 254.6 ± 0.2 vs. 254.5 ± 0.4 Mcl/l/l, p < 0.01, respectively) and the presence of Hp was lower (43% vs. 68%, p < 0.05) than that in the control group. Comparing histologic findings, neutrophic infiltration grade was less in the IM group, in spite of almost the same inflammation grade in both groups (p = 0.4 ± 0.5 vs. 0.4 ± 0.1, p > 0.05, respectively). However, there were no significant differences in Hp, serum G, PII, II, ratio, GET contraction rate of the gallbladder, food and drinking habits in the both groups. However, a significant difference in smoking habits (69% vs. 18%, p < 0.01) did occur.

Conclusion: These results indicate that HP was closely associated with the pathogenesis of IM. In addition, smoking might play an important role in the development of IM in this study.

1239 Esophageal Cancer with Airway Fistula: Palliative Treatment by Tracheobronchial Stent
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Esophageal stent is the palliative treatment of choice for esophageal cancer with airway fistula (AF), but it can be unsuccessful in patients with cervical le- sions, non-stenosing tumors, or recurrences at anastomosis. Combined use of a esophageal and a tracheobronchial stent (TBS) has recently been proposed. The purpose of this study was to assess the value of a TBS alone in 16 patients (mean age: 55 yr) presenting esophageal cancer with AF (15 squamous cell carcinoma, 1 adenocarcinoma). Before treatment 97.3% of patients presented invalidating cough and were unable to eat. Half had se- vere dyspnea. The esophageal tumor (mean length: 6.8 cm) was located in the upper third of the esophagus in 14 cases and in the middle third in 2 cases. In most cases the lesions were of high-grade dysplasia (84%) and correlat- ing (64%) tumor producing low-grade stenosis. The mean distance of the fistula from the dental arches was 22 cm. Two patients presented tracheo- bronchial involvement without fistula and 14 presented AF (esophago-tracheal in 9 cases, esophago-bronchial in 4 cases, and esobronchial in 1 case). After tracheobronchial disobstruction by laser resection or necessary, a silicone tra- cheal or bronchial stent was inserted using a rigid bronchoscope. Respiratory symptoms, dysphagia, and general status were evaluated before and after treatment.

Results: Nineteen stents (13 in the trachea and 6 in the main stem bronchus) were placed in 16 patients (2 stents in 4 cases). Placement was suc- cessful in 15 patients (84%) and achieved palliation (improvement of clinical symptoms and resumption of eating) in 11 patients (89%). The median du- ration of palliation was 53 days. Six patients required further bronchoscopy (4 stent replacements and 2 adjustments) due to enlargement of the fistula in 4 cases and stent migration in 2 cases. During follow-up all patients un- dertook other palliative treatment (radiotherapy in 2 cases, esophageal stent in 2, esophageal dilatation in 4, endoscopic gastroscopy in 8, enteral or par- enteral nutrition in 6). Median survival was 114 days. Fifteen patients died. In 10 cases the death was due to respiratory complications. Conclusions: Placement of a TBS for treatment of esophageal cancer with AF is an effec- tive palliative treatment, easy and safe to perform, but it does not achieve prolonged palliation throughout survival. This technique should be reserved to only in patients who are contraindicated for esophageal stent placement or present tumors producing low-grade stenosis.

1241 Terminal Constipation Due to Anismus. Analysis of Etiologic, Clinical, and Administrational Data and Results of Rehabilitation by Biofeedback Training
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Chronic idiopathic constipation is a frequent motive for medical consultation. It is often due to Anismus. The purpose of this study was to assess etio- logical and clinical criteria and anatomic of anorectal function associated with anismus and to report the results of rehabilitation by biofeedback training. Patients and Methods: This study included 50 patients (42 women and 8 men) with a mean age of 52 years, complaining of long-term treatment- resistant constipation (mean duration of symptoms: 14 ± 5.1 years). Ano- rectal manometry was performed in all patients, and defecography in 39 pa- tients. Rehabilitation by biofeedback training was done in all patients. Results: History of pelvic disease was noted in 86% of cases, especially among women with a history of obstetrical trauma being noted in 76% of the population (mainly benign congenital anomalies of the pelvis, 84%) any inflammatory, and pelvic floor abnormality in all patients with an anomaly of pelvic floor static in 85% of cases. Anismus was detected in only 51% of cases. Ano-rectal manometry demonstrated Anismus in all patients. The rehabilitation by biofeedback training led to disappearance of constipa- tion in 64% of patients after a mean of 10 weekly sessions. No factor was found to be predictive of failure of rehabilitation treatment. It is concluded that biofeedback treatment for constipation in the onset of terminal constipation due to Anismus. Postpartum anorectal manometry would be useful to achieve early detection and allow preventive treatment by biofeedback training.
**Secondary Aortoenteric Fistula After Placement of an Aortic Prosthesis: Evaluation of Clinical Criteria and Various Modes of Investigation**


Aortoenteric fistula (AEF) is a rare (0.8 to 2.6% of cases) but serious (early mortality: 30 to 70%) complication of aortic prosthesis reconstruction. Based on cases of 12 patients (11 men and 1 woman) with a mean age of 63 years (range: 22 to 77 years) treated surgically for AEF in our departments between 1987 and 1993, we assessed the usefulness of clinical criteria and investigation techniques.

1. There was a delay between prosthetic placement and AEF ranged from 1 month to 2 years (mean: 8 years). The indication for reconstruction was occlusive arterial disease in 8 cases, aortic aneurysm in 3, and aortic dissection in 1. The presenting signs were digestive tract hemorrhage in 11 cases (92%) sepsis in 4 (33%), and low limb ischemia in 4 (33%). Endoscopy was performed in 8 cases and allowed diagnosis in 4 (50%). CT scan allowed diagnosis in 5 of 6 cases (83%). Arteriography allowed diagnosis in 2 of 5 cases (40%). The fistula was located in the duodenum in 8 cases (65%), small intestine in 2, colon in 1 and esophagus in 1. Treatment consisted in extraanatomical bypass and removal of the prosthesis in 5 patients. In this group, early mortality was 60% and only one patient survived to 18 months. Seven patients were treated by replacement of the prosthesis with early mortality in 28% and long term survival in 17%.

Initial diagnosis of AEF is based on clinical signs. AEF should be suspected in any patient with an aortic prosthesis who develops digestive hemorrhage. Endoscopy and CT-scan, which is the most sensitive examination, should be performed immediately.

**Cell Kinetic Analysis of Colorectal Cancers by the Monoclonal Antibody MIB-1**

T. Miyashita, G. Nishimura, Y. Michiwa, I. Miyazaki, Surgery II, Kanazawa University, Kanazawa City, Japan

K-67 was found to be present in the late G1, S G2 and M phase of the cell cycle, that is, in proliferating cells. We studied the proliferative activity in biopsied materials by means of immunohistochemical examination with the monoclonal antibody MIB-1, defining the Ki67 antigen, and the MIB-1 labeling rate in relation to the clinicopathological findings and the prognosis in patients with colorectal cancers.

One hundred and fifteen specimens obtained by endoscopic biopsy from patients with colorectal cancers were stained with the monoclonal antibody MIB-1 (IMMUNOTECH S. A.) by the labeled streptavidin biotin method. All labeled nuclei demonstrated by use of MIB-1 were regarded as positive. Between 500 and 1,000 cells were counted in each of 10–15 microscopic fields to determine the average of MIB-1 labeling rates.

The average of MIB-1 labeling rates in 145 specimens was 43.7 ± 9.9%. There were significant differences in liver metastasis, peritoneal dissemination and clinical stages in MIB-1 labeling rates. The survival rate of MIB-1 labeling rates (greater than 44%) group was significantly lower than that of the low MIB-1 labeling rates group.

The immunohistochemical staining of proliferating cells in biopsied specimen of colorectal cancers using the MIB-1 monoclonal antibody may be useful in predicting the prognosis of colorectal cancer.

**Is Chemosensitivity Affected by WAF1/CIP1 Expression?**

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The tumor growth suppressor gene WAF1/CIP1 was recently shown to be induced by p53 and arrest cell growth by inhibition of cyclin-dependent kinases. This gene is induced by DNA damaging agents and occur to G1 arrest or apoptosis in cells with wild-type p53 but not with mutant p53. In the present study, we used gastric cancer cell lines to determine relationship between WAF1/CIP1 expression, cell cycle analysis and chemosensitivity by northern blot, flow cytometry and MTI assay. We found weak or no expression of WAF1/CIP1 in cells with mutant p53 except MNK28. Under 0.2 μg/ml of adriamycin, MNK28 did not occur G1 arrest and was found higher sensitivity. It was suspected that there was functional disorder of WAF1/CIP1 in MNK28. In MNK45 with wild-type p53 WAF1/CIP1 was induced under 0.2 μg/ml of adriamycin and occur G1 arrest but found high sensitivity. In the presence of adriamycin, we found induced WAF1/CIP1 but did not found G1 arrest and high sensitivity in other cell lines with wild-type p53. We electrophoresed MNK45 DNA incubated with adriamycin and found DNA fragmentation. It was suspected that MNK45 was damaged by adriamycin and induced WAF1/CIP1 by p53. Other cell lines occurred G1 arrest but failed to repair MNK45 died by apoptosis.

We also performed northern blot analysis for mdr1 gene, it was connected with adriamycin resistance, but we could not found over expression of mdr1 in all cell lines. This results support the idea that there is no relationship between WAF1/CIP1 expression and chemosensitivity.
toelectronic device which converts the light into an electrical signal. In vivo studies were performed to evaluate the drift of the system, the response time of the probe, and the threshold bilirubin concentration that could be detected. In addition, the effect of various environmental pHs on bilirubin absorbance was assessed. Finally, the linearity of the response was studied by measuring bilirubin absorbance simultaneously with both the system and a lab spectrophotometer.

Results. Bilirubin (5–100 μmol/l) absorbance was stable over 24 h, with a maximum drift of only 3%. Once immersed in different bilirubin concentra-
tions, the probe detected their correct absorbance almost immediately (i.e. within 4 s). Regarding the experiment performed in 10 different concen-
trations, the minimum bilirubin concentration that could be detected by the sys-
tem was 1 μmol/l. When bilirubin was diluted in HCl or gastric juice at pH varying from 2 to 8, no significant changes in its absorption were observed. The response of the system to increasing bilirubin concentrations in both HCl and gastric juice was linear over the range 0 to 120 μmol/l. A good correla-
tion (r² = 0.99) between absorbance measurements by the probe and the spectrophotometer was observed.

Conclusions. The above results show that the Bili*te® system is a stable, sensitive and reliable device for measuring bilirubin concentration in the gas-
tric environment.

1252 Are the Characteristics of Acid Reflux Episodes Associated with Different Esophageal Symptoms Different?

C. Scarpignato, G. Shi, S. Bruley des Varannes, J.P. Galmiche. Department of Gastroenterology and Hepatology, University of Nantes, France.

Some studies, including ours, have shown that symptom-free episodes last longer and are more acidic than the asymptomatic ones. Whether the characteristics of reflux episodes associated with different esophageal symp-
toms are similar or different is presently unknown.

Methods. Symptom and reflux episodes occurring during 42 consecutive 24-h pH-monitorings in patients with GERD were analyzed. For each individual reflux episode (either symptom related or symptom free) the duration, the minimum pH and the reflux area were calculated.

Results. During pH monitoring, a total of 435 symptom events (see below) were reported by the patients. The characteristics (Mean ± SEM) of reflux episodes either asymptomatic or related to different symptoms are shown below:

<table>
<thead>
<tr>
<th>Reflux episodes related to:</th>
<th>Number</th>
<th>Duration (min)</th>
<th>Min-pH (Units)</th>
<th>Reflux Area (pH-min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>1308</td>
<td>3.03 ± 0.12</td>
<td>2.86 ± 0.02</td>
<td>1.37 ± 0.11</td>
</tr>
<tr>
<td>Heartburn</td>
<td>50</td>
<td>3.97 ± 0.78</td>
<td>2.13 ± 0.10</td>
<td>0.49 ± 0.71</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>25</td>
<td>3.20 ± 0.137</td>
<td>2.54 ± 0.13</td>
<td>3.16 ± 1.58</td>
</tr>
<tr>
<td>Belching</td>
<td>70</td>
<td>2.02 ± 0.15</td>
<td>2.59 ± 0.09</td>
<td>0.92 ± 0.14</td>
</tr>
</tbody>
</table>

For all the reported symptoms reflux episodes were more acidic than those not perceived by the patients. Reflux episodes associated with heartburn and regurgitation lasted longer while those related to belching were shorter than the asymptomatic ones.

Conclusions. These results are consistent with the idea that acid con-
tact time as well as pH of the refluxate are important contributing factors to esophageal sensitivity. The short duration of belching related reflux episodes suggests that belch could by itself induce the reflux, and so should therefore not be considered in the analysis of symptoms.

1254 Gastric Emptying Measurement by 13C-Octanoic Acid Breath Test

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Scintigraphy is considered as the gold standard for gastric emptying (GE) measurement. However, its use is frequently restricted by the limited access to Nuclear Medicine Departments. Moreover, because of the radiation burden, scintigraphy is contra-indicated during childhood and pregnancy. Re-
cently, a non-invasive breath test (BT) was developed using octanoic acid labelled with 13C (i.e. a stable isotope easily detected by mass spectrome-
try) as a marker of the solid phase of the meal (1). The aim of this study was therefore to compare the diagnostic yield of this new method with that of the scintigraphic technique taken as the reference.

Methods. GE of solids was simultaneously measured by scintigraphy and 13C-octanoic acid BT in 23 patients (9 with functional dyspepsia, 2 with diabe-
etes, 4 with dyspepsia after surgery, 8 with gastro-esophageal reflux). The weight of one of the meals was kept to 500 g and the boil of the meal was doped with 13C-octanoic acid (1750 Kj test-meal). Gastric acquisitions were taken every 20 min, whereas breath samples were collected at 15 min intervals. Results were expressed as half-emptying times (T50). 13C concen-
trations were determined by isotope ratio spectrometry.

Results. Scintigraphic and BT T50 were significantly correlated (r = 0.69, P = 0.0003). Results were very closed (i.e. differences less or equal to 20 min) in 15 patients (r = 0.975, P = 0.0001). Using 98 min as the upper limit for normality, the results expressed in terms of normal GE or gastroparesis (GP) were consistent in 13 cases (9 normal/4 GP). In contrast, discrepancies were observed in 10 cases (8 normal GE at scintigraphy while delayed at BT versus 2 GP at scintigraphy while normal at BT). However, in 3 of these 10 cases, the differences between T50 were only 4, 13, and 20 min, respectively. Finally, the agreement between the two methods was good or excellent in 16/23 cases (70%).

Conclusion. These results confirm the value of 13C-octanoic acid BT for GE assessment. However, studies are still necessary to further explain the reasons for discrepancies between BT and scintigraphy. (1) Ghoss et al. Gastroenterology 1993; 104:1640–7.

1255 Effects of Changes in Transit Time on the Activity of Human Fecal Flora in Vitro


The purpose of this study was to assess the effects of changes in the mean transit time (MTT) induced by drugs on the activity of human fecal flora in vitro.

Methods. The activity of fecal flora was estimated by the ability of a fe-
cal inoculum to ferment in vitro in a batch system one substrate (best fibre) for 24 h. The inoculum was collected from 8 healthy volunteers studied for three week periods during which they received either a controlled diet alone (control period), the same diet with cisapride, or loperamide. Cisapride and loperamide were adjusted in order to half and double MTT measured in the control period. At the end of each period, the % of the initial substrate added disappeared, the concentration and the profile of SCFAs was determined.

Results. (n = 10 ± SEM) are tabulated:

<table>
<thead>
<tr>
<th>Control</th>
<th>Cisapride</th>
<th>Loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTT(min)</td>
<td>73 ± 1</td>
<td>147 ± 1*</td>
</tr>
<tr>
<td>SCFA(A1)</td>
<td>140 ± 8</td>
<td>121 ± 3*</td>
</tr>
<tr>
<td>% Acetate</td>
<td>67 ± 2</td>
<td>62 ± 2*</td>
</tr>
<tr>
<td>% Propionate</td>
<td>19 ± 2</td>
<td>15 ± 1*</td>
</tr>
<tr>
<td>% Butyrate</td>
<td>11 ± 1</td>
<td>8 ± 1*</td>
</tr>
<tr>
<td>% of disappearance</td>
<td>94 ± 3</td>
<td>76 ± 5</td>
</tr>
</tbody>
</table>

*p < 0.05 versus control period by ANOVA and t-test.

MTT was inversely related to the % of disappearance of substrate (r = −0.79, p < 0.005); to the production of SCFA (r = −0.85, p < 0.005) and to the percentage of butyrate produced (r = −0.71, p < 0.005)

Conclusion. Changes in MTT alter bacterial activity and modify bacterial pathways affecting the proportion of individual SCFAs.

1256 Heartburn but not Other Reflux Induced Esophageal Symptoms is Related to Preceding Acid Burden


Acid burden over an extended period preceding a reflux episode has been suggested as a critical factor for heartburn development (Janssens et al., Gastroenterology 1992; 102: A90). However, although heartburn is the most typical symptom of GERD, other reflux related complaints are commonly re-
ported by the patients. We therefore looked at the extent of esophageal ex-
posure to acid during the period that preceded the reflux episodes related to the different symptoms.

Methods. 42 patients with symptomatic GER underwent 24-h pH monitor-
ing and indicated the occurrence of symptoms (detailed on a diary card) with an event marker. Acid burden (area under the curve) was calculated for each individual reflux episode for different time intervals preceding it.

Results. Of 435 symptom events reported by the patients during pH recordings, 145 (i.e. 33%) were reflux-related (i.e. occurring during or within the two min following the reflux episode). The more frequently reported symptoms are shown in the Table. The acid burden (mean ± SEM) at various time windows preceding the different symptoms is reported below:

<table>
<thead>
<tr>
<th>Reflux episodes Number</th>
<th>Reflux area (pH min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before reflux episode</td>
</tr>
<tr>
<td>No symptoms</td>
<td>0.70 ± 0.03</td>
</tr>
<tr>
<td>Heartburn</td>
<td>1.20 ± 0.30</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>0.89 ± 0.23</td>
</tr>
<tr>
<td>Belching</td>
<td>0.68 ± 0.14</td>
</tr>
</tbody>
</table>

Conclusions. These results show that heartburn is the only reflux-related symptom which is associated with a significantly (p = 0.06) higher acid bur-
den over an extended period of time. This would suggest that priming the esophageal mucosa with acid is a prerequisite for heartburn to develop.
1257 Expression of trk Family in Normal Stomach and Gastric Cancer
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Purpose: The trk family is encoding receptors for nerve growth factor and brain derived growth factor. Localization and immunohistochemical reactivity of trk family in non-neural tissue have remained elusive. In this study, we evaluate expression of trk A, B, and C in normal gastric mucosa and gastric carcinoma of 27 cases.

Method: The antigens in formalin-fixed and paraffin embedded sections were retrieved by microwave heating in 50 mM citrate buffer (pH 6.0) and subjected to immunohistochemistry using the streptavidin-biotin peroxidase complex method using polyclonal trk A, B and C antibodies (Santa Cruz Biotechnology).

Results: In normal stomach, parietal cells stained for trk A and C, whereas trk B expression was negative. Immunohistochemical staining of trk A and C was seen in the carcinoma cells related to intestinal metaplasia. Expression of trk B seemed to correlate with differentiation of carcinoma cells.

Conclusion: trk family was successfully detected in the formalin-fixed and paraffin embedded materials. Their expression was not restricted to neural tissue and, in stomach, was seen in peculiar cell types. They seemed to play a role in intestinal metaplasia and, in cancer, differentiation of the carcinoma cells.

1259 Is Delayed Gastric Emptying More Frequent in GERD Patients Unresponsive to Medical Treatment?
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Several studies, including ours, have shown that, compared with healthy subjects, GERD patients display — as a group — a significant delay in gastric emptying of solids. Whether the proportion of subjects with delayed emptying rate differs between patients resistant and responsive to medical treatment is presently unknown.

Methods. Gastric emptying of solids (by radioisotopic technique) and postprandial esophageal exposure to acid (through esophageal pH-meter) were studied in two groups of GERD patients resistant (n = 28) and responsive (n = 31) to medical therapy (high dose ranitidine or omeprazole), respectively as well as in 10 healthy subjects.

Results. 21 out of 28 (i.e. 75%) patients resistant to medical treatment had an emptying half-time outside the normal value (mean ± 2SD) of our laboratory (70 ± 20 min). Of the 31 patients who were responsive to medical management, only 14 (i.e. 45%) displayed an abnormal emptying rate, the difference between the two groups being significant (p = 0.03) at both the Fisher’s exact test and Chi-square test with Yates’ correction. The emptying half-time of patients resistant and responsive to medical therapy was 148.5 ± 11.9 min and 147.5 ± 15.0 min, respectively. These values were significantly (p < 0.05) different from that (81.5 ± 4.2 min) found in 10 sex and age-matched healthy subjects. In both group of patients, subjects with delayed gastric emptying spent a longer time at pH < 4 than those whose emptying rate fell within the normal range.

Conclusions. These results show that delayed gastric emptying is more frequent in GERD patients unresponsive to medical treatment and demonstrate that enteral exposure to acid is dependent also on emptying rate. In addition, they suggest, that by increasing the intragastric volume available for reflux, gastric retention can account for by resistance to medical treatment.

1260 The Expression of Growth Factors and Cell Kinetics During Gastric Ulcer Healing in Rat
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Repairing process of gastric ulcer accompanied with both cellular proliferation and differentiation. TGF α is well known as a potent stimulator of cellular proliferation in stomach. On the other hand, apoptosis seems to play an important role for the regulation of cellular kinetics during differentiation. In this study, we evaluated the expression of TGF α and EGFR by immunohistochemistry, and examined the cellular kinetics by double staining of BrdU and nick end labeling (NEI) in normal and ulcerated stomach. Regenerative epithelium of gastric ulcer appeared immature adjacent to ulcer margin, but tended to mature and differentiate gradually apart from ulcer margin. The expression of TGF α positive cells increased in mature epithelium, but not in immature site. Immature epithelium, however, expressed EGFR intensely, which was consistent with the localization of proliferative cells. BrdU positive cells increased in immature epithelium. On the other hand, apoptotic cells, which were identified as NEI positive cells, increased in matured epithelium, but not in immature site. These results indicated that in this model of experimentally induced ulcers, TGF α exerted its action of stimulation of proliferation though EGFR in immature epithelium with paracrine manner and that apoptosis might play an important role for the regulation of cellular kinetics associated with cell differentiation during gastric ulcer healing.

1262 The Expressions of EGFR and C-Met During Gastric Ulcer Healing in Rat
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Background. Several growth factors regulate cellular proliferation and differentiation during gastric ulcer healing. TGF α is demonstrated to stimulate cellular proliferation of the stomach via EGFR. Recently, HGF and its liganded receptor, c-met, have been identified in the stomach. Then, we investigated the expressions of EGFR, c-met, TGF α, and HGF in rat experimental gastric ulcer immunohistochemically. Methods. Male S.D. rats were applied in order to make experimental gastric ulcer. Specimens of rat stomach were prepared after 1, 2, 4, and 8 weeks of gastric ulcer induction. BrdU was administered before preparation. Specific antibodies for EGFR, c-met, TGF α and HGF were employed for immunohistochemicals. Results. In the normal stomach, immunoreactivities of EGFR and c-met was identified on parietal cells and the proliferative zone recognized by BrdU uptake. TGF α was identified in surface epithelium and parietal cells where HGF also showed positive staining. Neither TGF α nor HGF were detected in the proliferative ulcer zone. During gastric ulcer healing, EGFR was expressed on proliferative cells in immature regenerative epithelium adjacent to ulcer margin. Whereas, c-met was expressed at the mature site of regenerative epithelium adjacent to ulcer margin, and also in granulation tissues. TGF α was observed in mature epithelium away from ulcer margin, and HGF was detected in granulation tissues. Conclusion. Our results indicated that EGFR was closely related to proliferative process, whereas c-met was associated with repairing events during gastric ulcer healing. TGF α and HGF might react through their liganded receptors with paracrine manner.

1263 Nizatidine Protects Gastric Mucosa from Acute Aspirin Damage Through an Acid-independent Mechanism
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It was recently shown [Silecchia et al., Scand J Gastroenterol 1994; 29 Suppl 206: 8-13] that, conversely from ranitidine, nizatidine is able to increase significantly prostaglandin concentration in gastric juice of duodenal ulcer patients. This property, together with the compound ability to enhance mucus, secretion, could confer to this drug a gastroprotective activity, independent of its main antisecretory action.

Methods. Gastric potential difference (GPD) and intragastric pH were measured simultaneously in the anaesthetized rat. Data were continuously recorded on a data logger and results analyzed automatically through a specially developed program (PGProgram®). The maximal increase in PD values (ΔPDmax), the time at which the maximal PD increase occurred (time to ΔPDmax), the time spent under baseline (AUB) and the irritating index (Reiz’s index) were calculated. Nizatidine was administered orally or intravenously 120 and 30 min before aspirin administration respectively.

Results. Pre-treatment of animals with the nizatidine strongly and significantly (p < 0.01 versus saline) reduced the barrier-breaking effect of aspirin (see Table below):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ΔPDmax (mV)</th>
<th>Time to ΔPDmax (min)</th>
<th>Reiz’s Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>23.2 ± 1.4</td>
<td>11.0 ± 1.0</td>
<td>1112 ± 1/6</td>
</tr>
<tr>
<td>Nizatidine (100 mg/kg)</td>
<td>30.0 ± 2.9</td>
<td>7.8 ± 1.5</td>
<td>413 ± 2/1*</td>
</tr>
<tr>
<td>Nizatidine (30 mg/kg)</td>
<td>7.7 ± 1.8*</td>
<td>7.4 ± 1.5</td>
<td>223 ± 2/6*</td>
</tr>
</tbody>
</table>

The H2-antagonist was able to reduce aspirin-induced GPD increase before any detectable change of intragastric pH. Conclusions. Nizatidine decreases acute aspirin damage through an acid-independent mechanism.

1264 Mineralocorticoid Receptors in Parietal Cells of Human Gastric Mucosa
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Background. The influence of mineralocorticoids on the gastrointestinal tract has been demonstrated. In the stomach, it is possible that aldosterone regulates various electrolytes transport systems associated with gastric acid secretion. The presence of mineralocorticoid receptors (MRs) in human stomach was therefore investigated with [3H]aldosterone binding assay and immunohistochemistry. Methods. Specific [3H]aldosterone binding sites were assayed in human stomach specimens (ten cases of gastric body and
five cases of antrum) by incubating cells with various concentrations of (H)aldorphore in the presence of a 200-fold molar excess of RU38486, a glucocorticoid receptor antagonist. The dissociation constant (Kd) and the maximum number of binding sites (Bmax) were calculated from Scatchard analysis. The localization of MRs was examined by immunohistochemistry with a polyclonal antiserum to the human MR in stomach specimens from 25 individuals. MR-positive cells were characterized by electron microscopy. Results: Specific (H)aldorphore binding sites were detected in gastric fundic mucosa, but not in the antrum. In fundic mucosa, Kd was 0.72 ± 0.05 nM (mean ± S.E.) and Bmax was 5.99 ± 1.38 fmol per milligram of protein. MR immunoreactivity was detected only in parietal cells. Conclusions: Parietal cells of human stomach contain MRs. Thus, aldosterone may regulate various functions of parietal cells including the gastric acid secretion.

1265 P2Y and P2U Purinoceptors Expressed on Rat Gastrointestinal Longitudinal Myocytes Mediate Contraction Through Ca2+ Mobilization
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Adenosine 5'-triphosphate (ATP) is an extracellular messenger which can bind to four distinct receptor subtypes in neural or non-neural cells including smooth muscle cells. The purpose of this study was to characterize the functional purinoreceptors expressed by longitudinal smooth muscle cells all along the gastrointestinal tract and to study the effect of the phosphorylation of their activation.
Methods. After exposition to ATP, variation of cell length was measured using image analysis. Moreover, free cytosolic calcium concentration was monitored using fluorescent calcium-sensitive molecule Indo-1 in cells exposed to ATP, 2-methylthio ATP, 2-methylthio ATP or uridine 5'-triphosphate (UTP). Isolated myocytes from the rat stomach, jejunum, ileum, caecum and colon were included in this study.
Results. ATP (30 μM) reduced cell length in a similar manner than acetylcholine (10-7 M) or ATP (a P2Y purinoreceptor agonist) transiently increased free cytosolic calcium concentration in myocytes from the 5 segments, whereas a β1 methylene ATP (a P2X purinoreceptor agonist) had no effect. This rise in free cytosolic calcium was abolished by thapsigargin (10-6 M), but was maintained in calcium-free extracellular solution. Moreover, gastric, caecal and colonic myocytes also responded to UTP in a similar way. Individual smooth muscle cells responded to these agonists in an all-or-nothing manner.
Conclusion. Smooth muscle cells from the longitudinal layer of gastrointestinal muscular tissues express P2Y receptors which mediate contraction through calcium mobilization from the intracellular stores. Moreover, gastric, caecal and colonic myocytes express P2U receptors mediating similar physiological effect.

1266 Dietary Factors Short Chain Fatty Acids Induce Procyclic and Extracellular Proteins Modification on Primary Culture of Rat Intestinal Myocytes
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Short chain fatty acids (SCFA) are the main endproducts of the anaerobic bacterial fermentation of carbohydrates. Although these anions are characteristic of colonic contents, they are also present in lower concentration in the ileum. Their role on the metabolism and biology of colonocytes is now well characterized. However, the functional consequences of their presence on intestinal smooth muscle cells remain poorly studied. The purpose of this study was to assess the effect of different SCFA (especially butyrate) on smooth muscle cells in culture.
Methods. Intestinal myocytes were put into culture after collagenase digestion of longitudinal muscle strips for a week in DMEM supplemented with 10% fetal calf serum. The mucosal origin of the cells in culture was controlled by immunostaining with antibodies against a smooth muscle actin, desmin, smooth muscle myosin and vimentin. Cell proliferation was studied by incorporation of 3H-thymidine. Collagenous and non-collagenous protein synthesis was quantified by incorporation of 3H-proline. Actin and myosin concentrations and isoforms were analyzed by SDS-PAGE and Western blot.
Results. At low concentration (0.1 mM) butyrate significantly stimulates cell proliferation but inhibits it at higher concentrations (≥ 1 mM). Protein synthesis was less efficient and accelerated no effect. Collagenous and non-collagenous protein synthesis was stimulated by butyrate. Moreover, butyrate stimulates a smooth muscle actin expression, whereas no effect was observed on SM1/SM2 myosin heavy chain ratio.
Conclusion. SCFA which are produced by dietary fiber fermentation may affect intestinal muscles by directly acting at the molecular level on myocytes.

1269 An Antecedent of Sexual Abuse is more Frequently Reported by IBS Patients than by Patients with Organic Disease: Consulting In Gastroenterology or Healthy Controls
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Many recent studies have indicated that the prevalence of an antecedent of sexual abuse was higher among patients with Irritable Bowl Syndrome (IBS) consulting in Gastroenterology than in patients with organic disease (OD). However, in at least one study, this prevalence was reported to be as high in IBS patients as in patients with OD. The aim of the present study was to evaluate, in a multicenter trial, the prevalence of sexual abuse in IBS patients consulting a gastroenterologist and to compare it to that observed in healthy controls and in patients with OD.
Patients and Methods. All patients consulting between June and September 1994 for IBS (Rome Criteria), in 8 University Hospitals (Bordeaux, Clermont-Fd, Grenoble, Marseille, Toulouse, Tours) have been included (n = 176, Mean age 39 ± 15 y; 38 females, 78 males). Control groups were: (i) patients consulting in the same units for the follow-up of a non-neoplastic OD (n = 119; 41 ± 17 y; 51 F; 68 M); (ii) patients consulting in Ophthalmology (n = 200; 44 ± 21 y; 108 F; 92 M), (iii) healthy people asking for a check-up in the control centers of the National Health System (Niort, Orleans, St Brieuc) (n = 135; 42 ± 16 y; 66 F, 69 M). Each patient received an anonymous questionnaire and was required to fulfill it after the consultation, without help of anybody. The questionnaires were retained, the cover being deleted and blindly filed. Prevalence of sexual abuse among patients in the various groups was compared by the chi-2 test with Yates correction.
Results. 56 cases of sexual abuse (49 F, 6 M) have been recorded among the 96 IBS patients (51.3%); 7 women show aggressions, 5 cases of exhibitionism, 2 sexual harassments, 24 cases of sexual touches, 17 rapes. The prevalence of sexual abuse was 13.5% for the patients with OD (P = 0.0005 versus IBS), 12.5% among patients consulting in Ophthalmology (P > 0.0001) and 6.7% in healthy controls (P < 0.0001). Mean age at time of sex abuse was 13.5 ± 7.2 y. Sexual abuse was accompanied by physical abuse in 16 IBS patients and 17 controls (NS). 28 IBS patients reported isolated physical abuse (14.7%) versus 40 from control groups (8.8% — P = 0.041).
Conclusion. The study confirms the high prevalence of sexual abuse among IBS patients consulting in Gastroenterology. These patients could probably benefit from an adequate therapy in some cases.
Material and Methods. TNB/ethanol 50% (80 mg/kg) or saline was injected in the intestinal lumen of fasted male guinea pigs. Animals were sacrificed at various time intervals from this procedure. Smooth muscle cells from the ileum circular layer were isolated by enzymatic dispersion. Cell contraction was assayed in the presence of increasing concentrations of PAF or PGE2 for 30s. Contraction was evaluated by measuring the length of 50 cells and expressed as % decrease in cell length from unfixed to 10 min after reagent addition. Results. PAF and PGE2 induced a contraction of ileal smooth muscle cells from saline-treated animals with a maximal effect (21.2 ± 1.9% to 23.6 ± 2.1%). At 10 min after reagent addition, EC50 was about 3 ± 0.4 μM for PAF and 12 ± 4 μM for PGE2, similarly to those previously observed in cells dispersed from untreated animals. In TNB-treated animals, PAF and PGE2 also provoked a cell contraction in a concentration-dependent manner. However, when the animals were treated between Day 1 and Day 4 from the TNB injection, PAF-induced contraction was not altered while the effect of PGE2 was modified with a maximal contraction observed at 1 μM and an EC50 of 0.2 μM (right shift of 2 logM). Between Day 4 and Day 6, the dose-response curve of the PGE2-induced contraction shifted by only 1 logM while the PAF-induced contraction was markedly altered with a maximal contraction at 1 μM and an EC50 of 0.3 μM (right of 2 logM). At Days 10 and 15, PAF- and PGE2-induced contractions were similar to those observed in untreated animals.

Conclusion. After TNB treatment, desensitization of PAF and PGE2 receptors occurs sequentially; PGE2 receptors desensitize during the initial phase of inflammation while PAF receptors desensitize after several days. This desensitization of receptors for mediators involved in the inflammatory reaction could play a cytoprotective role for smooth muscle cells.

1273 Study of Superficial Colorectal Neoplasms with Depressed Lesions Observed Endoscopically (ER)
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Objective: Superficial depressed lesioned colorectal neoplasms with ER (17 carcinomas limited invasion into mucosa and 22 adenomas) were examined and studied in regard to their morphological comparison microscopically. Material & methods: 49 lesions of superficial depressed colorectal neoplasms (flat and central depressed lesions which histologically proliferate in a horizontal direction and show mucus formation of the neoplastic epithelium) were performed from July 1989 to December 1994. Macroscopically, they were classified as IIa + IIb + IIc according to Japanese regulation of colorectal neoplasms. The lesions were determined concerning the height from the muscularis mucosa, depth of depressed central portions and the height of circumferential mucosa. Then, using the image analyzing equipment of Rise Co. Ltd., following were determined with two dimensional analysis: 1) the size of neoplasms and size the size of whole mucosa regions which was calculated as a distance from the horizontal line perpendicular from the border of the neoplasms, and 2) the ratio of each region size was calculated. Results: The carcinomas and the adenomas were no difference morphologically. The size of carcinomas was found to be 7.8 ± 4.3 mm and the adenomas were observed to be of 4.8 ± 2.0 mm. As for the depth of depressed lesions, it was found to be of 324 ± 155 μm in the carcinomas and in the adenomas, it was noticed rob of 272 ± 98 μm. Concerning the ratio of carcinomatous region size in the mucosa it was found to be 74 ± 10% in the carcinomas, while in the adenomas, it was found to be 69 ± 10%. Conclusion: As for the superficial colorectal neoplasms with the central depressed lesions, it was found that compared with the adenomas, carcinomatous cases appear to have such tendency of larger in size, deeper depressed lesions and the ratio of their size in the mucosa is rather higher.

1274 Diosmectite Treatment Prevents Intestinal Permeability and Mucus Alterations Induced by Ingestion of a Pesticide in Rats
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Diosmectite (IPSEN, France) is known to protect the digestive mucosa by its high fixation power of bacteria and toxins. Intoxication with diquat, a widely used non-selective herbicide is primarily associated with erosions of intestinal mucosa and fluid hypersecretion. The aim of this study was to determine the effects of diquat on intestinal permeability and the spinnability (reflecting the polymerisation of glycoproteins) of gastrointestinal mucous and to evaluate the protective action of diosmectite on these parameters.

Four groups of eight male Wistar rats were used. Intestinal permeability was determined as the percentage of 51Cr-EDTA administered orally (0.2 ml, 3 μCi/ml) 1 h before sacrifice in the urine, for 24 h after administration. Mucus was collected by scraping the mucosa of the stomach corpus, duodenum and ileum with a blunt spatula and its spinnability was measured in quadruplicate on a 1 ml sample using a microviscosimeter (SEFAM, Paris). All animals were treated orally and daily for 2 weeks before intestinal permeability and mucus spinnability measurement. Group 1: vehicle (water, 0.2 ml/day for 2 weeks);

1275 Diagnostic Features of Early Esophageal Cancer with a Special Reference to the Detection at Curable Stages
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A purpose To elucidate the clinical features of early esophageal cancer, especially mucosal cancer, based on the histopathological evidence, taking into consideration its general poor prognosis. Methods 51 patients (40 males and 11 females) with early cancer detected over the 14 years of which cancerous depth invasion were diagnosed as m1 (27 cases), m2 (15), m3 (8) in mucosal cancer, and sm1 (6), sm2 (11), sm3 (9) in submucosal. c: results 72 males and 4 females. Average age in male 62 ranging from 42 to 79, in female 56. 53.8% of early cancer had no complaints. Types of gross appearance were I (4 cases), I + IIc (5), IIa (4), IIa + IIc (9), IIIb (11), IIIc (35), IIIc + IIb (6), IIIc + IIc (2), IIIc + IIId (4) and corresponds to protrusion, lla elevated or plateau, lla no level difference, lllc depressed, lllec excavated. 15 of 50 mucosal cancers only discernible with the iodine solution dying. With the lymphatic invasion, m1 (0%), m2 (13.3%), m3 (12.5%), sm1 (50%), sm2 (63.6%), sm3 (56.6%). 2 of 50 were lymph-plus in mucosal cancer, while in submucosal, 15 of 26 being lllc. With no pathological invasion, lllc in early cancer, 7 of 26 being lllc in submucosal. With the lymph node metastasis, no lllc in mucosal cancer, 6 of being lllc in submucosal. d: conclusions 1) male over 60 as a risk factor 2) More than half of early cancer had no complaints. 3) The fact that Type-I and Type-III proved sm cancer was extremely crucial because it is closely associated with prognosis. 1 mm in height and 0.5 mm in depth is being accepted as a border figure between Type-I and Type-II and between Type-IIc and Type-Ic. 4) Endoscopic mucusal resection can be indicated to m2, but generally not to m3 up to the nation-wide statistics. 5) Lugol dying was indispensable since 30% of mucosal cancer could not be discerned without iodine solution.

1277 The K-Agonist Fedotozine Increases Thresholds of First Sensation and Pain Perception to Colonic Distension in Patients with Irritable Bowel Syndrome
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Increased sensitivity to colonic distension plays an important role in the pathophysiology of the irritable bowel syndrome (IBS). Fedotozine, a selective agonist of K receptors, modulates the activity of afferent nerves in animals and relieves abdominal pain in IBS. Aim of this study was to evaluate the effect of Fedotozine on colonic sensory thresholds and compliance during intra-colonic isotonic distensions using a barostat. Patients and Method: In 12 IBS patients (5 men, 7 wo 50 ± 13 y) present- ing with chronic abdominal pain and mild constipation, a tube with the bag of a barostat was placed in the left colon and its position was verified radiologically. After an overnight fast, phasic isotonic distensions (4 mmHg increments, 5 min duration, 5 min interval) was performed until a threshold of 1st sensation and then until pain appeared. Statistical comparisons were performed on Days 1 and 2, a run-in distension was performed without treatment, followed after 2 hours by a second session with a random intravenous infusion of placebo or Fedotozine 100 mg, starting 30 min prior to the first distension step and continued over 90 min, in a double-blind, cross-over fashion. Bag volume was recorded at each pressure step to allow comparison of pressure-volume curves. Results: Thresholds recorded during run-in sessions on Days 1 and 2 were not different. During isotonic distensions, the thresholds for 1st sensation and pain were significantly lower in patients on Placebo than on Fedotozine.

Pressure-volume curves (compliance) during isotonic distensions were not different on Fedotozine and on Placebo.
The Role of Endogenous ET-1 in the Indomethacin-Induced Reduction in Gastric Mucosal Blood Flow  
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Recent studies have implicated endogenous endothelin (ET-1) as a mediator of the reduction in gastric mucosal blood flow but the exact mechanism of its involvement remains unclarified. Since reduction of gastric mucosal blood flow is considered a major pathogenic factor of indomethacin-induced mucosal damage, we studied the effect of a mixed endothelin receptor antagonist, BMS-189735, on the indomethacin-induced reduction of rat gastric mucosal blood flow as well as the tissue and plasma levels of ET-1 after intragastric administration of indomethacin.

Materials and Methods: Male wistar rats (200-250 g) were fasted overnight and anesthetized with urethane (1.5 g/kg ip). They were fitted on a surgical stand and a gastric chamber was constructed for measurement of gastric mucosal blood flow with laser Doppler and tissue spectrophotometry, while blood pressure was monitored. 30 min after recording baseline levels, indomethacin (20 mg/kg) was intragastrically injected and two other groups (n = 6) of rats were pretreated with bosentan (30-60 mg/kg) by gavage, 1 h before indomethacin. Venous blood and gastric mucosal samples were obtained before, 5 min-60 min after indomethacin administration for measurement of plasma and tissue levels of ET-1 by EIA (WAKO, Japan). Results: 10 min after intragastric indomethacin gastric mucosal blood flow started falling and after 60 min it decreased by a max 68.75 ± 13.14%. Bosentan pretreatment dose dependently antagonized the indomethacin-induced gastric mucosal blood flow reduction (7.5 ± 3.4% after 60 min, p < 0.01 vs the indomethacin only group, n = 6). Tissue levels of ET-1 increased 5 min after indomethacin (2.15 ± 0.17 ng/ml vs 1.30 ± 0.07 ng/ml of indomethacin only group, p < 0.01) but then returned to control levels after 1 h. Plasma ET-1 levels remained unchanged. Conclusions: These data suggest that ET-1 is mainly responsible for the indomethacin-induced gastric mucosal blood flow reduction, action not to be mediated by release of ET-1 but most probably to a reduction of other vasodilators that normally counter-balance the action of ET-1 in the regulation of gastric microcirculation. These data point to an important action of mixed endothelin receptor antagonists in the protection of gastric mucosa against indomethacin and underline the importance of the yet unknown factors that contribute to this type of gastric mucosal damage.

The Fate of the Liver Lobe with Impaired Blood Flow and Its Influence on Liver Function and Regeneration  
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[Abstract] This experiment was designed to discuss which is preferable, to remove the parenchyma of the liver with impaired blood flow or make it remain in liver resection or in liver transplantation.  
[Methods] Male S-D rats underwent 30% hepatectomies and divided into 3 groups. The blood flow in 54% of the remnant liver was disturbed either by ligation of the portal vein (PVL group) or both the portal vein and the hepatic artery (TIL group). Only 30% hepatectomy was performed on the control group. The fate of the lobe with impaired blood flow was evaluated by macroscopic and microscopic findings as well as by immunohistochemistry with anti single-stranded DNA antibody. Its effects on liver function and regeneration were examined by blood chemistry and BrdU immunostain. 48 hours after hepatectomy, 1 mg/kg of E. Coli derived endotoxin was challenged and the damage on remnant livers was investigated.  
[Results and Conclusion] The ligated lobe in the PVL group shrank and the remnant liver regenerated rapidly. Labeling index of anti single-stranded DNA antibody elevated as 10 times higher as the control, which indicated apoptosis took place in the ligated lobe. The ligated lobe in the TIL group eventually retracted to a half size of the intact lobe, the remnant liver was surgically resected in 2 weeks and the necrosis lobe became smaller than 30% of the previous volume in a month. Et challenge was lethal in 33% of the TIL group, while every rat in the other groups survived. Serum GOT level 6 hours after the challenge was 2337 U/l in the TIL group, 247 U/l in the PVL group, and 408 U/l in the control. In conclusion, disturbance of the portal flow and that of total hepatic inflow cause a fairly sufficient regeneration after heptectomy. However, total inflow disturbance is not preferable since it seems to augment vulnerability of the liver to endotoxin.
Fcm of colo-rectal polyadenomas (Pa) and of the adjacent healthy mucosa (Hm) to investigate its value in predicting recurrence of Pa. Materials and methods: 29 Pa(12 with slight dysplasia, 14 with moderate dysplasia, 10 with severe dysplasia and 3 with cancerous transformation in situ (Cis)) were resected in 32 patients. Biopsy samples of HM were taken simultaneously 3 cm from the lesions. PA were cut in two parts parallel to the wall and a fragment being used for histological analysis and the other frozen for Fcm. Cell suspensions were prepared by mechanical disruption and labelled with propidium iodide.

Results: The cell population of 4 of 39 PA (10.25%) had aneuploidy DNA content. The methods for identification of 10 with severe dysplasia (20%) and one of three with Cis (33.3%). Pa with slight dysplasia and their adjacent Hm didn't show aneuploidy. Aneuploidy did not appear to be significantly higher (p > 0.005) in Cis and in high grade dysplasia. Mean proliferation index (Pi) was 13.67% in slight, 14.2% in moderate, 17.36% in severe dysplasia and 22.4% in Cis. The Pi was significantly higher (analysis of variance, p < 0.001) in Cis and severe dysplasia compared with slight and moderate dysplasia. The Pi of adjacent HM was not correlated with that of the Pa. Polyp size was not correlated with aneuploid peak or with high Pi.

Conclusion: The existence of an aneuploid peak is not closely correlated with pathological grade. Pa proliferation index varies according to the severity of dysplasia. Thus it seems that FCM of healthy mucosa is of value in predicting the occurrence of metachronous PA.

1295 Discover of Some Established Cell Lines with the Indwelling Hepatitis C Virus and Effect of Some Drugs on the Culture of the Virus
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It is known that, compared with chronic hepatitis (type B), chronic hepatitis (type C) is more apt to progress into hepatocellular carcinoma through liver cirrhosis. Chronic hepatitis (type C) is difficult to cure. In Japan, about 160,000 patients with chronic hepatitis (type C) have received interferon therapy, but only about 30% of these patients have experienced complete remission and most patients suffer a recurrence of the disease. Hence, a new effective drug has been much anticipated. However, the study using chimpanzees is very expensive. Therefore, the hepatitis C virus (HCV) culture could be the most useful for the development of a new anti-HCV drug. We report that the indwelling HCV in the Chang cell could be replicated on some condition and there are some inhibitory drugs except IFN. Materials and Methods RNA fraction was extracted from HCV RNA infected Chang cell at the Tsukuba Cell Bank (Japan), and the cell of HepG2, HeLa, human fibroblast cells that human lung squamous cell carcinoma from Tsukuba cell bank. Subsequently, reverse transcriptase and polymerase chain reaction (RT-PCR) using sense and anti-sense primers to a portion of 5' non-coding region of HCV was carried out. The subtype of the HCV was determined by Okamoto’s method. Results and Discussion RT-PCR also was done. The staining of the indwelling HCV was carried out using indirect immunoperoxidase method (IPA) (by the method of Tsutsumi, Hepatology 19, 265, 1994). The analysis of base sequences was determined using dye terminator cycle sequencing (DTS). The minus and plus strand HCV RNA was estimated using asymmetric RT-PCR. The Chang cell was suspended in Eagle’s MEM solution containing 10% FBS, 100 units of penicillin and streptomycin, and the suspension was induced by <1 × 10^5 cells/ml. The suspension in a bottle was incubated at 37°C in 5% CO2 and 95% air for 4 weeks. The effects of the addition of IFN γ 2a, ursodeoxycholic acid (UDCA), actinomycin D (ACMD), dexamethasone (DX), β-methasone (β-Me) to the culture medium was studied. The effect of the irradiation of ultraviolet was also studied.

Results: The indwelling HCV were recognized by RT-PCR in the Chang cells obtained from ATCC, Tsukuba cell Bank and Danippon Pharmaceutical Co. Ltd. and in the HepG2 from Tsukuba Cell Bank. There were no target bands in the other cells. As control, the liver specimens of chronic hepatitis (type C) was positive for RT-PCR. This result shows that chronic hepatitis is negative for RT-PCR. The contamination could completely be denied. There were also rounded the positive staining cells (about 50% in the Chang cell) (ACMD) after 4 weeks of culture. The base sequence of the target HCV RNA. The amplified a portion of 5' non-coding region was according to the same DNA of the region of HCV RNA. The subtype was like Type III (Identity 92%). IFN γ 2a, UDCA, or baecaine made the amount of HCV decrease in RT-PCR. ACMD makes the cell number and the amount of HCV. The base sequences of the target HCV.
Results: Gastric cancer incidence was significantly higher in the ammoniatriated animals than in the control group. The labeling index of well-differentiated adenocarcinomas was also larger in the ammoniatriated group than in the water-treated group.

Conclusion: In Helicobacter-infected subjects, gastric juice consists of approximately 0.001% of ammonia, while it contains less than 0.005% in subjects uninfected with this bacterium. H. pylori is a promoter for MNNG-induced gastric carcinogenesis. The results also showed that ammonia significantly stimulates cell replication of gastric mucosa and of well-differentiated gastric cancer.

Results: Patients with duodenal ulcer (DU) took Lanso 30 mg/day until day 28. HPE was defined by the negativity of all the diagnostic methods.

Conclusions: (1) Triple therapy with Lanso-Amox-Clari can eradicate H. pylori in 95% of all patients. (2) Lanso-Amox is significantly more effective than double therapy with Lanso-Amox. (3) The HPE with DT is low despite the high dosage of Lanso used. (3) Side effects are greater in the TT group but are minor without decrease of efficacy.

Duality of \textit{Cyclooxygenase-2} in Cell-proliferation of Gastric Epithelial and Gastric Cancer Cell-lines


Background: \textit{Cox}-2 (COX-2) is one of two \textit{Cox} isozymes (i.e., constitutive \textit{Cox}1 and heat-not-inducible \textit{Cox}2). Although \textit{Cox}2 inhibitors decrease gastric mucosal blood flow and induce gastric injury in human and animals, the roles of \textit{Cox}2 in gastric epithelium have not been examined. We investigated gene expression of \textit{Cox}2 in gastric epithelial cells. We also examined the effect of a specific inhibitor for \textit{Cox}2 in the differentiation of gastric cancer cells and gastric epithelial cells.

Materials and Methods: \textit{MKN}-45, a gastric cancer cell line and \textit{RGM}, a cell-line derived from normal rat gastric mucosa established by Matsumoto and Ohno, Riken Cell Bank, were cultured in a 1:1 mixture of DMEM and Ham's F-12 containing 20% fetal calf serum (FCS). (1) The cells were deprived of FCS for 3 days. The cells in quiesence were stimulated by addition of 20% FCS. Total RNA was extracted with acid guanidium phenol chloroform and analyzed by Northern blotting using the \textit{Cox}2 cDNA. (2) Quiescent \textit{MKN}-45 and \textit{RGM} cells were cultured for 3 days with 20% FCS and 10^-10^-10^-5 M of \textit{NS}-398. The cell proliferation was assessed by counting cells. (3) \textit{NS}-398 inhibited cell proliferation of both \textit{MKN}-45 and \textit{RGM} in a dose-dependent manner. The maximal suppression rates were 32% for \textit{RGM} and 35% for \textit{MKN}-45, respectively.

Conclusion: The present results indicate that expression of \textit{Cox}2 gene is enhanced in gastric epithelial cells after growth stimulation. Inhibition of \textit{Cox}2 resulted in marked decrease in gastric epithelial cell proliferation, suggesting a pivotal role of this enzyme on normal gastric cell proliferation as well as gastric cancer development.

\textit{Mechanism of Ammonia-induced Promotion of Gastric Carcinogenesis}


Background: Helicobacter infection is closely related to gastric carcinogenesis, although precise mechanisms for cancer development remains unknown. The aim of this study was to clarify the gastric cell kinetics in rats exposed to ammonia, a Helicobacter-product.

Materials and Methods: Male Sprague-Dawley rats aged 5 weeks were given drinking water containing 83 mg/l of N-methyl-N-nitro-N-nitrosoguanidine (MNNG) for 24 weeks. They were then divided at random into the following two groups: a group drinking tap water and another drinking water containing 0.01% ammonia for 24 weeks. At the end of the study, the animals were administered bromo-deoxyuridine (BrdU), sacrificed and histologically examined in a blinded manner.

Results: Gastric cancer incidence was significantly higher in the ammoniatriated group than the water-treated group. In the ammoniatriated animals, the labeling index and proliferative zone index of gastric mucosa were significantly higher in the ammoniatriated group than the control group. The labeling index of well-differentiated adenocarcinomas was also larger in the ammoniatriated group than in the water-treated group.

Conclusion: In Helicobacter-infected subjects, gastric juice consists of approximately 0.001% of ammonia, while it contains less than 0.005% in subjects uninfected with this bacterium. H. pylori (Amo-d) is a promoter for MNNG-induced gastric carcinogenesis. The results also showed that ammonia significantly stimulates cell replication of gastric mucosa and of well-differentiated gastric cancer.

\textit{Seven Days Triple Therapies with Lansoprazole and Amoxicillin Plus Amoxicillin or Tindazole for Helicobacter pylori Eradication: Preliminary Results of a Randomized Study}

H. Lamouliatte, R. Cayla, F. Zerbib, P. Talbi, F. Mégraud, A. de Mascalier, Hôpital Saint-André, 33075 Bordeaux, France.

There is no gold standard treatment for Helicobacter pylori (HP) eradication (HPE). Previous studies showed an eradication rate up to 90% with low-dose short-term triple therapy including a proton pump inhibitor (PPI) in association with tindazole (Tinoliatte) and clarithromycin (Clari). In our center, the triple therapy with PPI — amoxicillin (Amo) and Clari have also obtained an HPE rate higher than 90%. The aim of this study was to compare in an open randomized pilot study the HPE of 2 triple therapies using Lansoprazole (Lanso) plus Clari in association with Tinoliatte (TLC group) or Amo (LCA group) for HP positive patients.

Results: HP infection was assessed by endoscopy at the inclusion and 4 weeks after the end of the treatment on antral and fundic biopsies by 4 different methods: rapid urease test (at the inclusion), histology, culture and PCR. Clari resistance was defined by contact resistance with an agar diffusion method. HP positive patients were randomly allocated to receive either: (1) Lanso 30 mg bid and Amox 1 g bid (LA group) or 2) the same regimen in association with Clari 0.5 g bid (LAC group) for 2 weeks. Patients with duodenal ulcer (DU) took Lanso 30 mg/day until day 28. HPE was defined by the negativity of all the diagnostic methods.

Conclusions: (1) Triple therapy with Lanso-Amox-Clari can eradicate H. pylori in 95% of all patients. (2) Lanso-Amox is significantly more effective than double therapy with Lanso-Amox. (3) The HPE with DT is low despite the high dosage of Lanso used. (3) Side effects are greater in the TT group but are minor without decrease of efficacy.
Methods: 63 HP positive patients (47 male, mean age 45.5 years old, 32 with duodenal ulcer) were treated with 1 or 2 weeks regimens including a PPI (omeprazole 20 mg or lansoprazole 30 mg bid with Amox 1 g bid and Clar 250 mg bid, 500 mg bid or tid. HP status was assessed on antbiotics trials at the inclusion and 4 weeks after the end of the treatment by 3 different methods: histology, culture and PCR. Clar resistant strain was defined by control discordance of an agar diffusion method and Clar resistant strain by a MIC > 8 mcg/ml (E-test). Eradication was defined by negativity of all the methods. Drug tolerability was evaluated at the end of the treatment.

Results: Pre-treatment HP Clar resistant rate was present in 10.5% (n = 6/57) and HP Metro resistance rate in 52.6% (n = 30/57) among the evaluable strains. 1. Compliance: 4 patients (6.3%) were not compliant (<80%) of the prescribed resistance rate for 10 days after the end of the trial Clari resistant strain. In evaluable patients, the Clar sensitive strains were eradicated in 98% (n = 48/49 - 95%/C: 93.9%-100%). In intention to treat, the cure of HP infection was 85.7% (n = 54/63). 3. Side effects: they were all minor and appeared in 30.1% (n = 18/63) with diarrhea in 11 metabolic, taste in 12, malnissis in 2, palpessional oedema in 1.

Conclusions: 1. The triple therapy PPI-Amox and Clar can eradicate HP infection in 91% in evaluable patients and in 98% on Clar sensitive strains. 2. Compliance seems to be very low between 2o 5% except in France with a rate near at 10%. The aim of this study was to investigate the incidence of Clar resistant strain to Clar in HP eradication (HEP) and their occurrence after eradication failure with regimens including Clar.

Methods: 108 HP positive patients (80 male, mean age 45.2 years old, 57 with duodenal ulcer and 52 with non-ulcer dyspepsia) without prior anti-HP treatment were treated with different regimens comprising a proton-pump inhibitor: omeprazole 20, 40, 60 mg or lansoprazole 60 mg and Clar 0.25, 0.5, 1 or 1.5 g without (dual therapy) or with (triple therapy) amoxicillin 2 g or tinidazole 1 g/day. All the patients underwent endoscopy with antral biopsies to test the strain sensitivity to Clar before and after 4 weeks after the end of the treatment. Clar resistant strain was defined by contact resistance with an ager diffusion method. Patients with bad compliance were not included in this study.

Results: The results of this study showed that the HP strain resistance rate to Clar in the patients treated before was very low between 2 to 5% except in France with a rate near at 10%. The main aim of this study was to investigate the incidence of Clar resistant strain in HP eradication (HEP) and their occurrence after eradication failure with regimens including Clar. The results of this study showed that the HP strain resistance rate to Clar in the patients treated before was very low between 2 to 5% except in France with a rate near at 10%.

Conclusions: 1. The triple therapy PPI-Amox and Clar can eradicate HP infection in 91% in evaluable patients and in 98% on Clar sensitive strains. 2. Compliance seems to be very low between 2 to 5% except in France with a rate near at 10%. The main aim of this study was to investigate the incidence of Clar resistant strain in HP eradication (HEP) and their occurrence after eradication failure with regimens including Clar.

Materials and Methods: The pancreas were obtained from 22 consecutively resected cases (7 females, mean age 62.5 years old). Pancreas and the ducts were taken in three directions using a soft X-ray apparatus and the length of the duct of Wirsung was measured. The pancreas was cut in parallel slices of approximately 3 mm from the head of the pancreas, vertical to the main duct of the body, and embedded in paraffin. The sections were stained with HE. Immunohistochemical studies for CF cells were performed.

Results: There are two apparently different categories of the embryological fusion of both ducts (see the figures below): 10 cases of type 1 and 12 cases of type 2. The type 2 is an unexpected way of fusion and has not been reported in the past. The mechanism of this fusion may be the beginning of the fusion between main papilla and the point of the fusion was significantly shorter than that of type 1. His 185.3 vs 28.2 ± 7.0, P < 0.01.

Discussion: The results may indicate the existence of an unreported type of embryological fusion as a not-uncommon process. Further studies will be needed.

Pre and Post-treatment Clarithromycin Resistance of Helicobacter pylori Strains: A Key Factor of Treatment Failure

R. Cayla 1, F. Zerbib 1, P. Taïbi 1, F. Méraud 2, H. Lamouliate 1 1. Hôpital St André, 33075 Bordeaux, France; 2. Pellegrin, 33075 Bordeaux, France

The resistance of Helicobacter pylori (HP) strain to antibiotics is an important factor of treatment failure. The HP strains resistance rate to Clarithromycin (Clari) before treatment seems to be very low between 2 to 5% except in France with a rate near at 10%. The main aim of this study was to investigate the incidence of Clari resistant strain to Clari in HP eradication (HEP) and their occurrence after eradication failure with regimens including Clari.

Methods: 108 HP positive patients (80 male, mean age 45.2 years old, 57 with duodenal ulcer and 52 with non-ulcer dyspepsia) without prior anti-HP treatment were treated with different regimens comprising a proton-pump inhibitor: omeprazole 20, 40, 60 mg or lansoprazole 60 mg and Clar 0.25, 0.5, 1 or 1.5 g without (dual therapy) or with (triple therapy) amoxicillin 2 g or tinidazole 1 g/day. All the patients underwent endoscopy with antral biopsies to test the strain sensitivity to Clari before and after 4 weeks after the end of the treatment. Clari resistant strain was defined by contact resistance with an ager diffusion method. Patients with bad compliance were not included in this study.

Results: The results of this study showed that the HP strain resistance rate to Clari in the patients treated before was very low between 2 to 5% except in France with a rate near at 10%.

Conclusions: 1. The triple therapy PPI-Amox and Clari can eradicate HP infection in 91% in evaluable patients and in 98% on Clari sensitive strains. 2. Compliance seems to be very low between 2 to 5% except in France with a rate near at 10%.

PPI-Amox and Clari can eradicate HP infection in 91% in evaluable patients and in 98% on Clari sensitive strains. Compliance seems to be very low between 2 to 5% except in France with a rate near at 10%.

1. Hôpital St André, 33075 Bordeaux, France; 2. Pellegrin, 33075 Bordeaux, France

Discussion: The results may indicate the existence of an unreported type of embryological fusion as a not-uncommon process. Further studies will be needed.
second procedure). The mean postoperative stay was 10.8 days in the group A vs 15.2 in the group B. This preliminary report assesses the feasibility of laparoscopically-assisted surgery for left colonic disease, avoiding a large incision with its proper complications.

**1312 | New Evidence of Amino Acid Substitution in HBV Core Region**

H. Ueda, M. Miyano, S. Yukawa. 3rd Department Internal Medicine, Wakayama Medical University, Japan

Hepatitis B virus (HBV) causes acute and chronic hepatitis. Some mutations in precore and core region are reported in chronic hepatitis B, but not in acute hepatitis B. In chronic active hepatitis B (CAHB), however, there have been no reported mutations in core region are studied according to serum GPT value. Therefore, CAHB was classified into two groups regarding to severity of serum GPT value, and the difference of mutations in core region was compared between two groups.

Eleven patients with CAHB were subjected to the study. All patients were positive for HBsAg but negative for both hepatitis C and hepatitis delta virus antibodies. CAHB was characterized according to serum GPT value. In group 1 (4 patients) and group 2 (7 patients), serum GPT were over 100 IU/L at least once a year and below 100IU/L, respectively. HBV DNA were extracted from patient’s sera, and core region was amplified by PCR. Specific primers were inserted into BlueScript vector and applied to Autosequencer (ABI373A, Applied Biosystem) with Dye Deoxyterminator Method. At least three clones were isolated for one case, and the DNA sequence was determined.

DNA and output of amino acid sequence of core region in subjects were compared with wild type adr. In all eleven patients, there were many mutations, but the numbers of amino acid substitutions were ranged from 2 to 7. A numbers of amino acid substitutions were smaller in group 1 than in group 2. No region of amino acid substitutions was found in group 1. The other hand, in group 2, it was found that codon 59 and 84 = 101 were specific regions for amino acid substitutions.

In this study, the amino acid substitutions of codon 59 and 84 = 101 were noted in group 2 but not in group 1, suggesting that the amino acid substitutions in these region may play an important role in CAHB.

**1314 | Laparoscopic Microwave Coagulo-necrotic Therapy for Hepatocellular Carcinoma**

Y. Watanabe, M. Sato, K. Kito, N. Iseki, S. Kimura. Second Department of Surgery, Ehime University, School of Medicine, Shigenobu, Ehime791-02, Japan

Hepatocellular carcinomas (HCCs) include a high incidence of coexisting liver cirrhosis in Japan, which limits the range of resection. PEIT has an advantage that it can be performed repeatedly with minimal invasion to the patients. However, the disadvantage is that the area, which can not be observed by US or CT, 57, can not be treated. With the development of laparoscopic US, some surgical procedures with the help of US have become possible to perform safely and exactly. Here, we report some cases, who were treated by laparoscopic MCNT (LMCNT) with the guidance of laparoscopic US. Among those cases, we selected because conventional therapies such as TAE and PEIT were not effective, however, the hepatic resections were not indicated because of their hepatic dysfunction. Five males and one woman, mean age of them were 53.8 years old. All cases suffered from liver cirrhosis after hepatitis B in two cases and hepatitis C in four cases. All of them were treated by several times of TAE and four cases were also treated by PEIT before LMCNT. Three cases had solitary and others had multiple HCCs. Case 5 was performed lateral segmentectomy former than LMCNT and then the remnant HCC in segment 7 was treated by thoracoscopic MCNT through the diaphragm. Procedures: In every case, laparoscopic color doppler US was used to monitor the blood supply to HCCs, which must be also coagulated by LMCNT. During the coagulation therapy, the US probe was placed beside the coagulator to monitor the effectiveness of coagulation of the tumor and also tumor vessels. Microwave coagulator with 10 mm in diameter and 20, 25, 30, 35 mm in length (Nihon Shoji, Co.) was used according to the depth from the liver surface and the size of the tumor. We selected the output of the coagulator as 60 to 80 W and the duration as 40 sec and the frequency according to the tumor size from the result of preliminary experiments by rats. Postoperative evalution of LMCNT was done by CT, Angiography. Results and Conclusion: No tumor stain was observed after MCNT estimated by angiography and also necrotic mass by CT and US were observed. AFP as a tumor marker returned to normal value after the operation in every case. In two cases, ascites was observed after the operation but was well controlled by diuretics. Liver function tests showed almost equal values, as compared with the preoperative ones. Thus, LMCNT can be an option for the therapy of HCCs, which are difficult to treat by conventional therapies.

**1315 | A New Hereditary Cause of Portal Vein Thrombosis: Arg506 → Gin Mutation in the Gene for Factor V**


Introduction: A new hereditary increased risk for deep vein thrombosis has been reported. It is associated with a single point mutation in the factor V gene that replaces the arginine in residue 506 with glutamine. This mutation induces abnormal resistance to anticoagulant activity of activated protein C (APC). We report two cases of portal vein thrombosis associated with this genetic disease.

Patients: the two patients had personal and familial history of deep vein thrombosis. An exhaustive investigation could excluded intraabdominal neoplasia or infection, myeloproliferative disorder, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria and coagulation inhibitor deficiency (antithrombin, proteins C and S).

An abnormal APC resistance was found and DNA analysis showed in the two cases the factor V Arg506→Gln mutation. The family study, made in one case, showed the same genetic disease in one of the relatives.

Conclusion: APC-resistance with factor V gene mutation should be sought for in patient family study and anticoagulant treatment are justified for symptomatic patients.

**1319 | Leukocytapheresis As New Therapy for Ulcerative Colitis**


Major inclusion criteria for leukocytapheresis (LCAP) therapy were active clinical condition and active disease stage shown by endoscopic findings, and either insufficient response to conventional therapy, allergic or severe side effect reactions to drug therapy or severe symptoms with no prior treatment by medication. Informed consent was obtained from all patients prior to their entry into the study. LCAP was performed with the Plasauto 1000 apheresis unit equipped with a Cellsorta (Aiki Medical Co., Ltd, Tokyo), leukocyte removal filter. LCAP was administered five times at 1-week intervals in 5 weeks of intensive therapy and 5 times at approximately 1-month intervals during approximately 5 months of maintenance therapy, for 30 patients with UC. We classified the response to the LCAP as: 1) excellent, colonoscopic endoscopy and clinical manifestations showed complete remission of disease, 2) moderately improved, endoscopy and clinical manifestations showed improvement but not remission, 3) no change, and 4) deterioration. Furthermore we evaluated the level of cytokines in culture supernate produced by patients’ mononuclear cells stimulated with Con A (IL2, IL4, IL6, IFNa, and IFNb) or by patients’ monocytes stimulated with LPS (IL1 and ILB). Clinical and blood examinations showed no side effects in, any cases. Clinical improvement was recognized in 24 of 30 patients (80%) including 8 with dramatic responses during the intensive therapy, and continued throughout the maintenance therapy in 23 patients (76.7%). The concentrations of the cytokines were compared between effective and ineffective group. The concentration of TNFa before LCAP in the effective group was higher than that of ineffective group and after LCAP was not observed. It was decreased to normal range after both intensive and maintenance therapies. In the effective group, the concentrations of IL1α after both intensive maintenance therapies and ILB after maintenance therapy were decreased, however, the concentrations of IL6 and IL10 intensities were maintained. However, increased IL6 at the very low levels was observed in patients with repeated dosage, and the levels were decreased with the number of LCAP therapy.

**1320 | Hepatic Resection for Synchronous and Metachronous Metastases from Colorectal Cancer**

H. Kagure, Y. Omori, K. Monma. Department of Surgery, Dokkyo University School of Medicine, Tochigi, Japan

Purpose: Hepatic metastases are fatal and the mean expected survival time for those patients is estimated to be less than one year. Surgical excision is now considered the only potentially curative approach. We review our results of hepatic resections for metastases from colorectal cancer.

Materials and Methods: Since 1982, a total of 39 hepatic resections were performed in 36 patients with hepatic metastases. Of these, 26 patients had colorectal carcinoma in one or more sites. There were synchronous metastases in 16 patients and metachronous metastases in 10. The age of the patients ranged from 28 to 73 years (a mean of 55.5 years). There were 16 men and 10 women. The primary tumor was cancer of the colon in 11 cases and cancer of the rectum in 15. The hepatic lesions were solitary in 13 cases and multiple in 14. Ten patients underwent metachronous hepatectomies. In metachronous metastases, the time between the excision of the primary lesion and hepatectomy ranged from 2 to 43 months. In 16 patients with synchronous metastases we carried out synchronous resec-
tions of metastases and the primary tumor in 12 (75%). The operative pro-
cedures comprised ten right lobectomies, five wedge resections of the liver, five lateral segmentectomies, two extended right lobectomies, two left lobec-
tomies, two right middle and left segmentectomies and one extended left lobectomy.

Results: Twenty-five patients survived the operation and one patient died (operative mortality: 3.8%). Postoperative complications were minimal except for hepatic failure. Twelve patients were completely alive with the survival time ranging from 11 to 76 months. Fourteen patients died between five months and 34 months. Survival rate at five years are 22%.

Conclusions: Hepatic resection for colorectal metastases is an accepted therapeutic option in selected patients. Even synchronous metastases, combined synchronous resection of hepatic metastases and the primary tu-
mor can be tolerated and should be the treatment of choice.

1321 In Duodenal Ulcer (DU) Patients, does Duodenal Gastric Metastasis (DGM) Depend on Ulcer Activity, Ulcer Shape or Duodenal Bulb Morphology? D. Popas1, C. Vissuzanne1, I. Sobhan1, Th. Vallet1, M. Mignon1, CHU Bichat, 75077 Paris Cedex 16

To establish the prevalence, location and extent of DGM in DU disease, 48 consecutive pts (30 with healed DU (HDU), 18 with active DU (ADU) were prospectively studied.

Method: Multiple pinch biopsies: median 8 (range 4–12) were taken from the 4 walls (W) of the mid first duodenum (antero (AW) posterior (PW), su-
perior (SW) and inferior (IW)). 2–3 additional biopsies were taken from the ulcer scar (US) or ADU margins and 2–3 from antral mucosa. PAS (DGM) and Giemsa (HP) colorations were performed. HDU pts were divided in 3 groups (G I: 14 pts with visible scar in deformed 1st duodenum; G II: 7 pts with deformed duodenum only; G III: 9 pts with normal duodenal shape).

Results:

<table>
<thead>
<tr>
<th>DGM</th>
<th>MPSA<em>DGM</em></th>
<th>Location (%)</th>
<th>HP+-/HP-</th>
<th>DGM+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDU total</td>
<td>16/14</td>
<td>21.9 ± 18</td>
<td>0/0</td>
<td>8/8</td>
</tr>
<tr>
<td>G I scar site</td>
<td>14/0</td>
<td>23.3 ± 5</td>
<td>100 US</td>
<td>7/7</td>
</tr>
<tr>
<td>extra US</td>
<td>5/9</td>
<td>18.8 ± 7</td>
<td>100 AW</td>
<td>4/1</td>
</tr>
<tr>
<td>G II</td>
<td>2/5</td>
<td>10</td>
<td>100 AW</td>
<td>3/2</td>
</tr>
<tr>
<td>G III</td>
<td>0/9</td>
<td>0</td>
<td>100 US</td>
<td>3/6</td>
</tr>
<tr>
<td>ADU total</td>
<td>18/0</td>
<td>32 ± 6</td>
<td>100</td>
<td>1/62</td>
</tr>
<tr>
<td>– 4 salami</td>
<td>4/0</td>
<td>47.4 ± 14**</td>
<td>100</td>
<td>6/8</td>
</tr>
<tr>
<td>– 10 tender</td>
<td>10/0</td>
<td>39 ± 5</td>
<td>100</td>
<td>6/8</td>
</tr>
<tr>
<td>– 4 linear</td>
<td>4/0</td>
<td>25 ± 8</td>
<td>100</td>
<td>6/8</td>
</tr>
<tr>
<td>– extra U sites</td>
<td>10/8</td>
<td>23.9 ± 5.3</td>
<td>100 AW</td>
<td>8/2</td>
</tr>
</tbody>
</table>

*Proportion of biopsied surface involved with DGM.

Conclusion: Prevalence of DGM was (%) 100 in ulcer margin and visible scars, 55 in extra ulcer sites in HDU (G I), 28 in deformed duodenal bulb without visible scar (G III), 0 in normal duodenal bulb (G III). Whatever the HP pattern, DGM extent was the largest in ADU notably at the margins of salami type ulcer (p < 0.05** vs all other DU categories).

1324 Systemic Lupus Erythematous (SLE) and Chronic Intestinal Pseudoobstruction (CIPO)

G. Perlemuter1, S. Cheussadade, M. Dapoigny, B. Wechsler, P. Godeau, A. Kahan, D. Couturier. Service de gastroentérologie, Hôpital Cochin-Paris, Clermont-Ferrand, Service de médecine interne, Hôpital de la Pitie, Paris, France

CIPO is a syndrome characterized by clinical features such as episodes of subocclusion, diarrhea, and weigh loss. Gastrointestinal manifestations as nausea, vomiting and abdominal pain are common in SLE patients. Intra-
abdominal vasculitis and chronic diarrhea are rare but life-threatening com-
lications of SLE. The aim of this study is to describe the clinical and man-
ometric features of 5 patients with CIPO and SLE.

Methods: 5 women (mean age: 33 years [19–39]) has been referred to our center for small bowel or antro-duodenal (AD) manometry. Vomiting, diar-
rhoea, intestinal obstruction and intestinal distension were present in respec-
tively 5, 4 and 3 cases. SLE was known in 3 cases (1, 7 and 11 years). In the 2 cases of CIPO revealing SLE, kidney biopsy ascertained the diagnosis. Bilateral hydrenephrosis and hydroureter associated with reduced bladder volume was seen in 4 cases. Antinuclear, anti-ENA and anti ENA titrab-
ies were + in 4, 2 and 2 cases. Manometry was performed during fasting state (3 hours), during post prandial state (n = 4) and after pharmacological stimulation (somatostatine 100 µg SC, n = 2, trametidine 100 mg IV, n = 2. erythromycin n = 3).

<table>
<thead>
<tr>
<th>Case No.:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weig loss (kg)</td>
<td>25</td>
<td>50</td>
<td>18</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Oesophageal manometry LES (P IN &gt; 14 cm H2O)</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Wave amplitude (N &gt; 45 cm H2O)</td>
<td>16</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anastomosis DGM</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phase 3/3 hour</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Integraditive pattern</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
</tr>
<tr>
<td>Post prandialpattern</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
<td>Hypo</td>
</tr>
</tbody>
</table>

ND = Not done, N = Normal, Hypo = Hypomotility

Perenteral nutrition was necessary in 5 cases. One patient died: post-
mortal examination showed cerebral and gastro-intestinal vasculitis. Under
steroid therapy, a complete (n = 3) or partial remission (n = 1) was seen.

Conclusions: (1) CIPO can complicate or reveal SLE. (2) Renal or urinary
tract abnormalities (intestinal cystitis or obstructive uropathy) are suggestive of CIPO during SLE. (3) SLE is a reversible cause of CIPO.

1329 Intestinal Manifestations during Antibiotic Treatments

Parenteral nutrition was necessary in 5 cases. One patient died: post-
mortal examination showed cerebral and gastro-intestinal vasculitis. Under
steroid therapy, a complete (n = 3) or partial remission (n = 1) was seen.

Conclusions: (1) CIPO can complicate or reveal SLE. (2) Renal or urinary
tract abnormalities (intestinal cystitis or obstructive uropathy) are suggestive of CIPO during SLE. (3) SLE is a reversible cause of CIPO.

1331 Ileal Absorption and Distribution of Bovine [15N]-Labelled Milk Nitrogen in Humans

C. Bos, S. Mehall, R. Benamoujz, C. Luengo, N. Gaussen, J. Rartauere, D. Tomé, INFRA, UNHP, Paris, France; Hôpital Avicenne, Bobigny, France

The aim of this study was to estimate true-digestibility and excretion of milk proteins. After fasting overnight, 6 healthy volunteers with an ileal tube were given an intake of 480 ml of [15N]-labelled milk (182.4 µmol of nitrogen). Ileal effluents and urine were collected for a period of time of 8 and 22 hours, respectively. The samples recovered in the ileum and urine were analysed by isotopic mass spectrometry for [15N]milk ratio to discriminate between exogeneous [15N]-milk and endogenous (unlabelled) nitrogen origins:

<table>
<thead>
<tr>
<th>Ingested</th>
<th>Nitrogen recovered</th>
<th>Digestibility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>182.4</td>
<td>44.6 ± 12.8</td>
</tr>
</tbody>
</table>

The amounts of exogenous nitrogen recovered in 480 minutes in the ileal effluent samples showed that net oro-ileoabsorption of milk was 91.8%. The urinary exogenous nitrogen excretion during the 22 hours following [15N]-labelled milk intake reached 44.2 ± 6.8 mmol, made up of 41.8 ± 6.4 mmol of urea (94.8 ± 8.9% of exogenous excreted nitrogen) and 0.55 ± 0.26 mmol of ammonia (5.4 ± 3.6%). Since urinary excretion of exogenous nitrogen represented 24.2 ± 3.7%, milk nitrogen deposition is estimated at 67.6 ± 3.7% of the ingested nitrogen. These results show the high digestibility of milk proteins at the ileal level as well as the good deposition occurring in the 22 hours following the ingestion.

1334 Prognosis of Cirrhotic Patients in Intensive Care Unit

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Introduction: Increase in ICU mortality among patients with cirrhosis is an established fact. However, existence of risk factors for mortality in this popu-
lation has not been yet studied. We primarily intended to create a prognostic score applied to mortality of cirrhotic patients in ICU and thereafter to validate this score in a prospective group.

Gut: first published as 10.1136/gut.37.Suppl_2.Pt_2.A121 on 1 January 1995. Downloaded from http://gut.bmj.com/ on September 15, 2023 by guest. Protected by copyright.
Patients and methods: 78 successive patients (study 1), with a proved cirrhosis were included in the first study (medical admission; n = 50, surgical: n = 28; P < 0.001; P = 0.03, C = 0.37), who needed 118 clinical, bi- ological and therapeutic parameters during the first 24 hrs. We performed an univariate analysis of each parameter concerning ICU mortality (Student t-test and Chi square test p < 0.01) then a multivariate regression among the previous significant ones to compute a score. We validated this score in the following 83 cirrhotic patients (study 2) ad- mitted in ICU. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), and well classified patients (WCP) were analysed from this score.

Conclusion: We define in this study a score made of 3 ordinary parame- ters registered at admission and linked with a high rate of mortality in ICU cirrhotic patients. This simple score may be kept in mind for admission of such patients on ICU.

1335 Food Intolerance — The Effect of Food Challenge E. Kettang 1, M.B. Jacobsen 2, L. Foss 2, A. Levik 2, M.H. Vatn 2, 1 Med. Dept. VSS, Tonsberg, 2 Dept. VSS, Rikshospitalet, Oslo, Norway

Double blind food challenge (DBFC) is partly based on subjective symptoms. In patients with typical allergic reactions, RAST and skin prick tests may be of great help in the verification of an antibody reaction, whereas more heter- eogenous mechanisms have been suggested for the majority of patients with food intolerance. Based on the hypothesis that a subgroup of these pa- tients may demonstrate objective signs of intestinal hypersensitivity, the fol- lowing tests were introduced in an open rechallenge of patients with previous gastrointestinal symptoms after intake of milk and wheat, relieved by a diet based on the confirmatory results of a previous DBFC: Urinary S1C/EDTA ex- cretion combined with lidoxanol, a new water soluble radiographic contrast medium, intestinal transit time by H-breathe test after lactulose and radi- ographic measurements with lidoxanol, measurements of cellular markers as eosinophilic cationic protein (ECP), tryptase and serotonin in fecal dialysate. ECP was also measured in serum. These assays were performed before and after 2 weeks of normal diet provocation. Patients symptoms were recorded on VAS. A small intestinal biopsy was taken by a telemetric capsule in three of the patients.

In the 6 patients, 5 women and one man, age 39–63 years, the average symptom score increased from 2.1 (SD 1.1) to 4.7 (SD 4.6). No significant ef- fects were seen on urinary excretion of S1C/EDTA or lidoxanol, on transit time measured by H-breath test or on ECP tryptase or serotonin levels in fecal dialysate. ECP in serum, which was increased above the reference limit in 5 of 6 patients (p = 0.05) by an average of 82.5 per cent, was reduced in 5 of 6 individuals (p = 0.05) by an average of 91 per cent after diet provocation. The small intestinal biopsies from three patients showed normal histology and immune histochemistry.

In conclusion, an open challenge in patients with an adverse reaction to milk and wheat had no effect on small bowel permeability, small bowel transit- time or fecal markers of cellular sensitivity. The serum levels of ECP with a reduction after provocation may suggest an activation of eosinophilic cells in these patients and a binding of activated eosinophils in circulation to the intestinal structure.

1336 Hemodynamic Effects and Evolution of Biological Parameters Following Perfusion of Allografted After Liver Transplantation J.M. Sab, C. Ract, Y.Q. Lab, J.L. Gaudin, D. Robert, C. Ducert 1, 1 Intensive Care Unit, Hospital de la Croix Rousse, Lyon, France, 2 Transplantation Surgical Unit, Hopital de la Croix Rousse, Lyon, France

Introduction: prostaglandin treatment was proposed in primary liver graft dys- function. Apart from primary nonfunction that requires retransplantation, a less se- vere graft dysfunction exists. It is revealed by a delayed decrease in serum transaminases, or by an early level of serum transaminases that is unusu- ally high. We study the hemodynamic changes and transaminases evolution following prostaglandin treatment (PG E1).

Patients and methods: we analysed 10 patients (6 males, 4 females) who underwent liver transplantation (alcoholic cirrhosis: 5, chronic active hepati- tis C: 2, autoimmune hepatitis: 2, fulminant hepatitis: 1). Immunosuppres- sive regimen included corticosteroids and cyclosporin (9) or FK506 (1) and was given immediately posttransplant. PG E1 infusion was started from 4 to 65 hours postoperatively (33.9 ± 16 hour). The infusion was begun at 0.21 μg/min/kg after bolus administration of 2 μg/kg (0.73 ± 0.58 μg/kg) and contin- ued for 1 to 8 days (4.2 ± 2.9 days). Liver function and hemodynamic profile were analysed every 8 hours, 24 hours before treatment until 48 hours after beginning; then every day until 5th day.

Results: There were no significant effect of liver dysfunction for 2 patients who needed retransplantation within 24 hours. The other 8 patients showed an improvement of enzymatic profile. ASAT significantly decreased at 16 hr (HO: 1165 ± 1150 U/l, M: 779 ± 680 U/l, p < 0.01, p paired test) as ALAT did at 32 hr (HO: 1085 ± 680 U/l, M: 164 ± 300 U/l, p < 0.05). This transam- inase kinetics is reproducible for all patients during the first 24 hours postPG E1 (r = 0.87, p < 0.05). No other parameter of liver function showed signifi- cant variation, neither cholesterol enzymes nor coagulation profile. Concern- ing hemodynamic profile, alprostadil seems to reverse liver cy- tolysis if introduced within 3 days postoperatively. Consequential effects of this treatment are not yet known according to rejection incidence and in- fectious complications, and need a further evaluation.

1337 Colonization of Human Lactobacillae and Bifidobacteriae in Patients Operated With ileoanal Pouch (IPAA) K.O. Laak 1, M.B. Jacobsen 1, A. Bjørneklett 1, T. Midtbø 2, E. Lungaas 1, T. Høvig 1, A. Axelsen 1, E. Jensen 1, A. Bakka 1, M.H. Vatn 1, 1 Med. Path., 2 Dept. Surg. Intl., Rikshospitalet, Oslo, Norway, 2 Dept. Karolinska Hosp., Stockholm, Sweden

Changes in the bacterial microflora may play an important factor in gastroin- testinal diseases. It has been suggested that human Lactobacillus and bifi- do bacteriae may stabilize the human microflora. The purpose of the present study was to see if ingestion of a fermented milk product containing live lac- tobacilli and bifidobacteriae (Cultura) would influence the ileo micro flora in patients with IPAA.

Ten patients, 3 males and 7 females, age 15 to 46 years, operated with colectomy and IPAA for ulcerotic colitis more than one year ago volunteered for the study. Two of the patients had minor complaints but none of them had clinical pouchitis. The number of daily soft stools varied between 2 and 15. The patients ingested 500 ml/d of Cultura for one week. Stools samples were collected before and after one and two weeks for selective cultures of lacto- bacilli and bifidobacteriae, as well as for analysis of short chained fatty acids (SCFAs), mucin degradation, urobilinogen, coproporphyrin, beta-sapta glycine and free tryptic activity (FTA). Breath hydrogen (H2) and methane (CH4) were quantitated after ingestion of 20 g lactulose at start and after one week. In addition the patients were examined endoscopically.

Five of the 10 patients reported on significantly reduced number of stools and improved consistency after ingestion of culture. The number of lacto- bacilli at start was 6.5 ± 10.8, 5 ± 10.4 to 2 ± 10.8 (median + range), in- creased significantly after one week to 2 ± 10.8, 1 ± 10.7 ± 10.8 (median + range), and was after 2 weeks still significantly above the baseline level, 2 ± 10.7, 4 ± 1.0 to 1 ± 10.9 (median + range). Bifidobacteria also increased significantly from the baseline level, 4 ± 10.8, 2 ± 10.4 to 9 ± 10.7 (median + range) to 6 ± 10.8, 9 ± 10.6 to 2 ± 10.9 (median + range) after one week, but was reduced to base line after 2 weeks. No significant change occurred in FTA and urobilinogen. None of the patients had beta-sapta-glycin. Only one patient converted cholesterol to coprostanol, and did so in all 3 samples. Mucin degradation occurred in 6 patients. SCFAs formation in stool, SFAs and breath excretion of H2 occurred in all but one patient and did not change significantly after ingestion of Culture. None of the patients excreted breath CH4. Histology revealed various degrees of inflammation from atro- phy to moderately increased cellularity, and no signs of bacterial growth was seen at electron microscopy from endoscopical biopsies.

In conclusion, the significantly increased content of lactobacilli and bifi- do bacteriae and the sustained elevation of lactobacilli in stools after inges- tion of Cultura may suggest an ability for intestinal culture formation. The clinical significance of the present results will have to be examined in further studies.

1338 Infection in Liver Transplantation: Evolution of Infectious Organisms and Influence on Outcome O.V. Lé, J.M. Sab, J.L. Gaudin, C. Ract, D. Robert, C. Ducert 1, 1 Intensive Care Unit, Hospital de la Croix Rousse, Lyon, France, 2 Transplantation Surgical Unit, Hospital de la Croix Rousse, Lyon, France

Introduction: since first studies describing infection in liver allografts recip- ients, microbial organisms isolated changed with evolution of peroperative care. This study describes the incidence of pathogens identified in infectious sites among liver recipients, and their effect on outcome.

Patients and methods: we retrospectively analysed 104 consecutive pa- tients who underwent liver transplantation between december 1991 and june 1994. Perioperative antibiotic prophylaxis (pipercillin, ofloxacin, metronida- zole) was systematically given intravenously before the first 48 hours and oral- selective bowel decontamination (tobramycin, polymixin B, amphotericin B) was performed for 3 weeks. Standard immunosuppressive regimen included cyclosporine or OKT3 and corticosteroids. Rejection was treated by corticos- teroid boluses or OKT3. The rate of infection, the timing and associated mor- tality of pathogens were ascertained.
The incidence of infection occurred in 45% (n = 47) of all patients following transplantation. 31% (n = 32) of this population had an infectious event within the first month post transplantation (early infection). 36% (n = 37) of them had an infection within the second month (late infection). Gram positive organisms (staphylococci) are essentially isolated in early stage of transplantation (47%). In a later period, we mainly isolated viruses (61%), especially CMV. The incidence of pathogens is significantly different between early and late infection.

### Pathogen

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Early infection</th>
<th>Late infection</th>
<th>p (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram + cocc</td>
<td>47%</td>
<td>9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gram - bacillus</td>
<td>22%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fungi</td>
<td>15%</td>
<td>3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>11%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Virus</td>
<td>5%</td>
<td>61%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The incidence of infection is different according to patient's survival.

### Conclusion

If compared to previous studies, pathogens involved in infection of patients who receive liver allografts shifted from gram negative bacilli to gram positive cocci, probably because of antibiotic prophylaxis. Moreover, early infection seems to affect more significantly outcome than late infection does.

1341 Lansoprazole 15 and 30 mg daily in long-term treatment of erosive reflux esophagitis


Lansoprazole 30 mg daily has been found to be effective in acute healing of erosive reflux esophagitis. In this single center, double blind randomised study, 118 patients with erosive reflux esophagitis, were given lansoprazole 30 mg daily for 12 weeks, and if endoscopically healed and asymptomatic at that time, randomized to treatment with either lansoprazole 15 mg or 30 mg o.m.. Endoscopy was repeated after 3, 6 and 12 months of maintenance treatment. An endoscopic relapse was defined as reappearance of grade 1 or more severe reflux esophagitis. 118 patients were included in the initial healing phase and received lansoprazole 15 mg daily. 52 patients received lansoprazole 30 mg daily.

At the end of the 12 months maintenance period, 13 patients (27.1%) receiving lansoprazole 15 mg daily had experienced a relapse of endoscopically verified reflux esophagitis, compared to eight patients (15.4%) treated with lansoprazole 30 mg daily (n.s.). A life table analysis showed no statistically significant difference between the two groups. In the 15 mg group, 70.8% were kept in symptomatic remission, compared to 84.6% in the 30 mg group. 81 patients experienced at least one adverse event, 77.1% of patients receiving lansoprazole 15 mg, compared with 84.6% of patients receiving lansoprazole 30 mg (n.s.).

Conclusion: Lansoprazole proved to be safe and effective maintenance treatment for reflux esophagitis, as both 15 mg and 30 mg daily kept the majority of patients in endoscopic and symptomatic remission. No statistically significant differences were found in endoscopic relapse, symptomatic relief or occurrence of adverse events.

1342 Interleukin 6 (IL6), Interleukin 6 Soluble Receptor (IL6sR), and Interleukin 1 Receptor Antagonist (IL1ra) Plasma Concentrations in Crohn’s Disease

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The aim of this study was to analyse the connections between the plasma concentrations of three proteins (IL6, IL6sR and IL1ra) and: 1) the clinical course of the disease; 2) erythrocyte sedimentation rate (ESR), C reactive protein (CRP), alpha 1 acid glycoprotein (AGP) and platelets; 3) the medications taken by the patients.

Methods: Serum levels of IL6, IL6sR and IL1ra were measured by an immunoenzymometric assay in 94 patients with Crohn’s disease (CD) 58 female and 36 male, mean age 34 years (n = 3) and 20 healthy volunteers. Disease activity was assessed by the Harvey Bradshaw index (HBI): 44 patients were in relapse (HBI > 3) and 50 in remission (HBI < 4).

### Results (mean ± SEM):

<table>
<thead>
<tr>
<th>Active</th>
<th>Inactive</th>
<th>Cortic. +</th>
<th>Cortic. -</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6 (pg/ml)</td>
<td>60 ± 8</td>
<td>50 ± 4</td>
<td>53 ± 5</td>
<td>71 ± 8</td>
</tr>
<tr>
<td>IL6sR (pg/ml)</td>
<td>77 ± 5</td>
<td>62 ± 5</td>
<td>75 ± 9</td>
<td>83 ± 9</td>
</tr>
<tr>
<td>IL1ra (pg/ml)</td>
<td>902 ± 283</td>
<td>545 ± 154</td>
<td>616 ± 225</td>
<td>549 ± 194</td>
</tr>
</tbody>
</table>

The differences are significative 1) between controls and patients with the three proteins; 2) between active and inactive patients for IL6 and IL1ra, but not for IL6sR, 3) between those with and without corticosteroid therapy for IL6 alone.

IL6 and IL1ra, but not IL6sR, are weakly (r < 0.5), but significantly, correlated to the HBI, the ESR, and CRP and AGP levels. There is no connection with white cell levels.

Conclusions: IL6 and IL1ra levels rise according to the clinical and biological activity of the disease, in contrast to the IL6sR, which increases independently of the disease activity in CD. Patients with corticosteroid therapy have diminished IL6.

1345 Patients with Symptomatic, Uncomplicated Gallstone Disease: Exhibit Findings Similar to Functional Dyspepsia. Volume Measurements Using Three-dimensional Ultrasonography

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Cholecystectomy in patients with uncomplicated gallstone disease is not always successful, as some patients still experience symptoms in the upper abdomen after the operation. We investigated gallbladder size, antral size, and symptoms in response to a standardized meal in 18 consecutive patients with symptomatic, uncomplicated cholecystolithiasis (GB). Methods: Volumes of the gallbladder and the gastric antrum were estimated with three-dimensional (3D) ultrasonography fasting and 10 min after ingestion of 500 ml meat soup. A mechanical ultrasound scanner (Vingmed Sound), coupled to a stepping motor, tilted the transducer through an angle of 80° while recording a total of 81 images. Volume estimation was performed digitally after interactive manual contour tracing and organ reconstruction in three dimensions. The results were compared with those obtained similarly in 17 patients with functional dyspepsia (FD) and 18 healthy subjects (C). Results: No significant differences in fasting gallbladder volumes (GB: 18.9 ml; FD: 16.2 ml; and C: 17.2 ml) or gallbladder emptying (GB: 25.3%; FD: 18.0% and C: 28.8%) between groups were found. Antral volumes both fasting (p < 0.05) and postprandially (p < 0.01) were wider in GB and FD than in C. The soup induced dyspeptic symptoms in 12/18 (67%) GB, in 15/17 (88%) FD, and in 2/18 (11%) C (p < 0.001). None of the gallstone patients experienced typical biliary pain in response to the soup. Conclusion: In symptomatic, uncomplicated gallbladder disease the size of the gallbladder and gallbladder emptying did not differ significantly from FD patients or healthy controls (C). However, such patients (GB) are similar to FD patients characterized by wide gastric antrums and dyspeptic symptoms in response to ingestion of meat soup. Thus, a part of the symptomatology of symptomatic, uncomplicated gallstone disease may be due to functional dyspepsia.

1346 Five Year Follow Up of 181 Consecutive Patients with Reflux Esophagitis

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Data on the natural course of erosive esophagitis are sparse. The purpose of this study was to precise symptoms on long term and to identify prognostic parameters.

The files of the 286 consecutive patients seen in 1987 recorded on computer were retrieved. There were 196 men and 90 women, with a median age of 57 years (range: 16-90). Ninety per cent had reflux symptoms (heartburn and/or regurgitation). Esophagitis was graded according to the Savary-Miller’s classification. The endoscopic grading was 1 in 80%, 2 in 9.5%, 3 in 5.5% and 4 in 5% (11 deep ulcer, 4 peptic stricture). The patients were interviewed by phone according to a standardized questionnaire by an experienced gastroenterologist (GB) 57 to 77 (mean: 64) months after diagnosis of erosive esophagitis. Thirty (10%) patients were lost, 75 (26%) had died and all causes of death were identified. In 17 (6%) patients antireflux surgery had been performed and 2 of them had died postoperatively. Only these 2 deaths were related to esophageal diseases. Data on the course of the disease could be obtained in 181 patients. In 48% of them the symptoms had completely disappeared, 38% considered their symptoms to be improved and 14% had the same or worse symptoms compared with the initial investigation. None declared symptoms to be worse and none complained of the occurrence of dysphagia. One hundred three (57%) of the remaining 181 patients had stopped medication, 78(43%) continued on medication of whom 58 (74%) on demand and 20 (26%) regularly. The drugs were mostly antacids and/or alginate. Less than 10% of the patients required antisecretory drugs.
Age, sex, the presence of a hiatus hernia and the grade of oesophagitis at initial endoscopy had no influence on the course of the symptoms. In conclusion, the long term outcome of erosive oesophagitis seems to be better than previously reported. More than half of the patients were im-
proved or completely relieved at 5 years without taking drugs any more. A large majority of patients under treatment used the drugs required to relieve their symptoms and we did not observe any complication of the disease.

Prevalence of anti-HCV antibodies in thyroid autoimmune disease has been diversely evaluated and controversy exists as to the pathogenic effect of HCV in TAIID. In contrary, many studies have reported a high prevalence of thyroid autoantibodies in CHC patients. The aims of our study, conducted between february 1994 and february 1995, were: 1) to assess the prevalence of anti-
HCV antibodies in consecutive patients referred to endocrinology or nuclear medicine unit for thyroid investigation and identified as affected by autoim-
mune thyroiditis (study 1); 2) to assess the prevalence of thyroid autoantib-
odies in all patients with thyroid autoimmune (Hashimoto) C patients admitted to the gastroenterological unit before interferon therapy (study 2).

Material and method — Study 1: The criteria for diagnosis of TAIID were: a) positive direct and indirect (Ab > 1000 U/ml or Ab > 150 U/ml/RIA or Ab > 15 U/ml/RIA TRAX assay). The detection of anti-
HCV Ab was performed by Elisa second generation (Abbott) and third gen-
eration (Orthodiagnostic systems). The study was: 1) initially retrospective in 140 consecutive patients fulfilling the inclusion criteria. The sera were collected and stored at −20°C, from january 94 to april 94. Among them, 81 were affected by autoimmune thyroiditis and 59 by Graves disease. 2) Then prospective in 59 patients admitted consecutively from may 15 to june 30 1994 (28 patients) and from july 01 to august 31 (31 of Graves disease). Study 2: a prospective study was conducted to assess the prevalence of thy-
roid autoantibodies (thyroglobulin and thyroid microsomal autoantibodies) in 52 CHC patients admitted to the hepatogastroenterological unit (37 men and 15 women; median age = 41 yr; range = 16-76 yr) before interferon therapy. Antibody to hepatitis C virus was detected with a second-generation enzyme immunoassay and then confirmed with recombinant immunoassay kit. Preva-
ence of chronic hepatitis C was confirmed with histological study of liver biopsy from all patients.

Results — Study 1: Anti-HCV Ab was detected in 199 patients with TAIID. Study 2: Two patients (3.8%) had thyroid autoantibodies. Among them, one had high titers of thyroid autoantibodies and had hypothyroidism.

Conclusions: This study doesn’t suggest a central pathogenic role for HCV in TAIID and shows that prevalence of thyroid autoantibodies is identical in chronic hepatitis C patients and in general population, suggesting no associ-
ation between chronic hepatitis C and prevalence of thyroid autoantibodies.

Insights into Stomach Mechanisms from Concurrent Gastric Ultrasonography and Manometry

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Gastric wall motion, sequencing of active luminal apposition, and intraluminal pressures are all believed to be major determinants of flow within and from the stomach. We have monitored these variables simultaneously in 6 healthy subjects (A.M, 2 F) for the first time by concurrent antropylorodu-
odenal manometry and transabdominal ultrasound. A 5 MHz sector transducer was positioned on the abdomen to image the antrum in longitudinal section from the pylorus to approx. 10 cm oral. A multilumen sleeve/side hole mano-
metric assembly was placed astride the pylorus and its position monitored ultrasonically with the acoustic shadow of two metallic rings fixed around the manometric assembly 3 and 5 cm above the sleeve (distal antrum). After subjects drank 500 ml of clear meat soup (20 kcal, 37°C), ultrasound im-
ages were stored on a video tape and synchronized with digitized pressures. Results: Within a 60 minute time period, satisfactory simultaneous record-
ings were obtained for 16 min/subject (12-26 min). Images were analysed independently by two radiologists. The time of occurrence of ACs at the marker and the onset of contraction at the corresponding side hole with variation 0.57 sec, SD 2.56 sec). Of a total of 276 ACs seen by ultrasound, 170 were recorded by manometry (p = 0.05). Only 6 PWs recorded by manometry, 96% of ACs appeared propagated on the ultrasound display (95% interobserver agreement). 77% of propagated ACs classified by ultrasound, appeared propagated by manometry (p < 0.05). ACs were evaluated as either lumen-occlusive or non lumen-occlusive (>90% interobserver agreement). 80% of all PWs were produced by lumen occlusive ACs. Conclusions: Concurrent ultrasound and manometry is feasible. A wide range of motility patterns were observed. Good agreement can be obtained with low interobserver variability. The two methods of measurement give dif-
ferent information about gastric motor function. Used in combination they should be effective in improving understanding of gastric mechanics in hu-
mans.

Peritoneal Carcinomatosis (PC) during the Course of Digestive Endocrine Tumors (DET)
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PC is considered as exceptional during the course of DET; the aims of this study were to determine its prevalence, symptoms and prognostic value. Pa-
ients and methods: 116 consecutive pts (86 M, 48 F, mean age 55 ± 14 years) with DET seen between January 1991 and December 1993 were followed during 44 months (median; range 1-348) 59 pts had gastrinomas (37% with liver metastases (LMI), 30 pts had carcinoids (90% with LM) and 20 pts had other DET (non-secretant pancreatic tumors: 17; secreting pan-
creatic tumors: 8; LM: 74%). The diagnosis of PC was regarded as certain if PC was seen during laparotomy, or in the presence of ascites containing tu-
mor cells, associated with suggestive anomalies on CT scan (ie. peritoneal nodules or masses). PC was highly probable in the presence of ascites with-
out tumor cells and metastasis in the liver (LM: 3). PC was considered 29 months (median) after the diagnosis of DET and was associated with LM (82%), lymph-node metastases (70%) and various other metastases (45%). No deaths related to PC were recorded, while 5 pts died due to LM progression. Conclusion. PC is more frequent than previously known in pts with carcinoid tumors and pan-
creatic endocrine tumors apart from gastrinomas; it is not observed in pts with gastrinomas. Such variations could be accounted for by differences in tumor-cell metastatic potential in the various tumor subtypes. PC has little prognostic implication as compared with LM.

Scintigraphic and Ultrasound Measurement of Gastric Emptying — Relationship to Appetite

K. Hveem, K. Jones, M. Horowitz, B.E. Chatterton. Med. Dept., Inherited Hospital, Leavenger, Norway; Depts. Medicine and Nuclear Medicine, Royal Adelaide Hospital, Adelaide, Australia

Introduction. Scintigraphy can measure gastric emptying (GE) and intragas-
tric meal distribution, but is associated with exposure and requires expensive equipment. The use of ultrasound to evaluate GE therefore has advantages over scintigraphy. The absence of a strong relationship be-
tween postprandial appetite and GE, suggests that other mechanisms, such as neural distension, may contribute to satiation. We have evaluated the relationship between ultrasonographic measurements of antral area and (i) scinti-
ographic measurements of total stomach emptying and intragastic distribu-
tion of liquids (ii) postprandial satiation. Materials. 7 normal volunteers (aged 20-27 yr) drank 350 ml of 20% dextrose (280 kcal) or beef soup (20 kcal), both labeled with 20 Mbq 99m sulphur colloid on separate days (and in randomised order) while sitting in front of a gamma camera. The amount of isotope in the total (T50), proximal and distal stomach was derived. Ultra-
sound measurements of antral area were made with a 5.0 MHz sector scan-
ner placed at the umbilical region immediately before meal ingestion and subsequently at 15 min intervals for 180 min or until 90% had emptied from the stomach. Postprandial antral areas were expressed as a % of maximum and the time when antral area had decreased by 50% (T50) was calculated. Satiation (fullness) was evaluated by a visual analogue scale. Results. Scinti-
graphic and ultrasonographic T50’s were comparable and much longer (p < 0.001) for dextrose than soup (dextrose 107 ± 16 min vs 108 ± 18 min; soup 24 ± 4 min vs 23 ± 5 min) and there was a close correlation between them (dextrose r = 0.94, p < 0.005, soup r = 0.97, p < 0.001). There was also a close correlation between the T50 for the distal stomach measured scinti-
ographically and ultrasonographically 1 T50 < 0.001). Fullness increased after dextrose (p < 0.05), but not soup. The score for fullness at 15 min was closely related (r = 0.92, p < 0.01) to the postprandial increase in antral area measured by ultrasound, but not to ultrasonographic measurements of the proximal stomach. Conclusions. We conclude that ultrasound measurements of gastric emptying are: (i) of com-
parable sensitivity to scintigraphy in measurement of emptying of low and high nutrient liquids (ii) correlate closely with postprandial satiation suggest-
ing that the latter is mediated by antral distension.
Toxicity was superior in arm A than in arm B: 41 pts (21.5%) experienced grade 3–4 toxicities in arm A against 18 pts (9.2%) in arm B, p = 0.0004. Grade 3–4 toxicities were in arm A versus B: neutrophils 7.9% vs 2%, diarrhoea 4.7% vs 3.1%, mucositis 2.9% vs 1.5%, pectins angina 0.5% vs 1.5%. Conclusion: The bi-monthly combination of SFU and continuous infusion with high-dose folinic acid is more active and less toxic than monthly SFU bolus with low dose folinic acid and should be tested against treatment, and compared to new active protocols.

Treatment of Helicobacter pylori (HP) with Low Dose Bismuth Subnitrate, Spiramycin and Metronidazole

In our hospital triple therapy with low dose bismuth subnitrate, oxytetracycline and metronidazole eradicated HP in 91.4% of the patients, is cheap, but hampered with side effects (light: 33%, moderate: 22%, severe: 16%). Some reports indicate that the combination of bismuth and metronidazole is crucial in low-cost regimes. We replaced oxytetracycline with spiramycin, a macrolid antibiotic with few side effects, to study the outcome and side effects of this modified regime.

Methods: HP status is determined with a rapid urease test in gastric biopsies. Indication for anti HP treatment was at the discretion of the treating physician. 135 consecutive patients were treated with bismuth subnitrate 75 mg qid, spiramycin 500 mg qid and metronidazole 400 mg tid for 10 days. Sixty patients recorded side effects in a diary card during treatment, whereas 62 were questioned on the follow up visit. The follow up was 6–8 weeks after treatment.

Results: Two patients stopped treatment, another 15 refused the second gastroscopy. A total of 120 patients were included in the intention to treat eradication rate was 68.8% and the per protocol 78.6%.

The tables indicate the number of patients with side effects for the two ways of registration, and the type of side effect.

Treatment of chronic hepatitis C (HC) by alpha-interferon (IFN) is indicated to avoid evolution toward cirrhosis. The aim of this study was to estimate the number of cases of cirrhosis (CIR) avoided among patients with non-cirrhotic HC by 3 different therapeutic strategies (ST), and to estimate the cost of each ST.

Methods: 3 ST were compared: ST1 = no treatment, ST2 = treatment with IFN (3 MU/3 times a week during 6 months) of chronic active HC (CAH), ST3 = treatment with IFN of every non-cirrhotic HC. A decision tree was built. The data published in medical literature allowed us to make the following estimations: about 1 million persons in France are infected by HC virus, patients chronically infected by virus C have either CIR (21%), CAH (39%) or chronic persistent HC (CPC) (40%); the risk of cirrhosis 10 years after diagnosis is 65% for CAH and 4% for CPC; 21% of the patients are responders to IFN; IFN has to be discontinued because of adverse effects in 17% of the patients. The risk of CIR was also considered to be reduced by half after treatment in responders to IFN. The cost of each ST was calculated from hospital fares. We estimated the mean cost of 1 case of CIR avoided by each ST.

Results: The risk of CIR 10 years after diagnosis of chronic HC is 29.0% for ST1, 26.0% for ST2 and 26.3% for ST3. Compared to ST1, ST 2 would treat 78 000 patients in order to avoid 4160 cases of CIR at a cost of 1.2 10^12 FF. Compared to ST2, ST3 would treat 160 000 patients, would avoid 160 additional cases and would cost twice more. The mean cost of each case of CIR avoided by ST2 would be 290 10^4 FF and 560 10^6 FF at ST3.

Conclusion: Compared to no treatment, treatment with IFN of CAH would reduced by 2.5% the number of CIR 10 years after diagnosis. Treatment of
every non cirrhotic active HC, regardless of whether it is active or persistent, would lead to treat twice more patients in order to avoid a few additional cases of CIR.

**1360** Interferon Reduces 5-HIAA in Carcinoid Patients Due to a Metabolic Rerouting

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A majority of clinical studies of interferon in carcinoid patients has revealed a discrepancy between serotonin-derived tumour markers and CT-measurements of tumour manifestations. To test the hypothesis that interferon may induce enzyme to cause a re-routing of the tryptophan metabolism towards the kynurenine pathway we treated primary carcinoid cell cultures with interferon-a 2-30 for 9, 15 and 30 days. Cells treated for the shortest period were allowed to recover for 9 days without treatment. Serotonin and Kynurenin were measured in the cell medium on HPLC with electrochemical or photometric detection. Measured values were related to the initial value and to the results of untreated control cells.

Interferon significantly increased kynurenin in the medium and serotonin was reduced in parallel (p < 0.05). The effect was seen after three days and persisted through all treatment periods. When the treatment was stopped kynurenin values returned to pretreatment levels. Intracellular amount of kynurenin was negligible compared to the medium values possibly indicating a constitutive secretion. Thus, decrease of serotonin-related tumour markers during interferon treatment do not necessarily indicate reduction of tumour mass.

**1362** Does a Chronic Supplementation of the Diet with Dietary Fibre Extracted from Pea or Carrot Affect Colonic Motility in Man?

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The effects of dietary fibre (DF) on colonic motility remain poorly known. Our aim was to compare in 6 healthy volunteers the 24-h motor profile of the unprepared whole colon recorded after a period of usual diet and after 2 randomized periods of a 3-week supplementation with 2 different DF extracted from pea and carrots (granulometry 3-100 μm) expected for good digestive tolerance. Colonic motility was recorded at 5 different levels from ascending to sigmoid colon to determine the site of initiation and the number of HAPCs and to quantify motor activity every 30 min during the 24-h recording with a particular analysis of the 2 h periods after dinner and breakfast. After chronic supplementation, nchytemeral variations of the 24-h motor profiles and the number of HAPCs were not significantly modified when compared with those obtained after the usual diet. Nevertheless, a significantly more delayed initiation of HAPCs was found with both DF and the colonic post-prandial motor response was more diffuse after dietary enrichment with carrots, the DF with the highest fermentescibility and hygroscopic properties.

In conclusion, in healthy volunteers, well-tolerated DF chronically added to the usual diet had limited colonic motor effects. The more distal stimulation of HAPC could be deleterious in constipated patients.

**1363** The Role of the ECL and Parietal Cell Masses in the Maximal Acid Secretion

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It is now accepted that the ECL cells play a central role in the regulation of oxyntic mucosal histamine release and thus acid secretion in the rat stomach. The present study was done to assess the role of the ECL and parietal cell masses in the maximal gastrin and histamine stimulated acid secretion.

Male Wistar rats were dosed for three months with gastrin given by osmotic miniimplants at a rate giving a plasma concentration of about 400 pM. Control rats had implanted miniimplants with saline only. At the end of the 3 month period, food, but not water, was withdrawn for 48 h and during the last 24 h of this period, the miniimplants were also removed. Then the acid secreting, vascularly perfused isolated rat stomach was prepared, and maximal gastrin followed by maximal histamine stimulated acid secretion was determined. Thereafter the stomachs were everted and filled with Pronase and incubated for 75 min. The mucosal cells were harvested, counted and a differential cytofluoimunocytochemistry was performed for ECL cells (histamine immuncytochemistry) and parietal cells (hematoxylin-eosin).

The three months period of hypergastrinemia induced an ECL cell hyperplasia. Gastrin-stimulated acid secretion was, in contrast to histamine stimulated acid secretion, increased after the three months period with hypergastrinemia.

**1364** Fedotizine in Irinitible Bowel Syndrome: Results of a 6 wk Placebo-Controlled Multicenter Therapeutic Trial

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Hepatogastroenterology department, Hôtel-Dieu, Clermont-Ferrand, coordinating center, France, 2 Institut de Recherche Jouvenal, Fresnes, France

Efficacy and safety of fedotizine (FZ), a peripheral 5 HT3 agonist, were compared to that of placebo (PL) in patients with Irritable Bowel Syndrome (IBS).

Methods: A phase III, double-blind, parallel group trial was carried out in France by 70 hospital or private practice centers. The entry criteria were: presence of lower abdominal pain occurring at least 3 times a week for more than 6 months; at least one other symptom of IBS had to be present, notably transit/defecation disorders and abdominal bloating. Each patient had normal findings on barium enema or colonoscopy, and only upper abdominal ultrasound and routine blood tests. Patients completed a diary card daily and rated the intensity of abdominal pain (main criterion) for the previous 4 periods of the day (night, morning, afternoon, evening) as well as the severity of the immediate adverse events. The number of withdrawals associated with adverse events was comparable on FZ (n = 13) and PL (n = 19). Biological tolerance was similar for both groups.

Conclusion: Efficacy of fedotizine is superior to that of placebo in the symptomatic relief of IBS lower abdominal pain as assessed by patients as well as on QoL. Safety of fedotizone was excellent.

**1365** A Comparison of the Early Symptomatic Effect of Single-Doses of Fedotizine Waver to Ranitidine Conventional Tablets in Gastr-Esoargosal Reflux Diseases

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Patients with gastro-oesophageal reflux disease (GERD) are likely to take single doses of histamine-receptor antagonists on demand to alleviate symptoms of reflux. In this study in general practice We compared the symptomatic effect of fedotizine 20 mg wafer and ranitidine 150 mg conventional tablet at 15, 30, 45, 60, 120, and 180 minutes, and the patients’ preference of drug therapy.

Methods: Patients had GERD for a minimum of 1 year, had required palliative treatment for at least 5 episodes per week during the East month, and had at least three of the following: clinical criteria of heartburn, acid regurgitations, burning epigastric pain, symptomatic relief from antacids, and the main dyspeptic disturbance being heartburn or acid regurgitation. A double-blind, double-dummy trial was performed with one active dose of either drug given in a randomized order. The patients were provided with an alarm clock to remind them about the measurements, which were indicated on a seven-point categorical scale (1 = worse, 7 = free of symptoms). Patients were also asked to nominate their preference for the wafer vs. the tablet.

Conclusion: Of 982 patients who had valid data for the analysis, their average age was 49.5 years (±14.6), 436 (52.5%) were males, 607 (73.1%) reported at least daily symptoms, 248 (29.8%) had suffered from constant symptoms during the last year, 192 (23.0%) had difficulties in swallowing, 597 (71.8%) occasionally woke up at night because of reflux symptoms, and 143 (17.2%) had a previous diagnosis of esophagitis.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fedotizine wafer</td>
<td>63 (7.9%)</td>
<td>128</td>
<td>204</td>
<td>287</td>
<td>364</td>
<td>400</td>
</tr>
<tr>
<td>Ranitidine tablet</td>
<td>54 (115)</td>
<td>185</td>
<td>260</td>
<td>259</td>
<td>422</td>
<td></td>
</tr>
</tbody>
</table>

The table shows the proportion of patients who obtained a clinical significant effect at the nominated time periods. A repeated measures ANOVA indicated that FW was significantly better (p = 0.03) than RT at relieving symptoms of reflux during the first hour of measurements, however there was no difference between the 2 treatments at 2 or 3 hours. Significantly more patients (p = 0.01) preferred the wafer (362, 43.4%) to the tablet (265, 33.4%).

Conclusion: We conclude that FW provided faster symptomatic relief in patients with GERD during the first hour, but the clinical implications of the difference have yet to be determined. FW was preferred by more patients than the conventional tablets. As timeliness is an important factor in manag-
ing patients with GERD, FW may be a more suitable alternative than RT that is preferred by patients for fast and convenient symptom relief.

**1366**

*Visible Abdominal Swelling and Functional Disorders of the Intestine (FDI): Should Medical Treatment be Given Along with Dietary Advice?*

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Abdominal swelling and ballooning are common complaints in FDI. It has recently been shown that following dietary advice, such as excluding certain foods, can help to relieve some of the symptoms [1]. The aim of the present study was to assess the effect of a diet excluding certain foodstuffs, and the possible therapeutic synergy of combining the diet with dismosomite (a cytoprotective and adsorbant drug), with placebo control. 

**Methods:** The double-blind study was conducted in comparable groups in five towns by 50 private-practice gastroenterologists. 350 subjects, corresponding to Manning's criteria, suffering from balloonning with at least moderate discomfort a minimum of 3 times a week, and without major constipation (more than 3 stools a week), were pre-included. Normal results for standard biological check up, normal colonoscopy over the past two years, and endoscopy with no clinically significant anomalies excluded an organic nature for the symptoms. Subjects scored the degree of balloonning (main criterion) on a visual scale in a self-assessment log book every day, and recorded the day's food consumption. The secondary assessment criterion was abdominal pain and transit disorders. At the end of the pre-inclusion period, 244 subjects (49 ± 1.2 yrs; sex ratio: 0.67) were randomized into two groups: n = 116 diet + placebo (dismosomite (D)) for 45 days. Clinical examinations were carried out on days 0 and 45 to assess the abdominal swelling objectively and describe the symptoms. Results: Analyzed from the treatment intention point of view, the results demonstrated that dietary advice was significantly better in both groups (p < 0.05). The subjects' overall clinical improvement (ballooning: 65%; abdominal pain: 55.5%; transit disorders: 40%) was similar in both groups, confirming a substantial treatment effect through time (p < 0.01). Concerning the abdominal swelling visible on clinical examination, 36/118 presented the symptom in group D against 47/116 in group P (p < 0.04) (x² test). Conclusion: Restrictive dietary advice during FDI was poorly observed. Dismosomite was an efficacious alternative for visible abdominal swelling.


**1367**

*Specific Life Quality Questionnaire in Gastro-oesophageal Reflux*


**Introduction:** To assess life quality (LQ) in patients with gastro-oesophageal reflux (GOR), a reliable specific questionnaire was sought, yet none was found in the literature. We therefore developed a self-administrated LQ questionnaire to assess the impact of GOR and treatment on LQ, so as to provide clinicians with useful data. Details of the on-going psychometric validation will be available in spring 95.

**Methods:** This was a 4-part 1-year study. 1 — individual qualitative interviews: six GPs, 6 pharmacists. 35 patients were interviewed to determine patients’ complaints and the specific ways they described their disease. The domains of daily life which were most impaired by GOR were identified. 2 — item generation: this was done by a panel of experts and 5 patients using keywords identified in 1. The corresponding response scale comprised 5 categories and the recall period was the previous month. 3 — item comprehension: for each of 14 patients each participant to check the relevance of the domains assessed by the questionnaire and to determine whether all concepts important for patients were present. Meanwhile, item understandability and acceptability were checked. 4 — item reduction: we used a cross-sectional study in which 223 GOR patients (GOR without complications and GOR with esophagitis grade 1 to 4) completed the questionnaire. The analysis used descriptive statistics, principal component analysis, multivariate analysis and stepwise discriminant analysis according to symptom severity.

**Results:** A 104-item questionnaire was created and was found to be well accepted through the cross-sectional study. Item reduction analysis was performed on the 223 questionnaires received. 66 items were deleted according to pre-established item selection criteria. The final questionnaire comprised 38 items evaluating 7 domains: daily activity (6 items), relationships (3), life quality (9), psychologic worries (5), sleep (6), and stool (4). Internal consistency reliability was met for all domains (co Cronbach > 0.70).

**Conclusion:** The 38-item questionnaire respected consensual guidelines, was well accepted by patients and met quality requirements. A longitudinal study now assessing its construct validity, reproducibility and responsiveness over time.

**1370**

*Comparison of Five Commercial Serological Tests for Helicobacter pylori Detection*


**Introduction:** Numerous serological kits are now commercially available to provide cheaper and more rapid diagnosis. In this study we compare 1 latex and 4 ELISA kits (Pyloset kit, Pyloset EIA, Launch Premier H, pylori Biog AG IgG & Shield Diagnostic Helico-G). 

**Method:** Dyspeptic patients aged 18 yr and over attending Gloucester Royal Hospital for a routine endoscopy were considered for the study. The gold standard used was microscopy of H&E and half Gram stained histological sections, culture on selective and non-selective medium and biopsy urease test. A 5 ml sample of venous blood was taken, spun and serum stored at -20°C.

**Results:** H. pylori was detected in 32 of 82 patients. Six of the 7 patients negative by the gold standard but antibody positive had a past history of ulceration or past proven H. pylori infection and antimicrobial treatment. The latex test was easy to perform but sensitivity was only 75%. Birolin and Shield were 100% sensitive but had a specificity of 67%. The Biolad had 10% of results in the equivocal range. Pyloset EIA and hunch were also very sensitive (94 ± 97%) and good specificity (7% ± 6%).

**Conclusion:** The Pyloset latex kit had a good specificity but poor sensitivity compared with the other ELISA kits. The hunch Premier kit had the best overall results and was the easiest ELISA to perform, but is only qualitative and expensive. A quantitative result is obtained from Pyloset EIA, Biolad GAP and Shield Helico-G, which may be useful in long term follow-up after treatment.

**1372**

*Helicobacter pylori Eradication in the Long Term Management of Peptic Ulcer Disease in General Practice*

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**Introduction:** Studies have shown that dual therapy using omeprazole combined with amoxicillin gives eradication rates of up to 80%. We aim to look at the use of long term acid suppressant treatment in general practice and find out whether dual therapy is effective in eradicating H. pylori in this group.

**Methods:** The study was carried out in the sole medical practice of Melton Mowbray. Patients found to have peptic ulcer disease, diagnosed by either barium meal or endoscopy and who were not taking NSAIDs were invited. They were treated with omeprazole 20 mg bid and amoxicillin 1000 mg bid for 2 weeks. Six weeks post treatment, a 14C breath test was performed. Serological testing was performed using the Helico-G kit (Sheilds Diagnostic).

**Results:** 126 of 394 patients on repeat prescriptions for anti-ulcer therapy were shown to have peptic ulcer disease. A total of 66 patients were entered into the study, (men 38–86 yr, mean 63.8 yr, women 36–85 yr, mean 61.5 yr). H. pylori was found in 13/66 (20%) of patients with a cure rate of 82% in 60 patients but 2 patients declined follow-up. Successful H. pylori eradication occurred in 42 of 58 patients (72%).

**Conclusion:** Of the 1.2 Melton GP population on repeat acid suppressant treatment, 32% had confirmed peptic ulcer disease. Dual therapy is effective in H. pylori eradication in the community. It is recommended that peptic ulcer disease patients in the community on long term acid suppressant treatment be treated with a course of H. pylori eradication therapy.

**1373**

*Faecal pH Depends on Intestinal Transit Time*

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Normally, short chain fatty acids (SCFAs), derived chiefly from bacterial fermentation of unabsorbed carbohydrates, keep colonic and hence faecal pH below 7, which limits the bacterial formation of putative co-carcinogens like deoxycholic acid. The determinants of faecal pH are unknown except for high intake of undigested carbohydrates. Theoretically, speeding up colonic transit could lower pH by limiting the absorption of SCFAs or raise it by limiting their formation.

We have measured faecal pH, stool form, weight, and total transit time (WGT) (using radiopaque pellets), stool weight and defections per week on 77 occasions over 7-days periods in healthy women eating their normal diets, with monitoring of dietary intake. These measurements were repeated in 39 subjects after taking either senna or imodium for 8 weeks in titrated quantities to speed up or slow down intestinal transit to the maximum tolerable level.

Under basal conditions faecal pH ranged from 5.55 to 8.24 median 7; WGT from 25 to 186 median 63 h; stool weight from 240 to 2977 median 945 g/day; and stool form from 1.4 to 5.5 median 3.8. Using the Spearman rank test between weight (r = 0.48, p < 0.001), form (r = 0.54, p < 0.001) and defections per week (r = 0.7, p < 0.001) correlated with WGT. In addition, there was a relationship between WGT and faecal pH (r = 0.34, p = 0.002).

Median faecal pH at three levels of WGT were as follows > 8 h, pH 7.43, 40-79 h pH 7.03 and <39 h, pH 6.78. There was no change in dietary fibre intake during senna or imodium treatment.
Conclusion. Efficacy of fedotozine is superior to that of placebo in the symptomatic relief of functional dyspepsia complaints as assessed by patients. Safety of fedotozine was excellent.

1378 24-hour Manometry is Essential to Diagnose Diffuse Oesophageal Spasm

The diagnosis of Diffuse Oesophageal Spasm (DOS) relies on manometry which, by convention, requires more than one simultaneous wet swallow in a series of 10 (interspersed with normal peristaltic contractions). The development of 24-hour manometry now allows the correlation of symptoms with oesophageal motor abnormalities.

Over the last four years, two conventional laboratory-based manometric studies and one 24 hour study (Gaetic recording system, Scotland) were carried out on 380 patients with oesophageal symptoms. Sixteen patients [seven male, median age 50 (range 37-65), were found to have symptomatic oesophageal contractions during the 24-hour study. These painful contractions ('spasms') were characterised by multiple peaks, long durations (>20 seconds) and excessive amplitudes (>230 mmHg) and frequently occurred at night. Twelve of these patients had normal conventional manometric studies. Two patients had normal peristalsis to the wet swallows but had other contractions of long duration, excessive amplitude and multiple peaks (spasms) at some time during the laboratory study. In only two patients would the diagnosis of DOS be made by conventional criteria.

Painful oesophageal spasms have long durations, excessive amplitudes and multiple peaks. Conventional manometry fails to diagnose the majority of these patients. New criteria based on 24-hour manometry are needed to define Diffuse Oesophageal Spasm.

1380 A Long-Term, Multicentre Double-Blind, Controlled Trial of Helicobacter pylori Eradication in Gastric Ulcer Disease

We have investigated the effect of Helicobacter pylori (Hp) eradication regimen on eradication rate and ulcer recurrence in patients with gastric ulcer (GU).

Methods: 171 consecutive GU patients entered the study. Hp infection was assessed by histology and microbiology. All patients received omeprazole 40 mg om for 6 weeks. Thereafter they were randomised to receive in addition either amoxicillin 750 mg bd or placebo for 2 weeks in the ratio 1:1. Patients with healed ulcers then entered a 12 month untreated follow-up. Hp eradication was assessed one month after stopping treatment. Unhealed patients were regarded as having zero remission days in follow-up. An all patients treatment analysis was done.

Results: 24 patients were Hp negative at entry, 19 had a malignant ulcer, 1 did not have a GU and 20 did not have a follow-up assessment. 107 (72 OM + AMOX, 35 OM) were eligible for the analysis. GU healing was achieved in 87% of patients overall. Hp eradication was achieved in 58% of patients who received antibiotic and in 6% of patients who received omeprazole alone.

Results in Hp eradicated and non-eradicated groups.

<table>
<thead>
<tr>
<th>Hp eradicated</th>
<th>Non-eradicated</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer recurrence</td>
<td>3/44 (7%)</td>
<td>30/63 (48%)</td>
</tr>
</tbody>
</table>

The patterns of recurrence were highly significantly different between the two groups (Logrank test, P < 0.001).

Conclusion: Eradication of Hp was successful in substantially reducing GU recurrence in a twelve-month period following healing.

1381 Colonic Tumors and Streptococcus Bovis Bacteria: A Prospective Study. Relationship with the Biotype

Several retrospective studies have reported a relationship between Streptococcus bovis (SB) bacteremia and colonic tumors. It has been suggested that one SB biotype (and not the other biotype II) is associated with a high frequency of colonic tumors (100 p. 100) and endocarditis (94 p. 100). The aim of our prospective study was to look for a digestive lesion for every new case of SB bacteremia.

Patients and methods: From 1987 to 1994, every case (n = 22, 15 men and 7 women, mean age: 68 ± 8 years) of SB bacteremia diagnosed in our hospital had a complete colonic evaluation by colonoscopy, completed eventually with a barium enema. The biotype of SB was identified from 1992 (n = 12). The diagnosis of endocarditis was based on clinical and echocardiographic findings.
Results: 13 out of 22 patients (59%) had one or several colonic tumors: tubular or tubulovillous adenoma (n = 7), intraepithelial carcinoma (n = 4), Duke A adenocarcinoma (n = 1) and Dukes C adenocarcinoma (n = 1). Other infectious diseases (sinusitis, dental infections) were found in three cases. Previous clinical digestive symptoms were present in a single case (rectal bleeding). The determination of the biotype showed 9 biotypes I and 3 biotypes II. The percentage of colonic tumors was 55 p.100 (n = 5) for the biotype I and 33 p.100 (n = 1) for the biotype II. Endocarditis was diagnosed in 66 p.100 (n = 6) of bacteremia with biotype I, and none for biotype II.

Conclusive prospective study confirms the association between colonic tumors and SB bacteremia. These cases emphasize the need for the detection of colonic tumors even if other infectious exist. Our study does not confirm the striking association between the biotype I, colonic tumors and endocarditis.

1383 Toxic Bile Acid Fractions in Reflux Oesophagitis
A new automated oesophageal sampler was developed to directly monitor the extent of duodenogastroesophageal bile reflux.

Ten healthy volunteers (Group 1) and thirty patients (Group 2 — minimal mucosal injury, Group 3 — erosive oesophagitis and Group 4 — stricture/Barrett’s) underwent 16 hour oesophageal aspiration studies with simultaneous pH monitoring. The samples were analyzed for bile acids using reversed-phase high performance liquid chromatography. By resolving 14 individual bile acid fractions, detailed bile acid profiles of the subjects were obtained.
A total of 2544 samples were analyzed. There was no significant variation in the number of samples or volume of aspirate obtained from individuals in the four groups. The highest levels of bile acids were found in patients of Group 1 (mean ± SEM: 21.9 ± 3.5 mg/dl) and Group 4 (mean ± SEM: 22.1 ± 4.0 mg/dl). The predominant bile acid fractions present in the refluxate of the symptomatic groups were the primary bile acids (CA, taurocholic (TCA) and glycocholic (GCA)) and taurocholic (TCA) acids. The secondary bile acids taurodeoxycholic (TDCA) and glycodeoxycholic (GDCA) acids, exclusively in patients with oesophageal stricture/Barrett’s (Group 4). Simultaneous pH monitoring revealed that patients in Group 4 also had maximum acid exposure (mean total % time pH < 4) = 23.9 ± 5.7% vs Group 1 — 5.9 ± 2.2, Group 2 — 9.3 ± 6.6 and Group 3 — 10.9 ± 2.7). There was poor correlation (r = 0.3) between bile acid and pH profiles.
We conclude that, in addition to acid, presence of toxic bile acids such as lithocholates may enhance the extent of mucosal injury in reflux oesophagitis.

1384 Specialized Bleeding Units are the Logical Way Forward in the Management of Upper Gastrointestinal Haemorrhage: A Two Year Prospective Study
Community studies continue to report the mortality of upper GI haemorrhage to be 10–15%. This is unacceptable high and reflects not only the increasing age and infirmity of the bleeding population but also the lack of a standardised approach to management. We present the initial 2 years experience of a specialized Bleeding Unit serving Grampian Region (population 430,000). The emphasis is on rapid assessment, aggressive resuscitation, prompt diagnosis and early surgery, according to an established protocol.
The Unit has an open-access policy for all suspected GI bleeds. There were 1324 suspected upper GI bleeds and of these 1098 were confirmed, leaving 17% (n = 226) who had not bled. Fifty-two percent (n = 573) of confirmed bleeds were significant of whom 2/3 were aged over 60 years. Duodenal ulcer accounted for 25%, gastric ulcer 14% and varices only 5%. The median time to endoscopy was 3 hours (mean ± SEM CI = 6.9 ± 0.55), and the source was found in over 90% of admissions.
Trivial bleeds with no serious concurrent illness went directly home (48%, n = 249), with a median hospital stay of 24 hours (31 ± 2). Severity of bleeding was linked to prior use of NSAID/Aspirin (Significant 41%; trivial 22%; no bleeds 20% p < 0.001) but not to smoking or alcohol. Fifty-seven percent of peptic ulcers had stigmata of recent haemorrhage and 75 (18%) went on to surgery with a surgical mortality of 8%. The overall 30 day bleeding related mortality was 3.9% with deaths confined to the elderly and those severe concurrent illness.
Centralized expertise and rapid triage directs clinical efforts on those with major bleeds, allowing early effective discharge of the remainder. Specialized bleeding units reduce mortality and thus provide cost effective management of GI haemorrhage and should be part of all major district hospitals.

1386 Lower Gastrointestinal Haemorrhage, Two Years Experience in a Dedicated Bleeding Unit
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Major colonic hemorrhage poses a difficult diagnostic and therapeutic problem. In contrast to upper gastrointestinal bleeding, colonic bleeding has no generally accepted plan of investigation and treatment. The literature on colonic bleeding is sparse, with most series detailing the application of a new treatment or diagnostic modality. We have community-based data accumulated prospectively on 1602 patients referred to an open-access bleeding unit with suspected gastrointestinal haemorrhage over a two year period.
During the 2 year period, 278 (17%) admissions were for suspected lower GI bleeding; 252 of these bleeds were defined as significant, with full in haemoglobin and cardiovascular compromise, and 85% of all of these significant bleeds occurred in patients greater than 60 years old. The gender ratio was predominately male in those under 60 years (M:F = 1.9:1), but this was reversed in the older group (M:F = 0.6:1). In those 102 significant bleeds over 60 years old, 29% rebled, and 20% required surgery. Deteriorative disease (24%) was the commonest diagnosis with tumours, infective colitis and inflammatory colitis each at 10%. The origin of bleeding was not identified in 25% of cases, confirming the diagnostic. Concurrent illness was common (80%) in patients over 60, but did not influence severity of bleeding. Smoking, NSAID use and alcohol were not related to severity in the young or elderly groups. The median blood transfusion requirement for patients with significant bleeds was 3 units (mean ± SEM CI = 4 ± 0.8), compared to the median requirements for trivial bleeds of 0 units (0 ± 0.1). The total hospital stay was a median of 9 days for significant and 4 days for trivial, with 38% of trivial bleeds being discharged home directly from the Bleeding Unit.
The overall 30 day bleeding related mortality for colonic bleeding was 5.1% (2/325) with only 1 death recorded in under 60 year group. These data provide a community database on the diagnosis and severity of lower GI bleeding which had not previously been available.

1388 Ana and Pouchitis in Ulcerative Colitis After Proctocolectomy with Ileo-anal Anastomosis
An association between the presence of ANCA and pouchitis has been recently suggested in ulcerative colitis (UC) patients after proctocolectomy and ileo-anal anastomosis (AA) [1,2]. The aim of this study was to assess this relation- ship in 86 UC patients with IAA (n = 41) and 25% were confirmed by using ANCA. Our study confirms that ANCA was present in 38% of UC patients and IAA in 33%. The predictive value of ANCA in the development of pouchitis was evaluated against the background of pouchitis.
UC patients with IAA: M/F, Age (years), UC onset (years), Surgery (months), ANCA+ (%) 0.3 vs UC patients without pouchitis at the time of the study

Among the 9 patients with an history of previous pouchitis but no pouchitis at the time of the study, only 3 (33.3%) had ANCA. The predictive value of ANCA in the development of pouchitis remains to be evaluated.

2) Landers et al. Gastroenterology 1993; 104: 774A.

1389 Surgical Management of Anorectal Incontinence Due to Internal Anal Sphincter Deficiency
Roger Morgan, Nick Carr. Department of Colorectal Surgery, Singleton Hospital, Swansea.
Anorectal incontinence (AI) due to failure of the external anal sphincter complex is well documented and treatment methods are established. By contrast, Internal Anal Sphincter (IAS) deficiency as the sole cause of AI is less well recognised and management is more difficult.
The present study outlines the aetiology surgical management and outcome in 13 patients (11 M:2 F; median age 46 years, range 32–67 years) who presented with AI due to isolated IAS defects as defects due to previous anal surgery (N = 120), or other trauma (N = 1). All patients underwent investigation by defecating proctography and endoanal ultrasound. Eleven of the 13 patients underwent either rotation (N = 5) advancement (N = 3) or island (N = 3)
anaplasty to correct the contour defect in the anal canal. Two of these 11 patients developed wound breakdown and defunctioning colostomy was necessary in 1 of these but this has subsequently been closed. All these patients have normal defecatory control and no longer wear a pad (median follow-up 32 months; range 3-60 months). In the remaining 2 patients direct IAS repair was performed. This procedure produced marginal symptomatic improvement in 1 but failed in the other patient who has since undergone corrective anaplasty with a good result.

It is concluded that anaplasty can produce satisfactory results in the treatment of fossa to discrete IAS defects but that the place of direct IAS repair remains uncertain.

**1391 Experience with Liver Biopsy as a Day Case Procedure**

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The growth of day-care activities and the need to relieve pressure on in-patient bed occupancy make percutaneous liver biopsy as a day case an attractive proposition. We report our experience with 40 patients who fulfilled strict inclusion criteria for day case liver biopsy. These criteria were:

1. Social circumstances sufficient to provide reliable support and supervision at home for 24 hours after discharge.
2. Adequate blood clotting parameters (INR 1.3 or less; platelets 100 or more).
3. Exclusion of cases with potential or definite vascular hepatic lesions (e.g. Hepatocellular Carcinoma).
4. No more than a small amount of ascites to avoid the problem of post-biopsy ascitic leak.

Twenty-eight females and 12 males were biopsied (mean age 55, range 29-80 yr), with the indications falling into 2 main categories, (1) assessment of previously diagnosed chronic liver disease (PBC 8 cases, chronic hepatitis 5, alcoholic liver disease 5, haemochromatosis 2) and (2) explanation for liver profile abnormalities (20). Three cases required admission with post-biopsy pain of which 2 were discharged next day while the third developed a haemothorax and stayed in for 1 week.

**Conclusions**

1. Day case liver biopsy seems to provide a well-tolerated and apparently patient-preferred alternative to the in-patient approach, making this important investigation more cost-effective and no longer susceptible to cancellation for lack of hospital beds.
2. To further evaluate this day-care activity a post-biopsy questionnaire to determine patient satisfaction and to document side-effects occurring after discharge is now being employed.

**1392 Lansoprazole in Maintenance Therapy for Resistant Duodenal Ulcers**

L. Harlet, J. Penson, E. Boesaert, M. Puttemans, E. Fouine. KUL Leuven, Menen, Roussel S.A., Brussels, Belgium

The aim of the acute phase of the study was to compare the efficacy and safety of lansoprazole (LAN) 30 mg od and omeprazole (OME) 40 mg od in the treatment of refractory duodenal ulcers. In the maintenance phase, the efficacy of maintaining ulcer relapse and the long-term safety of LAN 30 mg od were studied.

The trial was an international, multicentre, double blind, randomised, parallel-group design in the acute phase (4 or 8 weeks). Patients with proven resistant duodenal ulcer (ulcer of at least 5 mm still present after a minimum of 6 weeks on H2-antagonists at standard dose) were randomised into two groups: either LAN 30 mg od or OME 40 mg od. If the lesions were healed, the patient entered a 5 month (M) open maintenance phase with LAN 30 mg od. The study comprised 4 or — if healed at 4 weeks — 5 visits (M0, M1, M2, M3 and M6), with an endoscopy, biopsies and blood samples at each visit.

56 patients (31 LAN, 25 OME) were included in the acute phase. Both groups are equally matched for age, race, sex, height and weight.

Healing rates obtained at 4 and 8 weeks are 82% and 96% for LAN and 84% and 92% for OME respectively (no significant differences between the treatment groups).

Of the 56 patients, 49 were healed and 48 were included in the maintenance phase. During this 5 month period 3 relapses occurred: 1 patient stopped taking study medication for approximately 7 weeks because of diarrhoea. 2 others took NSAID’s.

6 adverse events possibly or probably related to study drug were reported by 6 patients (3 LAN, 3 OME) during the acute phase. Only one patient experienced a serious adverse event: presenting with bleeding, following aspiration (not related to study drug LAN). During the maintenance phase, 3 drug related adverse events occurred in 3 different patients (2 cases of diarrhoea and one of headache).

No abnormal findings in the histological examinations were observed.

**Conclusion:** Lansoprazole 30 mg od appears effective and well tolerated in a long term treatment of resistant duodenal ulcers.

**1393 Safety of Lansoprazole in Maintenance Therapy for Reflux Oesophagitis**

J. Penson, M. Puttemans, E. Fouine. Roussel S.A., Brussels, Belgium

The long term efficacy and tolerance of lansoprazole (LAN), a proton-pump inhibitor, are presently investigated in various studies aiming at the prevention of relapse of healed reflux oesophagitis (RO). Much concern is given to the safety aspects, including regular ECL-cell counts and measurement of gastrin levels performed every 3 months.

In Belgium, 108 patients with RO have been enrolled in two studies, both being part of multicenter international trials. Both trials consist of three phases. In the first phase each patient receives 30 mg LAN od for 8 weeks. If the erosions are healed, the patient enters a 12 month (M) double blind randomised phase: Study A: LAN 15 or 30 mg od (58 patients) or Study B: LAN 15 or 30 mg od or omeprazole 20 mg od (50 patients). Following both studies patients may continue treatment with LAN 30 mg od in an open label extension. Of the 108 patients presently 100 were evaluating the LAN 30 mg od group.

**Conclusion:** The long term evaluation of lanoprazole (LAN) 30 mg od in maintenance therapy for reflux oesophagitis showed a satisfactory safety profile with no relevant side effects, including regular ECL-cell counts and measurement of gastrin levels.
up to 8 weeks. On confirmation of ulcer healing patients were randomised to tracosaic lesions and biological activity. The purpose of this study was to examine a possible association between patient's perceived stress and their disease activity. Methods: We studied 82 patients with CD (36 males, 47 females, median age 30 years, range 19-68) and low disease activity (Crohn's Disease Activity Index [CDAI] < 150), attending our outpatient clinic for inflammatory bowel disease (IBD). We used the General Perceived Stress Questionnaire (gPSQ, covering the previous 2 years), a seven-factor checklist instrument (30 questions) developed to reflect the psychosocial factors that are believed to cause or precipitate relapses in patients with IBD. Clinical and biological disease activity were measured with the CDAI, C-reactive protein (CRP), orosomucoid (OM) and erythrocyte sedimentation rate (ESR). Results: We found a significant correlation (Kendall Tau = 0.27, p = 0.0005) between the CDAI and the perceived stress of patients at the time of testing. Patients with higher CDAI perceived more stress retrospectively. However, only the subjective parts of CDAI were significantly associated with the perceived stress (well-being: r = -0.0002, frequency of liquid stool p = 0.01 and pain p = 0.02). Objective parameters of inflammatory disease activity like CRP (p = 0.2), OM (p = 0.8) and ESR (p = 0.9) showed no significant correlations with the gPSQ and did not suggest a link between the biological disease activity and perceived stress. In conclusion our data indicate a possible relationship between new NSAID exposure and UGIH, and clinical symptoms of CD activity, independent of the biological disease activity. Therefore, the patient's perceived stress and psychological factors should be considered in the evaluation of Crohn's disease activity when using the CDAI.

**1407** The Pattern of Prescribing of Community-Dispensed Ulcer-Healing Drugs in Tayside, Scotland 1989-92

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Few data are available regarding the pattern of prescribing of ulcer-healing drugs (UHDs) in the community, despite their widespread use. The aim of this study was to analyze the pattern of UHD prescribing in Tayside, Scotland (population 240,000) between 1989-92. Methods: We prospectively collected data on UHD and non-steroidal anti-inflammatory drug (NSAID) prescriptions dispensed in the community throughout the region (except for a purpose-designed database). Results: Between 1989-92, 469,414 prescriptions (P) for UHDs were dispensed to 60,007 patients (n) (0.15% of the population). 36.9% of these patients received only one prescription for an UHD during the four year period, the percentages of prescriptions for H2-receptor antagonists (H2-RAs) and misoprostol, with proton pump inhibitor (PPI) for 100 years per person, 240,000 patients for a 20 yr old female without any risk factors, were 0.10 in NSAID users and 0.08 in non-NSAID users. Similarly, the event rates for a male, > 80 yrs old with all risk factors, were 5.90 in NSAID users and 0.05 in non-users. Conclusion: NSAID use carries a significant risk of UGI for subjects who have not used them in the previous six months. The event rates are highly dependent on individual patient characteristics.

**1408** Genotypes of Hepatitis C Virus in Austria, Dominance of subtype 1b


Introduction: Hepatitis C virus shows nucleotide sequence diversity distributed throughout the global gene pool, classified to six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. The distribution of viral genotypes shows geographic variations. Therefore it was of
Epidemiological interest to detect HCV-genotypes in the Austrian population in patients with chronic liver disease and proven HCV-infection.

Patients and methods: Hepatitis C virus genotypes were surveyed in patients in Vienna. 76 patients with histologically proven chronic hepatitis, positive for HCV-Ab as well as HCV-RNA. Other causes for chronic liver disease, especially alcoholism were excluded by serological testing. All patients were tested for the genotype of HCV by polymerase chain reaction, using type-specific primers. According to the classification of Simmonds HCV RNA samples were divided into genotype 1a, 1b, 2a, 2b and 4 (and mixed infections).

Results: The results were: 1a = 8 (10.5%), 1b = 47 (61.8%), 1 = 1 (1.3%), 1a1b = 3 (3.9%), 2a = 1 (1.3%), 2b = 1 (1.3%), 3 = 10 (13.9%), 4 = 3 (3.9%), 10d = 1 (1.3%), 1a1b2 = 1 (1.3%). The dominant subtype of hepatitis C virus in the population is 1b. Subtype 3 and 1a are on second and third place in frequency. The other subtypes are also found but quite rarely. Patients with subtype 4 were in two of three of egyptian origin.

Discussion: Austrian patients with chronic Hepatitis C infection are mostly infected by the subtype 1b.

1410 Release of TNFα and IL-1β from PBMC in Patients with Active Crohn’s Disease: No Effect of Budesonide

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Background: Active Crohn’s disease (CD) is associated with increased release of TNFα and IL-1β from peripheral blood mononuclear cells (PBMC). In this study we determined the effect of Budesonide (BUD), a novel oral methylprednisolone (PRED) on the release of these cytokines from stimulated PBMC.

Patients and methods: Nineteen patients with active CD (CDAI >150) were randomly assigned for treatment with either Bud or Prd Bud was given at a dosage of 3 mg, 3 times daily. The Prd group was treated with 48 mg/d, which was tapered to 32 mg in week 2. PBMC were separated by Ficol density centrifugation before and 2 weeks after treatment. After separation cells were resuspended in RPMI and stimulated with anti-CD3 (20 ng/ml) and Phorbolmyristate-acetate (1 ng/ml) for 24 h. TNFα and IL-1β were measured in the supernatants by ELISA (Immunotech). Clinical response to treatment was assessed by CDAI and C-reactive protein (CRP).

Results: At study entry both groups showed high concentrations of TNFα and IL-1β. The differences in cytokine concentrations between both groups were insignificant. In the Prd group a significant decrease of TNFα and a slight decrease of IL-1β production was observed after 2 weeks. In contrast, Bud treatment did not reduce release of TNFα and IL-1β. The clinical response in the Bud group was less pronounced than in the Prd group by a minor decrease in the CDAI. CRP was significantly reduced in the Prd group, only.

1411 Hepatitis C Virus Infection in Older Patients

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Since the discovery of hepatitis C virus (HCV) there have been many studies of its prevalence. It has been suggested that this increases with age but there have been few studies in the elderly. Study of HCV related disease in the elderly was therefore undertaken in a large group of elderly patients with chronic liver disease. The prevalence of infection on which the rationale of treatment is based.

Amongst the HVCAV positive patients seen at Freeman Hospital 25 were >65 years old. The median age at presentation was 67 years (range 50-91 years) and 4 were female. 9 were asymptomatic at presentation. 8 presented with varices, 5 with malaise, 3 abdominal pain, 1 pruritis and 1 oedema. Risk factors were 7 transfusion, 1 haemodialysis, 1 dentist, 2 tattoos and 1 Afro-Caribbean origin. There was no recognised risk factor for infection in 13 at all. 1 patient had a previous War. We found in addition 3 patients with other recognised other risk factors had a similar history. Lipoid biopsy was performed in 20; 2 chronic hepatitis, 12 cirrhosis and 6 cirrhosis and HCC. Genotyping was performed by INNO-LIPA, INNO-LiPA, in 19. 1a-4, 1b-15 and 1 untypeable. Genotype was not related to disease severity or mode of transmission. 9 have died median age 71 years (range 67-84 years) only 4 of liver related disease all with HCC.

HCV infection is usually asymptomatic with significant liver disease but does have a marked effect on life expectancy. A novel risk factor for this population may be overseas War Service.

1412 Evidence for a G-CSF Mediated Upregulation of the High Affinity Receptor for IgG (FcγRII, CD64) on Circulating Neutrophils in Active Crohn’s Disease

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We recently described an upregulation of CD64 on circulating neutrophils in patients with active Crohn’s disease (CD) indicating an enhanced cytotoxic potential of those cells. G-CSF and interferon-γ (IFN-γ) are the only known cytokines which induce by different mechanisms an increased expression of CD64 on neutrophils. Whereas IFN-γ acts on differentiated neutrophils to upregulate CD64, G-CSF stimulates neutrophilic progenitors leading to an enhanced mobilization of CD64 positive neutrophils from the bone marrow. The aim of the present study was to investigate the pathogenetic role of G-CSF and IFN-γ for CD64 expression on circulating neutrophils in patients with inflammatory bowel disease (IBD) in vivo.

The expression of CD64 (FcγRII) was studied in patients with active CD (CDAI > 150), inactive CD (CDAI < 150), active ulcerative colitis (UC) and healthy donors (HD) on peripheral blood PMN by whole blood flow cytometry and evaluated as percentage of positive cells (%). On the basis of absolute neutrophil counts (aN), absolute counts of circulating CD64+ neutrophils (aCD64 + N) were calculated. Serum levels of G-CSF and IFN-γ were measured by ELISA. Inflammatory activity was assessed by serum levels of C-reactive protein (CRP).

None of the patients received steroids or other immunosuppressive drugs within the last two months. IFN-γ could not be detected in the serum of HD and IBD patients. Compared to HD, G-CSF serum levels were increased in active CD (p < 0.001), whereas IFN-γ (p = 0.01) and IL-10 (p = 0.01) in active CD. Serum G-CSF was higher than in inactive CD (p = 0.005). No significant difference was measured between active CD and UC. The expression of CD64 was lower in patients with active CD and UC than in healthy donors, which was consistent with our previous results in patients with active UC.

1413 Non-hodgkin’s Lymphoma in Hepatitis C Virus Infection

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Hepatitis C virus (HCV) is associated with hepatocellular carcinoma and it has been suggested that it may be directly oncogenic. HCV also infects lymphocytes, is linked to cryptogloasma where there is clonal proliferation of lymphocytes and there have been reports of an association with non-Hodgkin’s lymphoma (NHL). We therefore examined for an association amongst our patients with HCV infection and NHL.

We describe the clinical and pathological details of two patients amongst 21 patients attending the Liver Unit at Freeman Hospital with HCV related cirrhosis and NHL. Patient 1 was a 68 year old female with asymptomatic transfusion acquired HCV cirrhosis and diffuse low grade centrocytic NHL. Patient 2 was a 68 year old male with active but not high grade large cell lymphoma of mucosal associated lymphoid tissue. HCV RNA was detected by PCR in 1 patient assessed in serum and lymphocytes. Genotype was 1b by INNO-LIPA (INNOGENETICS). We screened 53 consecutive patients with NHL of all ages >50 years old attending local lymphoma clinic; in none was HCV detected by second generation ELISA (ORTHO).

We conclude that HCV is an uncommon contributory factor for the development of NHL in the UK.

1418 Serum Procollagen Type III N-terminal Peptide (PINP) Levels and Histological Changes in Primary Bilary Cirrhosis (PBC)

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Assessment of collagen turnover may be of some help in monitoring progres-
sion and response to treatment in PBC. The measurement of serum procollagen I and III peptides, which are released during metabolism of collagen, is a non-invasive means of assessing this. Several assays, with varying specificities to the Col I–III peptide (reflecting mainly synthesis) and to the Col I peptide (reflecting both synthesis and degradation), are available for the measurement of sPIIINP, but confusion exists regarding interpretation of their results.

Biopsies from patients with PBC were assessed for Ludwig’s scores and for various histological parameters semiquantitatively, on a 0 to + + + scale. Blood was taken at the same time as the biopsy for sPIIINP measurement. Four assays were tested: Behring 238 and 239 (mono-specific for Col 1–3) and Behring Fab 226 (Col 1–3 and Col 1).

Significant correlations existed between all 4 assays, but the strongest were between sPIIINP 226 and Fab (p < 0.001, r = 0.877) and sPIIINP 238 and Fab (p < 0.001, r = 0.874). No significant correlations were observed between sPIIINP by any assay and lobular inflammation, lobular fibrosis or portal inflammation. There were significant increases in sPIIINP 226 and Fab, but not 238 or Orient with increasing severity of portal fibrosis (226: p < 0.001 and Fab: p = 0.011). sPIIINP Orient and 238, but not 226 or Fab levels, increased significantly in later stage disease (3 and 4) when compared with early stage disease (1 and 2) (Orient: p = 0.002 and 238: p = 0.009).

We have shown that the 238 and Orient assays give equivalent information regarding collagen turnover in patients with PBC, as do the 226 and Fab assays. Assays measuring only Col 1–3 reflect histological stage of disease whereas those measuring both Col 1–3 and Col 1 reflect the degree of portal fibrosis. In conclusion, the choice of assay greatly affects the interpretation of sPIIINP levels.

1419 Semiquantitative Assessment of Hepatic Fibrogenesis at the Transcriptional Level


Accumulation of collagen and other matrix proteins within the liver is, in part, responsible for the deterioration in hepatocellular function which is seen in chronic liver disease. A measure of hepatic fibrogenic activity would be a valuable indicator of prognosis and response to treatment. Since the rate of collagen synthesis is under transcriptional control, quantitation of procollagen mRNA in liver biopsy material offers an alternative approach to that of serum markers of collagen turnover.

In situ hybridisation (ISH) of type I procollagen mRNA, using a 35S labelled antisense RNA probe to rat a(1)I collagen, was performed on 50 routinely processed liver biopsies from patients with primary cirrhosis (PBC) and on 5 biopsies, reported as normal, from patients with only mildly abnormal transaminases. Sections hybridised with the corresponding sense probe were used as negative controls. Signal was semiquantitatively assessed by C J R G and R F T M, independently, on a scale of 0 to + + + (ISH score), over fibroblasts in and around portal tracts and lymphocytes in zones 2 and 3 of the hepatic lobule. Ludwig stage and other histological parameters were also semiquantitatively assessed by NYH independently.

A good correlation existed between total (fibroblasts + lymphocytes) ISH scores of the two assessors (p < 0.005, r = 0.632). Total ISH scores of PBC biopsies were significantly higher than the "normals" (p = 0.005). Fibroblast ISH scores increased significantly with both increasing portal fibrosis and inflammation (p = 0.003 and p = 0.009 respectively) There was a strong trend towards an increase in total ISH score in late stage disease when compared with early stage disease (p = 0.056). Also, significantly increased serum type III procollagen peptide levels were observed in those with greater fibroblast ISH scores.

The assessment of procollagen mRNA levels by ISH offers a new and direct method to evaluate fibrotic activity in patients with PBC.

1420 Expression of Hepatitis C Virus RNA: Response to a-Interferon Assessed by In Situ Hybridisation

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Liver biopsy and serum samples from 22 patients with chronic hepatitis C (HCV) were screened semiquantitatively by ISH for the presence of HCV RNA. Liver biopsies were tested from patients with PBC and for various histological parameters semiquantitatively, on a 0 to + + + scale. Blood was taken at the same time as the biopsy for HCV RNA measurement. Four assays were tested: Behring 238 and 239 (mono-specific for Col 1–3) and Behring Fab 226 (Col 1–3 and Col 1).

Significant correlations existed between all 4 assays, but the strongest were between sPIIINP 226 and Fab (p < 0.001, r = 0.877) and sPIIINP 238 and Fab (p < 0.001, r = 0.874). No significant correlations were observed between sPIIINP by any assay and lobular inflammation, lobular fibrosis or portal inflammation. There were significant increases in sPIIINP 226 and Fab, but not 238 or Orient with increasing severity of portal fibrosis (226: p < 0.001 and Fab: p = 0.011). sPIIINP Orient and 238, but not 226 or Fab levels, increased significantly in later stage disease (3 and 4) when compared with early stage disease (1 and 2) (Orient: p = 0.002 and 238: p = 0.009).

We have shown that the 238 and Orient assays give equivalent information regarding collagen turnover in patients with PBC, as do the 226 and Fab assays. Assays measuring only Col 1–3 reflect histological stage of disease whereas those measuring both Col 1–3 and Col 1 reflect the degree of portal fibrosis. In conclusion, the choice of assay greatly affects the interpretation of sPIIINP levels.

1421 Glutathione S-Transferase and Inflammation in Hepatitis C Infection

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Glutathione S-transferases (GST) are enzymes present at high levels in the liver, distributed evenly throughout the liver parenchyma. Several GSTs provide a sensitive index of hepatocellular damage and are an alternative to aminotransferase levels which have been shown to possess limited specificity and sensitivity for detecting hepatic inflammation. Chronic hepatitis C virus (HCV) infection with normal serum aminotransferase levels, despite advanced histological damage, is well recognised and may result from poor sensitivity of standard LFTs. This paper investigates whether serum GST levels are more sensitive than aminotransferase (ALT) in detecting hepatocellular damage in 40 patients with chronic HCV infection.

Serum GST levels were measured by enzyme immunoassay (Biotron) and correlated with serum ALT levels and the presence of histological damage in the liver (standard criteria and Knodell score).

Histological assessment revealed 2 normal biopsies (both with normal ALT/GST levels), CLH (8), CPH (7), mixed 11 and CAH (12). Seven patients with abnormal liver biopsies had normal ALT/GST levels. Elevated ALT levels (29/52: 72.5%) were more specific for abnormalities in GST levels (increased in 20/40: 50%) for lobular inflammation. No direct correlation was found between ALT and GST levels and histological damage.

In this study group ALT levels were more frequently elevated in association with abnormal ALT/GST levels. Although the combination of ALT and GST was more sensitive than either test alone for detecting patients with HCV who have abnormal liver biopsies a significant number of patients (7/40: 17.5%) with histological abnormalities still had no biochemical evidence of inflammation in both tests.

1422 Asymptomatic Blood Donors with Hepatitis C Virus (HCV) Infection: Response to a-Interferon Therapy

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This interim report details the progress of 51 asymptomatic blood donors (36 male, age range 19–64; median 34) screened seropositive for HCV receiving a-interferon (3–6 mega-units thrice weekly for 6 months). All were confirmed positive by immunoassay (RIBA-2/RIBA-3) and 50/51 were HCV RNA positive.

Histology and ALT levels at entry were as follows: CLH B (1/8 normal ALT), CPH B (3/8 normal ALT), mixed 13 (4/13 normal ALT) and CAH 19 (4/19 normal ALT). To date 32 patients have completed 6 months treatment and 14 have been reviewed at 3 months post-treatment (+3). Most patients reported flu like symptoms at the start of treatment and tiredness persisted in 39%. White cell and platelet counts fell in 27% but no serious side effects were encountered nor review of dose required (1 patient dropped-out after 4 months treatment due to fatigue).

Complete biochemical response (normal ALT at 6 months) was seen in 20/32 (63%) and no improvement in ALT levels was seen in 12/32 (37%). Relapse (abnormal ALT + 3) occurred in 10/14 (71%) of complete responders. Serial serum samples (0.6 and +3 months) have been tested for HCV-RNA in 12 patients to date. No response (viraemic all 3 samples) was seen in 4/12 (33%), 5/12 were transient responders (not viraemic at 6 months) and 2/12 (17%) remained non viraemic at +3 months (+3) (1 patient was negative in all 3 samples). Post-treatment histological assessment was improved in 19/26 (73%), unchanged in 6/26 (23%) and worse in a single biopsy. Treatment with a-interferon produces a response in most donors infected with HCV but the majority relapse when treatment is withdrawn. Completion of this study may help to identify sub-groups with a better prognosis.

1423 Are Symptoms in Gallstone Patients Related to Age, Sex or Gallstone Characteristics?

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Symptoms caused by gallstones are usually attributed to obstruction of the gallbladder neck, although other factors, such as inflammation, could be involved. Gallstones might be expected to cause more pain, by becoming lodged in the neck. Age and sex alter gallbladder contractility and might affect symptoms.
163 patients with symptomatic gallstones, and gallbladders that emptied after fatty meal stimulation, answered preparative visual analogue scale (VAS) questionnaires covering 14 symptoms commonly associated with gallstones, and Nottingham Health Profile (NHP) charts. After cholecystectomy, the number and volume of stones and the size of the largest stone were measured. Results were analysed separately for men and women and the effect of age was also noted.

The Spearman’s Rank Correlation Test gave the following significant associations between symptoms and characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Symptom</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Feeling sick (VAS)</td>
<td>-0.21</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Fatty food upset (VAS)</td>
<td>-0.23</td>
<td>0.005</td>
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<tr>
<td>Stones – number</td>
<td>Average VAS score</td>
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<td>0.05</td>
</tr>
<tr>
<td>Stones – volume</td>
<td>None</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stones – size of largest</td>
<td>Pain (NHP)</td>
<td>0.18</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Larger gallstones were associated with higher pain scores. Overall, age was not found to be related to symptoms. NHP scores for women were significantly higher than for men. No other associations were found.

### 1424 Do Sucinalide and Ceruleidate Have Different Effects on the Gallbladder?

R. Ahmed, A. Smythe, R. Chess-Williams, A.G. Johnson.

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Radiological studies have suggested that the use of cerulide, a synthetic decapeptide, as a stimulant for gallbladder contraction causes ballooning of the gallbladder, possibly due to an increased action of cerulide on the neck of the gallbladder compared to the body. Of 44 patients with acalculous biliary pain undergoing cerulide provocation tests in this department, 17 were found to have ballooning. Sucinalide is a synthetic cholecystokinin octapeptide. The ballooning effect has not been reported with Sucinalide.

The two preparations were compared by in vitro studies on muscle strips, to assess whether any clinical advantage for either could be predicted. Muscle strips from 6 gallbladders removed at routine surgery were used. 6 strips from the body and 6 from the neck were assessed for each of the two drugs. Both cerulide and sucinalide were used in concentrations of 3.5 x 10^-14M to 1 x 10^-11M. Mean EC50 values and 95% confidence limits were:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source of Issue</th>
<th>EC50 (nM)</th>
<th>Confidence Limits (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerulide</td>
<td>Body</td>
<td>2.22</td>
<td>1.54 - 6.72</td>
</tr>
<tr>
<td></td>
<td>Neck</td>
<td>2.42</td>
<td>1.18 - 4.96</td>
</tr>
<tr>
<td>Sucinalide</td>
<td>Body</td>
<td>4.42</td>
<td>1.43 - 13.72</td>
</tr>
<tr>
<td></td>
<td>Neck</td>
<td>3.44</td>
<td>1.24 - 9.54</td>
</tr>
</tbody>
</table>

Using the unpaired t-test, no significant difference could be demonstrated between the EC50 values of issue obtained from the body or the neck of the gallbladder, or between the values from the two preparations.

### 1425 Efficacy of Dual vs Triple Therapy and Symptom Relief in Patients with H. pylori Gastritis

M.M. Ozman, R.V. Patankar, C.D. Johnson. University Surgical Unit, Southampton General Hospital, UK

With standard triple therapy H pylori can be eradicated in around 90% of individuals. However, compliance is poor because of the complexity and the side effects of regimen.

The aims of the present study were first to compare the effect of dual therapy (DT) with Omeprazole 40 mgbd and Amoxicillin 500 mgbd for 14 days in eradication of H pylori as against a modified short-term triple therapy (STTT) with tetracycline 500 mgbd, colloidal bismuth subcitrate (De-nol) 120 mgbd for 7 days and metronidazole 400 mgbd on the last three days and second to evaluate the effect of eradication on symptom relief.

60 patients (36 M, 24 F) with NUD and H pylori gastritis were entered into the study. Median (range) age was 58 (22-85) years. Gastritis was graded according to severity and location. H pylori status was assessed by means of CLO-test, histology and C13-UBT in all patients. Patients in each gastritis group were allocated treatment either with DT or STTT. Eradication was defined as a negative C13-UBT 4 weeks after cessation of treatment. All patients completed a symptom based questionnaire before and 1 month after treatment.

H pylori was eradicated in 24/30 (80%) of patients in DT group and 25/30 (83%) of the patients receiving STTT. DT with side effects were seen in 5 patients (16%) whereas in the STTT group 11 patients reported side effects (30%). Diarrhoea and darkness of stool being commonest. 76% of patients (23/30) had symptoms related with DT whereas 63% of patients (19/30) improved after STTT.

In conclusion, the combination of Omeprazole and amoxicillin appears to be preferable to STTT for eradication of H pylori in NUD. Successful eradica-

### 1427 Prokinetic Effect of Bolus Intravenous Aminocids on Gallbladder Emptying


University Surgical Unit, Southampton General Hospital, UK, Kobe University, Japan

Prokinetic agents prevent gallbladder sludge formation in patients predisposed to gallstones. We studied 14 healthy volunteers (13 Male) median (range) age 39.5 (24-67) years in a double bind, prospectively randomised, placebo controlled study. Each subject was studied after an overnight fast and received either placebo on a day of 3.5 ml/kg body weight of a sodium tetracycline mixture, Clincet, UK intravenously over 5 minutes Gallbladder ejection fraction was calculated using the PICS system and 150 mgBq BrIlA. All images were corrected for background, decay and motion. Plasma hormones were measured in the fasting state and at 5, 10, 15, 30, 45, 60, 90 and 120 minutes after the stimulus using sensitive immunoradiomu

### 1428 Risk Factors for Development of Gastric Endocrine Cell Hyperplasia During Treatment with Lansoprazole

R. Esser, G. Brunner, B. Michel, E. Solica, R. Arnold. Dept. of Gastroenterology, Philipps University, Marburg, Germany

Long-term treatment with proton-pump inhibitors is the treatment of choice in patients with severe reflux-oesophagitis. In rats potent acid inhibition can induce gastric carcinoids. This effect must be excluded in man. The present study changes of gastric endocrine cells during long-term treatment with lan-

### 1430 Epidemiological Factors of Gastroesophageal Reflux (GORD) in 2033 Patients Followed by General Practitioners

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Data on factors associated with GORD occurrence are sparse. The objectives of this study carry out by 1171 general practitioners were to focus on the sign-

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*Gut* first published as 10.1136/gut.37.Suppl_2.A121 on 1 January 1995. Downloaded from [http://gut.bmj.com](http://gut.bmj.com) on 1 January 1995.
Materials and methods: Between October 1993 and December 1993 two consecutive patients complaining of GORD symptoms (heartburn and/or regurgitation) and two control patients were enrolled by each investigator of the study.

A standardized questionnaire including data on. . . size, digestive and extra digestive complaints, past history, drug intake and habits was completed for each patient.

Results: 2032 patients with GORD symptoms and 2032 control patients were enrolled in this study (52 ± 0.3 years, 59% of men). In the GORD population the digestive symptoms last for 5.2 (± 0.1) years, 80% of GORD patients presented symptoms at least three days per week and 30% patients daily symptoms. Each patient consulted his general practitioner 4 times a year for GORD symptoms. 75% of these patients had an endoscopy (56% in the last year) 36 X-ray upper tractus transit and 10% 24 hours pH monitoring.

Comparison of the two groups: Digestive symptoms of GORD were present during pregnancy in 38% of GORD women versus 16% in control group. Chronic respiratory symptoms and chronic ear infections in childhood were more reported by GORD patients than control patients.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>GORD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain</td>
<td>40%</td>
<td>11%</td>
</tr>
<tr>
<td>Nocturnal cough</td>
<td>37%</td>
<td>11%</td>
</tr>
<tr>
<td>Pharyngitis irritation</td>
<td>44%</td>
<td>12%</td>
</tr>
<tr>
<td>Peptic ulcer pain</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>Bad breath</td>
<td>38%</td>
<td>18%</td>
</tr>
<tr>
<td>Drugs intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Calcium inhibitors</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Antiinflammatory drugs</td>
<td>10%</td>
<td>19%</td>
</tr>
<tr>
<td>Habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>31%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Conclusion: Data on past history and extra digestive symptoms showed significant differences between the two groups. No difference in habits and regular drug intake appeared between the two groups.

1431 The Effect of Preoperative Short Term Mebendazole Therapy on Viability of Hydatid Cysts

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Although the long term treatment with mebendazole is highly effective on viability of hydatid cyst, the role of preoperative short term mebendazole therapy is still controversial.

We designed a double blind and prospectively randomised study to evaluate the effect of short term preoperative mebendazole therapy on the viability of hydatid cyst. We included 40 patients with hydatid liver cyst which was all diagnosed and classified using ultrasound. Patients with type V hydatid cyst were excluded.

20 patients (16 F, 4 M) median (range) age, 40 (11 – 70) were given 50 mg/kg mebendazole, for 10 days other two patients (9 F 5 M) median (range) age, 40 (19 – 70) years were given placebo for 10 days. All patients underwent operation after the therapy. Both groups were compared as regard the viability of hydatid cyst which was classified according to operative findings, microbiologic evaluation and histologic examination of specimens according to WHO guidelines (WHO, 1981).

In therapy group, cysts were classified as viable or probably viable in 14/20 (70%) patients and 6/20 (30%) were classified as non-viable. Whereas in placebo group 10/20 (50%) cysts were classified as viable or probably viable 5/20 (25%) cysts were classified as non-viable. (p > 0.05)

In conclusion, preoperative short term (10 days) therapy with mebendazole has no effect on viability of hydatid cyst. In order to evaluate the preventive effect of tissue mebendazole concentration on secondary intraabdominal hydatidosis related to spillage of the contents of cyst during surgery, it is necessary to follow all the patients both groups for long term.

1432 Lithium Gamma Linolenic Acid in Pancreatic Cancer

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Lithium salt of Gamma Linolenic Acid (LGLA), an essential fatty acids has been reported to prolong the survival of patients with inoperable pancreatic cancer. We tested the effect of LGLA on 2 pancreatic ductal cancer cells lines (Panc 1 and MIA PaCa2) and studied the dose response and timecourse of this effect. A human fibroblast cell line was used as the control.

Cells were seeded at 2500 cells per well in 100 μl medium containing 10% FBS in 96 well culture plates. LGLA (Scotia, Guildford, UK) was added 24 hours later (0.625 to 490 μmol/l) and Lithium Chloride (LiCl) (0.06 to 2 mmol/l) was used to exclude a non-specific fat overload effect and a Lithium effect respectively. Cell growth was assessed by a microculture tetrazolium (MTT) assay.

LGLA showed a selective and significant dose and time dependent growth inhibition effect on both cancer cell lines (LGLD = 4 μmol/l) and after 4 days 60% growth inhibition was seen with MIA PaCa2 at 5 μmol/l. Fibroblasts were unaffected up to a concentration of 50 μmol/l (LGLD = 120 μmol/l). PA and LiCl had no effect. LGLA can be administered IV, has no side effects of conventional chemotherapy and may prove useful in patients with pancreatic cancer.

1433 Comparison of Side Effects Between Intravenous and Intraperitoneal Administration of Anticancer Agents

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The side effects of anticancer agents were analyzed in two different administration methods, intravenously and intraperitoneally. Intravenous administration group (IV), as control, consisted of 48 patients with esophageal cancer, who were administered CDDP (80-150 mg injection at one or two stages) and 5FU (total 1000-5000 mg). Intraperitoneal administration group (IP) consisted of 13 patients, 6 with colon cancer, 3 with stomach cancer and 4 with other cancers. All the patients of IP group had peritoneal or serosa infiltration of cancer. IP was performed using implantable subcutaneous port and catheter system. 100 mg of CDDP and 1000 mg of 5FU were administered at one stage with 1000 ml of saline. In IV group, leukaemia (<3000) was recognized in 14 patients (29.2%) and other serious complications were seen in 5 patients (10.4%). In contrast, leukaemia was seen in only one patient (7.7%) and no other complications were seen in IP group. Though severe gastrointestinal symptoms, such as vomiting, were seen in most of patients of IV group, they were absent in the patients of IP group. The catheter troubles, severe pain and inflow obstruction, was seen in two patients. IP administration was superior to IV regarding side effects.

1435 Patients with Irritable Bowel Syndrome (IBS) have Alterations in the CNS-Modulation of Visceral Afferent Perception

H. Mönkikes, I. Heymann-Mönkikes, R. Arnold. Dept. of Medicine, Division of Gastroenterology and Endocrinology, Philipps-Universität, Marburg, Germany

The knowledge about pathophysiological mechanisms underlying IBS is still incomplete. Some studies report abnormal bowel motility, e.g. elevated tone of the colonic wall, and others enhanced visceral sensitivity. The pathways mediating visceral hypersensitivity as well as the role of neural modulation of visceral afferent information in IBS is incompletely understood. It has been shown however, that cognitive processes have an influence on upper-GI visceral perception in healthy controls. Also, it has been speculated, that IBS patients might have a visceral post-stress hypersensitivity. Thus, the aims of this study were to investigate the effect of 1) mental distraction and 2) experimenta1 stress on lower-GI visceral perception in IBS patients and healthy controls (HC). Methods: In IBS outpatients (N = 13) and HC (N = 8), all female, rectal sensitivity (“first sensation”, “urge to defecate”, “discomfort” or “pain”) to rectal balloon distension (inflation rate: 40 ml/min) and rectal compliance were determined using an electronic barostat. Consecutive measurements were performed in the following order: control condition, distraction, condition, post-condition condition, control condition. The measurements under control conditions took place while the patients rested quietly in a comfortable position. The measurement under distraction condition took place during an easy drawing task, and under post-condition distraction condition after a 5 minute stressful drawing task.

Results: The threshold of recto-visceral perception (RVP) was lower in IBS patients. Mental distraction increased the RVP-threshold in HC but not in IBS patients (see table).

<table>
<thead>
<tr>
<th>Patients</th>
<th>control condition</th>
<th>distraction</th>
<th>post-condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First sensation</td>
<td>6.7 ± 0.8</td>
<td>6.7 ± 1.2*</td>
<td>7.6 ± 1.2</td>
</tr>
<tr>
<td>Urge to defecate</td>
<td>10.6 ± 0.8</td>
<td>11.9 ± 1.4*</td>
<td>10.7 ± 1.3*</td>
</tr>
<tr>
<td>Discomfort or pain</td>
<td>124 ± 1.0</td>
<td>142 ± 2.0*</td>
<td>125 ± 1.4*</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First sensation</td>
<td>15.1 ± 4.3*</td>
<td>18.8 ± 5.7*</td>
<td>10.7 ± 5.1*</td>
</tr>
<tr>
<td>Urge to defecate</td>
<td>43.6 ± 7.9*</td>
<td>54.4 ± 13.3*</td>
<td>40.9 ± 9.2*</td>
</tr>
<tr>
<td>Discomfort or pain</td>
<td>74.4 ± 12.6*</td>
<td>84.5 ± 14.4*</td>
<td>74.1 ± 14.8*</td>
</tr>
</tbody>
</table>

HC control condition: distraction post-condition

Mean ± SEM; #p < 0.05 vs HC, t-test; *p < 0.05 vs control; paired t-test

Conclusions: The data show, that cognitive processes have a modulatory effect on lower GI-sensitivity in healthy controls. In contrast to HC,
cognitive distraction does not decrease GI-sensitivity in IBS-patients. These results suggest, that alterations in the CNS-modulation of visceral aff-
ert stimuli play a major role in the pathophysiology of the irritable bowel syndrome.

**1436** Interaction Between Gastrin-Releasing Peptide and the Cholinergic System in Regulating Gallbladder Contraction in Man

P Hildebrand, S. Ketterer, B. Angly, C. Beglinger. Div. of Gastroenterology and Dept. of Research, University Hospital, CH-4031 Basel, Switzerland

The neurotransmitter gastrin-releasing peptide (GRP), the human analogue of bombesin, has been identified to regulate various gastrointestinal functions. In humans, exogenous GRP potently stimulates gallbladder contraction, most likely mediated by cholecystokinin (CCK) release. We have recently shown in man that BIM26226, a potent and specific GRP receptor antagonist, reduced meal-induced gallbladder contractions in normal and in patients with functional dyspepsia. However, it was not clear to what extent inhibition of GRP decreases the pattern of inhibition that is seen in response to meal-induced contraction. The aim of the present study was therefore to further investigate the pathways by which GRP exerts its effects. We were specifically interested in the interactions between GRP and the cholinergic system in regulating gallbladder contraction.

Methods: 6 healthy male subjects underwent 4 studies on separate days and in random order. Gallbladder contraction was assessed every 15 min by measurement of the volume of gallbladder gas obtained by endosonographic aspiration in the fasting state. Subjects were fed one of the four test meals that were minor

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**1437** Hypermanganesaemia and Parenteral Nutrition: A Cause for Cholestasis?

A. Jawhén, C. Öng, S. Wood, A. Forbes. St Mark’s Hospital, Dept. of Internal Medicine and Dept. of Research, University Hospital, CH-4031 Basel, Switzerland

Manganese toxicity has been identified to regulate various gastrointestinal functions. Although manganese (Mn) is the second most abundant trace element in the human body, Mn toxicity is rarely described. In the present study, we measured Mn levels in patients on parenteral feeding solutions. We also measured Mn levels in whole blood of 26 patients with chronic renal failure, 5 patients with inflammatory bowel disease and 238 patients with IBD.

Results: GRP alone dose-dependently induced gallbladder contraction with a half maximal effect at 10 pmol kg⁻¹ h⁻¹, atropine completely inhibited this response, while betahanechol (BET) (2.5 10¹⁰ pmol kg⁻¹ h⁻¹) with or without i.v. BIM26226 (500 pmol kg⁻¹ h⁻¹) was ineffective. GRP was shown to be a potent and selective agonist of Mn uptake into the duodenal mucosa. The uptake of Mn was increased in those with hypermanganesaemia.

Conclusion: GRP and the cholinergic system interact in the regulation of gallbladder contraction in man. In this study, Mn levels in patients on parenteral feeding solutions were significantly increased compared to Mn levels in normal and in patients with chronic renal failure.

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**1438** Arthropathy of Inflammatory Bowel Disease and Restorative Proctocolectomy


The arthropathy associated with inflammatory bowel disease (IBD) remains enigmatic, but is thought to improve after proctocolectomy. The prevalence of arthropathy in surgically treated ulcerative colitis (UC) has been compared to that in patients operated on for familial adenomatous polyposis (FAP) in whom arthropathy is not expected. In the absence of good objective crite-

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**1439** Delayed Gastric Emptying of Patients with Insulin-dependent Diabetes Mellitus Analyzed by the 13C-Octanoic Acid Breath Test

J. Dreise, P. Hildebrand, T. von Buren, P. Maier, H. Schächinger, C. Beglinger. Dept. of Internal Medicine and Dept. of Research, University Hospital, CH-4031 Basel, Switzerland

The non-invasive and non-radioactive 13C-octanoic acid breath test has recently been shown to measure gastric emptying of solids (Ghose et al. 1993/1994). It seems to be sufficiently sensitive to detect pharmacologically induced changes of gastric emptying. The aim of the present study was to evaluate this new method in detecting clinically relevant changes of gastric emptying rates. Methods: 25 patients with a history of insulin-dependent diabetes mellitus with different stages of peripheral neuropathy, but well controlled blood glucose levels were studied. 12 healthy male vol-
unteers served as control group. After an overnight fast, the subjects con-
sumed a test meal consisting of two slices of white bread, an egg, the yolk of which was doped with 100 mg of 13C-octanoic acid, and 200 ml of water. After disintegration and absorption in the duodenum, octanoic acid is oxi-
dized to 13CO2 in the liver. Breath samples were taken before the meal and every 15 min thereafter for 4 h. Enrichment of exhaled 13CO2 was analyzed by means of isotope ratio mass spectrometry and expressed as % dose.

Half-emptying time and lag time were calculated using a power exponential model. Data were mean ± SD. Results: Half-emptying time of control subjects was 2.22 ± 0.21 h and significantly (< 0.02) increased in diabetic subjects (2.64 ± 0.71 h). The lag time was also significantly increased in diabetic subjects (1.86 ± 0.49 h) compared to controls (1.54 ± 0.19 h).

Conclusion: The non-invasive 13C-octanoic acid breath test is sensitive enough to detect delayed gastric emptying in patients with insulin-dependent diabetes mellitus.

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**1440** Colorectal and Anal Ambulatory Motility in Faecal Incontinence

F. Herbert, M.A. Kamm, J. Woloszko 1, R.J. Nicholls. St. Mark’s Hospital, London, UK. 1 Bakken Research Centre, Maastricht, The Netherlands

Faecal incontinence has traditionally been regarded as predominantly an anal sphincter problem. However, patients with "neurogenic incontinence" have impaired rectal sensitivity and reflex sphincter recruitment, and increased bowel frequency, suggesting a colonic abnormality. We have therefore studied colonic motility in this condition using ambulatory manometry.

Methods: Five women (mean age 60 years) without endosonographic structural sphincter damage were studied. Four had pudendal neuropathy (PNTML > 2.2 ms), 3 low resting pressure, and 4 low squeeze pressure. Af-

er an enema, a 6 sensor solid state transducer catheter was colonicoscopically inserted into the distal transverse colon, with five sensors in the colon span-
ning 60 cm and one in the anal canal.

Results: A mean of 42 hours (24–56) of uninterrupted recording time was accomplished. All patients had episodes of incontinence during study: one had passive incontinence only, the remaining four had a total of 8 episodes of urge incontinence. All episodes of urge incontinence were associated with one of three patterns of bowel activity: (i) high pressure (up to 450 cm H2O) propagated contractions starting as proximal as the transverse colon, (ii) multiphase high pressure contractions propagating distally, (iii) simultaneous high rectal and colonic pressure contrac-
tions. In each case the squeeze (external anal sphincter) response was in-
adequate (below colonic and rectal pressures).

Conclusion: The colon plays a fundamental role in urge faecal inconti-

nence. Extremely high colonic pressures and reflex sphincter recruitment of functionally deficient anal sphincter muscles lead to urge incontinence.

**1443** Histopathological Parameters Correlated to DNA Content and K-ras Mutation in a Study of 44 Colorectal Adenomas. N. Saraga, J. Benhattar, G. Dotta, P. Protiva, B. Sordat. All Blum, ChUx, Lausanne University, and ISREC, Epalinges, Switzerland.

**1444** Soluble Intercellular Adhesion Molecule-1: A Useful Marker of Histological Severity of Alcoholic Liver Disease. R.M. Beattie, S.H. Murch, P. Domizio, J.A. Walker-Smith. Academic Department of Paediatric Gastroenterology, St Bartholomew’s Hospital, London.

**1445** Longterm Home Enteral Nutrition in Switzerland (A Prospective 3 Years Study). B. Reiter1, M. Keller2, K. Schweingruber3 and Swiss Study Group for Home Enteral Nutrition. 1 Kantonsspital Liestal, Switzerland, 2 Basel, Switzerland, 3 SVK Solothurn, Switzerland.

Gut: first published as 10.1136/gut.37.Suppl_2 Pt_2.A121 on 1 January 1995. Downloaded from http://gut.bmj.com/
4th UEGW Berlin 1995

Biliary Lactoferrin is Increased in Active Inflammatory Bowel Disease — A Predisposing Factor to Primary Sclerosing Cholangitis?

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Primary sclerosing cholangitis (PSC) affects 3-10% of patients with inflammatory bowel disease (IBD). Although the pathogenesis of PSC is unknown, one theory suggests that an enterohepatic circulation of chemotactic factors or autoantigens, such as bacterial N-formyl peptides or lactoferrin (LF, stored in secondary granules of neutrophils), may play a role in the initiation of PSC. Normally, plasma LF concon are low but in active IBD, both circulating and farn-lactoferrin-concentrated in granulocytes anti-neutrophil cytoplasmic antibodies (P-ANCA) against LF are present in 22-79% of patients with IBD, and in 50-86% of patients with PSC. If the theory of an enterohepatic circulation of LF is correct, then resection of the diseased bowel should reduce biliary LF concentrations in IBD. Methods: To study this, we obtained gallbladder bile at laparotomy from 42 patients with ulcerative colitis (14 active colitis, 17 colectomy, 11 pouchitis) and 21 patients with Crohn's disease (7 active colitis, 5 post-colectomy with no ileal disease, 9 active ileitis or ileocolitis) — none of whom had clinical or biochemical evidence of PSC. Biliary LF was separated from high molecular weight glycopolymers by gel filtration, and quantitated by ELISA. Cross-reactivity of the assay with other biliary proteins was excluded by SDS-PAGE and Western blotting. To determine whether released LF or other farn-lactoferrin-concentrated in granulocytes also were secreted into the plasma, LF concentrations in control subjects, 16:0-20:4 and 16:0-22:6, were significantly higher than that in healthy controls (7.6 ± 0.5%, p < 0.001: and 5.3 ± 0.5%, p < 0.05; respectively). In the Crohn's disease patients, the mean lactoferrin colonic before treatment (2.8 ± 0.31 mg/l, range 0.9-5.0 mg/l) was significantly higher than that in the controls (0.05 ± 0.11 mg/l, p < 0.01). After 2 wk treatment, the SICDA in the Crohn's disease patients decreased to 3.0 ± 0.6 (p < 0.001), and there were corresponding falls in the ESR (to 12.6 ± 2.7 mm/h, p < 0.05) and concs were 3.0 mg/I: (1.3 ± 0.15 mg/l, range 0.32-3.2 mg/l, p < 0.001). In those with pouchitis, the mean biliary LF conc of 1.8 ± 0.34 mg/l was intermediate between that of the other two groups (p < 0.05). In patients with clinically active Crohn's colitis, the mean LF conc was 3.7 ± 0.9 mg/l, compared with 1.1 ± 0.24 mg/l in the post-colectomy group (p < 0.05) and 4.0 ± 0.98 mg/l in those with active ileitis or ileocolitis (p = 0.06 v post-colectomy value). In contrast, biliary myeloperoxidase concon were low and comparable in all groups, with a mean conc in the 63 patients of 12 ± 2.5 µg/l (range 0.2-60 µg/l).

Summary/Interpretation: In active ulcerative colitis and Crohn's disease, biliary LF concs are increased, but fall with colectomy/disease remission. These findings are consistent with the hypothesis that biliary chemotactic factors (which seem anti-neutrophil cytoplasmic antibodies (P-ANCA) against LF are present in 22-79% of patients with IBD, suggesting that farn-lactoferrin-concentrated in granulocytes may play a role in the pathogenesis of PSC.

Increased Plasma Arcarhodin Acid-rich Phospholipids in Active Crohn's Disease: Response to Treatment

S.P. Pereira, T. Ahmad, T.B. Cassell, J.L. Engelman, G.M. Murphy, G.E. Sieden, R.H. Dowling, Gastroenterology Unit, Guy's Hospital Campus, UMDS, London, UK

Increased concs of polyunsaturated fatty acids (PUFA), particularly arachidonic acid (20:4), in the plasma and intestinal mucosa have been implicated in the pathogenesis of active Crohn's disease. However, it is not known whether there are similar changes in the fatty acid composition of circulating phospholipids. We therefore compared the fatty acid composition of plasma phosphatidycholine (PC, the principal plasma phospholipid) in control subjects, with that in Crohn's disease patients studied before and during treatment, and measured the results to markers of disease activity. Methods: Fasted plasma samples were obtained from 17 control subjects (12 M; 5 F; mean age 31, range 22-55 yr) and from 13 patients (7 F; 6 M; 33 yr, range 23-54) with active Crohn's disease (8 ileal and 5 ileocolonic) before, and after two and eight wk treatment with either a peptide diet (Reptam 30-35 kcal/g) or prednisolone (0.5 mg/kg/d: n = 6). Disease activity was assessed by a simple index (Harvey & Bradshaw; SICDA). ESP and C-reactive protein. Plasma lactoferrin concs — which also correlate positively with Crohn's disease activity — were measured by ELISA. Plasma concs of LPD, from other plasma lipids by HPLC, and the molecular species (FA composition) determined by reverse-phase HPLC. Clinical remission was defined as a SICDA score of <6. Results: Before treatment, the Crohn's disease patients had mildly active disease (SICDA 9.8-3.0 SEM 0.8; ESP 23.8 ± 6.4 mmol/l; C-reactive protein 3.0 mg/l, normal < 1.0 mg/l). Their predominant plasma PC species were 16:0-18:2 (51.2 ± 3.0% of total PC), 16:0-18:2 (21.1%), and 16:0-20:4 (17%). In control subjects, over two-thirds of both polyunsaturated species, 16:0-20:4 and 16:0-22:6, were significantly higher than that in healthy controls (7.6 ± 0.5%, p < 0.001; and 5.3 ± 0.5%, p < 0.05; respectively). In the Crohn's disease patients, the mean lactoferrin colonic before treatment (2.8 ± 0.31 mg/l, range 0.9-5.0 mg/l) was significantly higher than that in the controls (0.05 ± 0.11 mg/l, p < 0.01). After 2 wk treatment, the SICDA in the Crohn's disease patients decreased to 3.0 ± 0.6 (p < 0.001), and there were corresponding falls in the ESR (to 12.6 ± 2.7 mm/h, p < 0.05) and concs were 3.0 mg/I: (1.3 ± 0.15 mg/l, range 0.32-3.2 mg/l, p < 0.001). In those with pouchitis, the mean biliary LF conc of 1.8 ± 0.34 mg/l was intermediate between that of the other two groups (p < 0.05). In patients with clinically active Crohn's colitis, the mean LF conc was 3.7 ± 0.9 mg/l, compared with 1.1 ± 0.24 mg/l in the post-colectomy group (p < 0.05) and 4.0 ± 0.98 mg/l in those with active ileitis or ileocolitis (p = 0.06 v post-colectomy value). In contrast, biliary myeloperoxidase concs were low and comparable in all groups, with a mean conc in the 63 patients of 12 ± 2.5 µg/l (range 0.2-60 µg/l).

Summary/Interpretation: In active ulcerative colitis and Crohn's disease, biliary LF concs are increased, but fall with colectomy/disease remission. These findings are consistent with the hypothesis that biliary chemotactic factors (which seem anti-neutrophil cytoplasmic antibodies (P-ANCA) against LF are present in 22-79% of patients with IBD, suggesting that farn-lactoferrin-concentrated in granulocytes may play a role in the pathogenesis of PSC.

Does Crypt Fission Account for the Monoclonality of G6PD Locus-Mutated Crypts After Treatment with Mutagens?

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Glucose-6-phosphate dehydrogenase (G6PD) gene is an X-chromosome linked non-essential gene. This enzyme is present in the intestinal crypt stem cells of the male C3H mice. Administration of mutagens leads to the emergence of crypts populated by cells with a G6PD-negative phenotype in the small intestine and colon. There is a transient rise in the frequency of partially-mutated pheno- type, followed by the disappearance of these partially-mutated crypts, con- temporaneously with the attainment of a plateau value of the wholly-mutated crypts. The plateau is reached at between 4.6 and 7 weeks in the colon and at 12 weeks in the small intestine of the same mice, using the mutagen ethyl nitrosourea (ENU). Explanations for this difference have included differences in the cell cycle time of a single ‘master’ stem cell and multiple stem cells occurring a stem cell ‘niche’ with random loss after stem cell division. However, we demonstrate that the incidence of crypts in fission, the crypt fis- sion index, is some four times higher in the colon than in the small intestine at the time of ENU injection, and therefore propose an alternative hypoth- esis to one crypt fission as the mechanism for the more rapid evolution of wholly-mutated crypts in the colon. Negative patches (two or more adjacent negative crypts) also appeared, later and fewer than single solitary mutated crypts. The frequency and size of patches increase with time. The growth rate of the small intestine with the colon.
The hypothesis predicts the results of future experiments — namely that the emergence of wholly-mutated crypts is proportional to the crypt fission index and that more deeply-mutated crypts may be attained by a process of crypt fission and the same process also leads to patches of mutated crypts.

### 1455 Spontaneous Seroconversion and the Role of Precore/Core Mutations in Chronic Hepatitis B

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**Background/Aims:** Spontaneous seroconversion is an important immunological event in patients chronically infected with hepatitis B virus (HBV) since it is often associated with a reduction in liver disease and vital elimination.

The mechanism of spontaneous clearance of hepatitis B antigen and the occurrence of anti-HBe in chronic hepatitis B has not yet been clarified.

In previous studies mutations within the precore/core (pre c/c) gene have been described and in frame deletions of the core gene have been observed several weeks before seroconversion. These data raise the possibility that core gene mutations may initiate spontaneous seroconversion by abrogating tolerance.

**Material and Methods:** To investigate this hypothesis, we studied three untreated, male caucasian patients with adult-acquired chronic HBV infection before spontaneous seroconversion. All patients had biopsy-proven chronic hepatitis, and direct sequencing and single stranded conformation polymorphism (SSCP)-analysis of the pre c/c gene on sequential samples before seroconversion. Briefly, the pre c/c gene of HBV was amplified by PCR. The PCR-product was labelled with 32P-ATP and after precipitation divided into 20 SSCP fragments. The labelled product was run on a 6% polyacrylamide gel under nondenaturing conditions and autoradiographed. Aliquots of identical samples were analyzed by direct sequencing the pre c/c gene.

**Results:** Direct sequencing in one patient showed a nucleotide change (from adenine to cytosine at position nt 2123 in addition to the preexisting viral strain) six months before seroconversion indicating the emergence of a new viral strain. In the other two patients no mutations or new strains could be detected. In a dilution series with known variants of the core gene SSCP-analysis detected the mutant strain when it represented 5% of total virions. Although more sensitive than direct sequencing SSCP-analysis of the three patients who seroconverted detected no novel strain that were not identified by direct sequencing.

**Conclusions:** In patients with adult-acquired chronic hepatitis B the appearance of nucleotide changes within the pre c/c region of the dominant viral strain is not a necessary prerequisite for the induction of seroconversion, although we cannot exclude a mutation in a subpopulation representing less than 5% of total virions.

### 1456 Porphyria Cutanea Tarda and Iron Overload

F. O'Reilly, C. Darby 1, R. O'Moore, M.G. Courtney, G. Murphy, J.F. Fielding. Depts of Medicine and Dermatology, Beaumont Hospital, Dublin, Ireland; 1 Dept Biochemistry, St James's Hospital, Dublin, Ireland.

Iron overload is found in all patients with haemochromatosis and 60% of patients with porphyria cutanea tarda (PCT). We therefore screened patients with iron overload for evidence of porphyric metabolic derangement. Patients with high serum ferritin: Group 1 (ferritin: 500-1000 ng/ml), and Group 2 (>1000 ng/ml) presenting to hospital over a four month period were identified from hospital records. Clinical and demographic history, ethanol consumption, haemoglobin, serum copper, liver function tests, Hepatitis A, B and C status and plasma, 24 hr urine and stool porphyrins were documented in relevant patients.

In this population identified by raised serum ferritin, we have detected 13 patients with haemochromatosis and 5 previously undetected patients with PCT. Three patients had both haemochromatosis and PCT as has been previously reported (Seymour DG, Elder GH, Fryer A, Gut 1990 Jun 31; 4: 719-21). A marked increase in direct sequencing and single stranded conformation polymorphism (SSCP) analysis of the pre c/c region of the dominant viral strain was not found in these patients.

**Treatment of Ulcerative Colitis with an Engineered Human Anti-TNF-α Antibody CDP571**

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Tumour Necrosis Factor is a pro-inflammatory cytokine whose expression is increased in the bowel wall of patients with active Ulcerative Colitis (UC). TNFα antibodies have previously been shown to be beneficial in animal models of bowel inflammation.

**Aims:** To assess the safety and efficacy of an engineered human anti-TNF-α antibody CDP571, in a preliminary open trial in patients with mild or moderately active Ulcerative Colitis.

**Methods:** Patients with mild/moderate Ulcerative Colitis were treated with a single intravenous infusion of 5 mg/kg of CDP571. Their disease was assessed by Powell-Tuck score, C-Reactive Protein (CRP), sigmoidoscopy score and biopsy score (to be assessed blind at the end of the study).

**Results:** At present, 10 patients are at least 2 weeks post-infusion. Mean age 46.5 y; male 6 and female, with left sided disease.

### Table

<table>
<thead>
<tr>
<th>Mean Values (SSD)</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell-Tuck Score</td>
<td>6.0(2.5)</td>
<td>4.4(2.5)</td>
<td>5.1(2.3)</td>
</tr>
<tr>
<td>CRP</td>
<td>15.2(13.7)</td>
<td>8.5(4.2)</td>
<td>9.8(7.3)</td>
</tr>
<tr>
<td>Sigmoidoscopy Score (0-4)</td>
<td>2.3(0.7)</td>
<td>Not done</td>
<td>1.0(0.8)</td>
</tr>
</tbody>
</table>

* *n* = 9 for this result. All other results *n* = 10.

The plasma level of the antibody was ≥130 μg/ml at the end of the infusion and was eliminated from the circulation with a half-life of 7±7 days.

**Conclusion:** All patients have shown improvement in the Powell-Tuck and sigmoidoscopy scores and in CRP! These beneficial effects are evident by one week after infusion. The initial results of this open study are encouraging and patient enrolment continues.

This work was supported by Celtech Therapeutics Ltd, 216 Bath Road, Slough, SL1 4EN.

### 1458 Porphyria Metabolism in Hepatitis C Infection Secondary to Anti-D Immunoglobulin

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Patients with porphyria cutanea tarda (PCT) have been found to have Hepatitis C antibodies ranging in prevalence from 10% in Ireland (3) to 79% in Spain (3). These studies suggest that hepatitis C virus may be a triggering factor for PCT (1, 2, 3). Porphyria metabolism is also perturbed in patients with both HCV and HIV infection acquired mainly as a consequence of intravenous drug abuse (4).

Thirty-four female patients, known to be HCV positive by Elisa (Ortho Diagnostic Systems) and RIBA 3 were studied. The year of immunization and an ethanol and drug history was obtained from all patients. Haemoglobin, serum ferritin and copper, liver function tests, hepatitis A, B and C status were assessed. Plasma porphyrinids and 24 hr urinary uroporphyrin, coproporphyrin,aminolevulinic acid and porphobilinogen were analysed. All patients had a liver biopsy. The mean age of the group was 44 yrs (range 30-56). The mean duration of HCV infection was 18.7 yrs (range 4-28). Liver function tests were abnormal in 27 (76.4%). Two patients had raised serum ferritin. Liver histology was abnormal in 31 (91.2%). There was no evidence of alcohol abuse in the group studied. One patient was on oestrogen. Porphyria excretion was normal in all patients.

Patients studied in Ireland with PCT and HCV infection had additional risk factors for PCT. HCV infection alone appears insufficient to induce porphyria metabolic derangement.

### 1460 Porphyria Metabolism in Hepatitis C Infection Secondary to Anti-D Immunoglobulin and Intravenous Drug Abuse

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Hepatitis C virus (HCV) has been implicated as a possible triggering factor for porphyria cutanea tarda (PCT) with hepatitis C patients having a higher prevalence ranging from 10% in Ireland to 76% in France. We therefore compared porphyrin metabolism in 2 groups of patients with HCV infection.

Group 1 comprised 34 Rhesus negative women immunised with anti-D immunoglobulin (age range 30-56, mean 44 yrs); Group 2, all HIV negative intravenous drug abusers (IVDA), included 14 male, 11 female (age range 16-43, mean 28 yrs) HCV positive patients (Elisa and RIBA 3). Haemoglobin, serum ferritin, liver function tests, Hepatitis A and B status and plasma uroporphyrin III were measured. One patient in Group 1 was on oestrogen therapy. Three in Group 2 abused alcohol.

Porphyria excretion was normal apart from 3 (12%) in Group 2 with elevated free erythrocyte protoporphyrin, ranging from 756-986 ng/ml (normal <590). Liver function tests were abnormal in 27 (76.4%) in Group 1 and 19 (76%) in Group 2. Ferritin levels were elevated in 2 (5.9%) at 267 ng/ml and 671 ng/ml (normal: 8-110) in Group 1 alone.

HIV and HCV infection are associated with significantly abnormal porphyrin metabolism. Four of 59 patients with HCV infection alone, had mildly abnormal porphyrin profiles. Other factors, including, progressive liver disease, genetic predisposition, older age, ethanol, iron overload and oestrogen therapy may be necessary to precipitate overt PCT.

### 1461 The Non Effect of Prepyloric Site and Multiple Sampling on the Diagnostic Yield of the CLO Test


**Aim:** to determine if the site of prepyloric biopsy or multiple sampling enhanced the diagnostic yield of the CLO test.
Methods: 100 consecutive patients undergoing upper intestinal endoscopy who had no contraindication to biopsy had 4 prepyloric biopsies taken. The biopsies were taken from between 2 and 5 cm proximal to the pylorus and from the posterior, inferior, anterior and superior aspects of the pyloric canal. The first 25 patients had the anterior biopsy sent for histology and the other three samples were CLO tested. The ensuing groups of 25 had retrospectively the posterior, inferior and anterior specimens sent for histology and their other three samples CLO tested. Thus each site had 75 CLO tests to compare with the histological result. The CLO tests were read at 5 and 20 minutes and at 1 and 24 h. The sensitivity specificity, positive predictive value and negative predictive value of the CLO test for each site read at 24 hours were: Anterior 80.5 (64.6–90.6) 97.1 (82.9–98.9) 97.1 (82.9–99.8) 80.5 (64.9–90.6); Superior 82.2 (67.4–91.5) 100 (85.9–100) 100 (88.3–100) 78.9 (62.2–89.9); Posterior 73.3 (50.9–91.9) 97.1 (82.9–99.8) 97.1 (82.9–98.7) 73.3 (43.8–83.4); Inferior 76.5 (60.8–85.2) 98.2 (78.4–99.8) 97.4 (84.9–99.9) 76.7 (50.1–81.1).

Conclusion: neither the prepyloric site nor multiple sampling influenced the diagnostic yield of the CLO test.

1462 Intrafamilial Transmission of Anti-D Associated Hepatitis C Virus — A Zero Risk?
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Hepatitis C virus (HCV) is predominantly spread by parenteral routes, but there may be significant intrafamilial transmission. Aim: we surveyed 60 women who had been infected with HCV after receiving contaminated anti-D immunoglobulin. These Rhesus negative women were infected in 1977 (45), 1979 (2), 1982 (1), 1987 (2), 1990 (2), 1991 (3). All were positive for HCV antibodies by ELISA (Ortho, Murex) and RIBA3 (Ortho) were viraemic by PCR for HCV-RNA (Roche). Liver biopsies were performed which revealed mild to moderate chronic liver disease in 55 and severe chronic liver disease in five. All had stable longterm relationships. Thirty partners and 109 children were tested for HCV antibodies by ELISA (Ortho, Murex). No other risk factors were elicited in the contacts.

Results: No male partners or children tested positive for HCV antibodies indicating no previous exposure over a combined time period of 544 years for partners and 1575 years for children.

Conclusion: This study suggests a zero female to male sexual transmission rate of HCV in contrast to the much higher transmission rate in men. This contrasts with previous studies and may possibly be explained by the HCV genotype, low inoculum at infection, the overall mild hepatic insult and other factors such as genetic and geographic variables. The rest of the partners (30) and children (99) are presently undergoing further testing.

1463 Lack of Evidence of Autoimmune Disease in Anti-D Associated Hepatitis C Virus Infection
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Previous studies have suggested that Hepatitis C Virus (HCV) infection is associated with a high prevalence of autoimmune disease. Aim: We have investigated patients chronically infected with HCV due to anti-D immunoglobulin injection with respect to symptoms and signs of autoimmune disease and presence of autoantibodies and cryoglobulins. Results: 55 female patients, mean age 45.0 years (range 25–56) years infected with HCV contaminated anti-D immunoglobulin in 1977 (45), 1979 (2), 1982 (1), 1990 (2), 1991 (3). 1991 (3) were surveyed clinically and by serology to ANA, AMA, LKM-1, SMA, Thyroid microsomal, Thyroid globulin, Panet cell antibodies, Rheumatoid factor and Cryoglobulins. The mean duration of infection was 15.1 years (range 13–17 years). There were no patients with specific symptoms or signs suggestive of autoimmune disease. Cryoglobulins were not detected in any patient. In 6 patients (11%) thyroid microsomal antibodies were detected, in 2 of these, thyroid globulin antibodies were also positive. These patients were clinically euthyroid. In 5 patients (9%) ANA titres were weakly positive and in 5 patients (9%) gastric pancreatic antibodies were positive. No antibodies to LKM-1 were noted. Eight patients (14%) were positive for rheumatoid factor. These levels of autoantibody seroreactivity are no higher than “background” levels in the normal population.

Conclusion: This unexpected finding of lack of autoimmune phenomena in chronic Hepatitis C may be explained by the HCV serotype, by the long period of infection, by the low HCV inoculum at infection and/or by host factors.

1464 Histological Abnormality in Chronic Hepatitis C does not Correlate with the Presence or Absence of a Single Anti Core IgM Antibody
S. Sachithanandan, S. Al-Bloushi, M.G. Courtenay, E. Kay, C. Barry-Walsh, D. Royston, M. Leader, J. Quinn, N. Perfrey, A.G. Shattock, J.F. Fielding. Dept of Medicine and Pathology, RCSI and Beaumont Hospital, Dublin and National Virus Laboratory, Laboratory, Dublin

Liver histology in chronic hepatitis C (HCV) infection remains the gold standard investigation, but is invasive and potentially hazardous.

1465 Two Year Old Hepatitis A Vaccine (Havrix) Retains its Immunogenicity

Results: 3-17 year old children tested negative for HAV and were given a single dose of Havrix. All 65 children tested negative for anti-HAV by ELISA at two years. The mean ELISA titre was 1:1,024 which is the same as in younger children.

Conclusion: This study shows that the hepatitis A vaccine is as effective in children two years old as in younger children.

1466 No Evidence of Hepatitis E Virus Infection in Irish Haemodialysis and Intravenous Drug Abusing Patients
M.G. Courtenay, M. O’Mahoney, S. Al-Bloushi, S. Sachithanandan, J. Walshie, M. Carmody, J. Donohoe, N. Perfrey, J. O’Connor, A.G. Shattock, J.F. Fielding. National Virus Research Laboratory, Dublin, Ireland; Dept of Medicine, RCSI & Beaumont Hospital, Dublin, Ireland

Hepatitis E Virus (HEV) is an enterically transmitted hepatotropic virus which causes acute or subacute hepatitis. Hepatitis E infection is distinctly uncommon outside Southern Europe, North Africa and Asia. It has been suggested that haemodialysis patients in Southern France have a high prevalence of HEV antibodies (11%) raising the possibility that transmission may occur at least partially by parenteral routes. Aim: to test this theory we have surveyed haemodialysis patients and intravenous drug abusing patients (IVDA) attending our hospital for evidence of previous HEV infection using a recently devised indirect enzyme immunoassay for total IgG to HEV (Abbott Diagnostics, Wiesbaden, Germany).

Results: 45 haemodialysis patients (20 males, 25 females, mean age 55.0 years, range 17–83 years) and 30 IVDA patients (22 males, 8 females, mean age 29.0 years, range 19–59 years) were screened for HEV antibodies. No patients (0%) tested positive for HCV IgM antibodies, suggesting no previous exposure to HEV. This is the first report of HEV antibody testing in Northern European haemodialysis and IVDA populations and is significantly lower than the 11% in the South of France haemodialysis study. This may indicate a pronounced north-south gradient in Europe for HEV positivity in haemodialysis patients or may be due to localized influences.

Conclusion: This study does not support the concept of parenteral transmission of HEV.

1467 Serum Bile Acids, Plasma Cholecystokinin (CCK), and Gallbladder Motility After Ileal Resection (IR)
J.M.J. Salamens, F.M. Nagengast, A. van Schaij, A. Tangerman, W.P.M. Hopman, J.B.M.J. Jensen. Dept of Gastroenterology, University Hospital Nijmegen, The Netherlands

IR is associated with bile acid malabsorption and an increased risk for cholelithiasis. A decreased duodenal bile acid output and increased bilary
ursodeoxycholic acid (UDCA) fraction have been found after IR. The aim of this study was to examine whether IR leads to alterations in bile acid ab- sorption, deconjugation, 7α-dehydroxylase, and formation of UDCA. Since intraduodenal bile acids may influence the release of CCK we further studied the effect of IR on plasma CCK and gallbladder volume (GBV). Methods: 8 patients with Crohn's disease and a history of IR (MF = 8/5, mean age 39, op- eration 1–14 yrs before this study, length of IR: 30–70 cm) and 12 healthy con- trols (MF = 8/4, mean age 43) were studied. None of the subjects were using cholestyramine. Fasting and postprandial blood samples were obtained at 15 min intervals (3 hours) for conjugated (c) and unconjugated (unc) (cholaric, chenodeoxycholic (CDCA), deoxycholic (DC), and UDCA (capsular gas-liquid chromatography) and GBV (RIA). GBV was measured using ultrasonography. Results:

**Aims.** An inverse relationship between appendectomy and Ulcerative colitis (U.C.) and smoking and U.C. has been proposed. Our study examines the frequency of common surgical interventions and of smoking in a group of IBD patients and correlates it with the need for surgical treatment (N.S.) and smoking.

**Methods:** 440 patients were interviewed in a prospective, questionnaire based case control study. The subjects comprised 148 patients with U.C, 117 patients with Crohn's and 175 controls derived from an Orthopaedic Trauma- clinic matched for age, sex and socioeconomic group. Subjects were questioned on all previous surgery and on smoking history. Results: The appendectomy rate amongst controls was 18.2% (32/175) While this was significantly lower than that of U.C. patients 10.3% (15/148) p < 0.05) 11 of the U.C. patients had appendectomy prior to the onset of disease. The appendectomies were evenly distributed through the 3 categories of disease extent (Proctitis, left sided and extensive colitis). There was no sig- nificant difference in appendectomy rate between Crohn's patients and con- trols. The 3 groups had comparable rates of Tonsillectomy and Choledoc- tomy. 83.2% of the U.C. patients were non-smokers at the time of diagnosis in contrast to 50.4% amongst the Crohns patients (p < 0.01).

Conclusions: U.C. is associated with significantly lower smoking rate than in controls. This is not true for other surgical procedures unrelated to treatment of U.C. The role of the appendix in the evolution of U.C. requires definition and clarification with large multicentre studies.

**1469 Unconjugated Serine Bile Acid Levels in Patients with Small Intestinal Bacterial Overgrowth (SIBO) and Other Malabsorption Syndromes**

J.M.J. Salesma, A. Tangerman, A. van Schaik, E.W. van der Hoek,
J.B.M.J. Jansen, F.M. Nagengast. Dept of Gastroenterology, University Hospital Nijmegen, 1 Department of Medicine, Carolus Hospital, Den Bosch, The Netherlands

Unconjugated serine bile acid levels have been found to be elevated in patients with SIBO. In order to assess sensitivity and specificity of unconjugated serine bile acid as a test for SIBO we studied individual and total fasting unconjugated serine bile acid levels in healthy controls, patients with SIBO, and in patients with other malabsorptive states. Methods: 24 healthy subjects, 11 patients with culture proven SIBO, 15 patients with other malabsorptive states (8 patients with untreated coeliac disease (CD), and 11 patients with chronic pancreatitis (CP) with pancreatic insufficiency), 10 patients with ileal resection (IR), and 11 patients who had undergone proctocolectomy with ileal pouch-anal Anastomosis (IPAA) participated in the study. Fasting serine bile acid were measured using capillary gas-liquid chromatography. Results: Ind- individual as well as total unconjugated serine bile acid levels were significantly elevated in patients with SIBO compared to the other groups. Total unconju- gated serine bile acid (μmol/l):

<table>
<thead>
<tr>
<th>Mean</th>
<th>Median (range)</th>
<th>p vs SIBO</th>
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<tbody>
<tr>
<td>Controls</td>
<td>0.03 (0.21–3.85)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>SIBO</td>
<td>3.57</td>
<td>3.96 (1.46–3.35)</td>
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<tr>
<td>CD</td>
<td>1.13</td>
<td>1.01 (0.56–1.86)</td>
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<tr>
<td>CP</td>
<td>1.31</td>
<td>1.07 (0.90–2.43)</td>
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<tr>
<td>IR</td>
<td>2.09</td>
<td>0.22 (0.33–3.54)</td>
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<tr>
<td>IPAA</td>
<td>1.10</td>
<td>0.96 (0.47–1.90)</td>
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</table>

**1470 Surgical and Smoking History in I.B.D.: A Case Control Study**

N.P. Breslin, C. MacDonnell, C. O'Morain. Gastroenterology Unit, Meath-Adelaide Hospitals, Trinity Medical School, Dublin

**Aims:** An inverse relationship between appendectomy and Ulcerative colitis (U.C.) and smoking and U.C. has been proposed. Our study examines the frequency of common surgical interventions and of smoking in a group of IBD patients and correlates it with the need for surgical treatment (N.S.) and smoking.

**Methods:** 440 patients were interviewed in a prospective, questionnaire based case control study. The subjects comprised 148 patients with U.C, 117 patients with Crohn's and 175 controls derived from an Orthopaedic Trauma clinic matched for age, sex and socioeconomic group. Subjects were questioned on all previous surgery and on smoking history. Results: The appendectomy rate amongst controls was 18.2% (32/175) While this was significantly lower than that of U.C. patients 10.3% (15/148) p < 0.05) 11 of the U.C. patients had appendectomy prior to the onset of disease. The appendectomies were evenly distributed through the 3 categories of disease extent (Proctitis, left sided and extensive colitis). There was no significant difference in appendectomy rate between Crohn's patients and controls. The 3 groups had comparable rates of Tonsillectomy and Cholecystectomy. 83.2% of the U.C. patients were non-smokers at the time of diagnosis in contrast to 50.4% amongst the Crohns patients (p < 0.01).

Conclusions: U.C. is associated with significantly lower smoking rate than in controls. This is not true for other surgical procedures unrelated to treatment of U.C. The role of the appendix in the evolution of U.C. requires definition and clarification with large multicentre studies.

**1473 Clarithromycin (CL) in Combination with Omeprazole (OM) for Treatment of Helicobacter Duodenal Ulcers (DU), Prevention of DU Recurrence, and Eradication of H. pylori (HP) in Two European Studies**

C. O'Morain, R. Hogan and the Clarithromycin European H., pyloki Study Group. Meath Hospital, Dublin, Ire., BHURG study, St. Mary's Hospital, London, UK

Patients with HP and DU were enrolled in two well-controlled, randomized, double-blind, multi-center studies. Patients received for two weeks either CL 500 mg TID and OM 40 mg QD or OM 40 mg QD alone; all patients received an additional two weeks of OM 40 mg QD in one study and 20 mg QD in the other. Patients were followed for 8 months. An endoscopy was performed at the end of the study and 14 patients were excluded. The results at the end of the study and 14 patients were excluded. The results at the end of the study and 14 patients were excluded. The results were: 5% (5/92) of HP negative CL + OM patients and 13% (5/39) of HP positive CL + OM patients had recurrence of ulcer while 53% of HP positive OM patients had recurrence of ulcer at the end of the 8 months follow-up.

Both studies failed to demonstrate statistically significant difference of CL + OM patients vs 2% of OM patients discontinued Rx due to adverse events.

**1474 Nutritional Evaluation of Non-Surgical Patients**

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Information concerning the frequency of malnutrition of patients at a ward for Gastrointestinal Diseases and a ward for Internal Lower Endoscopy appeared important to determine the need for a nutritional team. Data concerning non-surgical patients are lacking and data on surgical patients are sometimes inconsistent, partly because of differences in methods. At entry and at discharge we graded malnu- trition of non-surgical patients into “none”, “mild”, “moderate” and “severe” and used: Subjective Global Assessment (SGA); a clinical score, Nutritional Risk Index (NRI; 1498stb/L + 41.7*actual/usual weight), NEJM 325:325. Nutritional Index (NI), 20.1–0.24*alb-19.68*pre-alb-1.86*total lymphocytes-0.04*(ideal weight. Clin Nutr 4:81) and Nutricia Score (NS; which com- bines weight, skinfolds, arm circumference, grip strength, alb, pre-alb, lympho- cytes, creatinine-length index and changes in weight). If the results of the methods differed by more than one category, we considered the results as a significant discrepancy. In 34 gastrointestinal (GI) and 56 internal patients frequency of any grade of malnutrition was: SGA 41, NRI 52, NI 64, NS 80%. More malnutrition was observed in GI patients (SGA 61 vs 36% p = 0.003 and NS 56% vs 47% ns). In patients with liver index (≥ grade varied from 4% to 31%. At discharge nutritional status had improved according to NI (49% vs 64%, p = 0.05), NS (70% vs 80%, p = 0.06) but worsened non- significantly according to the SGA. In conclusion at least 41% of patients were well nourished at admission, but frequencies were dependent on the method used. During the stay at the ward a tendency towards an improvement of the nutritional status was observed.
**Effect of Sodium-chenodeoxycholate on Basal and CCK-Induced Gallbladder Motility, Pancreatic Enzyme Secretion and Plasma PP Levels**


Bile salt diversion from the gut modulates gallbladder motility and pancreatic enzyme secretion, possibly by interference with plasma cholecystokinin (CCK) release. To further elucidate the role of bile acids in the regulation of pancreatic-biliary function we studied the effect of intraduodenal (i.d.) perfusion of sodium chenodeoxycholate (CDCA) on basal and CCK-induced gallbladder motility, pancreatic enzyme secretion and plasma pancreatic polypeptide (PP) levels.

Methods: Two tests were performed in 7 healthy subjects (2 M, 5 F, 18–28 yrs.). Saline (5 mL/min) with or without CDCA (0.5 g/h) was continuously perfused i.d. for three hours. During the last two hour test CCK (0.3 I.U. kg −1) was infused i.v. (5 mL/min) (chro-matography), gallbladder volume (ultrasonography) and amylase output (spot sampling using PEG-4000 as a recovery marker) were measured at regular intervals.

Results: Plasma CDCA levels in the CDCA study were significantly (p < 0.01) increased when compared to the saline study (3.8 ± 0.9 vs 0.8 ± 0.2 µM and 12.6 ± 2.6 vs 4.7 ± 2.7 µM after 2 h and 3 h of perfusion respect.). CDCA increased basal gallbladder volume from 28 ± 5 mL to 35 ± 7 mL (p < 0.05). CDCA was without significant amylase effects and CDCA diminished CCK-stimulated values for integrated gallbladder contraction from 2365 ± 309% 60 min to 1133 ± 178% 60 min (p < 0.05), integrated plasma PP from 787 ± 300 pM 60 min to 138 ± 93 pM 60 min (p < 0.05) and tended to decrease incremental amylase output from 3.0 ± 1.6 to 1.8 ± 0.9 kU/L (NS).

Conclusion: Duodenal perfusion of CDCA decreases basal and CCK-stimulated gallbladder motility, abolishes the rise in CCK-induced plasma PP levels but without significant effect on pancreatic enzyme secretion. These data indicate that CDCA inhibits the effects of CCK on gallbladder motility and PP release.

**Effect of Intraduodenal Digestible and Non-digestible Fat on Gastrin Stimulated Gastric Acid Secretion**

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Fat in the small intestine stimulates cholecystokinin (CCK) and inhibits gastric acid secretion. It is not known whether intact or hydrolysed triglycerides are responsible for this enterogastrone effect. In the present study we have investigated whether digestible fat (frying-oil) or non-digestible fat (sucrose polyester, SPE) containing fatty acids of comparable chain length inhibits gastrin stimulated gastric acid secretion and stimulates plasma CCK.

Methods: 8 healthy volunteers (M 8, 23 ± 2 yrs) were studied. 3 experiments were performed in each volunteer in random order on different days. In all experiments gastrin-17 was infused for 180 min in a dose of 10 pmol/kg/h. This dose results in plasma gastrin concentrations comparable to those after a meal. After one hour the duodenum was perfused with equimolar amounts of fatty acids (62 mmol/h) of either digestible (fat) or sucrose polyester (SPE) for 90 min, at a perfusion rate comparable to the gastric emptying rate of fat after a meal. In the third experiment saline instead of fat was perfused. We have measured gastric acid secretion (henol red colour recovery technique) and plasma gastrin and CCK concentrations (RIA's) at regular intervals.

Results: Infusion of gastrin resulted in plasma gastrin concentrations ranging from 46 ± 2 to 55 ± 5 pM. Digestible fat (+66.3 ± 10.9 pM 60 min) but not SPE (+24.7 ± 14.5 pM 60 min) stimulated plasma CCK when compared with saline (−5.4 ± 13.9 pM 60 min; p = 0.0092). Gastrin-stimulated gastric acid secretion during saline perfusion (21.0 ± 1.6 mmol H+lh) was inhibited by SPE (17.9 ± 2.4 H+lh; p = 0.004) compared to saline (17 ± 4% LCT). CCK inhibited gastric acid output significantly more than CCK (p = 0.05). CCK failed to inhibit gastric acid output (18 ± 6%).

Conclusions. Intraduodenal CCK inhibits gastric stimulated gastric acid secretion significantly more than CCK. But not CCK stimulated the release of CCK. However, infusion of CCK to plasma concentrations somewhat higher than during perfusion of LCT did not inhibit gastrin stimulated gastric acid secretion.

**The Reliability of Saliva as a Sample for Diagnosis of Hepatitis A Infection Under Various Sampling Conditions**

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Experience has proven the usefulness of serum as a diagnostic sample. Saliva, however, would be superior to serum as a sample in a number of ways. Acquisition is simpler than venepuncture, is painless and non-invasive, and the sample itself presents less danger to those handling it than does blood. The usefulness of salivary immunoglobulin (Ig) as a diagnostic tool depends ultimately on its reliability as a source of information. One of the major and most basic advantages of serum in diagnosis is its reliability. The composition of saliva, however, is known to be extremely variable. Whether or not the salivary IgA A level is related to the incidence of disease in an area and the organism being obscured under certain conditions is largely unknown. In order for salivary immunoglobulin to be of diagnostic use, the level of the specific immunoglobulin detected must not vary too much to an extent that the response is obscured under a particular set of conditions.

We have investigated the effects of eating, brushing of teeth and circadian rhythm on the apparent salivary immune status of 35 individuals known to be infected and anti-HAV positive, and from an equal number of anti-HAV negative individuals. Saliva samples were obtained from the subjects before and after meals, before and after brushing of teeth, and at various timepoints throughout the day. To date, samples from 20 anti-HAV positive and 20 anti-HAV negative individuals have been assayed for total IgG and for total anti-
HAV using in-house assays. The salivary anti-HAV assay was known to have a 99% correlation with a serum based assay after the assay of 405 paired serum and saliva samples, of which 236 were anti-HAV serum positive and 234 saliva samples were positive for false salive positives and no false negatives.

The results to date indicate that there was no significant difference between the levels of total IgG in the saliva of anti-HAV positive and negative individuals, but the levels in both groups were subject to minor variation throughout the day and under varying conditions. The levels of specific anti-HAV in the subjects’ saliva also varied with time of day, chewing and brushing of teeth, but never to the extent that the immune status of the individual was obscured. These results appear to confirm the usefulness of saliva as a diagnostic sample for the detection of Hepatitis A infection.

1481 IgM Anti-HCV Testing may Reduce Need for PCR Testing
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Conventional serology for Hepatitis C Virus (HCV) by enzyme-immunoassay (ELISA) provides evidence of infection, past or present, but does not indicate infectivity. Recombinant immunoblot assay (RIBA) correlates better than ELISA with the presence of HCV genome by the polymerase chain reaction (PCR) which currently tends to be the “gold-standard” for infectivity. However, both RIBA and PCR are slow, subjective, labour intensive and therefore expensive. In most viral infections the appearance of IgM antibodies provides an indication of an acute infection, while persistently low levels are often found in chronicity.

**Aim:** To evaluate a new test for IgM anti-HCV (Abbott Diagnostics, Weisbaden, Germany) on 42 anti-HCV positive recipients of anti-D immunoglobulin, in comparison with “in house” PCR and Roche Amplicor PCR. Results: Of the 42 patients, 29 (69%) were positive for IgM anti-HCV and by both PCR methods. Five patients were negative for IgM anti-HCV and by PCR. In 7 cases PCR was positive but IgM anti-HCV was not found. In one case, IgM was positive but PCR was negative but the patient had been treated with interferon. Thus there was a 100% positive correlation between the presence of IgM anti-HCV and the presence of HCV genome in untreated chronic HCV infected patients (X2 11.1 0.001) but not necessarily the reverse. Conclusion: We conclude that IgM anti-HCV testing at approximately one-third of the cost of PCR may provide an economical aid to minimizing the need for a significant proportion of PCR testing in chronic HCV infection.

1482 Loperamide Modulates Basal and Amino Acid Stimulated Pancreatico-biliary Secretion, Plasma CCK and PP Release
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Loperamide, an opiate receptor agonist is clinically used to reduce chronic diarrhoea. Since opiate receptors are widely distributed throughout the gastrointestinal tract, we studied the effect of loperamide on pancreatico-biliary secretion.

**Methods:** Six healthy subjects (4 M, 2 F; 23 ± 1 y) were studied on 2 different occasions. In test 1, saline (SAL) was continuously perfused i.d. for 3 hours (300 mL/h). During the last test hour 6.9 g of an amino acid mixture (AA) containing valine, methionine, tryptophan and phenylalanine was also given i.d. Test 2 was performed according to the same protocol as test 1. However, 13 and 4 hours prior to the start of AA-perfusion, 8 mg of loperamide were ingested. At regular intervals plasma CCK and PP (RIA), duodenal amylase and bilirubin output (spot sampling using PEG-4000 as a recovery marker) were measured.

**Results:** Loperamide plasma levels at the start of AA-perfusion were 2.7 ± 0.2 ng/mL in test 2. Loperamide completely abolished basal bilirubin output when compared to SAL (167 ± 35 mmol/h) and decreased amylase output from 3.9 ± 0.06 to 1.1 ± 0.6 kU/h (p < 0.05). AA-stimulated bilirubin (37.0 ± 5.3 mmol/h) and amylase output (5.4 ± 1.0 kU/h) were also decreased (p < 0.001) by loperamide (14.9 ± 3.8 mmol/h and 1.5 ± 0.5 kU/h respectively). Loperamide had no effect on basal plasma CCK and PP. However, AA-stimulated plasma CCK (41 ± 23 pmol/60 min) increased (p < 0.05) after loperamide (116 ± 29 pmol/60 min) while AA-stimulated plasma PP levels (180 ± 69 pmol/60 min) tended to be reduced (NS) by loperamide (108 ± 42 pmol/60 min).

**Conclusion:** Loperamide inhibits basal and AA-stimulated pancreatico-biliary secretion despite an enhanced plasma cholecystokinine release. These data indicate that opioid receptors can modulate the effect of a meal on pancreatic enzyme secretion and gallbladder motility.

1483 Analysis of Fecal Short-Chain Fatty Acids, Using a Direct Injection Gas Chromatographic Method
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During the past decade there has been a growing interest in the role of short-chain fatty acids (SCFA) in colonic disorders. SCFAs have been difficult to analyze in biological samples. Gas chromatography, preceded by some kind of cumbersome pretreatment method such as vacuum distillation, is used most often. Many pitfalls have been found in the chromatographic analysis of SCFAs. The purpose of this study was to develop a simple, rapid and quantitative analysis of fecal SCFA.

The method involves direct injection of fecal water samples into the gas chromatograph, without any pretreatment. Contamination of the gas chromatographic column with non-volatile fecal material was prevented by the use of a glass-wool stoppered empty glass liner in the injector. Injection was performed inside the liner in the headspace above the glass-wool plug. The liner was replaced by a new one after 100 injections of fecal water. Peak tailing and ghosting was prevented by the use of formic acid in the fecal samples. Recoveries of the individual SCFAs from spiked samples of fecal water and feces ranged between 92% and 102%. The intra-assay and inter-assay reproducibility was excellent. Coefficients of variation fell below 5%. The detection limit amounted to 0.1 mmol/l for acetic acid and to 0.02–0.05 for the other SCFAs. Acetic acid, propionic acid and n-butyric acid are quantitatively the most important ones and constitute about 90% of intestinal SCFAs in molar ratios of ca. 68:20:12. The total concentration of SCFA in fecal water amounted to 119.5 ± 44.9 mmol/l (mean ± SD, n = 24).

In conclusion, the direct injection gas chromatographic method as presented here is a rapid, sensitive and reliable procedure for measuring fecal SCFAs. The complete SCFA analysis requires only 5 min. This method highly facilitates research in this field.

1484 HCV Viruria After Exposure to Anti-D Immunoglobulin: Quantitative Measurement and Histological Correlation
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**Aim:** Viruria was confirmed by qualitative PCR. Quantitative PCR was measured using the Roche HCV monitor on 3 different. Liver biopsies were scored by HAI and biopsies were stained for iron.

**Results:** Serum HCV RNA titre on presentation ranged from 2.0 × 10^6/mL to 4.0 × 10^5/mL. Serum ALT ranged from 8.49 to 14.04 u/mL. HAI ranged from 14 to 1 for inflammation (maximum possible score 18) and 0 to 3 for fibrosis (maximum possible score 4).

**Summary:** Significant variation in quantitative HCV RNA has been demonstrated in a group of women with chronic HCV infection. There is a low incidence of cirrhosis in the group.

**Conclusion:** Quantitative HCV RNA levels in serum of a chronically infected group of women show wide variations despite likely similar infective dose. Viral levels correlated poorly with serum ALT and HAI.

1485 Dynamic Rectal Examination: Clinico-radiological Correlation
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Many patients referred for a Dynamic Rectal Examination (DRE) appear to have severe complaints which interfere strongly with daily activities and normal social life. The main purpose of DRE is to provide both qualitative and quantitative information with respect to anorectal and pelvic floor function, anal sphincter function and effectiveness of rectal evacuation. DRE is a safe and cheap, relatively simple procedure which is well tolerated. The parameters which can be assessed from DRE include a number of features that can be measured, such as anorectal angle, the position of the anorectal junction, perineal assessed and perineal descent. Anatomic changes such as rectocoele, enterocele and intussusception can be observed. To date hardly any study correlating radiological findings and patients complaints has been published.

We prefer the term DRE to defecography, since we consider this type of examination not only as recording the emptying of the rectum, but also as an evaluation of the dynamic factors. In DRE in contradistinc- tion to defecography, all patients routinely ingest liquid bariumcontrast two hours before the examination to opacify the small bowel during the examina-
In female patients vaginal opacification is carried out with Amidotrizoic acid gel.

We performed DRE on 248 consecutive patients (193 females and 55 males ratio 3.5:1) and 14 control subjects.

The total patient group was divided into 4 categories according to the dominant symptom pattern: constipation mainly characterized by obstructed and interrupted defecation, incontinence, perianal pain, miscellaneous.

Conclusions: Based upon our findings the following conclusions can be drawn: There is no indication for measurement of the central and posterior anorectal angle. There is no indication for measurement of the perineal descent and anorectal junction level. Anterior rectocoeles occur very frequently in females and are relevant only when they are large and the patient needs digital pressure to facilitate defecation. DRE is essential in diagnosis and characterization of these conditions.

In conclusion, cAMP production is similar in villus and crypt enterocytes with respect to PGE2 stimulation. Since cAMP plays an important mediatory role in duodenal HCO3 secretion, HCO3 production likely occurs from the villus and crypt after PGE2 stimulation.

4191 Gallbladder (GB) Emptying In Vivo and Contractility In Vitro of Gallstone Patients on Ursodeoxycholic Acid (UDCA)

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UDCA increases fasting and residual GB volume in gallstone patients and normal controls. Whether this is due to decreased GB smooth muscle contractility is unknown. We therefore studied GB emptying (in vivo) and contractility (in vitro) in gallstone patients treated with UDCA.

Methods: 9 symptomatic gallstone patients (age ± SD: 48.7 ± 11.8 yrs; M/F: 18/1) were treated with UDCA (110 mg kg−1 day−1) during 5 weeks.

The results were, however, not significantly different from controls. UDCA increases fasting GB volume and residual GB volume in gallstone patients treated with UDCA.

Conclusions: UDCA increases fasting and residual GB volume in gallstone patients. However, GB contractility appears not to be influenced by UDCA since smooth muscle sensitivity to both CCK and ACH is unchanged in vitro.

4192 The Effect of Different Osmolalities of the Sugars Absorption Test Solution on the Intestinal Permeability

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We evaluated the effect of the osmolality of the sugar absorption test (SAT) solution on the 6 hours urine excretion of the components lactulose and mannitol, in healthy subjects and in different SAT-solutions, successively. After an overnight fast, each subject ingested the SAT solution immediately after evacuating the urine bladder. This SAT solution comprised 2 g mannitol (M), 5 g lactulose (L) and 40 g sucrose made up to 100 ml with demineralized water to make it hyperosmotic (1560 mosmol/L). This procedure was repeated with the SAT solution, which comprised 0.5 g mannitol and 10 g lactulose/100 ml (375 mosmol/L). For the first 2 h after drinking the test solution no food or fluids allowed and all urine passed in the 5 h following ingestion of the test solution was collected.

The amount of mannitol in the urine, expressed as percentage of the ingested dose, was higher significantly in the hyperosmolar solution of 1560 mosmol/L, (0.0103 and 0.0023, respectively, p < 0.005). The amount of lactulose in the urine, expressed as percentage of the ingested dose, was significantly higher in the hyperosmolar solution of 1560 mosmol/L, (0.049 and 0.012, respectively, p < 0.005). We conclude that hyperosmolar SAT solution results in a higher lactulose excretion. For standardization of sugar absorption tests, we suggest to express the excreted sugars as percentage of the ingested dose, and to measure the osmolality of the test solution.

4193 Screening for Barrett’s Carcinoma, a Labour of Sisyphus?

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In order to ascertain the incidence and outcome of Barrett’s carcinoma (BC) in patients with Barrett’s Esophagus (BO), 186 patients with BO > 3 cm and without carcinoma were identified between 1973 and 1988 at our upper GI endoscopy. Their vital status or cause of death was ascertained by post or telephone in 1986 and 1994. In both studies 155 patients (95%) were traced. In 1986 4 cases of BC had developed, in 1994 another 4. The incidence of BC (patient years) was 1:170 and 1:180 respectively, the final follow up comprised 1440 patient-years.
Clinical Outcome of Anorectal Anal Repair in Patients with Fecal Incontinence

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Fecal incontinence following childbirth is usually treated by delayed overlapping external sphincter repair. However, the sphincter muscle injury, sustained during childbirth, is frequently associated with disruption of the perineal body and loss of the distal recto-vestigial septum. We started a prospective study to evaluate the clinical outcome of anorectal anal repair (AAR), consisting of restoration of the recto-vestigial septum and perineal body, overlapping external sphincter repair as well as imbrication of the internal anal sphincter. Another aim of this study was to identify factors preoperatively that could predict outcome. During the time period between 1989-1994, 37 patients (M/F: 1/36; median age: 47; range: 23–78) were operated on. The etiology of sphincter trauma was obstetric in 28 patients and surgical for 4 patients. In 10 patients incontinence was associated with rectocele or rectovaginal fistula. Prior to surgery, all patients underwent anal manometry in 28 patients and electromyography (EMG) of the puborectal muscle was performed, whereas in 24 patients pudendal nerve terminal motor latency (PNMT) was recorded. The mean duration of follow-up was 24 months (range: 1-64). In 30 patients continuity had been restored at 4 months of follow-up (81%). However, in 6 patients incontinence recurred after a mean period of 11 months. So the final outcome was good in 65%. Patients with incontinence, due to obstetric trauma, without previous surgery had the best result (82%). Maximal anal resting and squeeze pressures in patients with successful outcome did not differ from those obtained from patients without successful outcome (at rest: 61 ± 18 vs 55 ± 19 mm Hg; during squeeze: 86 ± 33 vs 70 ± 18 mm Hg). EMG-activity at rest and during squeezing showed no differences between both groups (at rest: 17 ± 12 vs 21 ± 16 mm H2O; during squeezing: 67 ± 31 vs 87 ± 3 mV). PNMT in both groups was similar (left: 2.3 ± 0.6 vs 2.5 ± 0.8 msec; right: 2.5 ± 0.8 vs 2.2 ± 0.4 msec). Conclusion: The clinical results of AAR are not better than the reported results after delayed overlapping external sphincter repair.

Pathophysiological Aspects and Clinical Outcome of Intra-anal Application of Isosorbide-di-nitrate in Patients with Chronic Anorectal Fissure

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Recently we have demonstrated that local ischemia, due to increased activity of the internal anal sphincter (IAS), is a major contributing factor in the pathogenesis of anorectal fissure. Relaxation of the IAS can be achieved by local application of exogenous nitric oxide donors, such as isosorbide-di-nitrate (ISDN). Aim of this study was to evaluate the influence of local application of 1% ISDN-ointment on anal pressure, anodermal bloodflow and fissure healing. Sixteen consecutive patients (male/female: 10/6; median age: 35; range: 18–51) with a chronic anal fissure were studied. Prior to treatment, ambulant anal manometry was performed in 6 patients. Because sleep was associated with a reduction of anal pressure to 39% of ambulatory values, we decided to apply the ISDN-ointment only by day (5-6 X daily; maximum duration: 12 weeks). Before treatment and at 3 and 6 weeks all patients underwent conventional manometry and laser Doppler flowmetry of the anodermal area, which remained unaltered. Samples were analyzed in a blinded fashion. Relaxation of the anal sphincter was detected in 16 of 17 patients experienced mild, transient headache during the first 2 days. Within 10 days the fissure related pain was resolved in all patients. At 6, 9 and 12 weeks anal fissure was completely healed in respectively 9, 11 and 15 patients. Pressure reductions were not directly correlated with resolution of the fissure. The maximal anal resting pressure (MAP) decreased within 5 minutes (median pressure drop: 50%; median duration: 39 min). This pressure reduction represents the acute effect of ISDN itself. At 3 and 6 weeks manometry revealed at least one hour after the last ISDN application. These recordings revealed also a reduction of MAP (mean values: pre: 116 ± 36 mm Hg; 3 weeks: 87 ± 18; 6 weeks: 97 ± 30; p < 0.03, paired t-test). This pressure reduction represents the late long-term effect of ISDN itself. At 3 and 6 weeks manometric decompensation at least one hour after the last ISDN application. These recordings revealed also a reduction of MAP (mean values: pre: 116 ± 36 mm Hg; 3 weeks: 87 ± 18; 6 weeks: 97 ± 30; p < 0.03, paired t-test). Conclusion: local application of ISDN reduces anal pressure and improves anodermal bloodflow. This dual effect results in a healing rate of 94% at 12 weeks.

Recurrence and Survival After Resection of Adenocarcinoma of the Gastric Cardia

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New techniques such as endoscopy and laparoscopy with ultrasound offer information on tumour penetration and locoregional lymphatic involve- ment and can thereby improve pre- and perioperative staging in cardiac carci- noma. To assess the relevance of this information, the effect of these and other parameters on recurrence and survival after resection of cardiac carci- noma was studied.

Between January 1, 1983 and December 31, 1993, 184 patients un- derwent resection. Most patients underwent partial or total gastrectomy with distal or subtotal esophagectomy. Until 1986, esophagectomy was per- formed by laparotomy and separate thoracotomy, thereafter by blunt dissec- tion via the transhiatal approach.

Eight patients (4.3%) died preoperatively. Follow-up averaged 26 months (range: 2-72). The 5-year cumulative overall recurrence rate (cal- culated by the Kaplan-Meyer method) was 72%. Both uni- and multivariate analysis identified the presence of tumor-positive locoregional lymph nodes (82% recurrence as compared to 52% when absent) or metas- tases (100% versus 68%) as significant predictors of tumor recurrence. The 5-year survival rate was 23% for all patients, 38% vs 15% (p < 0.001) in node-negative vs node-positive patients and 25% vs 0% in the absence or presence of metas- tases (p < 0.006). Also, in multivariate analysis, these factors appeared to be significantly related to survival. In this study no significant influence of T-category or exact localization of the positive lymph-nodes (N1 or N2) on tumour recurrence or survival could be detected.

The survival rates are still disappointingly high, especially in the presence of locoregional lymph node involvement or metas- tases. Pre- or perioperative identification of these patients, before resection has been carried out, might alter the therapeutic strategy.

Nicotine Inhibits the Production of Cytokines by Peripheral Blood and Lamina Propria Mononuclear Cells

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Ulcerative colitis (UC) is predominantly a disease of non-smokers and nico- tine patches improve the symptoms of this type of inflammatory bowel dis- ease. To find a explanation for the beneficial effect of nicotine in UC we stud- ied its influence on cytokine production and examined whether MNC possess receptors for this substance. Mononuclear cells were isolated from periph- eral blood of healthy volunteers and from surgical specimens, obtained from patients undergoing colectomy for cancer. The segments used for isolation of MNC was taken at least 5 cm from the tumour. MNC were incubated for 90 minutes after which the non-adherent cells (NAC) were collected. NAC were preincubated with nicotine (NIC) for 24 hours followed by addition of PHA (10 µg/ml) and incubation for another 24 hours. A proportion of the NAC were used for receptor binding studies.

Nicotine significantly inhibited the production of IL-2 and TNFa by non- adherent MNC in a dose dependent fashion in the range 10-8 to 10-6 M, with a maximum inhibition of 51% and 48% respectively. This inhibitory effect could not be antagonized by the nicotine receptor antagonists hexametho- nium and pancuronium. The NAC had 2420 ± 360 NIC receptors per cell. The NIC-receptors on the MNC had no affinity for hexamethonium, pancuronium, atropine or carbachol, indicating a non-cholinergic origin.

In conclusion, NIC inhibits the production of IL-2 and TNFa by mononu- clear cells, but this effect does not seem to be mediated by the cholin- ergic NIC receptors known. The suppression of the production of IL-2 and TNFa provides a explanation for the beneficial effects of smoking and nico- tine in ulcerative colitis.

Corticosteroid Resistance in Colitis is Characterized by a Low Glucocorticoid Receptor Content of Mononuclear Cells

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Most patients with inflammatory bowel disease (IBD) will respond to treat- ment with glucocorticosteroids (GC) but some do not improve even with high doses of oral prednisolone. Variation in anti-inflammatory response to corti- costeroids could be due to variation in the number of the glucocorticoid re- ceptors (GR) on mononuclear cells (MNC). In order to test this hypothesis we assessed the number of GR on CD4+ and CD8+ T-cells in 24 IBD patients. (1) I.B.D-patients who had responded to GC-treatment (responders) and (2) I.B.D-patients who had undergone colectomy because their colitis failed to respond to high dose GC (non-responders). MNC were isolated from heparinized peripheral blood from each individual and GR number was deter- miner by means of a whole cell binding assay with tritiated dexamethasone. Samples were analyzed in a blinded fashion.
Patients who do not respond to treatment with high dose GC have a significantly lower number of GR in their MNC, a comparison to responders and healthy volunteers. Responders do not differ from healthy volunteers as far as the number of GR is concerned. These findings strongly suggest a correlation between GR number in MNC and the effectiveness of corticosteroid treatment in IBD.

This research project was supported by the Netherlands Digestive Diseases Foundation.

1502 Allergic Condition as a Risk Factor for Crohn’s Disease and Ulcerative Colitis
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Allergic conditions have been mentioned as risk factors in Crohn’s disease (CD) and ulcerative colitis (UC). To investigate this hypothesis a case-control study was performed. As controls 471 IBD-males (44%), median age 38 (13-83) as well as 470 controls of UC (males 55%, median age 42 (16-87)) equal numbers of age and sex matched population-controls (C) were included in the study. Results are given as the percentage of positive findings in cases/controls and the calculated Odds Ratios (OR) with the 95% Confidence Interval. Smoking was controlled for by logistic regression analysis.

Crohn’s disease Ulcerative colitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>CD(%)</th>
<th>OR (95% CI)</th>
<th>UC(%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>6/3</td>
<td>1.9 (1.0-3.8)</td>
<td>4/3</td>
<td>1.3 (0.6-2.0)</td>
</tr>
<tr>
<td>Hay fever</td>
<td>13/17</td>
<td>0.7 (0.5-1.3)</td>
<td>13/17</td>
<td>0.7 (0.5-1.3)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5/6</td>
<td>1.0 (0.5-1.8)</td>
<td>5/6</td>
<td>1.0 (0.5-1.7)</td>
</tr>
<tr>
<td>Eczema</td>
<td>25/26</td>
<td>0.9 (0.7-1.3)</td>
<td>25/24</td>
<td>1.1 (0.8-1.4)</td>
</tr>
</tbody>
</table>

Summary and conclusion: The results of this first case-control study do not support the hypothesis that allergic conditions are risk factors for either CD or UC. A weak association between atopic eczema and CD was found; however, the few positive cases do not suggest that it has an important role in the development of CD.

1503 Modern Life’ Nutritional Factors in the Epidemiology of Inflammatory Bowel Disease
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In the industrialised world, the incidence rise of inflammatory bowel disease (IBD) during the last half century coincides with changes of the dietary pattern. To investigate the possible role of some characteristic “modern life” dietary factors a case-control study was performed. To reduce recall bias, only cases with the first symptoms within the last five years were included. Data on average consumption of nutrients, during the five years before the first symptoms of IBD, were collected by means of a mailed questionnaire in 159 patients with Crohn disease (CD), males 46%, male age 29 (30-73), and 226 patients with ulcerative colitis (UC), median age 37 (15-81); and equal numbers of age and sex matched population-controls (C) during the same period.

Results: Cola drinks (OR: 1.7, 95% CI: 1.1-2.7), chewing gum (OR: 1.5, 95% CI: 1.0-1.4), and chocolate consumption (OR: 2.0, 95% CI: 1.3-3.2), but not citrus fruits and orange juice had significantly raised OR in patients with CD, while in UC cola drinks (OR: 1.4, 95% CI: 1.0-2.0), chocolate consumption (OR: 2.1, 95% CI: 1.4-3.1) and orange juice (OR: 1.5, 95% CI: 1.2-2.1) had OR with calculated 95% confidence intervals above 1. After controlling for smoking, in CD chocolate and cola drinks and in UC only chocolate consumption proved to be independent risk factors (logistic regression analysis).

Summary and conclusion: In this case-control study, some of the investigated “modern life” nutritional factors were found to be possible risk factors in IBD. The investigated items with high OR all share a high sugar content and possibly also reflect the changed post war consumption pattern preceding the rise in incidence of CD. Confounding was reduced by use of age and sex matched population-controls and by limiting the dietary recall period to 5 years. It proved to be important to study risk factors in coherence with each other.

1504 Validation of the Dutch Translation of the ‘Inflammatory Bowel Disease Questionnaire’
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The Inflammatory Bowel Disease Questionnaire (IBDQ), a disease specific quality-of-life questionnaire, has been developed and validated in Canada. The aims of our study were, firstly, to investigate whether a translated version of this questionnaire could be used in a Dutch IBD population and, secondly, to compare an interview with a mailed version. Patients and methods: 97 IBD patients, 52 males and 45 females, median age 43 years (16 to 81). 39 with Crohn’s disease (CD) and 58 with ulcerative colitis (UC) completed the Dutch IBDQ and a Visual Analog Scale (VAS) concerning disease activity, emotional function and general well-being twice at an interval of six weeks. The second questionnaire included specific questions on change of those items. Linear regression analysis, Student’s t test for paired observations and calculation of intraclass correlation coefficients were used for statistical evaluation.

Results: Completeness: Of the mailed version (17 cases) 98.5% of the questions were fully completed versus 98.2% of the questions of the interview (20 cases). Content validity: Linear regression analysis of the VAS and IBDQ showed a significant correlation (r values > 0.73; p < 0.005) for all categories (bowel and systemic symptoms; emotional and social function). Responsiveness: (sensitivity to change): In patients reporting improvement (or deterioration) (n = 33) a significant change (p < 0.05) to the better (to the worse) in the total IBDQ score as well as the four subcategories of the IBDQ was observed between the two moments. Reproducibility: No significant difference between the two measurements was observed in 64 patients with stable disease activity (r = 0.93).

Summary and conclusion: The Dutch IBDQ was shown to be valid, responsive and reproducible. No major difference in completing rate between an interview and a mailed version was observed. This questionnaire can be used in the Dutch IBD patient population. Our results suggest that it will be feasible to use translations of the IBDQ in other non-English speaking populations.

1505 Duodenogastro-oesophageal Reflux is Increased in Gastro-oesophageal Reflux Disease (GORD), Complicated by Metaplasia in Barrett’s Oesophagus; A Fiberoptic 24-hour Bilirubin Monitoring
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Purpose. Does duodenogastro-oesophageal reflux (DGOR) predispose to the development of oesophageal complications, including Barrett oesophagus and oesophageal adenocarcinoma? The aim of this study was to compare the DGOR in GORD patients with and without oesophageal metaplasia. As an indication for DGOR, the oesophageal bilirubin exposure is measured.

Method. Measurements were made with a fiberoptic sensor and portable data collection unit (Giletlab 2000, Synectics medical Inc.). The fiberoptic electrodes were placed 5 cm above the lower oesophageal sphincter. The absorbance threshold was set to 0.14, corresponding to 10 µm of bilirubin. Studies were performed in 11 patients with uncomplicated GORD, 10 patients with GORD complicated by inflammatory metaplasia below the squamo-columnar mucosal junction (in normal position), and in 13 patients with Barrett oesophagus.

Results: In uncomplicated GORD patients, the mean percentage of the total recording time of oesophageal exposure to bilirubin was 11%. In patients with oesophageal metaplasia or with a Barrett oesophagus, the oesophageal bilirubin exposure was strongly (and statistically significantly) increased. The mean exposure time fractions were 55% and 60%, respectively. Similar observations were made in patients in supine position: then the mean exposure time fractions were 8% in uncomplicated GORD, 71% in GORD with metaplasia, and 69% in Barrett oesophagus.

Conclusions. In uncomplicated GORD, the oesophagus is exposed to bilirubin during 11% of the registration time; according to the literature, this is somewhat larger than in symptom-free control persons. In GORD patients with complications (metaplasia, Barrett), the oesophageal bilirubin exposure is much higher than in uncomplicated GORD patients. These findings may have consequences for the management of patients with GORD.

1506 Study with Two Prokinetics in Functional Dyspepsia and Gastrooesophageal Reflux
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Introduction: Cisapride (CIS) and domperidone (DOPM) are effective in the treatment of functional dyspepsia (FD) and gastroesophageal reflux (GOR). However, CIS is a H1-receptor and DOMP is a peripheral O2-antagonist. Therefore it was considered of interest to compare the two substances in patients with FD or GOR. Patients and Methods: Patients presenting to their primary care physician with upper abdominal complaints of more than 1 month were referred for upper gastrointestinal endoscopy (UGE). Patients with...
negative UGE were allocated to the GOR-group (predominance of heartburn, acid regurgitation or retrosternal pain) or to the FD group (predominance of epigastric pain). Both groups received PPI therapy. During 1 month with the trial medication and thereafter during 2 months without therapy, Pts. received in a double blind fashion tablets containing 10 mg of CIS or 20 mg of DOMP. GOR was treated on a qid schedule, while FD was treated on a t.i.d. basis. Pts. were considered responders of the improvement was ≥ 20% of the initial symptoms’ score; they were considered to have relapsed if the score returned to 1/2 of the initial value. Results were analyzed using the LOCF method. Results: 43 pts. were allocated to GOR and 84 to FD. In GOR at the end of treatment, the response rates (DOMP = 84%, CIS = 85%), global ratings (p < 0.05) and mean improvement of the symptoms’ score (p < 0.1) were in favour of CIS; the differences persisted but were no longer significant after follow up. No difference could be shown in the FLD group. Conclusion: In functional dyspepsia cisapride offers better symptomatic relief than domperidone, especially in reflux symptoms.

1507 | Is the Cellobiose/Rhamnose Ratio the Optimal Way to Express Intestinal Permeability Data?


The ratio of cellobiose (CE)to rhamnose (RH) or other inert sugars of similar size is frequently used to quantify the presence of pathogens. This permeability leads to increased damage in the urine during the test period in contrast to lower recovery of the monosaccharide. The ratio gives information on the permeation between pathogens and controls.

We used the permeation of CE and RH to measure changes in intestinal permeability resulting from the carbohydrate-bypass (CPB) procedure in cardiac surgery patients. As a result of the increased intestinal permeability, intraluminal endotoxins (ET) may gain access to the circulation and contribute to postoperative morbidity.

In a consecutive series of 16 patients the urinary CE/RH ratio measured during CPB was highly abnormal, 0.459 ± 0.36 (mean ± SEM) vs 0.011 ± 0.001 in healthy controls.

In the same 6-h sampling period during and immediately after CPB five blood samples were taken for ET determination. Endotoxemia was detected in all patients and an area under the curve (AUC) was calculated with the ET data. A mean of 122.6 ± 8.1 EtU/ml was found. No significant correlation existed between the CE/RH ratio and the ET AUC, nor did the rhamnose recovery show a correlation with ET.

Only the recovery of the larger sugar CE correlated significantly (r = 0.68, p = 0.0005) with the ET measured in blood, indicating the gut as the probable source for the circulating ET.

Conclusions: CE and RH permeate the gut via different pathways, which are altered by CPB. The circulating ET, probably originating from the gut, is correlated only to CE permeation. Expression of permeability data only as a CE/RH ratio may obscure important mechanistic relationships also in other studies.

1510 | Helicobacter Eradication Affects the Natural Course of Duodenal Ulcer Disease; 11 Years Follow-up


H. pylori infection causes chronic gastritis, a precursor lesion to duodenal ulcer disease. Several studies have demonstrated that duodenal ulcers (DU) recur in only a small number of cases following successful H. pylori eradication, compared with a recurrence rate of 50% or greater within the course of one year when H. pylori infection is not treated. These studies have followed these patients for one year or less and only a little is known of the outcome over a longer period. Therefore we studied Hp-positive patients with endoscopically proven duodenal ulcers, enrolled in HP eradication trials in between 1984 and 1995. From then on patients underwent repetitive endoscopies during a follow-up period of minimal 1 year. Relapse of DU was defined as recurrent DU at follow-up endoscopy. Patients using NSAID’s, or maintenance antacids therapy were excluded. Hp eradication was achieved using bismuth- or omeprazole/antibiotic combination therapies. H. pylori eradication was assessed by culture and histopathology of antrum biopsies. Data of 348 patients were analysed, of whom 183 had duodenal ulcer. The mean follow-up was 4.7 years (1.14–10.9 yrs). Hundred thirty one DU patients were successfully eradicated. In the Hp-positive follow-up period (mean 2.52 yrs (0.5–10)), 50 patients had a DU-relapse in 461 2 patients: 10.8% relapses per patient per year. In the Hp. pylori negative follow-up period (mean 2.95 yrs (0.1–9.8)), 4 patients had recurrent DU during 330.1 patient years, 1.2% relapses per patient per year. The difference in incidence of relapse rates between both groups was highly significant (log rank test p < 0.001).

Conclusion: Even after an Hp eradication, there is a great difference in ulcer relapse rate, between Hp-positive and Hp-negative, thus changing the natural history of duodenal ulcer disease dramatically.

1514 | p-Anca as a Marker of Genetic Heterogeneity and in Relation to Other Non-organ Specific Autoantibodies in Primary Scleroderma Cholangitis


As yet, the etiology of Primary Scleroderm Cholangiitis (PSC) remains unknown, although the finding of cellular and humoral immune abnormalities as well as the association with antineutrophil cytoplasmic antibodies (ANCA) of the perinuclear type (p-ANCA) in 66% of PSC patients, is of great interest. ANCA) have been described in all point to an auto-immune based pathogenesis. Humoral immune abnormalities in PSC patients (pts) include the presence of circulating smooth mus-