Expression and Distribution of Nitric Oxide Synthase in Patients with Portal Hypertensive Gastropathy (PHG)

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Nitric oxide (NO) is associated with hyperdynamic circulation and development of collateral vessels in portal hypertension. However, some controversies exist in the involvement of NOS in the pathogenesis of PHG. The distribution and expression of NO synthase (NOS) have not been explored in detail in patients with portal hypertension. The aim of this study was to investigate whether NO synthase (NOS) is activated in the PHG. The subjects composed of 19 patients, admitted due to complications of PHG, hematemesis, or melena, and 19 normal controls showing normal looking gastric mucosa at endoscopy (H. pylori -). Obtainings - 5 pieces of mucosal biopsied tissue, cNOS and iNOS activities were measured by using the conversion of L-arginine to L-citrulline, respectively. Western blotting and immunohistochemical staining were performed using antibodies against iNOS and cNOS, recorded by Affinity Bioreagent Co. (1:250, 1:500 dilutions). MPO activities were measured according to the method by Bradley. The cNOS activities were significantly elevated as compared to those of normal controls (0.98 ± 0.14 vs. 0.12 ± 0.02, P < 0.01). However, iNOS activities were not different between the PHG and normal controls (0.06 ± 0.03 vs. 0.018 ± 0.009, P = 0.001). The cNOS activities were correlated with Child classification grade and total bilirubin levels. In 80% of the PHG, strong cNOS staining was noted in the endothelium of congested, dilated lamina propria capillaries and gastric glands, whereas positive iNOS staining was observed in only 20% of PHG. The results of immunostaining were correlated with the results of western blotting. In conclusion, NOS didn't show causative role in the development of PHG in portal hypertension. Increased cNOS activities and expressions seemed to be the consequence of shear forces of portal hyperdynamic circulation.

Evaluation of Haemodynamic Parameters of Portal Vein as Indicators of Portal Hypertension – An Echo Doppler Study

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Over the past few years special attention has been paid to the haemodynamic parameters of the portal vein in the assessment of portal hypertension. The aim of this study was to evaluate the maximum velocity in the portal vein and cV/Q ratio index of the portal vein, recorded by duplex-ultrasoundography, in patients with various degrees of liver fibrosis.

In 75 patients with liver disease who underwent liver biopsy, the cross sectional area, mean and maximum velocity in the portal vein were recorded with Toshiba SSD-160. The maximum velocity index of the portal vein was calculated (CI = cross sectional area/mean velocity). Based on a semi-quantitative evaluation of hepatic fibrosis according to Knodell’s scoring system, we divided the patients into two groups; one with mild fibrosis (grade 1) and another with severe fibrosis (grade 3–4). We compared the above mentioned haemodynamic parameters in these two groups.

The patients with extensive fibrosis: grade 4 (cirrhosis) had the maximum velocity in the portal vein which was significantly lower than patients with mild fibrosis (16.7 ± 3.5 cm/s vs 25.7 ± 7 cm/s; p = 0.001) and the congestion index of the portal vein was significantly higher (0.08 ± 0.02 cm/s vs 0.1 ± 0.01 cm/s; p = 0.001). When we compared patients with grade 1 fibrosis to those with grade 3 (bridging fibrosis) the difference remained statistically significant: 25.7 ± 7 cm/s vs 18.5 ± 3.7 cm/s; p = 0.001 for maximum velocity and 0.03 ± 0.01 cm/s vs 0.06 ± 0.02 cm/s; p = 0.001 for congestion index of the portal vein.

We think that this haemodynamic parameters of portal vein could be good predictors for extensive fibrosis.

Postprandial Portal and Splenic Flow is Related to the Severity of Portal Hypertension in Chronic Liver Disease

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The purpose of this study was to determine if the combined analysis of portal and splenic flow in the postprandial state is related to the severity of portal hypertension in cirrhotic patients.

In 113 patients with chronic liver disease portal and splenic flow were measured by Doppler sonography. Flow and cross-sectional area were assessed before and 30 minutes after a standardized liquid meal (Fresubin 5 ml/kgbw). Measurements were compared to parameters reflecting the severity of liver disease (decompensation: Child-Pugh classification, splenomegaly, ascites, melena, gastric varices, iNOS expression, the level of iNOS activity, and iNOS concentration). Healthy volunteers (n = 12) and patients without liver disease (n = 8) served as controls.

Baseline portal (BPF) and splenic (BSF) flow were equal in the control group (BPF 3.8 ± 4.2 cm/s, BSF 13.8 ± 3.4 ml/min). The postprandial increase of portal flow (PPIF) exceeded the increase of splenic flow (PSIF) significantly (PPIF 1.65 ± 0.29, PSIF 1.15 ± 0.2; p < 0.05). BPF was lower in cirrhotic patients but not significantly different compared to the control group. In most patients with esophageal varices (82.9%), an increase of splenic flow (PSIF) exceeded BPF whereas in 90% of controls BSF was lower than BPF. PPIF was inversely related to the severity of liver disease (Child’s score, p < 0.002) and portal hypertension (esophageal varices, p < 0.02; bleeding vs. non-bleeding, p < 0.005; PHG, p < 0.02). In contrast to the controls, postprandial splenic flow decreased in most cirrhotic patients. The maximal reduction of splenic flow was observed in severe cirrhosis (Child C, p < 0.005; EV III, p < 0.005; severe PHG, p < 0.001).

Patients with chronic liver disease and a splenic flow exceeding portal flow had a high prevalence (> 80%) of esophageal varices. The postprandial increase in portal flow is related negatively, the decrease in splenic flow positively to the severity of liver cirrhosis and portal hypertension.

Hemodynamic Alterations in Decompensation of Liver Cirrhosis and Portal Hypertension

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Alterations in splanchic hemodynamics play key role in the natural course of liver cirrhosis and portal hypertension. The aim of the study was to evaluate results of serial determination of hemodynamics in 30 cirrhotic patients subjected to surgical treatment. Measurements were performed using duplex system, dynamic scintigraphy, venous phase of superior angioscintigraphy and direct portomanoametry and includes different times parameters: splenic arterial flow (SAF), splenic venous flow (SVF), portal venous flow (PVF), hepatic arterial flow (HAF), portal congregate index (PCI), hepatoportal index (HPI), degree of portal perfusion (DPP), portal pressure (PP). Results given in the table are means.

<table>
<thead>
<tr>
<th>N</th>
<th>Normal</th>
<th>Child A</th>
<th>Child B</th>
<th>Child C</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAF m/min</td>
<td>185.9</td>
<td>34.9*</td>
<td>293.8*</td>
<td>232.3*</td>
</tr>
<tr>
<td>SVF m/min</td>
<td>206.2</td>
<td>949.0*</td>
<td>616.8*</td>
<td>595.0*</td>
</tr>
<tr>
<td>PVF m/min</td>
<td>916.8</td>
<td>883.3</td>
<td>542.2*</td>
<td>459.0*</td>
</tr>
<tr>
<td>HAF m/min</td>
<td>210.0</td>
<td>174.0</td>
<td>100.0*</td>
<td>69.0*</td>
</tr>
<tr>
<td>PCI cm/s</td>
<td>0.04</td>
<td>0.10*</td>
<td>0.15*</td>
<td>0.16*</td>
</tr>
<tr>
<td>HPI %</td>
<td>66.2</td>
<td>45.5</td>
<td>30.5*</td>
<td>18.5*</td>
</tr>
<tr>
<td>PP mHg</td>
<td>6.7</td>
<td>23.6*</td>
<td>25.0*</td>
<td>21.4*</td>
</tr>
<tr>
<td>DPP</td>
<td>1.0</td>
<td>1.3</td>
<td>2.7*</td>
<td>3.5*</td>
</tr>
</tbody>
</table>

* p < 0.05 compared with normal. # p < 0.05 compared with group A

These results suggest, that major hemodynamic alterations responsible for decompensation of liver cirrhosis and deterioration of functional hepatic reserve are the following: change of hyperdynamic state of splenic circulation into congestive, gradual reduce of total and effective hepatic inflow and decrease of portal pressure.

Role of Sensory Neurons and Nitric Oxide in the Control of Hepatic Blood Flow

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An evidence exists that sensory nerve terminals (C-fibers) which contain different vasodilator peptides are found in the liver vasculature. In the present study the acute utilizing of neurotoxin-capsaicin (CAP) was used to explore the role of C-fibers in the maintenance of hepatic blood flow. The mediatory role of endogenous nitric oxide (NO) in the regulation of hepatic vasculature tone was also determined. Experiments were performed on rats under nembutal anesthesia. Hepatic blood flow (HBF) was registered continuously by Laser Doppler flowmeter (Perfusor 4001 Master). Portal blood flow (PBF) was measured ultrasonically (Transonic System 206T). Systemic arterial pressure (AP) was measured with a strain gauge transducer. Topical application of CAP (0.5 mg) to perinarial nerves located in the hepatic porta evoked an initial vasodilation (at minute HBF and PBF increased 77 ± 4 and 48 ± 4%, respectively, while blood pressure decreased (19 ± 3%). The apparent vasodilation was succeeded by vasoconstriction (at 30 min, HBF and PBF were decreased 31 ± 5 and 55 ± 3% respectively from control). Injection of NO synthase by N-nitro-L-arginine (L-NAME) (15 mg/kg iv.) decreased HBF by 38 ± 7 and PBF by 29 ± 7% respectively and increased AP by 28 ± 4%. Pretreatment of the animals with L-arginine (L-Arg) (100 mg/kg iv.) was without any hemodynamic effect. However L-Arg reversed all circulatory effects of L-NAME. We conclude that acute responses to CAP of the hepatic circulation reflect release of peptide neurotransmitters (initial vasoconstriction) and their subsequent depletion (late vasoconstriction). These findings also suggest that primary sensory afferent nerves are physiological modulators of blood flow and vascular tone in the liver. The results presented also emphasize an important role of endogenous NO as a tonic vasodilator of hepatic vasculature.
Evaluation of Portal System by Color Doppler Ultrasonography in Patients with Liver Cirrhosis

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Portal hypertension is the most important complication of liver cirrhosis. The development of portal hypertension usually becomes evident by the appearance of splenomegaly, ascites, encephalopathy, and/or esophageal varices.

Aim: In this study, portal system was evaluated by color Doppler ultrasonography in liver cirrhosis.

Methods: All patients were postnecrotic (HVB, HDV, HCV) cirrhosis. Portal system was evaluated by color Doppler ultrasonography (Toshiba SSA-270) in 40 cases (13 female, 27 men, mean age 42.7 years) with decompensated liver cirrhosis. Thirty three persons were taken as control groups (9 female, 21 men, mean age 40.2 years). In both groups, diameter of portal and splenic vein, portal vein flow direction (hepatopetal or hepatofugal), portal vein thrombosis were investigated. In addition, all collateral veins were investigated in patients with portal vein thrombosis.

Results: Portal vein diameter was between 7–23 mm (mean 13.5 mm) in all cases and portal vein thrombosis couldn’t be found in any cases. PV flow direction was hepatopetal in 39 cases. Parametrical vein (PUV) was established in 22 cases (55%), left gastric vein was established in 11 cases (45%). Retropitoneal collaterals in 17 cases (40.5%), LGV in 11 cases (27.5%), renal vein collaterals in 15 cases (37.5%), peripancreatic collaterals in 1 case (2.5%), perigastric collaterals in 4 cases (10%) were established in cases with liver cirrhosis. 30 healthy persons, their portal diameter was between 7.2–15 mm (mean 9.5 mm), splenic vein diameter was between 3–12.5 mm (mean 5.5 mm). There was a meaningful difference between liver cirrhosis and healthy persons (p < 0.001).

Conclusion: The results conclude that ultrasonography gives very useful informations about portal hypertension.

Pulmonary Circulation Time in Patients with Chronic Liver Disease


The hepatoportal syndrome (HPS) is an clinical entity characterized by abnormalities of arterial oxygenation in patients with chronic liver disease, without cardiopulmonary disorders. The pathophysiology of this syndrome is thought to involve intrapulmonary vascular dilatation. We measured pulmonary circulation time (PCT) using contrast echocardiography and evaluated the relationship between PCT and arterial PO₂ (PaO₂).

Patients and Methods: 21 patients with chronic liver disease (cirrhosis n=14, chronic hepatitis n=7, age 27–77 yrs) were studied. PCT was measured by contrast-enhanced echocardiography using Albunex® (human serum albumin micro air bubble complex, mean diameter 4 μm). PCT was defined as the time lag of opacification between right and left atrium observed in video-records. Cardiac output (CO) was also determined by doppler echocardiography. Pao₂ was measured insipinse and sitting position.

Results: Patients were divided into two groups; PCT ≤ 4 sec. (S-PCT, n = 7, mean ± S.D. 2.8 ± 1.0 sec.) and PCT ≥ 4 sec. (NS-PCT, n = 14, 5.2 ± 0.6 sec.). PaO₂ in supine position in S-PCT was significantly lower than in NS-PCT (83.3 ± 5.6 mmHg vs 95.2 ± 12.4, p < 0.05). In S-PCT, PaO₂ in sitting position was significantly decreased in supine position (77.9 ± 8.0 vs 83.9 ± 5.6, p < 0.05). No significant change in PaO₂ was observed between two positions in NS-PCT. PCT significantly correlated with PaO₂ in sitting position (r = 0.56, p < 0.01). PCT also significantly correlated with CO (r = 0.62, p < 0.01).

Conclusion: Orthoexemia was observed in patients with S-PCT. Thus PCT may detect potential HPS.

Portal Hypertensive Colopathy - A Prospective Study

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The term Portal Hypertensive Gastroenteropathy was chosen to describe the spectrum of gastrointestinal mucosal changes associated with Portal Hypertension (PH). The aims of our study were: to detect the prevalence of Portal Hypertensive Colopathy (PHC) in patients with PH; to describe the colonicoscopic and histological features and to correlate such findings with a variety of clinical, biochemical and endoscopic parameters.

Patients and Methods:Thirty patients with PH and with clinical indication for colonoscopy were studied prospectively. The study included anamnesis, laboratory data, abdominal ultrasonography, upper gastrointestinal endoscopy, colonoscopy and biopise, when possible.

Results: Nineteen of the 30 patients (63%) with PH had colonicoscopic findings suggestive of PHC. Seven of these 19 patients had also varices of the rectum and/or sigma. We didn’t find any correlation between the severity and extension of the lesions and Child-Pugh classification. We performed biopises in 16 patients and in 15 dilatation and capilar congestion were found, associated with a chronic inflammatory infiltrate in 12. PHC was associated with Portal Hypertensive Gastroopathy (PHG) in 13 patients, with esophageal varices in 15 and with gastric varices in 5. Thirteen patients had had upper gastrointestinal hemorrhage, but only 3 had been previously submitted to variceal sclerotherapy.

Conclusions: PHC is found in approximately 2/3 of patients with PH and it is not always associated with PHG or with esophageal varices. A hepatic entity must be included in the differental diagnosis of lower gastrointestinal hemorrhage and ferropenic anaemia in patients with PH. The gravity and extension of lesions have no correlation with the severity of hepatic insufficiency.

Plasma Interleukin-8 Levels in Patients with Post-hepatic Cirrhosis: Relationship to Severity of Liver Disease, Portal Hypertension and Hyperdynamic Circulation


Background/Aims: This study investigated plasma interleukin-8 (IL-8) levels in patients with post-hepatic cirrhosis and correlated it with the severity of liver diseases and hemodynamic methods. Methods: Plasma IL-8 levels were determined by ELISA and hemodynamic studies were performed using Swan-Ganz catheterization. Results: Plasma IL-8 levels were significantly higher in 57 post-hepatic cirrhotic patients (7.5 ± 1.8 pg/ml, p < 0.005) than those in 41 healthy subjects (2.0 ± 0.2 pg/ml). Elevated plasma IL-8 levels (plasma IL-8 > 5 pg/ml) were found in up to 30% of the cirrhotic patients. In cirrhotic patients, significantly progressive increases in the plasma IL-8 levels were observed in conjunction with the severity of liver dysfunction (Pugh’s class A/B/C = 4.5 ± 1.04 ± 4.2 ± 0.53 ± 8.3 pg/ml, p < 0.005). A significant correlation was observed between plasma IL-8 levels and serum bilirubin levels (r = 0.72, p < 0.001). There were no obvious differences in the hepatic venous pressure gradient (r = 0.26, p < 0.05) and systemic vascular resistance (r = 0.24, p < 0.05). Conclusions: These results demonstrate that plasma IL-8 levels are increased in patients with post-hepatic cirrhosis. The severity of liver cirrhosis is an important factor for the occurrence of enhanced IL-8 levels. IL-8 does not play a role in the hyperdynamic circulation observed in patients with post-hepatic cirrhosis.

Long-Term Follow-Up of Intrahepatic Portal Flow Change in Normal Volunteers and Patients with Chronic Liver Diseases


The summation of portal blood flow (SBF), measured from the left umbilical portion and the right anterior branch by Doppler, was applied to investigate the long-term intrahepatic portal flow change in normal volunteers and patients with chronic liver diseases. Serial SBF measurements were performed in 14 normal volunteers and 25 patients with chronic liver diseases. The duration of follow-up for patients and volunteers were 13.9 ± 6.36 months and 17.89 ± 4.51 months (mean ± SD) respectively. The SBF result obtained when both AST and ALT were within their normal limits was used as a baseline to compare with the subsequent data. Each SBF result was compared with baseline and the coefficient of variation (CV) > 11% was defined as significant change of the SBF. SBF of 0.95 mmHg × mm/s × cm², p < 0.05) and systemic vascular resistance (1119 ± 118 vs 1119 ± 54 dyne·cm⁻², p < 0.05) between cirrhotic patients with and without elevated plasma IL-8 levels. In addition, plasma IL-8 levels did not correlate with hepatic venous pressure gradient (r = 0.26, p < 0.05) and systemic vascular resistance (r = 0.24, p < 0.05). Conclusions: These results demonstrate that plasma IL-8 levels are increased in patients with post-hepatic cirrhosis. The severity of liver cirrhosis is an important factor for the occurrence of enhanced IL-8 levels. IL-8 does not play a role in the hyperdynamic circulation observed in patients with post-hepatic cirrhosis.

The Laparoscopic Cholecystectomy Associated With Operation for Hernia or Incisional Hernia

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The association of cholelithiasis with hernia or incisional hernia poses a problem for the surgeon in evaluating whether laparoscopic cholecystectomy, a classic cholecystectomy followed by hernia or incisional hernia operation or a simultaneous operation is the preferred approach for this particular condition. The best choice is not always easily decided by the surgeon due to lack of appropriate laparoscopic techniques in this situation.

In the First Surgical Clinic Timisoara in the period 1.01.94–15.01.96 we performed 296 laparoscopic cholecystectomies (L.C.) and we found at 7...
cases the association of cholecystitis with herna: —2 cases with intraabdominal incisional hernia (one was a giant one); —4 umbilical hernias, —1 epigastric supraumbilical hernias. The 7 patients were females, age between 31-68. We chose the solution of simultaneous operation: L.C. and operation for herna.

Under general anesthesia we performed an incision at the level of the herna, we isolated the peritoneal sac. Through a direct cutout onto the peritoneum we controlled the presence of adhesion and we prevented a visceral injury as and in a open laparoscopy we inserted laparoscopic port. A purse string suture is placed around the fascia and peritoneum in order to prevent excessive CO2 leak. We inserted the laparoscope and the other 3 additional ports. In the case of under-umbilical herna we reduced the peritoneal contents without separate incision in the umbilical hernia we introduced the first port through the umbilical sack. At the epigastric herna we introduced the first port through the epigastric herna and the 2 nd port infraumbilical. We performed normally the laparoscopic cholecystectomy and we finished by repairing the abdominal wall, closing the fascial defect. In 1 incisional herna we performed also the hernia repair.

The postoperative evolution was good in all the cases.

702  Comparison between Ultrasonographic Diagnosis and Intraoperative and Histological Findings in Patients with Laparoscopic Cholecystectomy

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Since 1992 laparoscopic cholecystectomy is a method of choice for treatment of the gallstone disease. Ultrasonography is a basic method for exact diagnosis and indications for operative treatment. The aim of this study was the comparison between the preoperative ultrasonographic diagnosis and intraoperative and histological findings. We used Braghetto's classification to divide our patients according to the ultrasonographic diagnosis to 4 groups:

I. Usual chronic calculous cholecystitis: 368 patients.
II. Acute calculous cholecystitis type II A with thickness of gallbladder wall < 5 mm: 21 patients.
III. Type II B with thickness of gallbladder wall < 5 mm: 15 patients.
IV. Sclerotic chronic cholecystitis: 46 patients.

There is the high level of coincidence of the preoperative ultrasonographic diagnosis with videoendoscopic and histological findings. Our experience demonstrated that patients with cholecystitis type II B and type III had need from the prolongation of the operative time, between them the frequency of complications is higher, more frequent is the conversion to open cholecystectomy. Braghetto's classification proposes the possibility for determination of course of surgical intervention and estimation of probability for conversion and intraoperative and postoperative complications.

705  The Use of Ultrasonic Surgical Destructor-Aspirator in the Laparoscopic Cholecystectomy

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The purpose of the ultrasonic surgical destructor-aspirator (USDA) is to explore Calots triangle by fragmentation and aspiration of the fatty tissue without damaging the vessels, and cystic duct.

The serosa of the Calots triangle is cut via electrocautery with the sharp-angle hook dissector. Then the cystic duct and artery are efficiently exposed by the USDA.

Laparoscopic cholecystectomy with USDA was performed successfully in 45 cases including 17 cases with an acute cholecystitis. Using USDA the stones in the gall bladder were destructed and gall bladder was removed without wound distension.

The USDA is suitable for skeletonizing the cystic duct and cystic artery, and the procedure is perfectly safe.

706  A Comparison of N2O and CO2 Pneumoperitoneum during Laparoscopic Cholecystectomy, with Special Reference to Postoperative Pain

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Nitrous oxide (N2O) pneumoperitoneum has been shown to be less pain provoking than carbon dioxide (CO2) pneumoperitoneum during laparoscopy under local anesthesia. There are no reports of whether N2O has that benefit also on major surgical laparoscopic procedures under general anesthesia. In the present study we compared the effects of N2O and CO2 pneumoperitoneum on postoperative pain and on cardiorespiratory variables during laparoscopic cholecystectomy.

Forty patients scheduled for laparoscopic cholecystectomy due to symptomatic cholecystitis were randomised to either N2O or CO2 pneumoperitoneum groups. Heart rate, blood pressure, pulse oximetry and end tidal CO2 were continuously monitored during the operations. Arterial blood gases were analysed three times during the procedures. Serum cortisol, epinephrine and norepinephrine concentrations were measured before intubation, at the end of and 8 hours after the operations. The intensity of postoperative pain was measured using visual analogue pain scale.

No differences between the two groups in baseline or perioperative blood pressures, heart rate or pulse oximetry values were found. The patients in the CO2 group had significantly lower pH values than the patients in the N2O group at the end of the operation. In the CO2 group a respiratory acidosis developed as seen in significantly increased arterial and end tidal CO2 values and decreased pH. No differences between the groups in serum cortisol or epinephrine levels were found. At the end of and after the operations norepinephrine levels were higher in the N2O group than in the CO2 group. The patients in the N2O group required less anesthetic agent (enturane) during the operations and at the end of the operation they had significantly lower pain scores one hour, six hours and the next morning 23 and 24 hours postoperatively.

Patients operated with N2O pneumoperitoneum had no side-effects of CO2 and were less painful postoperatively than those operated with CO2. Nitrous oxide is a good alternative for patients suffering from chronic cardiopulmonary diseases.

707  6 Years of Laparoscopic Cholecystectomy: Results on 1778 Patients


Aim of the Study: Laparoscopic cholecystectomy is today the standard therapy for gallstone disease. Improved experience with this technique allows to achieve better results. Aim of this study was to analyse our large series to evaluate the results achieved.

Methods: Between 1991 and 1996 1778 patients were submitted to laparoscopic cholecystectomy for gallbladder lithiasis. Preoperative imaging study consisted of US in all cases, i.e. cholangiography in 134 cases and ERCP in 81 cases. The lithiasis was complicated by acute cholecystitis (39 cases), empyema (16 cases), hydrophic (24 cases) and adenomia (5 cases). 565 patients had been submitted to previous laparotomies (25 upper abdomen, 540 lower abdomen). 1724 (97%) of pts underwent IOC A bile duct lithiasis was associated in 165 cases (9.3%) whose 4.2% unsuspected.

Results: Intraoperative complications occurred in 65 cases (3.6%): most common were bleeding (18 cases) and loss of small stones (43 cases) but we also observed a small bowel lesion, a diaphragm lesion and two lesions of biliary tract (1 choledochal and 1 common hepatic duct). Our conversion rate was 1.4% (25 cases) and it was due to bleeding (10 pts), visceral lesions (4 pts), cholecystitis (2 pts), multiple visceral adhesions (5 pts) and bile duct lithiasis (4 cases). Postoperative complications were 71 (3.5%): 15 parietal abscesses, 26 parietal hematomas, 6 incisional hernias through umbilical port, 15 subhepatic bile collections, 8 intraperitoneal bleeding and 5 residual VBP lithiasis. We also report a case of mortality due to cardiacogenic shock.

Conclusions: Laparoscopic cholecystectomy performed in experienced centers can achieve optimal results in terms of morbidity, in-hospital stay and recovery to normal activities of the patients shorter than open cholecystectomy.

709  Bile Duct Injury during Cholecystectomy in the Era of Laparoscopy

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The development of laparoscopic cholecystectomy (LC) has been associated with a rise in the incidence of bile duct injury (BDI). The aim of this study was to assess the changes in the presenting features and management of BDI in the era of LC.

Methods: All BDI cases (primary or secondary referral) treated at our center since January 1979 have been included for analysis.

Results: Between 1979 and 1988, 31 patients (average: 2.8 per year) were treated for BDI after cholecystectomy vs 39 patients from 1990 to 1995 (average: 6.5 per year). Of these most recent 39 patients, 16 (41%) had an abnormal cholangiogram (OC) (23/50%); 23/62% of which were operated a LC. In 12 (31%) patients, the BDI was discovered during the operation: 6 (38%) during OC and 6 (26%) during LC. The presenting features in the 27 patients in whom BDI was not discovered at the time of surgery were as follows:

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<th>OC</th>
<th>10 (10%)</th>
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<tr>
<td>LC</td>
<td>17 (84%)</td>
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</table>

Of the 16 (46%) patients undergoing an angiography, 9 (50%) had a lesion of the hepatic artery or of the portal vein; 4 (46%) after OC vs 5 (66%) after LC. The type of biliary lesion according to Bismuth's classification was identical in the both groups. Endoscopic treatment was not attempted in any case after OC but was attempted in 9 (29%) cases after LC. Seven (78%) of these patients were finally operated. Roux-en-Y hepaticejjunostomy was performed in 11 patients (69%) after OC and 16 (70%) after LC.
Conclusion: This study confirms an increase in the incidence of BDI in patients undergoing laparoscopic cholecystectomy, although 40% are still related to open cholecystectomy. Bile duct injury after laparoscopic cholecystectomy is diagnosed later, notably through septic and peritoneal complications, and are more frequently accompanied by vascular lesions. But these findings and the attempt of per-cutaneous or endoscopic treatments do not seem to have changed the type of repairment.

710 Incidence of Bile Duct Stone Disease Occurring after Prophylactic Cholecystectomy Incorporated in Curative Gastrectomy for Cancer

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Background and Aim: We reported a 6 to 10 times higher incidence of gallstone disease in curatively resected gastric cancer patients (Dig Surg 6: 39–45, 1989; Gastronterology 104: A362, 1993). One possible factor for this lithogenesis is impaired gallbladder (GB) motility brought about by vagal denervation (Dig Surg 6: 39–45, 1989), and another possible factor to be altered GB bile composition related to bile infection (Gastroenterology 104: A371, 1993; 106: A340, 1994). Since 1985, we have employed concomitant cholecystectomy for its prophylaxis, especially when total gastrectomy or a duodenum-bypassing subtotal gastrectomy plus hepatoduodenal lymph node dissection were performed. A study has indicated that prophylactic cholecystectomy is effective. However, the possibility of increasing incidence of bile duct stone disease after prophylactic cholecystectomy remained to be settled. Methods: We performed a follow-up study employing periodic ultrasound (PUS) monthly for the incidence of bile duct stone in a series of 150 patients having undergone a curative gastrectomy for cancer and cholecystectomy. The patients consisted of 106 males and 44 females aged 60.0 ± 10.3 y. Cholecystectomy in these patients had already been performed before gastrectomy in 8 patients (Group A), was concomitantly performed in 28 patients in 59 patients (Group B) or for prophylaxis in 77 patients (Group C) or for other reasons (Group D). The follow-up period (duration) was 44.4 ± 58.0 for Group A, 53.4 ±33.7 for Group B, 33.2 ± 23.0 for Group C and 16.3 ± 10.0 mo to this reclassified period, respectively. Results: Bile duct stone was diagnosed in only one of the 150 patients (1/150, 0.7%) and that in Group C (prophylactically cholecystectomized patients). The patient (62 y aged male) had undergone total gastrectomy, distal pancreatectomy, splenectomy and prophylactic cholecystectomy. A bile duct stone developed 39 mo later. Discussion and Conclusion: The low incidence of bile duct stone (0.7%) demonstrated in the present study may verify the concomitant cholecystectomy as a sufficient means for the total prevention of gallstone disease occurring after curative gastrectomy for cancer.

711 Can Preoperative Variables Predict Symptomatic Outcome after Cholecystectomy?

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Cholecystectomy for symptomatic gallstone disease results in pain relief in most of the patients, but for 20–30% abdominal pain is present also after the operation, the so-called postcholecystectomy syndrome. The aim of this study was to investigate whether preoperative variables could predict the symptomatic outcome after cholecystectomy.

Methods: 102 patients were referred to elective cholecystectomy in a two-year prospective study. Median age was 45 years, range 20–81. A preoperative questionnaire on pain, symptoms, history etc. was completed, and the questions on pain and symptoms were repeated postoperatively after 6 weeks and one year, respectively.

Preoperative cholecystography, potential stone detection, and sonography evaluated gallbladder motility, gallstones and gallbladder volume. CCK-profile was measured after meal stimulation. Bile, gallbladder and stones were analysed after the operation. Preoperative variables in patients with or without pain were compared by unpaired Student’s t test and significant variables were combined in a logistic regression model to predict the postoperative outcome.

Results: 80 patients completed all questionnaires. Of the 80 patients 21 had abdominal pain after the operation, whereas 59 had no pain postoperatively. Patients with pain one year after cholecystectomy were characterized by preoperative presence of a high dyspepsia score, “irritating” abdominal pain and an introverted personality. Further by absence of “agonizing” pain and absence of increased appetite, and that significant variables were combined in a logistic regression model to predict the postoperative outcome

Conclusion: In this prospective study on postoperative outcome after cholecystectomy preoperative symptoms were able to predict abdominal pain after cholecystectomy. Since reclassification gave too optimistic results, the model should be validated in independent patients.

712 Hepatocyst for Metastatic Liver Tumors from Colorectal and Gastric Cancers

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Purpose: Long-term survival after hepatectomy was examined between patients with metastatic liver tumors from colorectal and gastric cancers.

Methods: Between January 1990 and February 1996, 50 patients underwent hepatectomy for metastatic liver tumors from colorectal (10 patients) and gastric (40 patients) cancer.

Results: The median duration of follow-up was 30 days in 7 patients, 12 months in 10 patients and 1 year in 3 patients. The median follow-up time for the remaining 30 patients was 4 years. The overall survival rate at 1, 5, and 10 years was 80.5%, 65.0% and 67.5%, respectively. The 5-year survival rate for patients with colorectal cancer was 71.1% and that for gastric cancer was 77.8%.

Conclusion: Hepatectomy can provide long-term survival for patients with metastatic liver tumors from colorectal cancer.

713 Surgical Treatment of Liver Echinococcosis: Our Experience

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Between January 1991 and March 1996 we operated 94 patients with liver echinococcosis. There were 79 (84%) females and 15 (16%) males. Average age was 39.2 years (SD 16.5 years). Diagnosis was made by ultrasound, computed tomography and serological testing. More common the right liver lobe has been affected (70.7% vs. 29.3%). Partial pericystectomy with drainage was the most common operation performed in 44 (46.7%) cases. Partial pericystectomy with choledochotomy, “T-tube” drainage and suturing of open biliar ducts were performed in 10 (10.6%) cases, where cysts were centrally situated or biliary leakage was seen. Liver resections were done in patients with liver cysts or neoplasma destruction, mostly in the right liver lobe. Right hepatectomy, left hepatectomy and atypical resections in 9 (9.6%), 7 (7.4%) and 17 (18.1%) cases respectively. In one patient marsupialization was performed because of his bad condition and cyst infection. Six (6.4%) patients had secondary peritoneal echinococcosis, so besides liver procedures, total pericystectomies of these cysts were done, too. Nine patients were operated because of recidive of the disease, and one patient was reoperated four times. During postoperative course we did not have heavy complications. In eight (8.5%) patients abdominal collections have occurred, and ultrasound and drainage were performed. In one case relaparotomy, drainage, suturing of the biliar duct and “T-tube” drainage were necessary due to subhepatic abscess. It could be concluded that liver echinococcosis can be managed with partial pericystectomy in the majority of cases, with good curative effect and low postoperative complications course. Choledochotomy with “T-tube” drainage is additional method for centrally situated cysts or evident biliar leakage, and liver resections for a large degree parenchyma destruction or inadequate drainage openings.

714 Immunohistochemical Investigation in Occurrence of Endocrine Cells and Lysozyme in Chronic Cholecystitis

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 Aim: We investigated the functional significance of the occurrence of endocrine cells and lysozyme in cholecystitis by using the histochemical and immunohistochemical methods to clarify the etiology of chronic cholecystitis.

Materials and Methods: The subjects consisted of 120 cases of chronic cholecystitis surgically removed in our department and we selected 100 cases to show histologic evidence of metaplasia for study. Of the 120 patients, 53 were men and 67 were women, they ranged in age from 34 to 86 years, mean, 56.2 years. All histologic specimens were fixed in 10% neutral buffered formalin immediately after cholecystectomy, embedded in paraffin and sectioned at 5 µm. Grimelius reactions were used to bring out the argyrophil cells. Special modifications of Grimelius reactions were performed, “T-tube” drainage was followed by alcin blue. For the immunohistochemical demonstration, we used an streptavidin-biotin immunoperoxidase procedure (SAB) by monoclonal antibody.

Results: In normal gallbladder mucosa, endocrine cells and lysozyme were not demonstrated. In chronic cholecystitis, non-metaplastic group in 20 cases also were not observed these cells. The expression rate of the occurrence of endocrine cells and lysozyme of metaplastic group were found in 48 (48%) and 43 (63%) of 100 cholecystitis, respectively. These cells were apparently

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Cholangitis is a common bile duct stone disease that is frequently followed by cholecystokinin, somatostatin, gastrin and pancreatic polypeptide. Various hormone-containing cells showed a high correaltivity between the development of metaplasia and degree of cholecystitis. These cells were apparently formed by the metaplastic differentiation. And lymphocyte also showed a close relationship to the metaplasia.

Conclusions: It was recognized a strong correlation between endocrine cells and risk of metaplasia and cholecystitis. And it is suggested that endocrine cells has strongly influence on the occurrence and development of chronic cholecystitis. Therefore, there is much hope to the clinical application of hormone therapy in the treatment of cholecystitis.

715 Differences in Pain and Dyspepsia after Cholecystectomy and Symptomatic Gallstone Disease


Abdominal pain occurs in 20-30% of patients after cholecystectomy. The main cause of this pain remains unclear. Patients with acute cholecystitis (AC) could perhaps be expected to benefit more from surgical treatment than patients operated due to uncomplicated gallbladder stone disease (UGSD), as the necessity to operate is more unquestionable in patients with AC.

Purpose: To compare pain and dyspepsia after cholecystectomy for AC with patients dyspepsia for cholecystectomy, UGSD patients.

Methods: All patients (223 women, 122 men) cholecystectomized for AC at 4 Danish University hospitals during the period from 1986 to 1990, and a control group of age and sex-matched patients (213 women, 83 men) cholecystectomized for UGSD, were invited to participate in a questionnaire concerning the occurrence of abdominal pain and dyspepsia before and after cholecystectomy.

Results: 534 patients (83%) completed the questionnaire. Complains of abdominal pain were found in 32% with equal frequency in the AC and UGSD group (37% vs 38%). Women suffered more often from abdominal pain after cholecystectomy than men (42% vs 29%, OR = 1.75). Although more than one third complain of abdominal pain after cholecystectomy, 93% were improved or cured by the operation and this occurred more often in UGSD than AC (50% vs 89%) (P = 0.02). In general cholecystectomy reduced nausea (P < 0.0001) and vomiting (P < 0.0001) but aggravated flatulence (P < 0.0001). Abdominal pain was significantly correalted to dyspepsia after cholecystectomy in both groups.

Conclusion: Pain occurs with equal frequency in AC and UGSD after cholecystectomy.

716 Therapeutical Approach to Acute Cholecystitis

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Purpose of the Study: Laparoscopic cholecystectomy (LC) is the gold standard for uncomplicated cholecystitis: more debated are indications and timing in acute cholecystitis (AC). Aim of our study was to evaluate results of LC in patients with present or previous acute cholecystitis.

Methods: Between 1991 and 1995 1778 pts. were submitted to LC for symptomatic cholelithiasis. Of these 158 pts. (8.9%) were admitted with the diagnosis of AC identified by clinical, lab and ultrasonographic signs. 5 of these presented with signs of cholangitis and in four of them common bile duct stones were detected. Among the AC group, 39 pts. underwent LC within 48 hours from the clinic onset of symptoms (Group A). 119 patients, including elderly or high risk pts as well as pts. referred to us more than 48 hours after the onset of symptoms and pts. treated in the first two years of this study, underwent medical treatment and surgery was delayed for 5-7 weeks (Group B).

Results: Conversion rate was 7.7% in Group A and 0 in Group B. Mean operative time was significantly shorter in Group B (49.2 minutes vs. 78.5 minutes of Group A). In both groups common bile duct injuries were observed. Mortality was 8.3% in group A (2 port site infections and 1 hemoperitoneum, treated conservatively) and 4.2% in Group B (3 port site infections, 1 parietal herniation and 1 bile duct injury). Early postoperative period was observed. Mean postoperative hospital stay was 4.2 and 2.5 days respectively in Group A and B.

Conclusion: Our results suggest that LC can be safely performed by skilled surgeons within 48 hours from the clinical recovery of liver function was evaluated by bilirubin levels.

717 Prognostic Factors of Liver Excretory Function in Patients Undergoing Bilary Decompression for Obstructive Jaundice

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Aim: We conducted this study to identify the predictors of recovery of liver excretory function in patients with obstructive jaundice.

Materials and Methods: Twelve consecutive patients were recruited, with mean age 60.5 ± 9.0 years, male 9, female 3. The underlying diseases were common bile duct stone; 4, and biliary malignancy: 8. They received naso-biliary drainage (NBD, 4) or percutaneous transhepatic chole ductal drainage (PTCD, 8) according to clinical indications. Serum and bile were collected for biochemistry tests. The recovery of liver function was evaluated by indocyanine green retention test (ICG R50). Patients with a ICG R50 reduciton ratio less than 50% were considered as poor recovery (group 1, n = 6) while a good recovery was thought if the reduction ratio higher than 50% (group 2, n = 6). The clinical parameters were compared between two groups.

Results: Sequential change of serum & biliary content are as follows:

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile AC</td>
<td>Bile UGSD</td>
<td>Bile AC</td>
</tr>
<tr>
<td>Gr. 1</td>
<td>Gr. 2</td>
<td>Gr. 1</td>
</tr>
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</table>

718 Role of Atrial Natriuretic Peptide on the Pathogenesis of Renal Dysfunction in Patients with Obstructive Jaundice


Purpose of the Study: To investigate the sodium regulating hormones status and the role of the atrial natriuretic peptide (ANP) on the pathogenesis of the extracellular water (ECW) depletion and renal dysfunction in patients with obstructive jaundice (OJ). Methods: Forty patients with OJ were evaluated. There were 21 women and 21 men with an age range from 30-90 years. Twenty-four patients had benign conditions and 28 peripapillar tumours. Plasma ANP, Aldosterone (AlD) and Renin (Ren) concentrations were measured by radioimmunoassay. Extracellular fluid volume was determined using tetrapolar bioimpedance. Fractional sodium excretion (FNaEx) and creatinine clearance (CrCl) were also measured. A control group (CG) of 14 healthy subjects matched for age (mean age 64 years; range 37-84) and sex (8 women and 6 men) were used as controls for hormonal measurements.

Results: Ninety-one percent of OJ patients had elevated ANP ( > 60 pg/ml) vs 7% in CG ( < 0.001). Mean values were 119 ± 46 pg/ml in OJ group vs 40 ± 18 in CG ( p < 0.001). Plasma Ald concentrations compared with CG was 156 ± 72 vs 43 ± 21 pg/ml (p < 0.001). Forty seven percent of OJ patients had elevated Ald concentrations ( > 160 pg/ml) (p < 0.001). CrCl was 95 ± 65. Twenty eight percent of patients had low CrCl (< 50 ml/min). FNaEx was 0.63 ± 0.49. Patients with CrCl < 50 ml/min had higher Fractional sodium excretion (0.84 vs 0.56, p < 0.15). Sixty five percent of patients had ECW lower than 22% body weight. Plasma Renin concentrations was also higher in OJ patients than CG (41 ± 54 vs 16 ± 9 U/l/min; p < 0.01). Conclusion: The present study reveals that plasma ANP is increased in patients with obstructive jaundice. Endocrine and extracellular water alterations could related to renal dysfunction. These findings are relevant to the peripervative management of patients with obstructive jaundice.

719 Polypeptides from Red Cell Membranes: Electrophoresis Reveals Effects of Biliary Obstruction with High performance Electrophoresis

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Experimental biliary obstruction in Wistar rats leads to differences in the polypeptides of the red cell membranes that can be detected by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate. Here we
compare the pattern obtained in ghosts from normal rats and rats with high bilirubin levels in plasma, 5–11 days after experimental biliary duct obstruction. Ghost membranes from normal human subjects were also examined. After surgery, rats with coluria were sacrificed and biochemical tests for bilirubin, transaminase and amylase in plasma and an analysis of biliary/digestive tract histology were performed. Ghost membranes were solubilized and the polyepptides were separated on 75% polyacrylamide gels (staining gel 4.9%) according to Laemmli (Nature 227: 680, 1970), and stained with Coomasie blue.

The operated rats exhibited coluria, colangitis, ductal dilatation with cysts, and pancreatitis, and in liver, portal fibrosis with ductal proliferation. The biochemical results were consistent with the obstruction: high levels of bilirubin and of all the enzymes tested. Electrophoresis of ghosts revealed differences from normal rats between 75 and 25 kDa. At 53 kDa, a prominent band (designated 4.6) was found in normal rats between the bands 4.9 and 4.2, but disappeared with prolonged biliary obstruction. This band is not found in humans. Band 4.9 (35 kDa) present in humans, is absent from normal rats but appears after prolonged biliary obstruction. The intensity of bands 7 and 8 (29 and 25 kDa) increases in operated rats. Partial reversal of this profile was observed when the obstruction reversed spontaneously. We conclude that biliary obstruction with high bilirubin levels can affect red cell membrane polyepptides, depending on the severity and duration of the obstruction.

**Support**: CAPES, FIOB, UFRJ.

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**720 Factors Associated With Increased Biliary Pressure in Bile Duct Obstruction**

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**Purpose**: Increased bile duct pressure is the major factor responsible for acute cholangitis and bacteraemia. Therefore, prompt medical or surgical decompression of bile under high pressure should be accomplished as fast as possible. But, measurement of bile duct pressure is invasive. So, the present study was undertaken to find out the clinical factors to predict the increased biliary pressure in patients with bile duct obstruction.

**Methods**: Thirty-three patients with bile duct obstruction underwent percutaneous transhepatic bile drainage (PTBD). Intraductal pressure was measured as soon as bile duct pucture was performed. Bile cultures were performed in 24 patients and blood cultures were performed in 21 patients. Correlation of bile duct pressure and severity of pain, duration of symptoms, fever, leucocyte, serum bilirubin, serum alkaline phosphatase, or bile duct diameter was statistically analyzed.

**Results**: Bacteremias were noticed in 5 of the 17 patients with positive bile culture. Bacteraemia was associated with the increased biliary pressure. Bacteraemia was demonstrated when the biliary pressure was 22 cmH2O or more. Biliary pressure was associated with the severity of pain and body temperature. Significant correlation was not found between the duration of symptom, leucocitosis, serum bilirubin, serum alkaline phosphatase, or bile duct diameter and biliary pressure.

**Conclusion**: Increased biliary pressure in patients with bile duct obstruction is more likely to be associated with severity of pain and fever than leucocytosis, bilirubin level, alkaline phosphatase level, or bile duct diameter.

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**721 Bilirubinate Conjugates in Common Duct Bile of Patients with Choledocholithiasis**

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Common bile duct stones are mainly brown with Ca-bilirubinate as a major component. Deconjugation of bilirubinate glucuronides by bacterial betaglucuronidase in bile seems to be of importance. Our aim was to analyse the composition of common bile duct stones and relate this to bilirubinate conjugates in common duct bile. Material and methods: Common bile duct stones and common bile duct bile were collected endoscopically from 56 patients (29 women) with mean age 75 years (range 50–95). The stones were dried and mg of each stone was crushed and dissolved in N,N-dimethyformamide/dimethyl sulphoxide and cholesterol concentration was measured enzymatically on a Cobas Bio centrifugal analyser. Stones with < 50% cholesterol were considered pigment stones. Biliary pH was measured. Bilirubinate conjugates were analysed immediately by high performance liquid chromatography. A 25 minutes gradient on a C18 column and detection at 440 nm was used. Concentrations were calculated as a relative area under the curve on a computer.

**Results**: Forty-four stones (78%) were pigment stones. All 25 patients with duodenal diverticula had pigment stones (p < 0.01).

<table>
<thead>
<tr>
<th>Total bilirubin (µmol/L)</th>
<th>% Bilirubin digluconide*</th>
<th>Biliary pH</th>
</tr>
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<tr>
<td>Pigment stones (n = 44)</td>
<td>613 ± 472</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>Cholesterol stones (n = 12)</td>
<td>504 ± 311</td>
<td>67 ± 28</td>
</tr>
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</table>

*P-test, p = 0.005

No significant differences were found for the other conjugates.

**Conclusion**: The percentage of the main bilirubinate conjugate, bilirubin digluconide, is decreased in common duct bile of patients with pigmented compared to cholesterol stones.

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**722 Symptomatic Gallstone Disease: Which Patients Should Have ERCP?**

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For selection of patients with symptomatic gallstone disease to ERCP, clinical indicators of common bile duct stones (CBDS) (history, biochemical tests, ultrasoundography (USG)) are too insensitive to predict the frequency of negative ERCP. In the present study a discriminant function (DF) for the probability of CBDS (confining age, bilirubin, ALT, GGT) was tested prospectively, and compared to ultrasoundography (USG). 192 patients were included, 32 proved to have CBDS, and 160 not. Blood sampling was done mean 1.7 days prior to cholecystectomy or ERCP. Ultrasonography (USG) was performed in 171 patients (25 with and 146 without CBDS), ERC in 71 patients, and both procedures in 4 cases.

**Conclusion**: For CBDS criteria was positive in 152 patients (79.2%), 21.1% of them actually had stones, and there were no false negatives (sensitivity 100%, specificity 25%). DF was positive in 50 patients (26.0%), 60% of them had CBDS, and there were two false negatives (sensitivity 93.8%, specificity 87.5%).

At USG mean bile duct diameter was 4.8 mm in patients without CBDS and 6.4 mm in patients with CBDS. In patients with diameter 6 mm or less (normal range) nine had stones and 116 not, with diameter > 6 mm, 16 had CBDS, 30 had not. Sensitivity of USG was 68.0% and specificity 79.5%. There was a correlation between diameter at USG and ERCP (p < 0.001), but r was 0.504.

**Clinical characterisation** is most sensitive for CBDS detection, but has low specificity. DF is more specific and sensitive than USG, is easy to use, and seems efficient in selecting symptomatic gallstone patients to ERCP.

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**724 Bacterial Biofilm Formation: Clinical Bacteriology and SEM Analysis**

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We studied basic mechanism of biliary stent clogging to investigate on faeces involved in it. Material and Methods: In one year period 22 biliary stents (10 for transhepatic access) of different plastic materials (polyethylene, polyurethane and teflon) and different diameters (10–12 F) were implanted. They were out, before transversally from the duodenal and the biliary extremities (5 mm), then lengthwise; two parts, dipped into PBS solution to be sonicated, therefore they were analyzed by quantitative microbiology. The others were immersed into gluteraldeide 1:10, to be analyzed by scanning electron microscopy. 12 stents were substituted for dislocation or for charge therapy, while 26 were explanted due to infection (mean implantation time was 65.8 days, range 18–210) Results: microbiological analysis didn’t reveal a bacterial colonization in 7 out of 22 stents (mean implantation time 12.8 days, range 2–45 days, median 8). Only one of them was removed because of blockage, and SEM revealed heavy deposit of organic material. During the whole period of implantation an antibiotic therapy was administrated. Cholangitis episodes occurred in four patients, while the other patients presented symptoms of jaundice or cholestatis. 15 stents (mean implantation time 73.3 days, range 4–210, median 21) revealed: 14 Enterococcus spp., 3 E. cloacae, 2 E. coli, 2 candida and 1 C. freundii, Bacillus, Veillonella, Corynebacterium spp. SEM analysis provided indications in three cases that microorganism were present though culture had resulted negative. Conclusion: bacteraial cells were attached to both the inner and outer stent surface enclosed into a fibbrial matrix, suggesting that the first event of stent clogging is the development of an adherent bacterial biofilm. Microorganism of duodenal origin, Enterococcus spp. 64% mainly represented as component of the biofilm deposited on stent. Nevertheless in the case of stent with transhepatic access, biliary side resulted more early colonized then the duodenal side. We can speculate biliary stasis plays a fundamental role in the drainage failure.

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**725 The Presence of CaCO3 in the Gallbladder Stones Is a Marker for the Bile pH at which Cholelithogenesis Occurs**


Cholesterol cholelithiasis etiopathogenesis remains an uncertain and controversial subject. We determined during surgical exploration the pH of the gallbladder bile, and its relationship to cholesterol stones. Nevertheless in all cases when the bile pH was above 8, we discovered cholesterol crystals or conglomerates. In all cholesterol stones we found precipitates or
crystals of calcium carbonate. In layers of lighter colors of the stones the CaCO₃ concentration is increased up to 18% and the radiopacity more evident. The dissolution of bilirubin micelles by reducing the volume and making thinner the double electric layer that keeps the particles in suspension, favoring the sedimentation and conglomeration of cholesteryl. Constant identification of CaCO₃ in all cholesterolic stones resulting from HCO₃ ions in blood serum above 8 in bile – represents a marker of the moment of the cholesterol sedimentation. The phenomenon of bile alkalization (pH above 8) disturbs the stability of the colloid micelles and represents the initial moment of the lithogenesis. The conglomeration of the precipitate (cholesterol + bilirubin) is the final result of the process of various colors and radioopacity of the gallbladder sections. Such gallstones implanted steril in a dog’s gallbladder are dissolved and eliminated in several weeks. In humans bile acidification determines the same process that can be followed by ultrasonography.

**726 Changes in the Excretion of Bile Acids into the Greater Circulation System with the Continuous Infusion of Bile Acids into the Portal Vein of the Rat: A Biochemical and Microangiographic Study**

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**Purpose:** We continuously infused taurocholic acid (TCA) and a-HTC into the portal vein and measured microangiographically the changes in the process of its excretion into the greater circulation and the distribution of a-HTC in hepatic lobe. We examined this basic research might become one test method in the evaluation of hepatic function.

**Material and methods:** Male Sprague-Dawley rats weighing 250-300 g were used. We continuously infused 2 mM-TCA into the portal vein of rat over 30 minutes under the following condition.

- (the infusion speed of TCA was 10 ml/h, 15 ml/h; 20 ml/h)
- We sampled the venous blood of the rat at 5 minutes interval from the cava in the portal vein to study the excretion of bile acids into the greater circulation system.

We infused 2 mM-a-HTC into the portal vein of rat under the 15 ml/h. The liver of rats were removed at 3, 6, 12 minutes after infusion, and we made frozen tissue samples. We microangiographically observed the continual changes in the distribution of a-HTC in hepatic lobe. Result and discussion: The following results were obtained.

**Conclusion:** When 2 mM-TCA was continuously infused through the portal vein, that the upper limit of infusion speed to which the hepatic cells were able to treat the TCA, and prevent its excretion into the greater circulation system, was 15 ml/h.

**727 Treatment of Gallstones in the Elderly by Oral Bile Acids G.I.S. Co. (Interdisciplinary Group for the Study of Cholelithiasis). Italy**

An oral bile acids treatment of symptomatic uncomplicated gallstone disease in the elderly can be proposed as alternative approach to surgery, which presents in the elderly higher risk of mortality and morbidity as compared to young adult subjects.

**Aim of this study was to evaluate the clinical efficacy of two different treatment of gallstones in elderly subjects by means of bile acids (Taurocholsocholeoylacid-TUDCA- and Chenodeoxycholic acid and Ursodeoxycholic acid -CDCA+UDCA).**

124 elderly patients with symptomatic uncomplicated gallbladder stones were studied: 66 (11 male, 55 female, age range 65–90) were treated by: CDCA-UDCA (5 + 5 mg/Kg/day) and 58 (25 male, 33 female, 65–92) by TUDCA (500 mg/day) for 1 year. The diagnosis was made by Bilary US, Plain Abdomen X-ray and Oral Cholecytography. All subjects presented one or more episodes of acute pain in the six months prior to the study. 44 were also affected by diabetes (27 in TUDCA, 17 in CDCA-UDCA group). Patients were followed-up clinically every 3 and by US every 6 months.

42/66 subjects in CDCA-UDCA (24 drops: 9 operations for pain or complications, 9 deaths unrelated to gallstones, 3 side effects, 7 follow-up unattended) group completed the study. 4 total and 2 partial dissolution in CDCA-UDCA and 8 total dissolution in CDCA+UDCA can also involve bile duct anomalies resulting in 25cm or in duct of patients group symptoms could be followed-up: CDCA-UDCA: 38 had become asymptomatic, 4 had dyspepsia and all still asymptomatic were operated: TUDCA: 25 had become asymptomatic, 1 suffer from dyspepsia and 3 were still symptomatic (1 of whom operated).

**Conclusion:** 1) Gallstones dissolution in the elderly by oral bile acids seems to be scarcely effective; 2) no difference between the two bile acids was observed; 3) during oral bile acid therapy the majority of elderly subjects with gallstones show an improvement of their symptoms.

**728 Effect of the Combination of Chenodeoxycholic and Ursodeoxycholic Acid in Gallstone Dissolution**

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Combination of two bile acids (CDCA+UDCA) has been described as capable of dissolving cholesterol gallstones in more than 60% of cases. Recently a low percentage (5% after 21 months) has been reported.

The aim of this study was to evaluate the efficacy of the combination of CDCA+UDCA in dissolving cholesterol gallstone in a large number of symptomatic unselected patients and to compare the efficacy of two different types of drug administration (single dose at bedtime or two doses at meals).

A total of 212 pts (71 male, 141 female, mean age 46.4 yrs, range 18–65) with radiolucent gallstone in a functioning gallbladder was enrolled in 9 centres in North East Italy. All gallstones were asymptomatic (5 mg/day each) for 12 months or until dissolution. The drug was randomly administered in a single dose at bedtime or in two doses at main meals. Follow-up was performed by clinical evaluation every 3 months and biliary ultrasound every 6 months.

- 121 pts completed the study; 96 patients; 18 were operated because of severe biliary pain and/or complications; 11 stopped the treatment for adverse reactions; 31 dropped-out. Complete and partial dissolution were observed in 18.4% and 8.9% patients (intention to treat) or 25.6% and 12.6% (per protocol) respectively. The success of therapy was inversely related to the diameter of stone. No difference in dissolution was observed according to the different administration schedules (chi square = 0.015, p < 0.05).

- Conclusion: 1. The combination of CDCA+UDCA is effective in dissolving radiolucent gallstone in less than one fifth of unselected patients. 2. The drug administration scheme does not affect the results of the therapy.

**729 Effect of Age, Choleystokinin and Erythromycin on Gallstone and/or Biliary Sludge Formation in the Guinea Pig**


In this study we aimed to evaluate the effect of age, cholecystokinin and erythromycin treatment on gallstone and/or biliary sludge formation. Guinea pigs (30-1 mo-old and 30-3 yd-old) were placed on a cholelithogenic diet for 4 weeks while 10 guinea pigs of each group remained on normal diet. Ten guinea pigs of each group received respectively: cholelithogenic diet and daily intraperitoneal injection of 0.9% saline (control group), cholelithogenic diet and daily intraperitoneal injection of CCK (0.5 nmol/kg), cholelithogenic diet and daily erythromycin stearat (2 mg/kg) by nasogastric tube.

- After 4 weeks guinea pigs were killed and gallbladders were examined for gallstones and/or biliary sludge. The concentrations of bile constituents were determined. We observed no gallstone and/or sludge in 1-1 mo-old group. In the 3-13 years-old group; control 9 out of 10, cholecystokinin 5 out of 10, erythromycin 4 out of 10. In two age groups cholelithogenic diet significantly reduced the concentrations of bile salts and increased the cholesterol concentration and increased bile protein in 3-13 yd-old group. Treatment with cholecystokinin and erythromycin didn’t alter the bile salt concentration in both and reduced cholesterol in 1-1 mo-old. The ratio of bile salts/bile cholesterol reduced in both. However, treatment didn’t alter this ratio in 3-13 years-old group but increased in 1-1 mo-old group. We conclude that major factors in the increased incidence of gallstones formation in an adult guinea pigs are increased; concentrations of bile protein, bile cholesterol and reduced concentration of bile salts and ratio of bile salts/bile cholesterol. Treatment with CCK and erythromycin decreased the incidence by decreasing bile protein and increasing bile leasin and probably by increasing gallbladder motility.

**730 Effects of Nitric Oxide Donors on Gallbladder Motility in Humans**

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The gallbladder emptying is controlled by complex nervous and humoral mechanisms. It has been previously reported that endogenous nitric oxide (NO) is a neurotransmitter in the gallbladder (GB). The inhibition of NO synthase results in the increase of the intraluminal pressure of GB and this effect can be reversed by the pretreatment with L-arginine (L-Arg). The aim of this study was to evaluate the effects of Glycyl Trinitride (GTN), Molsidomine (MO) and L-Arg as potential sources of NO on lasting GB volume and on GB emptying rate, which was induced by feeding carbohydrate (ravens). The healthy subjects (9 men and 8 women), age range 25–37 years participated in this study. GB volume was examined by means of an ultrasonic method. Volumes were calculated as described by Everson and co. GB volumes were measured every 10 min for the first 45 min, there after at 15-min intervals up to a total observation period of 2 h. After recording of control values (26.3 ± 4 cm3), 0.5 mg GTN was administered sublingually, or 4 mg MO orally or L-Arg (100 mg/kg in 1 ml/kg) was infused intravenously, respectively. After the experiment was completed it was found that the fastest GB volume was significantly increased after GTN by 22 ± 2 and after MO by 25 ± 6%. MSF-induced GB emptying was completely inhibited by GTN and MO. Whereas, postprandial GB emptying was reduced maximally by 35.6 ± 9% (p < 0.1) after treatment with GTN and by 40.3 ± 5% (p < 0.1) after L-Arg. L-Arg was without any effect on resting or stimulated
the cisapride-induced changes in the GBV were calculated. After 120 min, caerulein was administered i.v. and the determinations of GBEF and GBR were performed.

Results: The mean caerulein-induced GBEF in the basic study was in the normal range (50.99 ± 18.6%). Cisapride administration significantly increased the fasting GBV (45.0 ± 21.7 vs. 33.6 ± 19.5 ml, p < 0.02). The cisapride-induced GBEF improved after cisapride administration as compared with the basic study: 60.42 ± 18.3% and 50.99 ± 18.6%, respectively (p = 0.003). The cisapride administration enhanced GBR (229.8 ± 55 vs. 163.3 ± 24.5%, p = 0.015).

Conclusions: The prokinetic effect of cisapride increases the fasting GBV by approximately 36%, and causes a significant improvement in the caerulein-induced GBEF and GBR. (Supported by a grant from the Ministry of Social Welfare: ETT 609/1993/02).

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Purpose: To describe the relation of gallbladder emptying (GBE) to gastric emptying (GE), antroduodenal postprandial motor index (PDMI), B-glucose and P-insulin in 8 healthy males and 8 patients with IDDM. Methods: Continuous antroduodenal pressure recordings. GBE and GE were measured scintigraphically. For GBE a continuous infusion of 99mTc-Me3Tc-galactosyl RBCs (40 MBq) was used with GE a standard meal (1 mg pimeti tagged with 40 MBq 99mTc-sulphur colloid and 150 ml water mixed with 8 MBq 111mIn-DTPA) was ingested in phase I of MMC. P-insulin was measured by RIA. Results: In normals as well as in patients meal ingestion elicited gallbladder emptying after a short lag-phase, however, in 3 out of 7 patients with NIDDM a reduced emptying rate and augmented residue at nadir was found. In this subgroup of patients the characteristics of GBE and PMI were similar to those patients with normal GBE and the control group. GBE in the subgroup of patients with abnormal GBE was median 15.7 mmol (9.6-16.0) compared to a median value of 7.4 mmol (5.7-17.3) in the patients with normal GBE. The values for P-insulin were 10.1 pMol (7.7-14.8) and 14.1 (4.7-20.4), respectively.
Conclusions: The abnormal gallbladder emptying in patients with NIDDM was related to elevated B-glucose but not to changes in GE. These findings indicate that hyperglycemia may impair GBE.

736 Postprandial Gallbladder Kinetic in Normals, Type 1 (IDDM) and Type 2 (NIDDM) Diabetics
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Purpose: To compare the characteristics of gallbladder emptying (GBE) in normal persons (NPN) (4 young and 4 elderly males) with the characteristics of GBE in otherwise healthy male diabetics (8 young IDDM and 6 elderly NIDDM) with a short daytime duration and without late complications.

Methods: GBE was measured by scintigraphy during 5 h using a continuous infusion of 200-500 MBq. The standard meal, which consisted of an omelet (100 g, 1400 kJ, 60% fat) and 150 ml water, was ingested in a meal phase.
Results: The pattern and characteristics of GBE in NPN was an unobstructed emptying after a lag-phase (t = time at 10% GBE) of median 11 min (octiles 6–19) with a rate of 0.85%/min (0.73–0.81) until the nadir was reached after 150 min (90–210). In NPN > 10%, the lag phase was between 15 and 20 min. In patients with a short daytime duration and without complications, the GBE was performed. The patients were classified into four groups based on the characteristics of GBE in NPN.

737 Real Time Ultrasonography for Measurements of Gallbladder Motility in Children with Upper Gastrointestinal Symptoms
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Motility disorders of gallbladder are a problem in pediatric gastroenterology. Early diagnosis by real-time ultrasonography is applied in measurements of gastrointestinal motility particularity of this of gallbladder. Study’s aim was: to establish the disorders of gallbladder motility & their structure according to modern noninvasive diagnostic method; to reveal the role of prokinetic in milk digestion and in hyperkinetic gallbladder. In 1996, 25 children (14 girls and 11 boys) aged 9–14 years with upper gastrointestinal syndrome were investigated. They were examined clinically and by real-time ultrasonography. The ellipsoid method was applied in measurement of gallbladder motility. After 30 min, 10 g chocolate control ingestion was performed. The patients with hypokinesia were treated with Motilium (0.5 mg/kg 2 ml). These with hyperkinesia with Spasmalgin (synthetic cholinolytic –20 mg/kg 1 ml). After 2. the same method of measurement of gallbladder motility was applied. Interestingly, gallbladder was established in 1625 cases (64%); hypokinesia-in 14/25 cases (56%) and hyperkinesia-in 2/25 cases (8%). After 2. in 1/214 hypokinesia patients clinical symptoms were not observed. 50% of gallbladder ultrasonography was normal. Complete healing (clinical & ultrasonographic) was established in hyperkinetic patients. It was concluded that real-time ultrasonography should be the diagnostic method of choice in childhood gallbladder motility disorders. These disorders are very common in children. Prokinetic or spasmolytic reduce the symptoms & motility changes.

738 Spontaneous Bacterial Peritonitis in Brazil: Prevalence, Predictive Factors and Prognosis
Background/Aim: Spontaneous Bacterial Peritonitis (SBP) is a common and potentially fatal complication of cirrhosis. Multiple variants of this infection have been described during the past decade. Few studies have investigated SBP in Brazil. In order to investigate prospectively prevalent, predictive factors and prognosis of the episode of SBP, we studied 143 in and outpatients with cirrhosis admitted to UFRJ and UERJ between January, 1995 and January, 1996.
Methods: All patients were submitted to a questionnaire, phasic ultrasound, blood analysis and abdominal paracentesis with ascitic fluid analysis. Seventy-four patients were analysed. The patients were followed for a mean follow-up period of 4 months and survival was determined.

Results: The prevalence of SBP was 20%. Culture-positive SBP. Culture-negative Neutrophilic Asciotes and Bacteriocytes were identified in 24%, 66% and 10%, respectively. After anti- and multivariate analysis, only anterior gastrointestinal hemorrhage, serum albumin and ascitic fluid C4 reached statistical significance (p = 0.05) as predictive factors for the development of the SBP. The in-hospital and follow-up mortality rates were 33.3% and 53.8% for the SBP patients and 8.5% and 31.9% for the non-SBP patients, respectively (p = 0.01 and p = 0.04). The cumulative probability of survival in the SBP group was significantly lower than the probability of the non-SBP group (p = 0.05).

Conclusions: We conclude that SBP is a frequent complication, depends on the severity of liver failure and is a marker for poor prognosis in patients with liver cirrhosis.

739 The Effect of Erythromycin and Cisapride on Postprandial Gallbladder Emptying in Healthy Humans
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Background: Cisapride and erythromycin exhibit prokinetic properties and increase the rate of postprandial gastric emptying. The aim of the study was to evaluate the potential effects of erythromycin and cisapride on gallbladder postprandial emptying in healthy volunteers.

Subjects/Method: Ten healthy male subjects (age: 25–33, mean age: 29 years) had their gallbladder emptying assessed by real-time ultrasonography on three different occasions, two days apart each, and in a random order as follows: a) after ingestion of 300 ml of fresh milk (lipids 4%) (postprandial emptying) b) after giving 200 mg erythromycin intravenously followed immediately by the ingestion of 300 ml of milk and c) after giving 10 mg of cisapride per os followed 30 min later by the injection of 300 ml of milk. Gallbladder volume was calculated every 5 min for 60–90 min. From the emptying curves (plotting of volume against time) the pattern of emptying was assessed, and the lag phase duration, the ejection fraction and time by which maximal emptying was achieved were calculated.

Results: Erythromycin significantly reduced the lag phase duration from 3.6 ± 4.2 SDmin (milk alone) to 1.3 ± 3.5 SDmin (milk plus erythromycin) (p < 0.04) and increased the lag phase duration of postprandial gallbladder emptying from 60.6 ± 8.5 SDmin (milk alone) to 78 ± 8.5 SDmin (milk plus erythromycin) (p < 0.0006). Cisapride increased the ejection fraction of postprandial gallbladder emptying from 60.6 ± 8.5 SDmin (milk only) to 67.1 ± 8.8 SDmin (cisapride plus milk) (p < 0.005). The effect of erythromycin on postprandial gallbladder emptying was significantly more pronounced than that of cisapride (ejection fraction: 78 ± 8.5 SD% after erythromycin and milk vs 67.1 ± 8.8 SD% after cisapride and milk; p < 0.005).

Conclusions: Erythromycin and cisapride significantly enhance the postprandial gallbladder motor response, by increasing the extent of emptying.

740 Intestinal Gas Volume Measurements of Gut Motility Measured in Healthy Volunteers
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Aim: Spontaneous gallbladder contractions occur in phase II of the migrating motor complex. This study compares these contractions in gallstone patients and controls. Method: We evaluated a new technique using a fixed finger in the mouth (Piekker, Holtheim, Germany). Dimensional analysis of symptomatic gallbladder volume was followed in 8 asymptomatic (n=8) gallstone patients, as well as healthy controls (n=10) were registered continuously. After a fasting period of at least 6 hours we measured all individuals every 5 minutes over a 6-8 hour period. Gallbladder volumes were estimated by the ellipsoid method. Minor oscillations less than 30% were excluded. To calculate the total amount of bile released per hour (gallbladder-index) we added all contractions and divided them by the total measurement time in hours. Exclusion criteria: cholecystitis, cholelithiasis, liver cirrhosis, thoracic or abdominal surgery, diabetes mellitus, age > 65 years, relevant medication. Results: Spontaneous gallbladder contractions of up to 86% and 35% were observed in all individuals except in 4 asymptomatic patients. Compared to the controls we found a significant reduction in frequency and magnitude of the contractions in asymptomatic but not in symptomatic gallstone patients.
Can Cisapride Overcome the Effects of Octreotide (OT) on Gallbladder Emptying?

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Background: We and others have shown that OT inhibits meal-stimulated gallbladder (GB) emptying and induces the formation of cholesterol-rich GB stones. The effects of the prokinetic drug, cisapride, on the GB are controversial and it is not known whether cisapride can overcome the inhibition of GB emptying caused by OT and thereby prevent the formation of OT-induced GB stones.

Methods: We, therefore, used a randomised, double-blind, placebo-controlled, crossover study to test the effects of cisapride (10 mg qds for 2 weeks) on GB emptying, assessed by real-time ultrasound after a fat-rich liquid meal, in 8 acromegalic patients (age range 21–69 yrs; 4 women) receiving long-term (>3 months) octreotide (100–200 μg tds) and in 8 non-acromegalic patients (age range 37–74 yrs; 5 women) from the Gastroenterology Unit of the University College London Clinic. Fasting (VF) and residual (RV) GB volumes, the extent of GB emptying – as assessed by the ejection fraction (EF) – and the rate of GB emptying (RBGE) were calculated.

Results: Mean values ± SEM

<table>
<thead>
<tr>
<th>Acromegalic patients</th>
<th>Non-acromegalic patients</th>
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<tbody>
<tr>
<td>Cisapride</td>
<td>Placebo</td>
</tr>
<tr>
<td>VF (ml)</td>
<td>56 ± 6.5**</td>
</tr>
<tr>
<td>RV (ml)</td>
<td>38 ± 7.2*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>31 ± 6.8</td>
</tr>
<tr>
<td>RBGE (ml/min)</td>
<td>0.46 ± 0.19*</td>
</tr>
</tbody>
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*p < 0.05, **p < 0.005 compared to placebo

Summary/Conclusions: These results show that cisapride increases the VF and, in the acromegals, the RV, but leaves the EF unchanged, whilst significantly increasing the RBGE. Since stasis (large RV) and EF are probably more important than RBGE in GBS pathogenesis and if GB dysmotility is rate-limiting, cisapride is unlikely to prevent the formation of OT-induced GBS.

Obesity and Rapid Weight Loss: Effect of Different Very Low Calorie Diets on Gallbladder Motility and Gallstone Formation

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Obesity is considered a risk factor for gallstone formation. Very low calorie diets (VLCD) represent a common treatment for morbid obesity; however an increased risk of gallstone formation has been reported during rapid weight loss induced by VLCD. Impaired gallbladder motility is considered among the pathogenetic factors for gallstone development. Since diet composition, and mainly its fat content, modifies gallbladder contractility and most of the commonly used VLCD are characterized by a low fat content, this study was aimed at evaluating in obese subjects during weight loss the effect of different VLCD on gallbladder emptying and composition and formation. Sixteen gallstone-free obese subjects (4 males, 12 females, age 35.5 ± 2.8 yrs; BMI: 41.3 ± 1.4 kg/m², mean ± SE) were studied. Gallbladder motility was evaluated by an ultrasonographic (US) technique in response to a standardized liquid meal. Subjects were randomly allocated to two weight reduction programs, each lasting 90 days; each program (A and B) was characterized by a different VLCD: A - 520 kcal, 3.1 g of fats, 39.1 g of proteins, 123.2 g of carbohydrates; B - 570 kcal, 12.5 g of fats, 51.1 g of proteins, 60.4 g of carbohydrates. Since a fasting analysis of gallbladder contractility was not investigated by US and gallbladder motility study repeated as at baseline; in 4 subjects for each group biliary lipid composition was also evaluated. Statistical analyses were performed using Mann-Whitney test (independent samples) and Wilcoxon test (paired samples); results were expressed as mean ± SE. BMI significantly (p < 0.05) decreased in each group during the program: A, from 40.3 ± 1.5 to 33.8 ± 1.2 kg/m², B, from 42.3 ± 2.0 to 35.4 ± 1.6 kg/m². Gallbladder motility, expressed as percent emptied, remained unaltered during the program in both groups (A, B). However, the percent emptied during weight reduction but this decrease was significant (p < 0.04) in group B (57.5 ± 4.6 ml before, 23.4 ± 3.8 ml at day 45, 66.4 ± 5.2 ml at day 90). Fasting gallbladder volume decreased during weight loss and this decrease was significant (p < 0.04) in group B (57.5 ± 4.6 ml before, 23.4 ± 3.8 ml at day 90) but not in group A (34.6 ± 4.5 ml before, 28.5 ± 3.7 ml at day 45, 26.9 ± 4.2 ml at 90). The emptying of the GB was, therefore, significantly increased during weight loss in group B, but not in group A. The composition, volume, and calcium content of gallbladder stones decreased during weight loss, though this decrease was not significant. Though not tested, it is possible that the use of weight reduction programs that are high in carbohydrates and low in fat. However, this study was not designed to evaluate the effects of VLCD on gallbladder motility.
Conclusions: Cholesectographic HBDT is delayed in some cholecystectomized patients with typical biliary type pain. This group may require further investigations or therapy (e.g. sphincterotomy).

747 Incidence of Colorectal Adenomas (CRA) in a Cohort without Prior Personal or Family History of CRA or Colorectal Cancer (CRC)
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Although people without history of CRA or CRC constitute the vast majority of the population, it is difficult to recommend a definite attitude towards prevention for this group which is considered at low risk, according to prevalence studies. The aim of this study was to evaluate the incidence rate which has not been determined until now. The study includes 450 persons enrolled in a colonic screening cancer prevention program since 1979 to 1992 who had at least 2 flexible sigmoidoscopies. Participants who had at the 1 exam present or past personal or first degree relatives history of CRA or CRC were excluded. The material consist of 298 women (66%; 170 people were less than 50 years old (36%) while 26 were older than 65 (10%). The mean annual incidence rate was found to be 2.65% (95% CI: 1.2-3.5% vs. 2.5% (95% CI: 1.0-3.0%). It was higher for men than for women (p < 0.03), and it increased with age (p < 0.01). These rates are much lower than those known for people with prior CRA or CRC which are about 10%/yr, and could be taken into consideration when screening the general population by sigmoidoscopy.

748 Negative Influence of Homologous Blood-Transfusions on the Evolution of Patients with Colorectal Carcinoma. (A Meta-analysis)
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Several publications mainly based on retrospective data, had shown a Negative influence of homologous blood-transfusions (HBT) on the evolution of patients with colorectal carcinoma. Several prospective studies have tried to clarify the issue and this analysis is an attempt to quantitatively assess the current knowledge.

Material and Methods: This analysis concerns only prospective studies in colorectal Ca. listed in Medline between 1984 and 1996. Patients were classified as receiving homologous blood (HBT), autologous (ABD) or no blood transfusion (No BT). The time of transfusion considered was the immediate pre-until the post-operative period. The parameters analyzed were 1) the incidence of post-operative infections and 2) Recurrence rates (both local & distant) at study end-point (usually 5 years). Data were analyzed using the Mantel-Haenszel method. The significance was accepted if p < 0.05.

Results: Rate of infections: 5 Studies compared HBT to No BT (N = 1594) and 3 studies compared HBT to ABD (N = 694). Rate of infections were 32% vs. 12% (p < 0.001) and 16% vs. 10% (p < 0.04). Rate of infections: 3 Studies compared HBT to No BT (N = 1556) and 2 studies compared HBT to ABD (N = 338). Rate of recurrence were 41% vs. 24% (p < 0.001) and 41% vs. 31% (n.s.). The combined risk of an infection and/or recurrence is almost significant as found after HBT than after ABD (Odds Ratio = 1.32; p = 0.064).

Conclusions: Patients requiring a BT appear to be at higher risk of infection or recurrence than No BT, but the comparability of these pts. is questionable. Patients receiving HBT appear to be at a somewhat greater risk of infection or recurrence than receiving ABD. Larger studies are needed in order to give a final answer to this question.

749 | Human Papillomavirus (HPV) and Colon Cancer: No Viral DNA Sequence Found Neither in Tumors nor in Normal Adjacent Mucosae
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The presence of human papillomavirus 6, 16, 18 and 33 was previously reported in up to 50% of colorectal carcinomas (Chang et al, Gut 1995). The E6 protein of these high risk types was shown to bind to the tumor suppressor p53 protein and to impair its degradation. The aim of our study was to further investigate the putative role of these HPV types in colorectal carcinogenesis.

Tumoral samples stored in liquid nitrogen from 55 patients were used. Normal adjacent mucosae was also available in all these cases. All clinicopathological data including age, sex, histological differentiation, immunohistochemical p53 status, tumor stage, tumor location, metastatic status and survival years were recorded. Samples were groomed in liquid nitrogen. DNA was extracted with phenol-chloroform after lysis in buffer with detergent and protease K. Two PCR experiments were performed: i) multiplex PCR using 3 sets of primers (E6 gene of HPV 16, 18 and internal control target located into the embryonic myosin heavy chain gene) (ii) another one using consensus L1 primers. PCR products were analysed after restriction mapping on 5% polyacrylamide gel stained with ethidium bromide. This multiplex HPV 16/18 PCR shows a sensitivity of 1 viral copy per sample. HPV DNA sequences could not be detected in any of the tumoral sample nor in the normal adjacent mucosa by any of the PCR techniques used.

These results suggest that HPV are not involved in colorectal carcinogenesis at least in French patients.

750 The Role of Cholecystectomy in the Oncogenesis of the Digestive Tract
Daniel Tuculanu 1, Ioan Romo§an 2, Josip A. Szucsk 3, Constantin Tudor 1, Leila Susan 1, C!lin Desplau 1, 4, A.M. Martin, Gut, 1996; 39 (Suppl 3) A121

The present study estimates the oncogenic risk after cholecystectomy, starting from the fact that the duodeno-gastro reflex (commonly noticed in cholecystectomized patients) is one of the major factors involved in the occurrence of gastric epithelium metaplasia.

The authors have carried out a retrospective analysis of 462 cases that were consecutively diagnosed in our medical department with cancers of the digestive tract: 67% of these pts. were operated in the years 1979-1992 for cancer, 223 cases with gastric cancer and 172 cases with colo-rectal cancer.

Seventy-nine patients had cholecystectomy in their history (9% of those with oesophageal cancer, 17% of those with gastric cancer, and 20% of those with colo-rectal cancers). In all three localisations the subgroups of cholecystectomized patients presented certain features that differentiated them from the rest of the patients: in the case of the oesophageal cancer we noticed the predominance of the feminine gender, of the localisation in the lower third, and of the adenocarcinoma histological type; in the case of the stomach we noted the predominance of the fungating endoscopic type and of intestinal histological type; in the case of colo-rectal cancer the localisation in the right half of the large bowel were predominant. A common characteristic for all localisations was the earlier age when the cancer set in and a long period since the surgical intervention.

All these data suggest that cholecystectomy plays a role in the oncogenesis of the digestive tract, either through the direct action of the biliary contaminants (lithocholic, biliary acids), or through the sensitisation of the mucosa to the action of other aggressive factors.

751 Family Study on Colorectal Cancer from the Digestive Cancers Registry of "Calvados": An Intermediate Report
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In France, colorectal cancer (CCR) is the most frequent cancer for both females and males (26000 new cases each year). Although an increased risk has been associated with a family history of CCR in nearly all epidemiological studies, few population-based family studies have been performed. A population-based family study has been carried out in Calvados, France, from September 1, 1993.

The main aim of this study is to define the role of genetic factors in the disease transmission accounting for environmental factors from a sample of systematically recorded family data. Results of a feasibility study connected with the above study showed a high proportion of contacted people who agreed to participate and a good representativity of the recruited cases compared with the registered cases.

A report of the definitive study progress is presented in this paper. During 30 months, 837 new cases of colorectal cancer have been diagnosed in Calvados. Four hundred three families have been included today. A high proportion of included persons (index cases and relatives) accepted being taken a blood sample (about 80%). The mean age for the index cases is 68.1 years for men (age range: 39 to 91 years) and 69.8 years for women (age range: 34 to 94 years). Twenty two per cent of the families have at least one colorectal cancer in addition to the index case. For 14 per-cent of them, at least one colorectal cancer occurred in the first degree relatives (i.e. sibling, children or parents). Fifteen per-cent of the families have at least one breast cancer, 13% a stomach cancer. For 7 per-centage of the families, one breast or one stomach cancer occurred in the first degree relatives. The recruitment of new cases will stop in September 1997. About 670 families are expected to be included.

752 Selenium Status in the Patients with Colorectal Adenoma and Colorectal Carcinoma
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Selenium is increasingly recognized as a versatile anticarcinogenic agent.
Selenium appears to operate by several mechanisms depending on dosage and chemical form of Selenium (Se) and the nature of the carcinogenic stress. Se prevents the malignant transformation of cells by acting as a “redox switch” in the activation/inactivation of cellular growth factors and other functional proteins through the catalysis of oxidation/reduction reactions.

We investigated Se status in the colorectal adenoma (CA) group of patients (pts.) who underwent endoscopic polypectomy, and operated group of pts. with colorectal carcinoma (CC). The control group were healthy volunteers from the same region. Concentrations of Se were examined in polyp tissue, carcinoma tissue, plasma, erythrocyte, lymphocytes, hair and 24-h urine samples. Malondialdehyde (MDA) was also investigated as an indicator of oxidative stress. The results showed that CA group and CC group of pts. had significantly lower concentrations of Se in Er and in plasma, Se concentrations were increased in urine, and it was lower in hair and Ly, but not significantly. Se concentrations in CA tissues was higher, in CC tissue was lower, comparing with healthy volunteers. Concentrations with Se were lower in the examined operative edge of the colonic tissue in the CC group, comparing with healthy volunteers. Values of MDA were 200–1000 times higher in the CC tissue and 6–40 times in the CA tissue, comparing with healthy volunteers.

753 Familial Adenomatous Polyposis in Lithuania


Purpose of the study: While establishing the polyposis register, to present data on familial adenomatous polyposis patients (FAP) in local population.

Methods used: From March 1995 to March 1996, possible data on polyposis patients in our republic was collected and information disseminated via professional and public sources about the register and disease itself. Screening of the first 112 and attempts to coordinate prophylactic treatment were made. Criteria of registration followed international guidelines.

Results: 23 polyposis families were registered with known 54 affected persons. 9 of these families have been isolated cases. A detailed information on 17 patients with colorectal cancer revealed 4 (23.5%) to have synchronous cancers. Earliest onset of colorectal cancer was in a 21 year old male. From 16 patients 12 (83%) had duodenal adenomas, from 16 patients 4 (2%) had mullardian osteomas and 13 (89%) of 14 patients had CHRPE (congenital hypertrophy of retinal pigment epithelium). First DNA tests have been performed for our polyposis patients.

Conclusion: Increasing collaboration with medical professionals and knowledge about FAP should be an important factors influencing further successful registration and treatment of FAP patients.

754 Screening for Hereditary Non-Polyposis Colorectal Cancer within a County Register in Romania

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One of the most important roles of the hereditary non-polyposis colorectal cancer (HNPCC) Registry is to coordinate the screening programs. It provides the opportunity for colorectal cancer (CRC) prevention in family members who are at high risk. The aim of this projective controlled longitudinal study was to evaluate the efficacy of the screening within a county HNPCC Registry (established in early 1989) in Bucharest area in Romania.; 21 families fulfilling “the Amsterdam criteria” were extracted from a cohort of 808 CRC between March 1990–March 1996. For the ascertainment of probands, information were collected about all types of malignancies, age at onset, location and histology. The genealogical studies and pedigrees construction were made as accurate as possible. The family members at risk were identified and call-up into the study. The screening group consisted in 54 subjects undergoing periodic examinations (full colonoscopy/sigmoidoscopy and barium enema) at 2–3 yr. interval whereas 87 subjects of the control group had no screening examinations. The adenoma/CRC detection and survival curves were compared by the Kaplan-Meier product limit method between the two groups of asymptomatic at-risk subjects. Adenoma/CRC occurred in 10/6 screened (16.5% positive examinations) vs 2/20 control subjects. The tumor Dukes stage (A + B vs C + D) was more favorable in screened group with one case of death caused by CRC vs 10 in control group at the end of the study. Although the adenoma/CRC occurrence did not differ significantly (p < 0.81), survival curves showed a significantly better survival in screened vs non-screened subjects (p < 0.04).

Conclusion: the 2–3 yr. interval screening programs on HNPCC, although detecting a similar rate of neoplastic colorectal changes, demonstrate a significant survival benefit in screened vs non-screened subjects with HNPCC, contributing to a more favorable prognosis.
Methods: To determine optimal conditions, we used five different kinds of germination medium among six HNPCC pedigrees and two somatic mutations in a single RER+ sporadic endometrial cancer, which had been already revealed by others. We discovered, by this method, the entire coding regions of MLLH in DNAs isolated from affected individuals belonging to two HNPCC kindreds and four HNPCC-like kindreds, and from four patients with multiple primary cancers as well as eight RER+ sporadic colorectal cancers.

Results: Two kinds of primers used as positive controls were detectable by the 2-D DNA methods. Twenty-one spots covering all 19 coding exons were visualized on a single gel, and we could envisage whether and where any mutations existed. We discovered novel germination mutations in one HNPCC proband and one RER+ sporadic colorectal cancer, and one polymorphism into HNPCC-like kindreds.

Conclusion: This new diagnostic method is very useful and offers a major improvement over current approaches.

758 The Influence of Intestinal Transit Rate on Colonic Luminal pH and Stool Short Chain Fatty Acid Concentration

S.J. Lewis, K.W. Heaton. Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW

Populations at low risk of colonic cancer consume large amounts of fibre and starch (fermented by bacteria to short chain fatty acids (SCFA)) and pass acid bulky stools. Traversing the colon SCFA are absorbed and luminal pH increased to neutral. One SCFA, butyrate, is the colon's main energy source and inhibits malignant transformation in vitro. Low colonic pH should be associated with high levels of butyrate and thus decreased predisposition to cancer. We aimed to test two hypotheses: 1. Altering colonic transit alters colonic pH. 2. Distal colonic luminal pH is correlated with the SCFA (especially butyrate) content of the stools.

13 healthy volunteers took in turn supplements of wheat bran (mean 28.3 g/day), senna laxative and loperamide, each for nine days with a 2 week washout period. Before and in the last 4 days of each intervention period dietary intake, whole gut transit time (WGTT), stool pH, stool SCFA concentrations (by GLC) and intracellular pH (using a radioisotope capsule for continuous monitoring) were assessed.

There was no difference between dietary intakes specifically total fibre, NSP or fat at the start and end of each intervention period. pH measurements were similar in the distal colon and stool. WGTT decreased and stool output increased with wheat bran and senna, vice versa with loperamide. Changes in WGTT were least impressive for wheat bran. Baseline stool SCFA concentration correlated with distal colonic pH (r = -0.417, p = 0.01) and WGTT (r = -0.623, p = 0.001). Similar correlations were seen for baseline stool butyrate (distal pH r = 0.434, p = 0.007 & WGTT r = 0.610, p = 0.001).

Colonic pH and stool SCFA concentration: effect of transit altering agents

<table>
<thead>
<tr>
<th>Colonic pH</th>
<th>Stool SCFA (umol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle</td>
<td>Total</td>
</tr>
<tr>
<td>Distal</td>
<td>Butyrate</td>
</tr>
<tr>
<td>Wheat bran</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>End</td>
</tr>
<tr>
<td>6.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Senna</td>
<td></td>
</tr>
<tr>
<td>6.9</td>
<td>6.4*</td>
</tr>
<tr>
<td>Loperamide</td>
<td></td>
</tr>
<tr>
<td>6.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Mean <em>p</em></td>
<td>0.05</td>
</tr>
</tbody>
</table>

There is a relationship between bowel transit rate (diet being constant) and stool pH, stool SCFA concentration and distal colonic pH. This may explain the associations between colonic cancer and dietary fibre, stool output and stool pH, in that stool pH is a marker for SCFA levels including butyrate.

759 Non-Invasive Recording of Colonic Electrical Activity Based on Experimental Investigations


The study was aimed at non-invasive recording of the electrical activity of the human colon, i.e., electrooculography (EOcG). Experiments were made on dogs with silver, bipolar, ball-shaped electrodes connected to the rectal wall. Stimulation electrodes were placed on the abdominal wall in the beginning of each experiment. Slow waves were led off in the electrooculomogram (EOcMG), corresponding to low-amplitude waves in the non-invasive electrooculogram (EOcG). The bursts of spontaneous activity are followed by a reproducible wave amplitude in the EOcG. Thus the functional state of the colon could be judged by the differences in the amplitude of the EOcG waves.

The electrical activity of the descending colon of fifteen healthy volunteers was recorded by the abdominal wall along the descending colon projection. The electrooculogram (EOG) was led off too. The activity of the colon and stomach was recorded on an original 2-channel electrooculograph. A method for complete elimination of the cardiac artifacts was elaborated and successfully implemented. The means ± S.E.M. of the frequency of colonic and gastric waves were calculated. Two kinds of EOcG waves according to the frequency were identified: i) waves with a frequency in the range of 5.85 ± 0.50 cpm and ii) waves with a frequency in the range of 2.37 ± 0.31 cpm. The analysis of the EOcG waves was compared with that of the EGG waves. There was a significant difference between the frequencies of the EOcG waves and the frequency of the EGG waves – 3.26 ± 0.26 cpm (n = 7).

Thus the proposed electrooculographic method proved to be suitable for non-invasive registration of the electrical activity of the human colon. It also could provide reliable information on the EOcG wave frequencies at visual inspection.

Supported by Grant L-539 from the National Fund "Scientific Research", Bulgaria.

760 Characteristics of Cecal Circular Smooth Muscle Cells from Guinea Pigs with Carrageenan-Induced Colitis

H. Akho1, Y. Chijiiwa2, H. Okabe3, H. Harada4, Y. Motomura2, Y. Iwakiri2, H. Nawata1, H. Akiho1, H. Okabe1, H. Carrageenan-Induced Colitis

No invasively recorded cecal circular smooth muscle cells from guinea pigs with carrageenan-induced colitis (UC-like colitis).

The smooth muscle cell length in the basal state of animals with colitis was compared with that in normal animals. In addition, the effect of contractile agents (cholceystokinin-8 (CCK-8), carbachol and relaxant agents (N6, O-Dibutylyl adenosine 3',5'-cyclic monophosphate [dBCAMP] and N2, O-Dibutylyl guanosine 3',5'-cyclic monophosphate [dBGMP]) on isolated muscle cells with or without colitis was assessed.

In the basal state, the mean cell length in animals with colitis was significantly (p < 0.001) shorter than that in normal animals. CCK-8 and carbachol-induced contraction with colitis was significantly decreased by 72.2% (p < 0.05) and 60.3% (p < 0.001), respectively, compared with that in normal animals. dBCAMP and dBGMP had no significant effect on smooth muscles from animals with colitis.

The data showed that the weak contractile response in animals with colitis was due to the basal cell length was significantly shorter than that in normal animals, and suggested that the relaxing mechanism of smooth muscles in animals with colitis was disturbed.

761 Histopathology of Hypoganglionosis in Whole Mount Preparations of the Human Colon

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Traditional histopathological methods like the acetylcholin-esterase reaction on sections of the colon bowel are normally used to diagnose and to investigate the histopathology of abnormalities of the enteric nervous system including the hypoganglionosis. The hypoganglionic is only defined as a reduction of nerve cells of about 50%.

In contrast to these methods we have investigated the histopathology of the enteric nervous system in whole mount preparations of resected segments of the colon of 10 patients suffering from severe constipation caused by aganglionosis and hypoganglionosis by NADPH-diaphorase reaction.

We could recognize that the meshwork of the enteric plexus is very irregular. The density of the ganglia and nervestrands is reduced. The ganglia are very small and contain a small number of nerve cells. The morphology of the nerve cells is very uniform in contrast to normal enteric nerve cells. Functionally the nerve cells are characterised by week NADPH-staining as expression of low NOS-content, which can cause constipation.

We may conclude that NADPH-diaphorase reaction on whole mount preparations of the human colon is a simple and reproducible method for the histopathological investigation of congenital defects of the ENS. Using this methods we could provide a completion to the previous histopathological image of the hypoganglionosis.

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762 Direct Contractile Effect of CCK on Cecal Circular Smooth Muscle Cells Via Both CCK1 and CCK2

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Cholecystokinin (CCK) contracts gastrointestinal smooth muscle cells. However there has not been sufficient investigation about receptors for CCK on smooth muscle cells. Receptor for CCK has been divided into two subtypes: CCK1 and CCK2. This study was designed to investigate the CCK receptor subtype responsible for cecal circular smooth muscle contraction by CCK.

Methods: Smooth muscle cells were isolated from cecal circular smooth muscle layer of the guinea pig. Cells were stimulated by test agent. At the end
of incubation, acrolein was added. The length of 50 cells in microscopic fields was measured by image splitting micrometry, and the percent decrease in mean cell length was determined by comparison with the control. Kinetic studies were performed. Cells were incubated with CC-K and M for various length of time. For subsequent experiments, the optimal incubation time was used. A dose–response curve for CC-K (10⁻¹⁰⁻¹⁰⁻⁸ M) was determined. We assessed the inhibitory effect of various concentrations of CC-K on the contractile effect of CRH. FK480 on 10⁻⁹ M CC-K-induced contraction; the inhibitory effect of various concentrations of CC-K on CRH-induced contraction; and the inhibitory effect of a combination of 10⁻¹⁰ M FK480 and 10⁻¹⁰ M MY202 on each of concentrations of CC-K-induced contraction.

Results: Both FK480 and MY202 inhibited 10⁻⁹ M CC-K-induced contraction in a concentration-dependent manner. A significant inhibition was observed at a concentration as low as 10⁻¹⁰ M FK480 and 10⁻¹⁰ M MY202. At a concentration of 10⁻¹⁰ M, both FK480 and MY202 shifted the concentration–response curve for CC-K to the right. In addition, a combination of 10⁻¹⁰ M FK480 and 10⁻¹⁰ M MY202 shifted the concentration–response curve for 10⁻¹⁰ M FK480 alone or 10⁻¹⁰ M MY202 alone to the right.

Conclusion: Our results strongly suggest that the guinea-pig caecal circular smooth muscle cell contains both CC-K and CRH receptors and the contractile effect of CC-K is mediated by both of these receptors.

**Faster Intestinal Transit is Associated with Lower Serum Oestrogens**

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Any factor limiting reabsorption of oestrogens from the colon should lead to increased faecal excretion of oestrogen and reduced serum oestrogens. High fibre diets and wheat bran supplements reduce serum oestrogens, perhaps explaining associations between a high fibre intake and reduced risk of breast cancer. We hypothesised that fibre reduces serum oestrogen concentrations by speeding colonic transit, reducing the time for bacterial deconjugation (by β-glucuronidase a pH dependent enzyme) and/or reabsorption of oestrogens. To test this we altered whole gut transit times (WGT) in 3 ways and looked for changes in serum oestrogen and in stool pH and β-glucuronidase activity.

40 healthy premenopausal volunteers were randomised to one of 3 groups. Ten subjects took senna then after a washout period wheat bran, both for 2 menstrual cycles. Another 10 did the reverse. A third group of 20 subjects took loperamide to slow down transit for two cycles. All supplements were taken in the maximum tolerated dose. At the beginning and end of each study period blood was taken for oestrogens (day 6 of the menstrual cycle), a 4 day dietary record was kept, WGT was measured and stools were analysed for pH and β-glucuronidase activity.

Serum oestrone sulphate, the major storage form of oestrogen, fell with wheat bran (average dose 20 g/day) and with senna; both un conjugated and non-protein bound oestrone fell only with senna. No significant changes in serum oestrogens occurred with loperamide. Senna and loperamide caused significant alterations in WGT; changes in those taking wheat bran supplements tended towards a reduction (p = 0.06). No significant changes were seen with loperamide–β-glucuronidase activity. Stool pH changed only with senna, where it fell. There was no significant change in dietary intakes.

Changes in geometric means of serum oestrogens (pmol/l)

<table>
<thead>
<tr>
<th></th>
<th>Oestriol</th>
<th>Oestrone</th>
<th>Oestrone sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td>End</td>
<td>Start</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>281</td>
<td>262</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>1745</td>
<td>1523*</td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>233</td>
<td>249</td>
<td>219</td>
</tr>
<tr>
<td></td>
<td>1641</td>
<td>1820</td>
<td></td>
</tr>
</tbody>
</table>

Speeding up intestinal transit can lower serum oestrogens. Faster intestinal transit may explain the epidemiological association of low risk of breast cancer with a high fibre intake.

**Differential Sensitivity of Isolated Smooth Muscle Cells from Normal and Inflamed Human Colon to Contractile Agents. Effects of Calcium Channel Blockers**

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Contractile activity of colonic smooth muscles from patients with IBD yielded conflicting results: some of them showed a decreased activity as compared to normal muscles, others reported no significant changes. We compare contractile response to different agonists of smooth muscle cells (SMC) enzymatically isolated from normal (n = 32) and inflamed (n = 33) human colon. The effects of calcium channel blockers (diltiazem and pinaverium bromide) were also evaluated. Contractile responses to CCK (1 nM), CCh (1 nM) and KCl (20 mM) were evaluated by video-microscopic measurements of the mean length of 100 isolated SMC. The contractility of SMC induced by catecholamines, CCh and KCl was decreased with age in IBD patients (p < 0.05). In contrast, the contractility of SMC induced by CCK was decreased with age in IBD patients. Significant changes were only observed in patients with inflamed tissues, (ii) calcium channel blockers significantly reduced cell contraction in cells from human colon.
767 Relations between Methanogenesis and Sulfate Reduction in the Human Colon

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Sulfate-reducing bacteria (SRB), which could be important in the pathogenesis of ulcerative colitis and inflammatory bowel diseases, are normal inhabitants of the human colon where they represent the major source of sulfide (S^2-) from the reduction of dietary and mucous sulfur. Since they can use H2 as electron donor, authors hypothesized that SRB outcompete the obligate methanogenic methanogens for H2, leading to a mutual exclusion between methanogenesis and sulfate reduction (Srd).

Aim: To test this hypothesis, we compared fecal SRB, Srd, and Srd between methane-excreters (CH4+) and non-methane-excreters (CH4—). Methane-excreters were capable to use H2 as electron donor (Desulfovibrio and Desulfofusobus) were enumerated by the agar shake dilution method, Srd measured using the methylene blue method and Srd by incubation at 37°C under anaerobic conditions in a tube with an excised human colon (35 mm). All SRB counts were expressed as log10 CFU/g wet weight, results are mean ± SEM.

Results: 1) All CH4+ harboured SRB ranging from 4.9 to 8.0 log10 CFU/g. 2) None of the differences between the two groups were statistically significant.

Group | SRB (log10 CFU/g) | Srd (μM/ml) | Srd (μM/ml/h)
--- | -- | -- | --
CH4+ (n = 17) | 6.6 ± 0.3 | 0.9 ± 0.1 | 3.2 ± 0.5
CH4— (n = 16) | 6.5 ± 0.3 | 1.1 ± 0.4 | 2.2 ± 0.4

Discussion: These results do not support the hypothesis of a mutual exclusion between methanogens and SRB in the human colon. Like in other intestinal methanogenic environments, normal inhabitants of the human colon do not coexist. The latter may actually behave as H2-producer using lactate as electron donor and transferring reducing equivalents to methanogens, as it has been shown in vitro using low sulfate concentrations, conditions usually prevailing in the human colon.

768 Composition of the Caecal Flora in Healthy Humans and Comparison with the Faecal Flora

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Most studies of the human colonic flora concern the faecal flora. Ecological conditions such as substrate availability, pH, and residence time differ greatly between the caecum and the left colon. The composition of the human caecal flora is poorly known due to the difficulties of sampling.

Aim: To assess the composition of the caecal flora in man using an in vitro technique, and compare the caecal and faecal flora.

Subjects and Methods: The caecal flora was collected under anaerobic conditions using a 4 mm in diameter intestinal tube with a tractable balloon. Faecal samples were collected on the same day. Serial dilution of the samples were prepared in an anaerobic chamber, and plated on the specific media. Comparisons between the caecal and faecal flora were done using the Wilcoxon test. Results: Log cfu/g; means (95% confidence intervals)

<table>
<thead>
<tr>
<th>Total anaerobes</th>
<th>Facultative anaerobes</th>
<th>Bifidobacteria</th>
<th>Bacteroides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caeacum</td>
<td>8.0 (7.5–8.5)</td>
<td>7.4 (6.9–7.9)</td>
<td>6.7 (6.2–7.7)</td>
</tr>
<tr>
<td>Faeces</td>
<td>10.4 (10.0–10.7)</td>
<td>7.8 (7.1–8.4)</td>
<td>8.9 (8.4–9.5)</td>
</tr>
</tbody>
</table>

Conclusion: 1 – studying the composition of the caecal flora is feasible; 2 – facultative anaerobes represent 25% of the dominant flora of the caecum; 3 – their concentrations are stable throughout the colon while strict anaerobes increase more than 100 times between the caecum and the faecal flora; 4 – our method should allow determining on the regulation of the caecal flora which is more prone than the faecal flora to be influenced by ingested substrates.

769 Urosodeoxycholic Acid Treatment in Patients with Primary Constipation and Hypercholesterolemia

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Ursodeoxycholic acid (UDCA), the 7 beta epimer of Chenodeoxycholic acid (CDCA), is a dihydroxy bile acid widely used in the treatment of chronic liver disease, cholesterol gallstones, hypercholesterolemia and dyspepsia. UDCA is able to inhibit the secretion of LDL cholesterol and it has a strong cholesteric effect but, in contrast to CDCA, it does not cause any increase of LDL cholesterol, nor diarrhoea, nor abnormal results in liver function tests.

Aim of our study was to investigate the effect of UDCA treatment in patients with primary constipation and hypercholesterolemia. Methods: Eleven subjects (4 males, 7 females; age: 58.7 ± 7.4 mean ± SD) with primary constipation (basal number of bowel movements BM = 2.55 ± 0.52 and report of hard stools in all cases; HS > 100%) and hypercholesterolemia (> 200 mg/dl; mean ± SD = 240 ± 21 mg/dl) were treated for 4 weeks with 8 mg/Kg/day of UDCA in a cross-over study vs. Placebo (4 wks). Differences between the two treatments and basal values were evaluated by means of the Wilcoxon matched pairs (BM and cholesterol) and the Kruskemn (BM and cholesterol) tests.

Results: During the study no patient complained about diarrhea, nor presented hypotransaminemia. BM was significantly (P < 0.01) higher after UDCA (4.87 ± 1.79) than Placebo (2.45 ± 0.32), while the presence of HS was lower (18.2% vs. 10.1%; P = 0.01). During UDCA treatment the n values of serum bile acids (n = 0.05) decrease in serum cholesterol (227 ± 0.5 mg/dl) was also observed. The relationship between the increase in the number of bowel movement and the decrease in serum cholesterol level showed an r value of 0.571 (P = 0.01). Conclusions: Our results show that the simultaneous administration of bile acids could be involved in the serum cholesterol lowering during UDCA treatment. In summary, since UDCA has been widely used without any side effect, it could be proposed in the management of patients with primary constipation and hypercholesterolemia.

770 Cost-Effective Treatment of Constipation in the Elderly: Comparison of Milk of Magnesia and Lactulose

Antonis K. Zacharid, C. Ptergiogiannopoulos, C. Fliavaros, J. Poulikos. Hellenic Red Cross Hospital, Athens, Greece

Purpose: To compare lactulose and Milk of Magnesia in the treatment of chronic constipation in elderly patients.

Material and Methods: 210 hospitalized elderly patients with chronic constipation after a 1-week washout period, were given Milk of Magnesia or lactulose at bedtime for 3 weeks; after another 1-week washout period, 3 weeks of treatment with the alternate agent was given.

Results: There was no significant difference between the efficacy of the two agents as assessed by a number of criteria, including frequency of stools, the number of days in which bowel movements occurred, the need for alternative laxatives or enemas, and symptoms such as bloating, cramping, excessive flatus, diarrhea, and fecal incontinence.

Conclusion: Milk of Magnesia and lactulose do not significantly differ for treating constipation; the use of Milk of Magnesia in the place of lactulose is cost-effective in that comparable results are obtained at greatly reduced costs.

771 Diurnal Motor Change in Canine Colostomized Segment

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Background: The colonic motor activity in dogs is characterized by recurring groups of contraction burst which are separated by motor quiescence. We reported in UEGW 94 that increased length of the motor quiescence may be the 'interdigestive motor pattern' of the canine colon (Gut 33: A18, 1994). Aim: To assess the diurnal motor profile in colostomized segment and to correlate it to that in the upper GI tract. Methods: Four force transducers (FT1, FT2, FT4) were implanted on the colon of 9 dogs at an equidistance from FT3 on the ascending colon and FT4 on the level of the caudal mesenteric artery. Another FT was implanted on the terminal ileum to distinguish the digestive from the interdigestive motor phase. The dogs were fed either 20 or 10 g meal to modify the duration of the digestive phase. Motor activity was assessed in each FT recording of the colonic motor activity was performed. The duration of each group of contraction burst (contractile state, CS) and the length of each motor quiescence state (QS) were sequentially plotted against the plate and their temporal profiles were correlated with the first meal MMC. Later the colon was transected between FT2 and FT3 to establish a double-barrelled colostomy and a 24 h recording was resumed. Results: In the intact dogs with either 20 or 10 g meal, CS at each FT except FT4 did not significantly change throughout the recording session. At FT4, shortening of QS occurred at 2–4 h and significant increase of QS occurred at 15.3 ± 0.3 h with 20 g meal and at 11.5 ± 0.8 h with 10 g meal. The onset of this QS prolongation was closely correlated with the appearance of the first meal MMC (r = 0.95 ± 0.02, p < 0.001). In the colostomized dogs, the motor profile in the oral colon (FT1 and FT2) was identical to that before colostomy, while no shortening of QS in the early postprandial period nor prolongation of QS in the interdigestive phase was observed in the distal colon (FT3 and FT4). Instead, CS and QS recorded periodically with a fixed value of 4.7 ± 0.1 min for CS and 32.6 ± 1.8 min for QS, respectively. Conclusion: Prolongation of QS in the colon is temporally locked with the interdigestive motor phase of the upper GI tract. Bowel continuity is essential for this QS prolongation to occur over the length of the colon. Each small segment of the colon has its own contractile rhythm which is, however, entrained by the rhythm in a more proximal adjacent segment so far as the bowel wall is continuous.

772 Pseudo-Obstruction of the Colon

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Pseudo-obstruction of the colon is an acute derangement of the intestinal motility with no evidence of any other obstruction or pathology. Since many controversies still exist in pathogenesis, diagnosis and therapy, the authors report their experience on the subject.
During the period January 1989–January 1996, 29 such cases were treated in our Department. Mean age was 71.5 years and there were 17 female and 12 male patients. Clinical picture was that of ileus, while in 15 patients palpation of the abdomen revealed diffuse tenderness. Radiology showed dilatation of the large bowel and on rectal examination air or feces were found. Diagnosis of pseudo-obstruction was established on these findings. First therapeutic attempt was conservative and consisted in administration of fluids and electrolytes, nasogastric suction and rectal tube insertion. Symptoms resolved in 8 cases, while urgent colonicoscopy decompression was successfully performed in 7 out of 29. Fourteen patients required operative treatment. Eight of them were submitted to caecostomy and 6 patients to loop colostomy of the transverse colon. Postoperative morbidity occurred in 4 patients, which included cardiac, pulmonary and renal insufficiency. One patient died from bronchopneumonia and heart failure.

In conclusion, pseudo-obstruction of the colon demands prompt diagnosis and correct treatment because of the high incidence of colon rupture and the elevated mortality rate this complication presents.

773 Cisapride in the Treatment of Functional Constipation Refractory to Previous Therapy

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Chronic functional constipation is a very common reason for consultation.

Objective: The purpose of this study is to assess the efficacy of cisapride in patients with functional constipation refractory to therapy (diet with fiber and laxatives).

Patients and Methods: A total of 32 patients aged 18–65 years were included. All of them suffered constipation, defined as less than 3 bowel motions per week and not improving on standard therapy (fiber-rich diet and laxatives). They also had no or low urge to defecate and hard stools. The patients underwent an anorectal manometric study and all of them showed an alteration in the rectal-anal inhibitory reflex (RIR) before starting therapy with cisapride 10 mg t.i.d. for two months. Clinical visits were made at 30 and 60 days to assess symptom response. After 30 days without treatment, efficacy was assessed both clinically and manometrically. The efficacy parameters were the number of weekly motions, the improvement in the urge to defecate, and the consistency of stools.

Results: All 32 patients participating in the study were women. The analysis of weight, age and height variables showed no statistically significant differences. Cisapride increased the weekly frequency of spontaneous bowel motions in 84% of the cases. The mean baseline value of weekly motions was 2.1/wk at the start of the study. After a 12-week follow-up, the average of weekly motions was 5.0/wk (p = 0.0001). The urge to defecate and the consistency of stools improved similarly to the frequency of motions. The clinical response was consistent with normalization or improvement in RIR in subsequent manometric controls.

Conclusion: The results show that cisapride is a useful drug for treating constipation related to an RIR impairment, since it significantly increases the frequency of spontaneous bowel motions, improves the urge to defecate and the consistency of stools, and its therapeutic effect persists 4 weeks after discontinuing therapy.

774 Feacal Incontinence Problem in Diabetic Patients


Feecal incontinence is a troublesome problem in diabetic patients. To unveil the extensiveness of faecal and gas incontinence, 250 diabetic outpatients (158 females, 91 males, mean age 53 ± 13 and mean diabetes age 10.6 ± 7.6) with good glycemic control (HbA1c < 8) and 250 age and sex matched non-diabetic (NDM) outpatients (161 females, 89 males, mean age 50 ± 13) were compared in terms of the below parameters using a visual scale analogue questionnaire. The people who had had abdominal operations and those with organic gastrointestinal, metabolic and hormonal diseases were excluded. All patients also filled in the neuropathy score questionnaire.

We found out that although the rate of stool incontinence is increased in diabetic patients than in non-diabetics, this does not interfere with social life considerably. Despite the presence of fecal incontinence, the preserved consistency of stool hinders incontinence be perceived as a major social problem in diabetics. Gas incontinence and its interference with social life seem to be much prominent problems in diabetic patients.

775 Effect of a Selective Calcium Antagonist Pinaverium Bromide on Rectal Distension-Induced Sensitivity during Experimental Inflammation in Rat

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The major features of functional bowel disorders, such as IBS (irritable Bowel Syndrome) are hypermotility and hypersensitivity of the gut characterized by a lower threshold perception. Pinaverium bromide (PB) a gastrointestinal selective calcium antagonist is indicated in the treatment of IBS. Recently it has been shown to inhibit intestinal contractions induced by GI hormones and mediators [1] suggesting an effect on visceral sensitivity. The aim of this work was to determine the effect of PB on rectocolonic inhibitor reflex and on visceral pain induced by rectal distension in rat in basal state and in hypersensitive state associated with rectal wall inflammation.

A series of 6 Wistar rats (250–300 g) was chronically equipped with 2 groups of 3 nichrome electrodes implanted in the wall of the proximal colon and 3 electrodes on the abdominal straitus muscle. Rectal distension was increasing volumes (0.4; 0.8; 1.2 and 1.6 ml) were performed, using an arterial embolectomy catheter, before and 3 days after TNB/ethanol administration (80 mg/kg in 1 ml/kg volume). Pinaverium bromide (10 mg/kg p.o.) was administered one hour before distension.

Rectal distension induced an inhibition of colonic motility and an increase in abdominal contractions in a volume-related manner. Pinaverium did not significantly modify the frequency of colonic nor abdominal contractions in normal conditions whatever the volume of rectal distension. Rectal inflammation reinforced the inhibitory rectocolonic reflex and enhanced the abdominal response. Pinaverium bromide significantly (p < 0.05) reduced abdominal contraction frequency induced by distension at 1.2 and 1.6 ml volume in inflammatory conditions; for a distension of 1.6 ml the number of abdominal contractions per 5 min was 16.5 ± 4.9 for PB vs 23.9 ± 8.0 for control.

In conclusion, pinaverium bromide (Dicetro™) has a marked effect on rectal distension-induced visceral pain in inflammatory conditions in rats. These findings further support the therapeutic value of pinaverium bromide, a GI selective calcium antagonist, in IBS given its effect on both hypermotility and hypersensitivity of the gut.


776 Influences of Dietary Fiber, Guar Gum, and 1,2-Dimethylhydrazine (DMH) on Prostaglandin (PG) Contents in Rat Colonic Mucosa

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Purpose. It has been reported that populations, who consume foods with much fibrous material and animals, have a decreased risk of colonic cancer. However, its precise mechanism remains unknown. This study was designed to clarify effects of dietary fiber, guar gum and DMH, a well known carcinogen, on rat colonic mucosal PG contents.

Materials and Methods. Five weeks old male Sprague–Dawley rats were divided into 4 groups; a) the non-fiber group: rats were fed a non-fiber diet, b) the guar gum group: rats were fed a fiber diet containing 15% guar gum, c) the non-fiber + DMH group; rats, which were fed a non-fiber diet, were infected with 60 mg/kg of DMH subcutaneously every 6 days 4 times for one month, d) the guar gum + DMH group; rats, which were fed a fiber diet containing 15% guar gum, were infected with 60 mg/kg of DMH as well as group c). All animals were fed each diet for 30 days and sacrificed. After colons were immediately removed, its length and weight were measured and mucosal tissues were assayed by high performance liquid chromatography.

Results. In the guar gum group and guar gum + DMH group, the length and weight of the colon significantly increased compared with those in the non-fiber group and the non-fiber + DMH group, but DMH did not affect them. Five kind of PGs, i.e., 6-keto-PGF1α, TXB2, PGFα, PGEP2 and PGD2 were detected in rat colonic mucosa. The intake of guar gum resulted in the increase in PGE2 contents significantly, especially in 6-keto-PGF1α, TXB2 and PGD2 contents. Administration of DMH increased significantly 6-keto-PGF1α, TXB2 and PGD2 contents. Guar gum cancelled DMH-induced increase in 6-keto-PGF1α, TXB2 contents.

Conclusion. These results suggest that 6-keto-PGF1α and TXB2 is likely to be involved to DMH-induced changes in the cancellation of these changes in PG contents by fiber diet might contribute to the prevention of occurrence of colonic cancer.
The Pattern of Distribution of the Intestinal Cells of Cajal (ICC) in the Human Colon

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Aim: The intestinal cells of Cajal are a population of cells in the gastrointestinal tract which are attracting increasing attention as their putative role in the control of gut motility is evaluated. The aim of this study was to establish the pattern of distribution of ICC in the wall of the normal human colon.

Methods: ICC express the proto-oncogene c-kit, a cell surface tyrosine receptor. ICC were identified in the colon by immunohistochemical staining, using a rabbit polyclonal anti-c-kit antibody (Oncongene Sciences). Normal colonic tissue was defined as non-involved tissue in surgical resection for a non-obstructing carcinoma of the colon. The regions of interest were right, transverse and left colon. Thirty nine cases were studied.

Results: The pattern of distribution of ICC in the colon was the same for all cases. In the intramural muscle layer ICC were identified in the muscle bulk in parallel orientation with the muscle fibres, and also in association with penetrating blood vessels. In the intramuscular plane, many ICC formed a network surrounding the myenteric nerve plexus. In the circular muscle layer ICC were again found in the bulk of the muscle in parallel orientation with the muscle fibres and in association with blood vessels, ICC were also seen lining the intramuscular septa. ICC were identified lining the inner layer of smooth muscle fibres at the submucosal border of the circular muscle. ICC were not identified in the submucosa, muscularis mucosa or mucosa.

Conclusion: The pattern of distribution of ICC is constant throughout the colon, showing no regional variation, and is consistent with a role in the control of colonic motility.

Anti-Endomysium, Anti-Reticulin and Anti-Jejunum Type Antibody Testing on Human Appendix

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Primates tissues seem to be important for the specificity of IgA type anti-endomysium (EmA), anti-reticulin (ARA) and anti-jejenum (JA) antibody determinations in the presence of specific antibodies (GSE). Substrate availability is, however, a frequent problem.

Methods: Frozen sections were made from appendices surgically removed because of the suspicion of acute appendicitis, but found to be histologically normal. Sections of non-rodent intestinal smooth muscle from patients (107 cases) were used to test against specific antibodies in the sera. A number of cases were tested by indirect immunofluorescence and by anti-protein A.

Results: Positive reaction on appendix (APP) is composed of staining of the endomysium, reticulin network and tonica propria fibres, each corresponding to the standard EmA, ARA and JA patterns.

Absorption studies resulted in fading of all components of APP+, irrespective of the fact whether oesophagus, liver or jejunum had been used. Conclusions: human appendix IF assay is a suitable and simple alternative to conventional EmA, ARA, JA determinations of comparable specificity and sensitivity yielding all the three results in the same procedure.

NK1- and NK2-Receptor Gene Expression during TNB-Induced Colitis in Rats

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Increasing evidence indicates that Substance P (SP) and neurokinin A (NKA) are involved in the regulation of several intestinal functions, including absorption, secretion, motility, and immune function. Due to the multiplicity of effects, they have been implicated in the pathogenesis of inflammatory bowel disease.

Methods: The effects on the jejunal tissues of specific receptor agonists (NK1 and NK2, respectively) and antagonists (NK1, NK2, and NK1/NK2) were analyzed on frozen sections by in situ hybridization using [35S]-labeled anti-sense and sense RNA probes and the autoradiographic signal was quantified by an image analysis system. Results: moderate NK1 and NK2 receptor gene expression was found in the normal rat colon. NK1 receptor gene expression was localized to smooth muscle cells of the muscularis mucosae and circular muscle, NK2 receptors were found to be expressed in the circular muscle and cells of myenteric plexus ganglia. De novo expression of both NK1 and NK2 receptor mRNA was observed during the acute phase of TNB colitis in mesenchymal cells around dilated submucosal vessels; in contrast, expression in smooth muscle cells of the muscularis mucosae and propria was clearly down-regulated, starting as early as 3 h after TNB and persisted until the 7th day. Tachykinin receptor gene expression gradually returned to normal thereafter. We were not able to identify any specific signal on epithelial cells, probably due to the very low, if any, basal expression and to the extensive necrosis of the mucosa following TNB administration. Conclusions: our findings suggest that reduced NK1 and NK2 receptor gene expression may play some role in the progressive colonic dilatation commonly observed during the acute phase of TNB-induced colitis.

Rectal Mucosal EGF Receptor Tyrosine Kinase (EGF-R tyr-k) Activity and Tyrosine Protein Phosphorylation Are Increased in Patients with Adenomatous Polyps (A.P.). Ulcerative Colitis (u.c.) and Colon Cancer (c.c.)


Tyrosine kinase (tyr-k) and a number of growth factors, like EGF and TGF-alpha are known to stimulate G1 tract proliferation. In humans increased colonic mucosal proliferative activity has been observed in A.P., u.c. and c.c. The aim of the presented study was to determine the differences in proliferative patterns and their correlation in patients with a.p., u.c. and c.c., as reflected by colonic mucosal EGF-R tyr-k, tyrosine protein phosphorylation and PCNA immunoreactivity.

The study population comprised 40 patients, aged 36-76 years (mean 56), in which 10 had a.p., 10 u.c. in remission phase, 10 c.c. and 10 were healthy controls. 6-8 rectal mucosal biopsy specimen were obtained at 10 cm from anal verge and at least 10 cm from any macroscopic mucosal changes during sigmoidoscopy. EGF-R tyr-k was increased in colonic mucosa by 35.2% in patients with a.p., by 40.6% in patients with u.c. and by 123% in patients with c.c. Tyrosine phosphorylation of several mucosal proteins (e.g. Mr of 55, 100, 155 and 170) in patients with a.p. and u.c. was 2-3 fold increased and in patients with c.c 5-6 fold increased, when compared to control levels. Expansion of proliferative zone towards crypt surface and significant increase (p < 0.01) of PCNA mean labeling indices were observed in patients with a.p., u.c. and c.c. as regards to the control group. Significant correlation between EGF-R tyr-k activity and PCNA LI values (p < 0.001) was observed within examined group of patients.

Increased values of EGF-R tyr-k activity in mentioned groups of patients may suggest, that tyrosine phosphorylation is involved in colon carcinogenesis.

Human Gastric Adenocarcinoma was Bioadhesinized in the Human Colon, But Not in the Small Intestine

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Purpose: Inflammatory bowel disease is thought to be associated with alterations in colonic mucus, which form the most important structural components of mucus. Nine human mucin genes, named MUC1–6, S/A/C, SF and MUC6 & B are known to be expressed in mucous layers in human colon. Among these, MUC2 (HpM) is the most abundant.

Results: HPB was previously reported to be expressed in a number of human colorectal cancer cell lines, and the human colon in vivo. The human colon consists of a number of distinct tissue types, which may have different biological properties. The aim of the present study was to evaluate the expression of HPB in various human colon tissue types.

Methods: Antibodies to HPB were generated in rabbits and were used to stain human colon tissue sections.

Results: The presence of HPB in human colon tissue was confirmed by immunohistochemistry. The staining pattern was consistent with the presence of HPB in the epithelial cells of the colon. The staining was stronger in the mucosa than in the submucosa.

Conclusions: HPB is highly expressed in human colon tissue and may be a potential target for immunotherapy.

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Sodium Channels are Present in the Upper Crypt but Not the Crypt Base in the Distal Colon of the Glucocorticoid-Treated Rat

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Sodium channels are induced in the rat distal colon by short-term corticosteroid treatment. It has been proposed that these channels are confined to luminal cells whereas chloride secretion is a property of crypt base cells. We used these methods to map the distribution of Na channels along the crypt-lumen axis.

Methods: Five colonicocyte populations (C1–C5) from lumen to crypt base were prepared by Ca\textsuperscript{2+} chelation (EDTA). Whole crypts were prepared using a modification of this method. Amiloride-sensitive \Na\textsuperscript{2+} uptake (le Na\textsuperscript{+} channel activity) was determined in specimens from each cell population using a K\textsuperscript{+} diffusion gradient. Similarly \Na\textsuperscript{2+} uptake by whole cells was performed on pooled luminal and crypt colonicocytes. A whole-cell patch clamp technique was used to measure the conductance (Gm) and voltage (Vm) of cells in mid-crypt and crypt-base colonicocytes during changes in Na\textsuperscript{+} concentration or with 10 micromolar amiloride.

Results: Glucocorticoid-naive rats showed no evidence of electrogenic Na\textsuperscript{+} transport. When Na\textsuperscript{+} was inhibited \Na\textsuperscript{2+} uptake in vesicles by 60%, 40%, 17%, and 11% and in colonicocyte populations C1–C5 respectively. In whole cells, amiloride-sensitive \Na\textsuperscript{2+} uptake was 20 pmol Na\textsuperscript{+}/mg protein in the luminal cell population and absent in crypt-base colonicocytes. Whole cell recordings of Vm showed depolarization and increase in Gm when bath Na\textsuperscript{+} was removed or amiloride was added indicating that Na\textsuperscript{+} channel activity was inhibited. The effect was maximal in luminal cells, absent in crypt-base cells and intermediate in the mid-crypt. Conclusion. Using 3 different methods we have shown that glucocorticoid-induced Na\textsuperscript{+} channel activity in rat distal colon exhibits a gradient with absent activity in the crypt and maximal activity at the luminal surface. This distribution may have implications for theories of cellular maturation along the crypt-lumen axis.

Human Colonicocytes from Endoscopic Biopsies: Isolation, Biochemical Characterization, and Expression of Human Stress Proteins

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Purpose: Biochemical and biological characterization of normal human colonic epithelial cells has been difficult due to lack of suitable methods for culture of epithelial cells from biopsy material. Therefore, colonic crypts isolated from surgically removed bowel or cancer cell lines have been widely used to study colonicocyte functions in vitro. We present here a simple method for the isolation of human colonic epithelial cells isolated from routine biopsies, and demonstrate that these cells metabolize butyrate and express human stress proteins, HSP 60 and 70.

Methods: Human biopsies obtained by routine diagnostic colonoscopy were treated with EGTA/EDTA and/or enzymes to separate the epithelial cells from the connective tissue. The cells isolated were grown for 1–3 days and the number of cells surviving was monitored by methyl tetrazolium (MTT) test and DNA quantitation. Colonicocyte metabolism of butyrate and glucose was quantitated by \14CO\textsubscript{2} liberation. The expression of HSP 60 and 70 was measured by PCR and immunoelectronmicroscopy.

Results: Electron microscopy showed that cells with the typical features of colonic epithelial cells could be isolated from a small number of biopsies and thios were not necessary and appeared harmful to the cells. The cells were viable for at least 3 days as judged from MTT and DNA measurements and were able to incorporate radiochromated amines and sugars into proteins. The butyrate metabolism had a K\textsubscript{m}-value of 0.6 mm. The cells also metabolized glucose. The cells expressed heat shock proteins, HSP 60 and 70 as judged by PCR as well as electrophoretic immunoblotting.

Conclusion: The experiments show that these primary cultures allow the study of human colonic epithelial functions in vitro. The possibility to establish primary cultures of colonicocytes from patients undergoing routine colonoscopy may be most valuable in the study of inflammatory bowel diseases.

Butyrate Transport in Rat Colonic Apical Membrane Vesicles

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Background: In order to study the specificity of the luminal butyrate-HCO\textsubscript{3}\textsuperscript{-} antiporter, the inhibitory potency of several SCFAs, their metabolite- and bro-
Results: Although inactive at 25 mg dose (data not shown), igmesine 200 mg strongly reduced the secretory flow of water and electrolytes during the PGE2 perfusion (Table, m ± s.e.m., \( p < 0.05, \text{ANOVA} \)).

\[
\begin{align*}
\text{Placebo} & \quad 285 ± 63 & \quad 39 ± 6 & \quad 2.0 ± 0.3 & \quad 32 ± 7 & \quad 7 ± 1 \\
\text{igmesine 200} & \quad 220 ± 58 & \quad 59 ± 8 & \quad 1.0 ± 0.3 & \quad 33 ± 7 & \quad 2 ± 1 \\
\end{align*}
\]

ANOVA for repeated measures over time showed that the effect of igmesine 200 mg was maintained during the PGE2 perfusion. No side effect related to igmesine was reported.

Conclusion: This study shows for the first time in man the intestinal antisecretory effect of a sigma ligand, suggesting the potential interest of this new pharmacological class as a therapeutic tool.

787 Distribution of CEA/FAS/FAS-Ligand/Tunnel in Normal and Ulcerative Colitis Colon

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The luminal epithelial cells of colon are positive for Fas antigen (Fas) and Fas-ligand (Fas-L) on their baso-lateral surfaces, contain TUNEL positive nucleus and undergo apoptosis. The apical surface of these cells are also positive for carcinoembryonic antigen (CEA), a maker of terminally differentiated colonic epithelial cells. Our finding that the Fas/FasL associated epithelial cells were found in the crypt of active ulcerative colitis (UC) prompts us to investigate whether CEA is also associated with these cells.

Portions of biopsies of normal colon and that of colon of active UC were fixed in 10% formalin and processed using a routine histology procedure. The breaks in nuclear DNA were detected by TUNEL method. Fas and Fas-L were localized using rabbit antiserum against an extra-cellular domain of Fas and an intra-cellular domain of Fas-L as the first antibody, respectively. For the localization of CEA using CEA, mouse monoclonal anti-human CEA was the first antibody.

The CEA was limited to the apical surface of the luminal surface epithelial cells of the normal colon. Whereas, in the UC colon, CEA was at the apical surface of the luminal and crypt epithelial cells. The distribution of the CEA positive cells coincided with that of cells with apoptotic markers, namely Fas/Fas-L/TUNEL.

The coincidental expression of CEA on cells with various apoptosis markers suggest that the cells undergoing apoptosis in the crypt of UC colon are fully differentiated and the hastened differentiation of epithelial cells in UC colon maybe a cause of apoptosis.

788 Corrections of Postoperative Incontinence in Children by Penna's Operation

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Introduction: Unsatisfactory functional results following operative treatment of anorectal defects constitute 30%–50%.

Materials and methods. Correction of postoperative incontinence was made in 20 patients (8 boys and 12 girls). All the children had been operated on previously by various techniques for anorectal defects and ensuing complications. Out of 20 patients 5 children were operated twice, 4 a third. A scary deformity of the anorectal area was revealed in all the children, out of them 5 patients showed anterior ectopy of the rectum with emiapment of the entrance to the vagina, the posterior wall of the distal third of the vagina was destroyed. Rectal tenesmus in all the patients decreased sharply or was aspned.

When choosing a technique of surgical correction of postoperative incontinence we preferred Penna’s operation which allowed to form a locking apparatus from the remaining elements of the pubo-perineal loop and the external sphincter of the rectum. 1 to 1.5 month prior to the operation all the children had been applied suspended two-trunc colostoma. If the patients had previously undergone abdomino-perineal proctoplasties, they were applied transversorossto (8 patients); anterior colostomy for perineal proctoplast (12 patients).

Soft parallelic ligature of the rectum was begun at 15 days, transrectal electrostimulation of the sphincter apparatus muscles was carried out 3 to 4 weeks later. Temporary colostoma was closed 1.5 months following Penna’s operation.

Results. 18 patients were followed up from 6 months to 5 years. Good results were received in 10 patients, satisfactory - 7 patients, unsatisfactory - only one patient. Undergoing the sacroccygeal portion of the spine was the major reason of the unsatisfactory result in the study.

Conclusion. We consider Penna’s operation in this category of patients to be the operation of choice.

789 Overlapping Sphincteroplasty for Anal Incontinence

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Surgical correction of anal incontinence is best suited to those patients with traumatic disruption of the sphincter ring. Such damage may result from obstetrical as well as iatrogenic injuries or, less frequently, road accidents or sexual abuse. Surgical repair by wrap-over technique has been shown to restore satisfactory function in most cases. The present study intended to assess clinical and functional results of overlapping sphincteroplasty.

From 1991 to 1995, a total of 40 repairs were performed in 39 severely incontinent patients (17 M, 22 F; mean age 34 ± 11 years, range 23–92). Preoperative and postoperative assessment included anal manometry, anosonography and electromyography. Mean follow-up was 23 months (range 5–54). Statistical analysis was performed using the Wilcoxon signed rank test. Aetiology of anal incontinence is shown in the table.

<table>
<thead>
<tr>
<th>Elitogy</th>
<th>N. patients</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Obstetric injury*</td>
<td>16</td>
<td>41%</td>
</tr>
<tr>
<td>Previous anorectal surgery</td>
<td>21</td>
<td>53.8%</td>
</tr>
<tr>
<td>Radioclaid surgery</td>
<td>2</td>
<td>5.2%</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>100%</td>
</tr>
</tbody>
</table>

*2 patients with associated recto-vaginal fistula

Endosonography was able to preoperatively reveal 36/39 external anal sphincter defects with a 92% correlation with surgery. Overall, 36 patients were clinically improved by surgery with 30 (78%) regaining normal continence and 6 (14.4%) showing fair function. Only one patient received a temporary colostomy. Septic complications occurred in 7 cases (18%). The procedure failed in three patients (7.6%) who were then submitted either to a neo-sphincteroplasty or to an electrically stimulated graciloplasty. All of them are totally continent after their salvage procedure. Endosonography is useful in mapping the anal sphincters and plan the best type of operation. Overlapping sphincteroplasty is the procedure of choice in the treatment of traumatic anal incontinence. Dynamic graciloplasty can be offered to highly selected patients in whom previously attempted conventional repairs had failed.

793 Balloon Expulsion Test and Perineometry as a Screening Test in Diagnosing Anismus

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Purpose: The aim of this study is to investigate the role of balloon expulsion test and perineometry as a screening test in diagnosing defecation disorder.

Method: The inclusion criteria was defecation disorder patients on Rome criteria, that is, excessive straining on more than 25% of occasions and sensation of incomplete evacuation on more than 25% of occasions. The all patients were diagnosed the cause of defecation disorder through balloon expulsion test in left lateral decubitus position and sitting position, perineometry, colon transit time, deficogram including ejection fraction of defecation, anal canal manometry and sigmoidoscopy to rule out organic disease. 10 asymptomatic persons were also examined as a normal control.

Result: Among 60 defecation disorder patients, anismus was (56%), descending perineum syndrome (7%), rectocele (3%), rectal intussusception (1%), combined disorder (7%) and normal pelvic function (25%). The weight that was needed to was expelled balloon in left lateral decubitus position in anismus patients was significantly higher than normal control (average 767 gm:330 gm, p < 0.05). The time that was needed to was expelled balloon in sitting position was significantly longer than normal control (average 5.6 min:3.5 min, p < 0.05). Perineal movement in anismus patients was significantly shorter than normal control (average 0.7 cm:1.3 cm, p < 0.05). The weight that was needed to was expelled balloon in left lateral decubitus position in anismus patients was inversely related to ejection time in defecation (p < 0.05).

Conclusion: Balloon expulsion test and perineometry are good screening test in the diagnosis of defecation disorder.

794 Visceral Sensitivity and Systemic Autonomic Responses to Rectal Distension in Healthy Volunteers

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Visceral sensitivity is claimed to be changed in IBS patients. In 18 healthy, female volunteers (19–57 years) we assessed retet reactivity and normal values for rectal visceral perception by a computerised barostat (Systecnic, Sweden) and sympathetic, and parasympathetic responses to rectal distension. Unechaged position of the barostat and was secured by intrarectal anal pressure registrations and the pressure values for feeling of gas, urge to defecate and discomfort were registered by a randomised, double staircase inflation procedure in phasic distension mode with 1 mmHg steps lasting 20 seconds with 30 seconds intervals. The intrarectal pressure function (5%). The weight that was discomfort was repeated was a singular inflation at the end of the study. Heart rate variability (HRV) and skin conductance (SC) were recorded throughout the study. Influence of posture changes were measured by positioning the subject towards an adjustable plate which could be tilted in 5 degrees intervals. The whole protocol was repeated after two days. First feeling of gas was at (mean ± SD) 11.8 ± 5.4 mmHg, urge to defecate at 13.5 ± 6.0 and discomfort at 29.3 ± 10.1 mmHg. 95% confidence interval for discomfort in healthy females is 20.2–38.8 mm Hg and for compliance 7.5–11.9 mmHg.

Correlation coefficients (r (Pearson) for these parameters were 0.89, 0.91 and 0.79 respectively. Student T-test showed no differences and coefficients of variation were 0.24, 0.20, and 0.24 respectively. Following exposure to
the discomfort threshold skin conductance increased 0.4 ± 0.5 μS compared to baseline at a latency of 4.6 ± 2.0 sec. The c.c. (test/retest) was 0.78.

Basal HRV was 70 ± 25 ms and remained unchanged following induction of rectal discomfort with a c.c. of 0.92. Changes in posture within 30 degree did not influence volumes in the balloon at high pressure levels, while large differences were noted at lower pressures. In conclusion, measurements of visceral sensitivity correlated peripheral responses to rectal discomfort were performed with high reproducibility.

795 Dynamic Graciloplasty for Fecal Incontinence: The One Stage Procedure


Dynamic graciloplasty is a new surgical option in the treatment of severe faecal incontinence. If most authors prefer a two-stage procedure (transposition of the gracilis muscle around the anus and implantation of the electrical stimulator and intra-muscular electrodes few weeks later), the construction of the neo-sphincter can be performed by a one stage graciloplasty and implant procedure. To assess this new technique we report the results of a prospective study conducted from June 1994 to May 1996.

Eighteen patients (8 women) of mean age 33 years (range 15–62) were operated on for severe faecal incontinence. The aetiology of incontinence was anal atresia (n = 6), surgical or obstetrical trauma (n = 6), non-surgical trauma (n = 2) and spinal cord injury (n = 1). Four patients had a previous unsuccessful Pickrell operation and were operated on in a two-stage procedure. Three further patients also had a delayed stimulator implantation because of a perineal operative complication. In all other patients a one-stage dynamic graciloplasty was performed.

There were no difference between the one-stage procedure (n = 11) and the two stage procedure (n = 7) with regard to:

- clinical functional result
- manometric results
- surgical complications (sepsis, pain, implant).

The advantages of the one-stage procedure over the two-stage procedure are: better electrode positioning, less risk to the nerve because it is more readily identifiable and one surgical act instead of two.

796 Perianal Bleeding, Pruritus Ani, and the Baboon Syndrome

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Background: Pathogenesis and aetiology of perianal bleeding, itching, pain and burning are often obscure. Inadequate cleansing (Smith 1982, Alexander-Williams 1983, Jones 1992) is accused as well as wet wipes (Harrington 1992) and moist toilet paper (Bryoziel 1992).

Methods: We asked two groups of patients by a 41-item-questionnaire about their daily cleaning habits (shower, bath, moist toilet paper or water after motions etc.). Those who came for gastroscopy (n = 130) without anal complaints and patients with a Baboon syndrome (BS) were asked about their cleaning habits. The BS is defined by the presence of daily bleeding lesions caused by overvigorous anal cleansing (n = 182) with bleeding, itching and burning. The latter had proctological investigation and endoscopy of the colon.

Patients with a BS were urged to refrain from using water to clear their anus. Follow up after four weeks by telephone interview (anal symptoms) and by haemocult test was performed in those 67 patients with a BS only and no lesions at total colonoscopy.

Findings: Rats

- In the BS group: many doctors see because of anal complaints (53% vs 15%), using a wet face-cloth after motions (40% vs 23%), water and fingers after motions (22% vs 8%), washing their anus before sleeping (45% vs 25%), being treated because of piles (40% vs 20%). At 4-weeks follow up pruritus ani of BS-patients had dropped from 45% to 5%, pain from 36% to 3%, haemocult testing became negative in all patients who changed their cleaning habits but symptoms and haemocult test remained nearly unchanged when this regimen was repeated.

Conclusion: To find out the cause of perianal bleeding, itching, pain and burning it is of utmost importance to ask patients about their daily cleaning habits. In contrast to most gastroenterologist we recommend only dry anal cleaning to prevent a Baboon syndrome.

797 Therapeutic Fiber and Bleeding Hemorrhoids

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Aim: To assess prospectively the effect of fiber addition on internal bleeding hemorrhoids and haemorrhoidal prolapse.

Patients and Methods: 50 patients (mean age = 48.3 ± 13 yrs., 29 M/21 F) were referred to our Department for endoscopic study of recurrent rectal bleeding. All patients underwent anoscopy before and after treatment to evaluate a) hemorrhoids bleeding on contact, b) the number of congested haemorrhoidal cushions and c) the degree of haemorrhoidal prolapse. Exclusion criteria were the presence of coagulation disorders or potentially bleeding colorectal lesion and the concomitant intake of laxative, anticholinergic or prokinetic drugs. Patients were randomised in two groups, in 23 the study group were treated with 35 g/d of Plantago Ovata and 27 in the control group with placebo. The treatment daily was started by 10 g/d at the first day of出血 episodes, congested haemorrhoidal cushions and degree of prolapse were analyzed with the Student’s test and the Welch Correction. A significance level of p < 0.05 was accepted.

Results: 1) patient from the study group and 3 from the control group were excluded. During the first 15 days of treatment, the number of daily bleeding episodes decreased from 5.2 ± 2.9 to 4.8 ± 3.8 in the study group versus 6.7 ± 3.0 to 6.4 ± 3.1 in the control group (n.s.). The next 15 days it decreased to 3.1 ± 2.7 and 5.8 ± 3.2 respectively (p < 0.005). A further reduction to 1.1 ± 1.4 was found after the last 10 days in the study group versus 5.5 ± 2.9 in the control group (p < 0.001). The number of congested haemorrhoidal cushions decreased from 2.5 ± 1.9 to 1.2 ± 0.9 (p < 0.001) in the study group, without differences in the control group. No change in the degree of rectal prolapse was observed after treatment in the study group nor in the control group.

Conclusions: 1) Fiber supplements significantly improved bleeding from internal haemorrhoids; 2) Therapeutic fiber effects are concentration-dependent appearing at least after a month of treatment; 3) Fiber does not reduce haemorrhoidal prolapse but significantly improves congested haemorrhoidal cushions.
group B regimen was comparable in MetR(90%) and MetR(95%) strains [12/13 (92.3%) vs 17/19 (88.5%), p = NS].

Conclusion: The efficacy of the newer, shorter, triple therapy involving two antibiotics (CL + Met) is probably dependent on the incidence of MetR Hp strains. In areas with low CL resistance of Hp, an alternative mono-antibiotic triple regimen may be equally effective and well tolerated.

**801 Omeprazole Based Dual and Triple Therapies for Eradication of Helicobacter Pylori**

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To investigate the efficacy of various omeprazole (Ome) (Ome)+antibiotic combinations in the eradication of Helicobacter pylori (Hp), duodenal ulcer or non ulcer dyspepsia patients with Hp infection were allocated to one of the following treatments:

- O 20 mg b.i.d. + amoxicillin (A) 1000 mg b.i.d for 2 weeks (OA).
- O 20 mg b.i.d. + Clarithromycin (C) 500 mg b.i.d for 2 weeks (OC50).
- O 20 mg b.i.d. + C 250 mg b.i.d for 2 weeks (OC25).
- O 20 mg b.i.d. + A 1000 mg b.i.d. + C 500 mg b.i.d for 1 week (OAC50).
- O 20 mg b.i.d. + A 1000 mg b.i.d. + C 250 mg b.i.d for 1 week (OAC25).

Endoscopic examinations were performed and six gastric biopsies (2 for histological examination, and 1 for urease test from both antrum and corpus) were taken before and one month after completion of therapy. Before treatment, both of the tests were positive for Hp in all cases. Eradication was defined by negativity of both the diagnostic methods.

**Results:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of cases</th>
<th>Hp eradication</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA</td>
<td>34</td>
<td>22 (64.7%)</td>
<td>5 (9.5%)</td>
</tr>
<tr>
<td>OC50</td>
<td>35</td>
<td>20 (57.1%)</td>
<td>12 (34.3%)</td>
</tr>
<tr>
<td>OC25</td>
<td>18</td>
<td>6 (33.3%)</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>OAC50</td>
<td>30</td>
<td>28 (93.3%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td>OAC25</td>
<td>23</td>
<td>27 (91.3%)</td>
<td>3 (13.0%)</td>
</tr>
</tbody>
</table>

Conclusions: 1. One-week OAC regimens achieved significantly higher eradication rates than two-weeks OA and OC treatments. 2. Eradication rates in one-week OAC regimens were found to be similar with less adverse events in cases treated with OAC25. 3. One-week OAC50 combination may become the treatment of choice for eradication of Hp.

**802 Intravenous Omeprazole Plus Antibiotics in Helicobacter-Related Peptic Ulcer Patients with Major Stigmata of Recent Hemorrhage – A Preliminary Report of a Randomized Controlled Trial**

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Aims: Eradication of Hp pylori significantly reduces the rate of ulcer rebleeding. Dual therapy with omeprazole and amoxicillin should be considered in all Hp pylori-positive patients with ulcer bleeding. The aim of the present study was to examine the efficacy of intravenous route of dual therapy in active ulcer bleeding.

Methods: In a prospective study, one hundred and thirty two patients with endoscopy documented ulcer bleeding with major stigmata of recent hemorrhage (active bleeding or non-bleeding visible vessel) were entered. Endoscopic injection therapy was performed in all patients with a mean volume of 7.5 mL of 1:10000 epinephrine. One hundred patients (75.5%) with documented Hp pylori infection (by rapid urease test and histologic findings) were randomly assigned to receive 40 mg omeprazole intravenously every day and amoxicillin-subbactam 750 mg three times daily intravenously for 3 days and 20 mg omeprazole twice daily and 500 mg amoxicillin three times daily for 11 days (Group A) or 20 mg omeprazole twice daily and 500 mg amoxicillin three times daily for 2 weeks (Group B). Subsequently, both group received 20 mg omeprazole daily orally for 4 weeks. Patients underwent a second endoscopy 3 days later and again at the end of 6 weeks.

Results: Early rebleeding occurred less in Group A (1/50 or 2% vs 5/50 or 10%, P > 0.05). All these 6 patients were excluded. Disappearance of major SRH was significantly higher in Group A (45/49 or 91.8%) than in Group B (32/52 or 61.5%, P < 0.05) at the second endoscopy. Hp pylori eradication rates were 89.7% (44/49) in Group A and 77.7% (30/40) in group B. (P > 0.05) Ulcer healing rates were 93.8% (46/49) in Group A and 95.5% (43/45) in Group B (P > 0.05).

Conclusions: Intravenous form of dual therapy can be started immediately in HP-positive ulcer hemorrhage with major SRH. Rapid disappearance of major SRH and lower early rebleeding rate could be achieved. It can be an alternative choice for Hp pylori treatment in active peptic ulcer bleeding.

**803 Relevance of Metronidazole Resistance in Predicting Failure of Omeprazole, Clarithromycin and Tinidazole to Eradicate Helicobacter Pylori**


Introduction: Omeprazole 20 mg o.d, clarithromycin 250 mg bid and tinidazole 500 mg bd for 7 days (OCT) is an effective regimen against Hp pylori but the effect of metronidazole resistance on regimens is unclear. Methods: Hp pylori positive patients were prescribed OCT and cure of the infection was assessed by 13C-UBT 5 weeks after therapy. Metronidazole resistance was determined by the disc diffusion method. Samples were stored at ~70°C for re-culture and MIC assessment by E test. Results: 141 H pylori positive patients were enrolled. The organism was successfully cultured in 118/141 (84%) cases and the overall eradication rate was 125/141 (89%). The incidence of metronidazole resistant strains was 121/141 (86%). OCT was successful in 69/70 (99%) patients harbouring sensitive strains of Hp pylori and in 42/45 (93%) of patients with strains that were resistant to metronidazole alone (p = 0.0). MIC was assessed in 23 samples. A cut-off point of > 4 mg/L to define metronidazole resistance gave eradication rates of 57% in sensitive and 96% in resistant strains. If the cut-off was re-defined as < 32 mg/L eradication rates were 70% in sensitive but only 30% in resistant strains. Conclusion: The disc diffusion method is not helpful in predicting OCT failure but the E test may be of value.

**804 Comparison of the Effect of Omeprazole, Clarithromycin and Metronidazole Combinations in Different Two Doses for One Week Therapy of Helicobacter Pylori Infection**

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Helicobacter pylori (Hp) is the principal cause of chronic active gastritis and duodenal ulcer, and has been linked epidemiologically with the development of gastric carcinoma. The aim of this study was to evaluate the efficacy and tolerability of low and high dose short-term triple therapies for cure of Hp infection. 60 patients with Hp infection (16 with duodenal ulcer disease and 44 with antral gastritis) were divided two groups (30/30) for different cures. First group was treated with omeprazole 20 mg o.i.d, clarithromycin 250 mg, b.i.d. and metronidazole 500 mg, b.i.d and second group was treated with omeprazole 20 mg b.i.d, clarithromycin 500 mg b.i.d. and metronidazole 500 mg b.i.d. for a week. Four weeks after the treatment withdrawal, cure of Hp infection was evaluated by urease test and histopathological examination. In eradication rate of Hp infection was 50% in the first group (16 patients were reported side effects; mel仇agic taste in 17 and pruritus in one) and 82% in the second group (24 patients were reported side effects; mel仇agic taste in 24, epigastric discomfort and mild nausea in 12 and diarrhea in 3) (p < 0.05). In conclusion: eradication rate of one week triple therapy with omeprazole, clarithromycin and metronidazole combination was increased with high doses but also side effects were increased with augmented doses.

**805 Comparison of Two One-Week Triple Therapy Regimens in the Eradication Rates of Helicobacter Pylori Infection with Associated Duodenal Ulcer. A Randomized Study (Preliminary Results)**

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Aim: To evaluate the efficacy and tolerability of two one-week triple regimens in Hp pylori eradication and duodenal ulcer healing. Methods: 171 consecutive patients with duodenal ulcer and proved Hp pylori infection diagnosed by rapid urease test, histology (2 biopsies from antrum and 2 from the corpus) and culture (2 biopsies from the antrum), were randomized in two short treatment groups. Group (OCC): patients (84) were given omeprazole 40 mg bd, clarithromycin 500 mg bd and colodial bismuth subcarbonate (CBS) 120 mg qd for 7 days (Group A: patients (87) were treated with the same dosage of omeprazole plus clarithromycin 1 g bd for 7 days. No patient received follow-up treatment. Ulcer healing and HP pylori eradication were assessed 4 weeks after cessation of therapy. Results: Three patients 2/OCA and 1/OCC group were lost to follow-up. H pylori was eradicated in 69/93 patients of the OCC group (89.1%); 95%-CI: 71%-88% and in 77/85 patients of the OCA group (90.6%); 95%-CI: 81%-96%. (OCC vs OCA: p =.
0.1). Duodenal ulcer healing was documented in 77/83 (92.8%) patients in the OCC group and in 80/85 (94%) patients in the OCA group (p = 0.7). Ulcer healing was more frequently observed in patients cured of H. pylori infection than in the group of the patients with persisting infection (96.5% vs 73.9%; p < 0.001). Side effects were infrequent and minor, one patient (OCA) suffered from slight diziness during the last two days of treatment that persisted for another 7 days, and one patient (OCC) had skin rash (clarithromycin was stopped on day 5 of therapy). Conclusions: 1. Both one-week regimens were effective in the eradication of H. pylori and duodenal ulcer healing. 2. They were well tolerated and their cost is similar.

806 High Eradication Rate of Helicobacter Pylori (HP) in Patients Unsuccessfully Treated Previously

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Aim: To estimate the effectiveness of a new regimen in eradicating HP in patients with duodenal ulcer (DU) unsuccessfully treated previously by the “classic” triple (tetraxotrimididotrimethadime (TDB) 120 mg qid, metronidazole 20 mg bid, amoxicillin 800 mg qid) therapy.

Patients and methods: 133 patients (M: 82; F: 51) aged 17–81 years with endoscopically diagnosed DU (diameter ≥ 5 mm) in whom “classic” triple or dual therapy failed to eradicate HP.

CLO test was done (at least two pieces from the antrum and the gastritic body) to confirm the presence and “eradication” of HP at the entry and at least one month after the end of the treatment respectively; in 31 patients, the presence and “eradication” of HP was confirmed by histology as well.

Patients were given omeprazole 60 mg (20 mg in the morning and 40 mg in the evening) plus amoxicillin 2 gr qid for 10 days and subsequently TDB (De-Novol) 120 mg qd for 6 weeks plus metronidazole 500 mg tid for 10 days.

Results: 1. Of the 133 patients, 85% of them (113) were follow up. Five of them (4%) withdrawal because of side effects (protracted diarrhoea, stomatitis, skin rash). One more patient presented mild diarrhea for 3 days but continued on the treatment.

HP eradication was confirmed in 113 of 118 patients examined (95%) and complete ulcer healing was observed in 119 of them.

Conclusion: This regimen seems to be highly effective in eradicating HP and in healing DU without major side effects.

807 Cost Savings Using the International Gastro Intestinal Primary Care Group (IGPCG) Management Plan


Upper gastrointestinal (GI) disorders are common in many countries worldwide and the costs of treatment represent a significant proportion of primary health care budgets. In the UK, for every 20 patients visiting their GP, one will have upper GI symptoms and therefore, optimal management is important. The IGPCG has devised an upper GI management plan of the form of a treatment algorithm which leads GPs logically through the paths of diagnosis and treatment options. This management plan allocates patients, based on predominant symptoms to one of the following subcategories: motility disorder likely, ulcer disease likely or gastro-oesophageal reflux disease (GORD) likely. A computer model was designed to evaluate whether using the IGPCG management plan can lead to cost savings in practice. Current upper GI treatment costs were obtained from International Marketing Statistics (IMS) Mediscus search of 47,303 patients taken from 728 GPs. Figures for overall cost per patient and for the different disease subcategories were established for current practice and the IGPCG management plan.

The overall cost per patient was £98.48 currently, compared to £96 for the IGPCG algorithm which represents a saving of 3.0%. For the two upper GI disease subcategories, motility and ulcer, the IGPCG cost per patient is considerably lower than currently. The estimated current cost per motility patient is to £152.53 cost of £54. IGCPG analysis of total costs including GP time and use of hospital services, revealed that of the three disease subcategories motility patients had the lowest cost per patient.

In conclusion, using the IGPCG algorithm significantly reduces treatment costs, particularly for those patients with an underlying motility disorder who are treated with prostkinetic drugs such as cisapride.

808 Does Initial Choice of Helicobacter Pylori (hp) Treatment Regimen Influence the Recurrence Rate of Duodenal Ulcer (D U)? A Meta Analysis

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DU has a one year recurrence rate over 60% in untreated patients and × 30% in patients on maintenance therapy (AMPT) 1990:4-283). Studies suggest that cure of HP infection reduces DU recurrence. However, data sets are small and results vary considerably between studies and regimens. We undertook a meta analysis to evaluate any differences in DU recurrence with respect to HP status

and the different drug regimens used for DU healing and eradication. Methods: A fully recursive, Medline search identified 126 articles from 1984 to 1995. 41 met inclusion criteria: i) DU healed by antisecretory drug and antimicrobial(s) and documented endoscopically; ii) ulcer recurrence diagnosed by endoscopy; iii) HP status ascertained by ≥ two methods; iv) adult patients and articles in English language. Studies were grouped by different regimens, HP status and time points following DU healing. Results:}

809 Effect of Omeprozole, Clarithromycin and Tindazole on the Eradication of Helicobacter Pylori and Healing of Gastric Ulcer


Background. Eradication of Helicobacter (H.) pylori is a key factor for the cure of peptic ulcers. Eradication of H. pylori seems to be more difficult to achieve in gastric ulcer (GU) patients than in patients with duodenal ulcer (DU) or gastritis. On the other hand general treatment regimens with a combination of an antisecretory drug and a single antimicrobial were reported to be lower in GU than in DU patients. Recently, we reported the high efficacy of a week low-dose triple therapy with Clarithromycin, Omeprazole and Tindazole on long-term eradication of H. pylori infection in patients with non-ulcer dyspepsia and DU. Purpose. The aim of the present study was to investigate the efficacy of a week low-dose treatment with Clarithromycin, Omeprazole and Tindazole followed by 3 weeks of Omeprazole in eradicating H. pylori infection and ulcer healing in patients with GU. Methods. 49 patients (28 males, 21 females; age (years) range 32–71, mean 49) without NSAID and H. pylori infection received Omeprazole 20 mg u.i.d. for 4 weeks and, during the first week, a combination of Clarithromycin 250 mg b.i.d. and Tindazole 500 mg b.i.d. H. pylori infection as well as eradication was assessed by histology (Haematoxylin-Eosin, Giemsa), quick urease test and 13C-Urea Breath Test (13C-UBT). Upper GI endoscopy with 3 antral and 2 corpus-fundus biopsies and 13C-UBT were performed prior to treatment at day 1 and 3 and 6 months after the end of the treatment. The healing rate in patients treated with antibiotics was compared to a H. pylori positive, non-NSAID GU historical control group (no. 53; 31 males; age (years) range 32–71, mean 49). On completion of the 3 weeks of treatment, eradication of H. pylori was obtained in 47/49 patients (95.9%, 95% CI: 90.3%–100%). Ulcers healed in 46/49 (93.9%, 95% CI: 87.2%–100%) of the patients treated with antibiotics and in 39/63 (71.7%, 95% CI: 59.8–83.8; p < 0.003) of the omeprazole patients control group. Follow-up evaluations performed at 3 and 6 months confirmed H. pylori eradication and persistent healing of GU in the patient treated with antibiotics. Conclusions: One week low-dose triple therapy with Omeprazole 20 mg u.i.d., Clarithromycin 250 mg b.i.d. and Tindazole 500 mg b.i.d. is also highly effective in H. pylori eradication in patients with GU. The GU healing rates in patients treated with antibiotics and antisecretory drugs are significantly higher than those reported in patients treated with only antisecretory agents.

810 Clarithromycin-Based Therapy Failure: What Comes Next?

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Purpose: Recently, eradication therapies containing clarithromycin have been extensively used and are associated with a high H. pylori eradication rate. However, it is still to be elucidated how to proceed when these therapies fail. This topic is of an utmost concern because of the ever increasing use of clarithromycin-based therapies. Therefore, we studied the efficacy of omeprazole + amoxicillin + metronidazole (OAM) in this situation, to avoid treatment with clarithromycin.

Methods: Eleven patients treated unsuccessfully one-week twice-daily therapy with omeprazole (20 mg), amoxicillin (1 g b.i.d.) and clarithromycin (500 mg b.i.d.) were included in this study. The patients (5 males, mean age 42 years) had been exposed to previous eradication therapies consisting of omeprazole (20 mg b.i.d.) and amoxicillin (1 g b.i.d.) and metronidazole (500 mg b.i.d.) (OAM) for one week. This same combination was administered to six patients in whom omeprazole (20 mg
Eradication of Helicobacter pylori (Hp), prevents duodenal ulcer (DU) relapse.

**Aim:** Study of evaluation: a double therapy regimen using high dose of Nizatidine (Axid) on Hp eradication and DU healing.

**Methods:** 60 consecutive pts with DU and biopsy proven Hp infection were randomized into the following therapy regimens:

A: Nizatidine 300 mg b.i.d + Amoxicillin 750 mg b.i.d., 14 days.

B: Collodial Bismuth Subcitrate (De-Nol) 240 mg b.i.d. one month, + Metronidazole 500 mg b.i.d + Amoxicillin 750 mg b.i.d., 14 days.

Endoscopy: Hp status (rapid urease test and histology) were repeated two months after cessation of therapy, and side-effects were evaluated.

**Results:** DU was healed in all pts. Hp was eradicated in 25 pts. (86.6%) in group A and 27 pts. (80%) in group B. Both cohorts A and B were formed by 30 pts. In group A, side-effects were negligible and pts. compliance very good.

**Conclusion:** Nizatidine in high dose associated to Amoxicillin cures Hp and DU, beside good drug tolerance.

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**Evaluation of the Combination of Omeprazole and Azithromycin with or without Metronidazole in Eradicating Helicobacter Pylori**

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**Purpose:** We evaluated the benefit of 7 therapeutic schedules with omeprazole (OME) and azithromycin (AZ) with or without metronidazole (ME) for eradication of Helicobacter pylori. Method: Helicobacter pylori status was determined by rapid urease test and histology before and 4 weeks or after therapy. 7 groups of H. pylori infected patients with peptic ulcer disease were studied. Group 1 (n = 25) and 2 (n = 25) received OME 20 mg/day for 14 days and AZ 500 mg/day for 5 days. Group 2 received and ME 3 × 500 mg/day for 5 days. Group 3, 4, 5, 6 and 7 received OME 40 mg/day for 14 days. Group 3 (n = 16) received AZ 500 mg/day for 5 days. Group 4 (n = 20) received AZ 500 mg/day for 9 days. Group 5 (n = 20) received AZ 500 mg/day for 9 days and ME 3 × 500 mg/day for 7 days. Group 6 (n = 19) received AZ 2 × 500 mg/day for 9 days. Group 7 (n = 15) received AZ 2 × 500 mg/day for 9 days and ME 3 × 500 mg/day for 7 days.

**Results:** The eradication rate in group 1, 2, 3, 4, 5, 6 and 7 was 64%, 72%, 62.5%, 70%, 75%, 73.7% and 86.6%, 21.4% (30/140) patients experienced mild side effects, mild discontinuation therapy because of side effects.

**Conclusion:** We conclude that omeprazole 40 mg/day for 14 days, azithromycin 2 × 500 mg/day for 9 days and metronidazole 3 × 500 mg/day for 7 days is effective treatment for eradication H. pylori infection.

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**Short-Term Therapy of Helicobacter Pylori Gastritis**

M.M. Döllinger, M. Kroesen, H.C. Döllinger. Department of Internal Medicine, University of Ulm, Germany

**Aim:** The study was designed to the effectiveness and tolerability of the Al-Mg-antacid hydroxide (HT) and the proton pump inhibitor (PPPI) pantoprazole given in combination with different antibiotics for the eradication of H. pylori in patients with chronic gastritis and non-ulcer dyspepsia (NUD). The study also examined the gastritis variables and the correlation between the H. pylori status and the dyspeptic symptoms.

**Methods:** Fifty-six patients with positive histology and positive 13C urea breath test who were found to have H. pylori were included. Group A: 11 pts were given two tablets of HT q.d.s. (total neutralization capacity 111.2 mmol/d) and amoxicillin 1000 mg b.i.d. for 10 days. Group B: 20 pts were treated with pantoprazole 40 mg b.i.d. and amoxicillin 1000 mg b.i.d. for 10 days. In both groups, metronidazole 500 mg b.i.d. was given for the last three days (days 8-10). Group C: 25 pts received pantoprazole 40 mg b.i.d. plus clarithromycin 500 mg b.i.d. and metronidazole 500 mg b.i.d. for 7 days. Eradication was determined using 13C-UBT one month after the end of treatment. Differences in the demographic and activity of gastritis between initial and final endoscopies were calculated with Wilcoxon matched pairs test. Symptom severity was scored by patients visual analogue scales (VAS) and by doctors' assessment.

**Conclusion:** Hp pylori eradication was achieved in 45% of group A, 70% of group B, and 96% of group C. Independently of the eradication regimen, cure of the infection brought a marked reduction in the degree of antral gastritis and an even greater improvement in the activity, with a resolution of symptoms in 88% of pts.

**Conclusion:** The results support the causal relation between H. pylori infection and gastritis. Furthermore, in chronic gastritis, H. pylori seems to play an important role in the symptoms of NUD. The success of antimicrobial therapy may be improved by effective control of gastric acid secretion, and the one-week triple therapy with PPI and two antibiotics not only is well tolerated, but also has high and similar efficacy in comparison with the eradication regimens in gastric and duodenal ulcer.

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**Evaluation of the Combination of Omeprazole and Azithromycin with or without Metronidazole in Eradicating Helicobacter Pylori**

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**Background:** Gastrointestinal hemorrhage is the most frequent complication of peptic ulcer disease. It has recently been suggested that HP infection may be a risk factors for the relapse of peptic ulcer and bleeding. Aim: we evaluated the effects of HP eradication on the recurrence of bleeding from duodenal ulcer (DU) in young patients with 46 to 70 months of follow-up. Methods: from June 90 to June 92, we analyzed 32 pts (all males, mean age 30.2 yrs, range 20-50 yrs), with endoscopically proved HP positive bleeding DU. All pts received Omeprazole (40 mg/day) for 4 wk followed by Collodial Bismuth (480 mg/day) for 2 wk associated with Amoxicillin (2 g/day) during the first wk, substituted by Metronidazole (750 mg/day) during second wk. After 6 wk all pts underwent upper digestive endoscopy. A status was assessed: HP eradicated (Giems staining and rapid urease test). Upper digestive endoscopy with antral biopsies was performed once a year for 46-70 months.

**Results:** Ulcer healing was found in 32/32 pts (100%). HP eradication was confirmed in 23/32 pts (71.9%). After 12 months 2 pts of the 24 HP eradicated pts had been reinfected (8.7%). In the following 24 month, ulcer recurred in 10/11 HP-positive pts (reinfected and eradicated). Rebleeding was noted in 5/11 (45%) HP-positive pts. These pts were treated with omeprazole 40 mg/day for 4 wk with complete healing. In the following 24–48 month ulcer recurred in 10/11 pts HP-positive pts. Rebleeding was noted in 7/10 (70%) of them.
Patients who were not reinfected by HP (21/32) did not show any evidence of DU relapse during follow-up. Thus, the rate of rebleeding episodes along the period of the follow-up was significantly lower in patients with long term eradication of HP, in comparison with those who did not. Conclusion: long term eradication of HP can decrease the rate of DU recurrence and rebleeding.

**816** Triple Therapy (Omeprazol + Amoxicillin + Clarithromycin) for Helicobacter Pylori Eradication in Patients with Peptic Ulcer. No Difference between Six or Twelve Days.

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**Intro:** Modern therapies for eradication of Helicobacter pylori try to be more effective and to achieve better compliance being shorter and cheaper. Some seven-days regimens with omeprozole, amoxicillin and clarithromycin have proved high eradication rates. In Spain available packaging of both antibiotics used carries 12 capsules in. If we use 7 days regimens we need double number of packages and lots of pills are wasted.

Aim: To ascertain the efficacy of a triple therapy with omeprozole, amoxicillin and clarithromycin for Helicobacter pylori eradication in regimens of 6 and 12 days.

**Patients and Methods:** We conducted a clinical trial to eradicate Helicobacter pylori infection in peptic ulcer. 132 consecutive patients (80 M/52 F, mean age: 49.7, range: 19–84) submitted to upper digestive tract endoscopy because symptoms of dyspepsia, were included in the study. Diagnosis of Helicobacter pylori infection was achieved when, at least, two of the following tests were positive: histologic examination of antral biopsy specimens in frozen tissue sections on HE and Giemsa, rapid urease test (Jatrox-test) and C13 urea breath test. Triple therapy consisting in omeprozole 20 mg bid, amoxicillin 1 g bid and clarithromycin 500 mg bid was given to patients at the time of diagnosis. Duration of treatment was non-randomly assigned for 6 and 12 days. Control of eradication was assessed by C13 urea breath test after 6 weeks of finishing treatment. Statistical analysis was performed using χ2 test with Yates correction.

**Results:** Eradication rates in the different groups are:

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 days</td>
<td>81.7%</td>
<td>66.6%</td>
</tr>
<tr>
<td>12 days</td>
<td>86%</td>
<td>80%</td>
</tr>
</tbody>
</table>

No statistical difference of eradication was found between both regimens (6 vs 12 days). Costs of the 2 regimens were 85 and 170 $, respectively for 6 and 12 days.

Conclusions: 1. Triple therapy (omeprazol + amoxicillin + clarithromycin) in a short course of 6 days is so effective for eradicating Helicobacter pylori in peptic ulcer than a 12 days therapy. 2. Cost-effectiveness for a 6 days regimen is excellent.

**817** Eradication of H. pylori Infection in Peptic Ulcers with Four Different Drug Regimens

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Aim: Four different therapeutic regimens for H. pylori eradication were compared in patients with gastric (GU) and duodenal ulcer (DU).

**Methods:** 70 GU (M/F 36/34, mean age 57) and 153 DU patients (M/F 90/63, mean age 49) who were positive for H. pylori underwent endoscopy, urease test, histology and serology at the beginning of the study and 4 weeks after the end of the treatment. They were randomly assigned to four treatments groups: A) Omeprazol 20 mg b.d., Amoxicillin 1 g b.d. for 14 days (n = 57), B) Omeprazol 20 mg b.d., Amoxicillin 1 g b.d. for 14 days, metronidazole 500 b.d. for, 10 days (n = 63), C) Omeprazol 20 mg b.d., Amoxicillin 1 g b.d., Clarithromycin 500 mg b.d. for 7 days (n = 48), D) Omeprazol 20 mg b.d., Amoxicillin 1 g b.d., Clarithromycin 500 mg b.d. for 14 days (n = 52).

**Results:**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. patients</th>
<th>Eradicated (%)</th>
<th>Healing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tot. GU</td>
<td>DU</td>
<td>Tot. GU</td>
</tr>
<tr>
<td>Group A</td>
<td>57</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Group B</td>
<td>63</td>
<td>17</td>
<td>46</td>
</tr>
<tr>
<td>Group C</td>
<td>48</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Group D</td>
<td>52</td>
<td>17</td>
<td>35</td>
</tr>
</tbody>
</table>

* p < 0.05, C and D in comparison with A and B

Conclusion: Follow-up Omeprazol + Amoxicillin had a low efficacy in the eradication of H. pylori. Two week Omeprazol + Amoxicillin + Clarithromycin therapy is the most effective, but one week of the same regimen is effective enough, simple and relatively well tolerated.

**818** Helicobacter Pylori Eradication with Dual and Triple Therapy: A Cost-Effectiveness Analysis

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Purpose: Helicobacter pylori (H. pylori) is broadly accepted as a major prerequisite for the development of peptic ulcer disease and its elimination prevents ulcer relapse in the vast majority of patients. This health economic study compares the cost-effectiveness of two extensively tested treatment schemata: a 14 days dual therapy with a proton pump inhibitor (PPI) and amoxicillin, which produced variable cure rates and a 7 days short term triple therapy (i.e. a PPI and two antibiotics), which resulted in very high cure rates.

Methods: Possible therapy courses for H. pylori cure were implemented by a decision tree model. The probabilities for the use of a particular course of treatment were determined by a survey of 100 office-based specialists in Germany. The underlying eradication and ulcer relapse rates were assessed by literature research and subsequent meta-analysis. For the analysis, direct costs (medication, diagnostics and consultations with the physicians) were considered.

Results: Taking only the medication costs into account, the daily costs of triple therapy were higher than those of dual therapy. However, the total medication costs of triple therapy were 34% lower than those of dual therapy. Carrying out a cost-effectiveness analysis, from the point of the German healthcare system, the total costs per year for a patient with successful H. pylori eradication treated with Clarithromycin were 682 and with dual and clarithromycin 868 for triple therapy. The robustness of this result was validated by several sensitivity analyses concerning the medication costs (price range) and the eradication rates (confidence intervals).

Conclusion: This health-economic analysis showed that triple therapy is not only more effective but also more efficient than dual therapy.

**820** What is the Best Rescue Therapy for Omeprazole Plus Amoxicillin?

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Introduction: Helicobacter pylori infection has change the natural course of peptic ulcer disease. Dual therapy with omeprozole and amoxicillin was the most popular therapy in the treatment of Helicobacter infection. Better compliance, few side effect and rapid disappearance of ulcer symptoms made it become the first line anti-HP therapy. However, variable success rate was results.

Patients and Methods: 425 patients with endoscopically documented peptic ulcer and positive H pylori infection were included. The definition of positive H pylori infection consisted of both positive CLO test and histological examination. Everyone received Omeprazol 20 mg bid and amoxicillin 500 mg tid for 14 days. Ranitidine 150 mg bid was given for 4 weeks. Repeat endoscopy was done to look for ulcer healing and H pylori eradication. The eradication rate of dual therapy was 76%. There were 102 patients who failed in initial H pylori eradication. We made randomization into three group: group A (36 patients): omeprazol 20 mg bid and amoxicillin 500 mg tid for 14 days, group B (33 patients): De-Nol 300 mg qid, amoxicillin 500 mg qid, metronidazole 500 mg qd for 7 days; group C (33 patients): Clarithromycin 250 mg bd, metronidazole 500 mg bid for 7 days. Repeat endoscopy examination with 4 biopsy (antrum and 2 body) for H pylori eradication was done 4 weeks after anti-HP therapy.

Results: Total eradication rate of H pylori in the second line therapy was 81.3% (83/102), including group A: 63.8% (23/36), group B: 90% (30/33), and group C: 90% (30/33). We further classified the eradication rate into the subgroups according to CLO < 1 hour (I), and CLO > 1 hour (II):

<table>
<thead>
<tr>
<th>CLO</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
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<tbody>
<tr>
<td>&lt; 1 hour</td>
<td>22/22 (52.1%)</td>
<td>11/14 (78.5%)</td>
<td>5/6 (83.3%)</td>
</tr>
<tr>
<td>&gt; 1 hour</td>
<td>57/34 (67.6%)</td>
<td>16/15 (630.3%)</td>
<td>27/30 (90.0%)</td>
</tr>
</tbody>
</table>

Conclusion: Black and traditional triple therapy both were good regimens for rescue of initial failure of dual therapy. Bacterial urease activity seemed not influence the H pylori eradication in the second line rescue therapy.

**821** Three-Day Octreotide-Assisted Helicobacter Pylori Triple Eradication Therapy. Six Month Follow-Up

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Purpose: Orally administered antibiotics for H. pylori eradication therapy exerts their effect by local diffusion into the gastric mucosa. However, gastric
emptying reduces antibiotic-mucosa contact time. We tested the hypothesis that a triple eradication therapy with concurrent proton pump inhibitor (PPI) administration may potentiate antibiotic effect by delaying gastric emptying.

Methods: 36 symptomatic H. pylori-positive patients with active duodenal (n = 20) or gastric (n = 16) ulcer participated in this pilot study. All patients received a three-day regimen that contained a proton-pump inhibitor (PPI), amoxicillin and metronidazole (500 mg orally q.d.s.) and colloid bismuth subnitrate (CBS) (240 mg b.d.). CBS treatment was continued for another four days. Endoscopy with antral biopsies for CLO-test, culture and crush tissue smears were performed on admission to the study, at 4, 8 weeks and six months post-treatment.

Results: 2A/26 (82.3%) ulcers were completely healed at 4 weeks and remained healed at 8 weeks. All 24 patients with a healed ulcer became H. pylori negative at 4 weeks. The eradication rate at 8 weeks was 88.5% (22/25). Almost all (94.3%) patients were symptomatic at 6 months. In 19/24 patients who accepted to have endoscopy at six months, ulcers remained healed, but the H. Pylori eradication rate dropped to 68.4% (13/19).

Conclusion: Our results show that a three-day octrotide-assisted H. pylori eradication therapy is not effective, to maintain a peptic ulcer in remission at six-month follow-up.
13 F; mean age 56, range 27–66) showing in the last 12 months at least one episode of bleeding duodenal ulcer, endoscopically documented, were enrolled. Eighteen subjects showed an intake of ulcerogenic drugs (NSAID+ve) causally related with bleeding episodes. From each patient smoking habit, alcohol intake, blood group and family history of peptic ulcer were also recorded. The Hp status was assessed by means of urease test, histology and serology. After an informed consent all patients received an eradication therapy (dual or triple regimen for 14 days); eradication rate was assessed 2 months after the end of the treatment as mentioned above. All subjects were followed-up by endoscopy (every 12 month and at any symptomatic recurrence) and clinical evaluation every six months. Results: Overall, in 36 out of the 50 patients (70%) Hp infection was eradicated (12 NSAID+ve and 23 NSAID−ve). One patient (Hp+ve/NSAID−ve group) showed a bleeding episode at the fifth month of follow-up. Seven patients showed ulcer relapse (3 in Hp+ve/NSAID+ve and 4 in Hp−ve/NSAID+ve group); no Hp−ve patient relapsed. No hematological differences were detected in Hp+ve vs Hp−ve as subjects regards clinical and epidemiological parameters. Conclusions: These preliminary data seem to confirm the importance of Hp infection eradication in preventing bleeding duodenal ulcer, both in NSAID+ve positive and negative groups.

827 Evaluation of Helicobacter Pylori Resistance to Five Antimicrobial Agents in Italy
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We evaluated the "in vitro" sensitivity to metronidazole, amoxicillin, tetracyclin, eritromycin and azitromicin of 66 strains of Helicobacter pylori (H. pylori) isolated from the gastric mucosa of dyspeptic patients. Susceptibility was determined by disc diffusion on agar plates. 29 patients (group A) had already been treated for H. pylori, while 37 patients who had previously received an unsuccessful treatment for the infection: 9 patients (group B) were treated with omeprazole + amoxycillin and 28 patients (group C) with tinidazole + amoxycillin + colloidal bismuth subcarbonate and/or omeprazole. All the isolates from group C were found to be resistant to metronidazole. The natural metronidazole resistance, evaluated in patient without previous anti-H. pylori treatments containing nitroimidazoles, was around 21% (7% and 3% in groups A and B respectively) and wasn't related to age or sex. No strains resistant to azitromicin were found. Tetracyclin resistant strains accounted for 4.5% (9%, 11% and 7% in group A, B and C respectively). The overall resistance to azitromicin was 15% (9%, 0% and 25% in groups A, B and C). Susceptibility to eritromycin, tested in 15 cases only, always matched with azitromicin susceptibility. The occurrence of strains of H. pylori resistant to nitroimidazoles as well as to macrolides is rather frequent in our geographic area. In our study a resistance to metronidazole was always found in case of failure of the therapeutic schedule containing a nitroimidaole: this suggests to avoid further alternative therapeutic combinations including nitroimidazoles in these cases. In vitro testing of H. pylori sensitivity seems to be important before embarking on treatments aimed at eradicating this bacterium. This holds true particularly in course of therapeutic trials, in case the eradication of this microrganism is of crucial importance as in low-grade gastric MALT lymphoma, and after a previous unsuccessful antibacterial treatment.

828 Second Regimen of Omeprazole (O) Plus Amoxicillin (A) Increases the Rate of H. Pylori (HP) Eradication in Patients with Duodenal Ulcer
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The combination of O + A has been proposed as an HP eradication treatment with controversial efficacy. It has been suggested that pre-treatment with O reduces the eradication rate. On the other hand, resistant to A, HP strains have not yet been identified. The aim of our study was to examine if a second administration of O + A increases significantly the overall success rate of HP eradication therapy in the pre-treatment with O or duration of antibiotic treatment influence these results. Patients and Methods: 149 patients with duodenal ulcer were enrolled in our study. They have been randomly allocated in 2 groups and received respectively: Group I (80 patients) Pre-treatment with O 20 mg for 10 days, followed by O 40 mg + A 2 gr for 10 days and O 10 mg for 20 days and Group II [controls]: (69 patients) who received both O 40 mg + A 2 gr from the beginning, subdivided in Ia: (29 patients): O + A for 10 days plus placebo for 30 days and Ib: (40 patients): O + A for 15 days plus placebo for 25 days. The patients of group I who failed to eradicate HP were randomly subdivided into Ia: 22 patients who received the same regimen and Ib: 28 patients who received both O + A from the beginning (O 40 mg + A 2 gr) for 10 days. As the treatment was estimated by histology (2 antral + 2 fundic biopsies) 4-6 weeks after the end of each treatment. Stat: Chi-square Results: 20% (Cl: 11–29) of group I (75 patients) and 37% (Cl: 24–49% ) of group II (63 patients) eradicated HP after the first treatment (p = 0.05) [11 drop out]. Additionally 12/22 patients of group Ia and 12/28 of group Ib eradicated HP after the second attempt of O + A [NS] [10 drop out]. There was no difference between Ia and Ib. The subgroup Ib was significantly different from group I ( p = 0.05). Conclusions: 1) The simultaneous administration of OM + A for 15 days has the best eradication rate, but remains low (37%). 2) The readministration of O + A has a substantial additional success rate, irrespective of pre-treatment with O.

829 Cimetidine and Amoxicillin – Clavulanic Acid for Ulcer Disease with Helicobacter and Herpes Simplex Virus
N.A. Vinogradov, M.A. Vinogradova, R.R. Gazziova. Hospital No 3, Moscow, Bacteriological Medical University, Ufa, Russia
Purpose: To evaluate the cimetidine and amoxicillin-clavulanic acid made by Smith Kline Beecham (Tagament and Augmentin respectively) for cases of peptic ulcer. To assess the influence of infection with Helicobacter Simplex virus (HSV) on ulcer disease. Patients: 55 patients aged 18–80, illness duration 1–20 years: 26 stomach ulcer (SU), 26 duodenal ulcer (DU), 3 with SU and DU at once. Concomitant reflux-esophagitis – 22, chronic pancreatitis – 18. Bleeding ( Forrest I–II) – 8 cases, when cimetidine was used i.v. 200 mg every 6 hour till hemostasis and then orally 800 mg per day alike the peptic ulcer exacerbation dose. Three comparable randomized groups: the 1st (n = 20) received cimetidine as monotherapy, the 2nd (n = 20) – cimetidine with Augmentin 375 mg 3 times a day for 10 days, the 3rd (n = 15) cimetidine with the triple therapy (bismut subcarbonate, metronidazole, ampicillin). Helicobacter pylori (HP) was isolated by histological or cytological methods. The presence of HSV in the mucosa biopsy samples was verified by fluorescent-iso-thio-cyanate-linked HSV-antibodies.
Results: Ulcer healing was sooner in the 2nd versus the 3rd group, and was the latest in the 1st. HP elimination occurred in 18 of the 2nd and in 12 patients of the 3rd group Cimetidine caused esophagitis and pancreatitis remission. The most resistant to therapy ulcers were characterized by laboratory evidence of HSV infection in patient with concurrent HSV simultaneous infection. Conclusion: Cimetidine and amoxicillin-clavulanic acid combined therapy is an advisable regimen for peptic ulcer with HP. HSV must cause immunosuppression with subsequent mucosa restitution depression and HP-infection aggravation.

830 Local Immune Response on Helicobacter Pylori Associated Gastric Ulcer before and after Eradication Therapy
R. G. Grivalos, A. Terrés, M. F. Bermejo, J. A. Moreno, J. M. Mateos, J. M. Pajares. Gastroenterology Department, Hospital de la Princesa, Madrid, Spain
The development of peptic ulcer is associated with the presence of Helicobacter pylori (HP). The aim of this study was to determine the phenotype, distribution, and expression of immunological phenotype markers and antigenic recognition molecules (HLA class I and II) in the gastric mucosa of peptic ulcer patients before and after the eradication treatment. Methods: Immunoperoxidase staining was performed in frozen cryostate sections from antrum gastric biopsies of 15 patients with HP associated gastric ulcer before and after eradication of the bacteria. Controls included mucosa from no infected healthy donors. Gastric biopsies were obtained through status endoscopy, and HP status was determined by rapid urease test, 13C urea breath test and histological examination. Sections were stained with the following monoclonal antibodies: anti-CD2, anti-CD4, anti-CD8, anti-CD45, anti HLA-DR and W6/32.
Results: Before treatment intraepithelial lymphocytes (IEL) and lamina propria T cells were CD8+ while CD4+ cells were predominant in folicles. Most of them, CD8+ and CD4+ cells expressed the activation marker CD2+ CD11b+ and high numbers of cells expressing this marker infiltrate the lamina propria. HLA-DR expression by epithelial cells was noticeable. After treatment the infiltration of mononuclear cells remain very similar to pretreatment status but expression by the epithelium was also noticed.
Conclusion: Helicobacter pylori eradication in patients affected of gastric ulcer does not affect the mononuclear infiltration in the mucosal lamina propria. However, a noticeable decrease of neutrophil-macrophagic infiltration can be observed in that location after eradication.

831 Decrease of Mucosal Interleukin 8 Contents in Patients with Helicobacter Pylori-Gastritis after Successful Eradication
T. Fujino, H. Kuwayama, M. Tachibana, M. Fukuyo, Y. Shijo, K. Chishima, N. Shimoyama, Y. Katayama, K. Kitazawa, K. Kawauschi, T. Saito, H. Mori. Department of Medicine, Dal-Ni University Hospital, Tokyo Women's Medical College, Tokyo
Although the precise pathogenesis is not known, infection of Helicobacter pylori (H. pylori) cases may occur by consumption of the stomach, leading to persistent chronic active gastritis. Gastric mucosal inflammation is characterized by neutrophil accumulation with abundant release of a number of cytokines including interleukin 8. In the present study we assessed mucosal interleukin 8 content before and after H. pylori eradication with special reference to histologic gastritis. Sixty gastritis patients with H. pylori infection was enrolled in this study. Four biopsies were taken each from antrum and gastric body. Three biopsies were processed for histology, culture, and rapid urease test
Conclusions. Gastric mucosal content of ILB was significantly decreased after successful eradication of H. pylori which was well correlated with improvement of histologic gastritis.

832 Usefulness of Symptomatological Pattern in Predicting the Outcome of Dyspeptic Patients after Hp Eradication: A Prospective Six Months Study

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The usefulness of H.p. eradication in NUD is still controversial. For a better evaluation of dyspeptic patients which could have an improvement of their symptoms after eradication, they were subdivided in three groups: A: ulcer-like discomfort; B: C: reflux-like. Methods: Included were subjects (61 M; mean age 51.5; range 25–76) entered an open, controlled prospective study. All underwent different treatment schedules with either Amoxicillin or Clarithromycin plus Metronidazole and Omeprazole for one week. Endoscopy: at baseline and two months after the end of therapy (T2): 7 gastric biopsies were taken from gastric antrum and body to assess H. pylori status by histology (Giemsa, Warthin Starry, immunohistochemistry) and rapid urease test (CLO test). All patients were evaluated for a six months follow-up period (T6). Results: Overall, 86/119 (74.5%) pts were cured and 96% showed a disappearance of gastritis activity at T2. Eradication rate in the 3 groups was 79.3% group A; 68.3% group B; 75.8% group C. Overall, 45% of eradicated subjects and 6% of non-eradicated subjects were asymptomatic at T2, 31% and 5% at T6, respectively. Subdividing the pts according to their symptomatological pattern, the percentages were as follows: Group A: T2 = 60.9%; T6 = 65.2% Group B: T2 = 36.5%; T6 = 74.6% Group C T2 = 43.5%; T6 = 39.2% (p = 0.001).

Conclusions: 1) Overall, 44.8% and 31% of dyspeptic pts were symptom-free and had no symptoms after 6 months after a successful H. pylori eradication therapy, respectively. 2) Higher asymptomatic rate was obtained in the ulcer-like group (60.9% at T2, unchanged at T6). 3) The disappearance of gastritis activity was confirmed in 96% of cured patients.

833 Effect of Eradication of Helicobacter Pylori on Gastric Histology and Gastric Function Parameters in Gastric Ulcer

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Aim. The evolution of gastritis and the behaviour of serum gastrin and pepsinogen (Pgl) levels and gastric emptying of solids were studied in 18 consecutive patients (11 males; mean age: 54.5 ± 9.1 yrs) with H. pylori (Hp) positive, uncomplicated, non-NSAIDs related gastric ulcer (GU) over a follow-up of three months after eradication therapy.

Patients and methods. Gastritis score was assessed according to the Sydney System on antral and corial biopsies before the treatment consisting of omeprazole 40 mg a day for 1 month and amoxicilin 1 g three times daily for 14 days, and 3 months after ulcer healing. In addition a series of functional tests including basal and meal-stimulated serum gastrin concentration, serum Pgl levels and an evaluation of gastric emptying of solids by means of serial ultrasonographic measurement of gastric antrum area were performed at the same visits.

Results. Double therapy for Hp resulted in successful eradication in 8 of 16 patients. In Hp-eradicated pts mean activity and inflammatory scores of gastritis in antrum and corpus significantly fell after 3 months. No significant changes of mean gastric emptying were observed in the antral and control group concerning intestinal metaplasia and atrophy both in the antrum and corpus. In contrast, pts with persistent Hp infection showed a significant worsening of gastritis activity in the corpus after treatment. In Hp-eradicated patients the means of integrated gastrin response to meal ([AUC pg/mlh]: 23428 ± 5727 vs 17623 ± 3993), but not fasting gastrin concentration ([pg/ml]: 67.7 ± 14.4 vs 59.6 ± 11.9), fell significantly during the follow-up and also serum Pgl levels significantly decreased as compared to baseline ([ng/ml]: 55.0 ± 27.8 vs 79.7 ± 32.3). In contrast fasting and maximal antral area and gastric emptying remained unchanged over time. In the control group, no significant modifications of any of the above mentioned parameters were observed during the follow-up.

834 Gastric Mucosal Nuclear Organiser Regions (AgNORs) and Helicobacter Pylori Infection: Impact of Eradication

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Despite the fact that the association of Helicobacter pylori (H. pylori) with an increased risk of gastric cancer has been well-documented, the exact mechanisms of this association, have not been elucidated.

Aim: The aim of the present prospective study was to contribute to the exploration of these mechanisms by studying the relationship between H. pylori infection and the silverstaining nuclear organizer regions (AgNORs) in endoscopic biopsies in gastric antrum as it is known that the number of AgNORs per nucleus has been positively correlated with proliferative rate and ploidy. To do that we studied a total of 28 H. pylori (+) patients and the results were compared with 22 endoscopically and histologically normal H. pylori (−) patients (control group), who were comparable to the H. pylori (+) group for age and sex. In addition a group of 10 H. pylori (+) patients were examined before and after successful eradication of H. pylori and normalisation of gastric histology.

Results: In the H. pylori (+) patients the mean number of AgNORs per nucleus was 5.43 ± 0.18 (SEM) and was significantly higher than the respective number in the control group (3.27 ± 0.13; p = 0.001). In patients studied before and after H. pylori successful eradication the corresponding numbers were 5.50 ± 0.31 and 3.20 ± 0.20 (p = 0.003) and the latter did not differ significantly from the control group of H. pylori (−) patients.

Conclusions: H. pylori infection alters the replication cycle of gastric mucosa inducing hyperproliferation and possible ploidy abnormalities. However, it remains unclear whether these alterations are induced directly by the bacterium or by the gastric inflammation.

835 Evolution of Histologic Lesions of Gastric Mucosa after Eradication of H. pylori in Duodenal Ulcer Patients. A Six-Month Follow-up Study

J.P. Gisbert, D. Boixeda, C. Redondo, Ranz F. Hernandez, Martin C. de Argila, C. De la Serna, L. De Rafael. "Ramón y Cajal" Hospital, Madrid, Spain

Purpose: To study changes in histologic gastritis at gastric antrum and body after H. pylori eradication in duodenal ulcer patients, at an early stage and after six months.

Methods: Seventy-six patients with duodenal ulcer disease were prospectively studied. At endoscopy biopsy specimens were taken from duodenal bulb, gastric antrum, body and fundus (H&E, Gram stain and culture). A patient was considered to be H. pylori+ when microbiology or histology demonstrated colonization in any location. An endoscopy with biopsy samples taken from antrum and body was performed one month after therapy completion and four months later. Different therapy regimens were used: amoxycillin/clavulanate plus omeprazole or ranitidin; classic triple therapy; and omeprazole or ranitidin alone.

Results: All patients were H. pylori+. Eradication was achieved in 47% (n = 36) of patients. In H. pylori eradicated patients, rates of chronic gastritis/chronic active gastritis prior to treatment and two and six months later were, respectively: 100/96%; 36/23%; 16/5.6% in gastric antrum, and for gastric body were: 54/38%; 12/12%; 12/5.6%. An histologic improvement, overall and in the acute inflammatory component, was observed one month after therapy completion (p < 0.001). Four months later, although histologic improvement was more marked, differences were not significant compared with results in the first month. No changes in histologic pattern was observed when eradication failed.

Conclusions: An improvement in gastric antral and body gastritis was associated with H. pylori eradication in duodenal ulcer patients. This successful evolution was observed immediately after eradication and confirmed six months after diagnosis.
Endoscopy was done before treatment and repeated at the end of treatment, 4 weeks, 4 months, 8 months and 12 months after treatment. At least two antral biopsy samples had been taken during every endoscopy. Activity of gastritis was described according to Sydney classification. Statistical analysis was performed by the Chi-square method.

Results: Seventy of antral gastritis during one year observation is presented on the table. Results are expressed as the percentage of patients.

<table>
<thead>
<tr>
<th>Degree of gastritis</th>
<th>Start of the treatment</th>
<th>End of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>95% 3.5%</td>
<td>60% 5% 95%</td>
</tr>
<tr>
<td>Moderate</td>
<td>20% 40% 30%</td>
<td>35% 20% 35%</td>
</tr>
<tr>
<td>Severe</td>
<td>70% 27.5% 10%</td>
<td>7.5% 7.5% 7.5%</td>
</tr>
</tbody>
</table>

No one of patients showed the relapse of the ulcer or H. pylori infection.

Conclusions: 1. Patients with cured H. pylori infection showed significant regression of antral gastritis. 2. The regression of antral gastritis was observed in the time of treatment and 4 weeks after the treatment of H. pylori infection. During later observation the severity of antral gastritis remained stable.

837 Erosive Duodenitis and Helicobacter Pylori Infection: Response to Eradication Therapy with Omeprazole, Amoxicillin and Clarithromycin

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Purpose: To study the prevalence of H. pylori infection in patients with erosive duodenitis, the associated gastric histologic lesions, and the response to an eradication therapy with omeprazole and two antibiotics.

Methods: Fifty-five patients with erosive duodenitis were prospectively studied (mean age: 55 yrs, 70% males). At endoscopy, biopsies from both gastric antrum and body were obtained for histologic study (H&E). A C13-urea breath test was also performed. Omeprazole (O) 20 mg b.i.d. plus two of the following antibiotics were administered for one week: amoxicillin (A) 1 g b.i.d., clarithromycin (C) 500 mg b.i.d., metronidazole (M) 500 mg b.i.d. Endoscopy (with biopsies) and breath test were repeated 1 month after completing therapy.

Results: All patients were H. pylori-positive (n = 55). Overall, eradication was obtained in 85% (95% CI = 74–92%). Eradication rates for different therapies were: OAC 94% (92–96); OCM 86% (11–113); OAM 64% (7/11) (p < 0.05 when comparing OAC and OAM). Overall, duodenal erosion healing was obtained in 80% (74–88%). Healing rates for different therapies were: OAC: 87% (27/31); OCM: 92% (12/13); OAM: 45% (5/11). Both OAC and OCM achieved better healing rates than OAM (p < 0.05). Duodenal erosion healing was achieved in 87% (75–94%) of cases with eradication therapy success, while only in 38% (n = 3) when eradication was not achieved (p < 0.01). An histologic improvement, both in the gastric antrum and body, was documented in 90% of H. pylori-negative patients (p < 0.01). Compliance of therapy was complete in all patients and no relevant adverse effects were reported.

Conclusion: A high prevalence (100%) of H. pylori infection in patients with erosive duodenitis treated with a one-week twice-daily therapy of omeprazole plus two antibiotics (OAC or ACM) was very effective in H. pylori eradication, duodenal erosion healing, and resolving associated histologic gastritis. These observations suggest that erosive duodenitis should be considered a variant form of duodenal ulcer disease and be treated accordingly, that is, with H. pylori eradication therapy.

838 Eradication of H. Pylori Infection in Patients with Corporal Atrophic Gastritis (CAG): A Consecutive Open Study

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CAG is a condition characterized by atrophy of oxyntic mucosa hypochloridria and fasting hypergastrinemia. It has recently been observed that a significant proportion of CAG patients are H. pylori-infected and that H. pylori infection is significantly associated with the development of corporal atrophy in patients treated long-term with proton pump inhibitors. No studies until now have been specifically addressed to prospectively investigate in CAG patients, if it is possible to get the infection since the lack of acid secretion, determine less favourable condition to its eradication.

Materials and Methods: 19 consecutive patients (15 F, 4 M aged 34–72) with H. pylori positive CAG (histology, culture, Ig G; at least two of these tests positive) were treated for 4 weeks with bismuth subcitrate 240 b.i.d.; amoxicillin 1 g tid post-adrandically and metronidazole 250 mg tid post-prandially were given during the first 2 wks of therapy. Endoscopy was again performed after 6 mos, to evaluate H. pylori status by histology and culture (antral n = 5) and body biopsies (n = 8). The gastritis status was scored according to the Sydney system. Fastening gastrin levels (pg/ml; specific RIA) and titre of IgG H. pylori (UI; Elisa GAP test, Biored) were also determined. Results are expressed as median (range), non-parametric test for pair analysis and p value based for statistical evaluation. Results: Overall eradication rate was 78.9% (15/19 pts). Minor side effects were recorded in about half of patients, but none determined therapy withdrawn. Gastrin levels decreased dramatically in eradicated patients (220 (49–1400) vs 42 (10–285); p < 0.001 as IgG H.p[80 (10–100) vs 31 (0–65); p < 0.005] Corporal chronic inflammation and atrophy were significantly reduced after eradication [respectively: 2 (1–3) vs 1 (0–2); p < 0.001 and 2 (1–3) vs 1 (0–3); p = 0.031]. Inflammation activity completely regressed [1 (0–3) vs 0 (0–0)]. Conclusions: These data show that is possible to eradicate H. pylori infection, obtaining a pronounced reduction of fasting gastrin levels and a significant reduction in the score of chronic gastritis.

839 Cure of Helicobacter Pylori Infection Does Not Affect Acidity in the Spontaneously Secreting Stomach of Duodenal Ulcer Patients

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Purpose: The present study was designed to evaluate the long-term effect of curing H. pylori infection on the intragastric acidity in duodenal ulcer patients.

Methods: Eleven duodenal ulcer patients infected by H. pylori were studied. 24-hour pH recordings were performed before treatment of the infection as well as 1 and year after the cure. Glass electrodes were placed 5 cm below the cardia.

Results: Cure of H. pylori infection was associated with a marked improvement of antrum and corpus gastrin and a decrease of the fasting gastrin levels. The acidity of the spontaneous secretion remained unchanged. The intragastric acidity remains unchanged after the cure of H. pylori infection in duodenal ulcer patients, suggesting that the net effect of the decreased acid output on the gastric pH is compensated by other mechanisms, e.g. the loss of neutralizing substances like ammonia generated by H. pylori.

840 Role of H. pylori Eradication in the Prophylaxis of Ulcer Bleeding Recurrence

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Purpose: Several studies have demonstrated that eradication of H. pylori (HP) is associated with a low rate of ulcer recurrence. Our purpose was to verify the effect of HP eradication on ulcer bleeding recurrence.

Methods: Patients with acute hemorrhage secondary to duodenal ulcer were included in this prospective study. Exclusion criteria were the administration of antibiotics, bismuth, or non-steroidal anti-inflammatory drugs within 30 days prior to endoscopy. After hospitalization a therapy with H2 antagonist at standard doses was administered. Biopsies were obtained (H&E) at diagnostic endoscopy, and a C13-urea breath test was also performed in the following days. At discharge, HP patients were randomised to receive 2 eradicating therapies (proton pump inhibitor (PPI) plus 1 or 2 antibiotics, for 2 and 1 week, respectively), followed by PPI for 6–9 months. Endoscopy with biopsies was repeated 1 month after completing therapy, and a breath test was performed again. Eradication was defined as the absence of HP by both diagnostic methods. Patients with therapy failure received a second course of therapy. Patients with therapy success did not receive maintenance-anti ulcer therapy and were controlled at 6 and 12 months with a C13-urea breath test.

Results: At present, thirty-three patients (mean age: 49 ± 12 years, 89% males) have achieved eradication (two of them required a second therapy). Ulcer healing was achieved in 88% (CI 95%: 76–95%) of patients. In the four cases with ulcer persistence, healing was reported in a 2 month endoscopy performed 1 month later. Follow-up of patients was: 2 months (n = 4), 6 months (n = 23), and 1 yr (n = 6). Reinfection was not demonstrated in any of 12 or 6 months. No bleeding episodes were observed in the follow-up period (mean: 6 months, range: 2–12 months).

Conclusion: This preliminary study suggests that rebleeding does not occur in patients with HP infection. A family of detection enzymes consisting of class Alpha, Mu, Pi and Theta isoforms, were inversely correlated with cancer risk. We investigated whether the NSAIDs idomethacin, ibuprofen, piroxicam, acetylsalicylic acid (ASA) and sulindac, incorporated in the diet

841 Effects of Nonsteroidal Anti-Inflammatory Drugs on Glutathione S-Transferases of the Rat Digestive Tract

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Nonsteroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to reduce cancer rates in oesophagus, stomach and colon of both humans and animals. Earlier, we showed that high human gastrointestinal tissue levels of glutathione S-transferases (GST) in rats fed with carbon tetrachloride (CCL4) was decreased in rats fed with GST induction enzymes consisting of class Alpha, Mu, Pi and Theta isoforms, were inversely correlated with cancer risk. We investigated whether the NSAIDs idomethacin, ibuprofen, piroxicam, acetylsalicylic acid (ASA) and sulindac, incorporated in the diet
Study.

with re-randomised C.J. Hawkev ated 0.001, re-randomised GST was levels in small intestine. Piroxicam enhanced gastric and hepatic GST Alpha levels as well. GST PI levels were raised in stomach by ibuprofen, ASA and sulindac in small intestine by indomethacin, piroxicam, ASA and sulindac. In conclusion, enhancement of morphological changes, resulting in a more efficient detoxification of carcinogens, may explain in part the anticarcinogenic properties of nonsteroidal anti-inflammatory drugs.

Site Specific Ulcer Relapse in Non Steroidal Anti-Inflammatory Drug (NSAID) Users: Improved Prognosis with H. Pylori and with Omeprazole Compared to Misoprostol

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Introduction NSAIDs cause gastric and duodenal ulcers and retard healing. We therefore compared healing and prophylactic efficacy of omeprazole and misoprostol in NSAID users and investigated whether H. pylori or the initial ulcer site predicted relapse.

Methods 935 patients with gastric ulcer (GU) or duodenal ulcer (DU), or > 10 gastric or > 10 duodenal erosions were randomised to receive omeprazole (OME) 20 mg, OME 40 mg, or misoprostol 200 μg qid under blinded conditions for 4 or 8 weeks until healed and open OME 40 mg for up to 16 weeks if unhealed. 732 evaluable patients with treatment success (no ulcer, and < 5 erosions at each site and no more than mild dyspepsia) were re-randomised to OME 20 mg, misoprostol 200 μg bid or placebo and followed for 6 months or to treatment failure (ulcer or > 10 erosions at either site or moderate/severe dyspepsia or discontinuation due to adverse events).

Results Overall treatment success was similar for healing with each active treatment but omeprazole was significantly better tolerated. Overall, omeprazole was significantly more effective than misoprostol for maintenance (p = 0.001, log rank test).

Treatmenl success (%) for patients with GU or DU at entry was:

<table>
<thead>
<tr>
<th></th>
<th>Initial GU</th>
<th>Initial DU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ome 20</td>
<td>Ome 40</td>
<td>Miso</td>
</tr>
<tr>
<td>n</td>
<td>131</td>
<td>140</td>
</tr>
<tr>
<td>Hp -</td>
<td>71%</td>
<td>61%</td>
</tr>
<tr>
<td>Hp +</td>
<td>82%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Of patients with GU at relapse, 73% had had GU initially compared with 72% of DU relapses who had DU initially.

Conclusions In NSAID users: (1) Initial ulcer site predicts relapse site. (2) Omeprazole 20 mg is similar to misoprostol for healing and maintenance of Hp negative ulcer patients, and for GU healing and maintenance in NSAID users. (3) Omeprazole is superior to misoprostol for healing and prevention of DU's associated with NSAID use and for all ulcer patients who are Hp positive. (4) Omeprazole appears to be more effective for the healing and prevention of NSAID associated ulcers in Hp positive patients than Hp negative patients.

Quality of Life (QoL) in Patients with Non-Steroidal Anti-Inflammatory Drug (NSAID) Associated Gastroduodenal Lesions During Healing and Maintenance. A Randomised Comparison of Omeprazole and Misoprostol

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Background Gastric and duodenal ulcers and erosions are commonly associated with NSAIDs, but there are few comparative QoL data that can be used to assist in identifying optimal treatment of such lesions.

Aim To compare the effect on QoL of omeprazole (ome) 20 or 40 mg or misoprostol (miso) 200 μg qid during healing. In the maintenance study ome 20 mg was compared with miso 200 μg bid or placebo.

Methods QoL was assessed in an international double-blind, parallel-group study. In the healing phase 618 male (40%) and female (60%) atritic patients, mean age 59 years, with ulcers or erosions, completed the Nottingham Health Profile (NHP) and the Gastroduodenal Symptom Rating Scale (GSRs) at baseline and after 4/8 weeks. In the maintenance phase, 513 patients were re-randomised and treated for 6 months. The NHP is a general health profile and measures the burden of illness, while GSRs, which uses a seven-graded Likert scale, evaluates the 15 gastrointestinal symptoms with 15 clusters describing Diarrhoea, Indigestion, Constipation, Abdominal pain, and Reflux.

Results Patients with arthritis generally have a poor health-related QoL, in particular regarding fatigue, sleep disturbances, mobility and pain. During healing, ome 20 mg om showed a significant advantage in relieving reflux symptoms (p < 0.0005), abdominal pain (p < 0.0005), indigestion (p = 0.04) and total GSRs score (p < 0.0005) compared with miso, while miso induced diarrhoea (p < 0.0005) was clearly superior. In the maintenance phase, ome was significantly more effective in relieving reflux symptoms (p < 0.0005), abdominal pain (p < 0.003), indigestion (p = 0.006), and overall symptoms (p = 0.0003) than miso. Also the lower dose of miso induced diarrhoea compared to placebo (p = 0.04).

Conclusion In arthritic patients, who are severely incapacitated in terms of QoL, omeprazole 20 mg om provided more effective control of dyspeptic symptoms and was better tolerated than misoprostol.

Increased Effectiveness of Omeprazole Compared to Ranitidine In Non Steroidal Anti Inflammatory Drug (NSAID) Users with Reference to H. Pylori Status

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Introduction Ranitidine is known to be inferior to both omeprazole and misoprostol in both healing and prophylaxis of NSAID-associated gastric ulcers. We investigated whether the site of initial lesion predicted relapse site and whether differences between ranitidine and omeprazole were attributable to ulcer site or Hp status.

Methods 541 patients with gastric or duodenal ulcer or more than 10 gastric erosions or more than 10 duodenal erosions were randomised to receive treatment with omeprazole (OME) 20 mg, or misoprostol (MISO) 20 mg or ranitidine (RAN) 150 mg bid and cumulative treatment success (no ulcer, < 5 erosions at each site, no more than mild dyspepsia) was recorded over 8 weeks. 432 patients were re-randomised to blinded maintenance treatment with OME 20 mg or RAN 150 mg bid and followed for 6 months or to treatment failure (ulcer or > 10 erosions at either site or moderate/severe dyspepsia or discontinuation due to adverse events).

Results Overall treatment success (defined as above) was significantly better for omeprazole than ranitidine during both the healing (p < 0.001, Mantel Haenszel test) and maintenance phase (p = 0.004, log rank test).

Conclusion NSAID ulcer patients tend to relapse at their initial site. Acid suppressing drugs are more effective for healing and prevention of NSAID associated ulcers in H. pylori positive than negative patients. Omeprazole is superior to ranitidine overall, and particularly for healing of NSAID-associated ulcers in H. pylori negative patients.

Short-Term Corticosterone Treatment: Different Effects In the Gastrointestinal Tract

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The feeding pattern and hormones are associated with tissue maturation in different systems, and the GI tract has been widely studied. Although glucocorticoids are thought to have a major importance in growth, a clear response is not yet established for the cell proliferation of the developing gastric and intestinal epithelia. The aim of this study was to evidence the effect of short-term corticosterone administration on the proliferative process of the gastric and intestinal epithelia of 18-day-old suckling rats.

For that purpose, we divided the animals into 3 groups: fasted and fed controls (i.p. injection of NaCl2); fed hormone-treated (i.p. injection of cortico- terone 50 μg/b.w.). We estimated the mitotic index (MI) (in both organs) and cell production rate (CPR) (in the stomach), which were achieved by vincristine blockade; b) gastric mucosal and gland thickness; c) possible morphological alterations. All these parameters were analysed in histological slides. Cell proliferation and thickness were subject of Mann-Whitney statistical test.
The MI was greatly inhibited in the gastric mucosa (P < 0.01), in opposition to the lack of effect observed in the jejunum. The CPR was also inhibited by corticosterone (P < 0.05), but no significant effect was detected in thickness. We did not observe any ulcer formation in either group.

These results suggest that the short-term corticosterone administration leads to a potent inhibition of the cell proliferation only in the gastric mucosa. These experiments light up the different responsiveness of the GI tract to corticosterone administration during fasting period.

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846 Gastric Parietal Cell Canalicul Index after NSAID Treatment in Osteoarthritic Patients
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Parietal cell canalicul index is related with the acid secretory activity of parietal cells. The aim of this study was to assess canalicul index before and after a 7 days treatment with indomethacin or d Roxicam. Patients: 32 osteoarthritic patients, randomly allocated to one of the two treatment groups, underwent endoscopy and biopsies of the gastric corpus mucosa. Methods: Biopsies were processed for transmission electronic microscopy. Images at 2500x of 20 parietal cells per patient were analyzed by computerized densitometric morphometry. The size of the secretory canalicul system was automatically measured. The rate of the size of the canalicul to the size of the cytoplasm was considered as the canalicul index (CI). Results: CI was (mean ± SEM) 17% ± 1.3 before treatment and reached 26% ± 1.6 after treatment (p < 0.001). CI in superficial parietal cells reached 27 ± 2 (p < 0.005), and 23% ± 2 in the profound parietal cells (p = n.s.). There were no differences between both therapeutics groups. Conclusions: Parietal cell canalicul index, an estimation of the secretory canalicul size, increased after 7 days treatment with NSAID in the most superficial parietal cells. This finding express a hyperestimulat state of the parietal cells which might be an important pathogenic factor in NSAID-induced gastritis, supporting the indication for preventive co-treatments with proton pump inhibitors.

847 Alteration of the Gastric Mucus and the Gastric Resistance Induced by Aspirin
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It is well known that the gastric mucosa plays an important role in protecting the stomach from noxious agents such as ethanol. However, we reported that oral administration of aspirin reduced the gastric mucosal lesions induced by absolute ethanol or 0.6 N HCl, although aspirin reduced the gastric surface mucosa (Gastroenterology 104 (4): A121, 1993). In this study, we attempted to examine the effects of aspirin on the gastric mucosa, mucous gel layer, surface layer and deep layer, and examined causality between the mucous movement and the gastric resistance.

Method: Male Wistar rats (180–200 g) were used. The gastric mucosa was examined histologically and biochemically 24 hr. after oral administration of aspirin (100–300 mg/kg, p.o.). Histochemical studies: Removed stomachs were opened along the greater curvature and fixed in absolute ethanol (−80°C). The paraffin tissue sections of both corpus and antrum were stained with AB-PAS, HID-BAD, UEA-I (Ulex europaeus Agglutinin I) and PNA (Peanut Agglutinin) stainings, and then observed histochemically. Each positive area was measured by our computer image processing system. Biochemical studies: Gastric mucins were prepared from gastric juice, mucous gel, surface and deep mucosa. Each sample was used for analysis of hexose and sialic acid.

Results: Surface mucus (PAS or UEA-I positive mucus) in both corpus and antrum significantly decreased at 0.25 to 12 hr. after oral administration of aspirin. Hexose contents also decreased in corpus mucosa. However, the deep corpus mucus (PNA positive mucus) significantly increased at 0.25 to 1 h. after administration of aspirin. Sialomucin was scarcely detected in normal mucosa but increased in the mucosa at 1 to 12 h. after oral administration of aspirin. Sialic acid increase in gastric juice, mucous gel, and surface mucosa at 1 h. after administration of aspirin. Moreover, acidic mucin (HID-BAD positive mucus) increased in surface mucosa at 6 to 12 hr. and recovered to normal range at 24 hr. after administration of aspirin.

Conclusion: We concluded that the aspirin-treated stomach enhanced the resistance to injury caused by strong irritants and this function is probably mediated by gastric mucus such as PNA positive mucus in deep mucosa and sialomucin in juice, gel layer and surface layer.

848 Low Dose Misoprostol as Prophylaxis Against Low Dose Misoprostol-Induced Gastric Mucosal Injury
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Introduction: Misoprostol, a prostaglandin analogue, given in conventional doses (200 μg bid – qds) prevents aspirin-induced-gastrroduodenal mucosal damage, but is associated with side-effects. In view of the increasing use of low dose aspirin for secondary prevention of vascular disease, we wished to study whether low dose misoprostol (100 μg) could prevent gastroduodenal damage and cause to low dose aspirin-induced side-effects.

Methods: 32 age and sex-matched healthy volunteers aged 18–45 were enrolled in this double blind, placebo controlled, parallel group study. Endoscopy was performed on days 0, 5, 14 and 28. Paired antral and corpus biopsies were taken for histopathological estimation and plasma samples for thromboxane estimation. Mucosal abnormalities and adverse events were noted. Volunteers were randomised to one of two drug regimens: 100 μg placebo misoprostol and aspirin 300 mg daily or 100 μg misoprostol and aspirin 300 mg daily for 26 days. Compliance was assessed by tablet counting, prostaglandin and thromboxane measurements. The primary endpoint was the total number of gastroduodenal erosions assessed endoscopically. Anatomical site and nature of erosions were secondary endpoints.

Results: Data were analysed using a generalised linear model.

<table>
<thead>
<tr>
<th>28 days results</th>
<th>Misoprostol</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Subjects with haemorrhagic erosions</td>
<td>12.5</td>
<td>50</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>No. of haemorrhagic erosions/subject</td>
<td>0.38</td>
<td>3.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Subjects with non-haemorrhagic erosions</td>
<td>18.8</td>
<td>18.8</td>
<td>NS</td>
</tr>
<tr>
<td>No. of non-haemorrhagic erosions/subject</td>
<td>0.38</td>
<td>1.19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% Subjects with petechiae</td>
<td>6.3</td>
<td>43.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of petechiae/subject</td>
<td>1.25</td>
<td>6.44</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

There was no significant difference in the side-effect profile between the placebo and misoprostol treated groups.

Conclusions: We conclude that low dose misoprostol provides effective prophylaxis against endoscopically assessed gastroduodenal mucosal damage caused by low dose aspirin and is free of significant side-effects.

849 Prostaglandin Enhances the Recovery of Mucin Content in the Surface Layer of Rat Gastric Mucosa at the Restitutional State after NSAID (HCl-Aspirin) Induced Mucosal Damage
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Applying the newly developed mucus-scraping method, the mucin content was measured in the different layers of rat gastric mucosa which had been injured by topical application of HCl-Aspirin, and the effect of a prostaglandin (PG) E2 derivative was estimated after its administration at 3 hrs following the injury.

Material and Methods: Male Wistar rats weighing 160–170 g were orally administered 0.15 N HCl-Aspirin (200–200 mg/kg) and killed at 1, 3, 5, and 7 hrs following the drug administration. Gastric lesions were macroscopically observed, and then the surface mucosa, deep corpus and antrum mucosa were separately collected. The mucin in each layer was extracted, and the content was determined as previously described (Gastroenterol Jpn 1992; 27: 493–472) 15, 16-Dimethyl PGE2 (30 μg/kg) was administered 3 hrs before aspirin administration, and the effect of this agent on the gastric mucosal restitution was estimated by determining the mucin content in each layer of the mucosa at 7 hrs.

1) Gastric macroscopic injury was observed in all cases of HCl-Aspirin treated rats at 3 hrs. 2) At 7 hrs after the administration, the macroscopic and light microscopically observable injury induced by the 50 mg/kg HCl-Aspirin was significantly recovered. 3) A considerable decrease and a notable recovery of the surface mucin content was observed 5 hrs after aspirin administration, but the mucin content of the deep corpus was not significantly changed during the experimental period by this HCl-Aspirin dose. 4) The PG treatment after 100 mg/kg HCl-Aspirin administration significantly recovered the surface mucin content. (126% vs. control, 200% vs. single HCl-Aspirin dosing) However, no significant change in the deep corpus mucin content could be achieved.

Conclusion: Changes in gastric mucin content induced by low dose (50 mg/kg) HCl-Aspirin were mainly limited to the surface mucosal layer. PG might participate in the restitution of the gastric mucosa by the accumulation of mucin mainly in the surface mucous cells. The estimation of mucin content in the different layers of the gastric mucosa could be a useful tool to study the restitution from gastric mucosal injury.

850 Alendronate Causes Gastric Mucosal Damage Similar to Aspirin
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Alendronate and pamidronate are primary amino-bisphosphonates used in the treatment of metabolic bone disease. Both drugs have been associated with enteropathy and gastrointestinal and renal injury is associated in the USA for parental use. In rats, alendronate causes gastric mucosal damage similar to aspirin or NSAIDs. Methods: We performed a blinded, crossover, randomized, single-center, placebo controlled comparison of alendronate (40 mg/day), aspirin (100 mg/day), and placebo using endoscopy to evaluate the presence and degree of mucosal damage to the esophagus, stomach, and duodenal bulb. Results: 12 normal volunteers were studied both before and after 4 days of drug therapy. Placebo caused no visible endoscopic damage. In contrast, both...
aspirin and enalaprilate were associated with visible gastric mucosal injury in the majority of those studied (75% and 50%, respectively) and both were significantly greater than placebo (p < 0.001). The gastric mucosal injury was deemed severe in 50% of those receiving either enalapril or aspirin. One enalapril-associated gastric ulcer was also seen. Esophagel and duodenal bulb injury was seen on histopathology and both were associated with enalaprilat.

Conclusion: The primary amino-bisphosphonate enalaprilate causes mucosal injury to the upper gastrointestinal tract similar to aspirin. Even when used according to manufacturer's dosing instructions enalaprilate should be used with caution.

851 Production of Inflammatory Mediators in Patients with NSAID-Induced Gastropathy
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Arthritis patients (AP) have an increased risk of the upper gastrointestinal tract mucosal damage because of their need of long-term non-steroidal anti-inflammatory drugs (NSAID) therapy.

The aim of this study was to investigate whether cytokines and arachidonic acid metabolites are involved in the inflammatory reaction of NSAID-induced injury of gastric mucosa (GM) and to determine the effect of cytoprotective therapy on GM in AP.

In 15 AP receiving Diclofenac (100 mg, daily, orally; 3 weeks) and 10 AP patients receiving Arthrotec (0.2 μg Misoprostol-PGE1 + 50 mg Diclofenac, orally, bid; 3 weeks), the GM production of IL-1, TNF, 6-keto-PGF1α-TxB2 and LTB4 was measured in biopsies and specimens obtained in special conditions. In the levels of IL-1, TNF, TxB2 and LTB4, was markedly increased (p < 0.05), whereas 6-keto-PGF1α production was significantly (p < 0.05) decreased in the GM in AP, before and 3 wks after start of Diclofenac therapy. No significant differences were found between the production of IL-1, TNF, 6-keto-PGF1α, TxB2 and LTB4 in the GM in AP before and after Arthrotec therapy.

The results of this study show that the GM injury mediators production in AP treated by Diclofenac differs from those receiving Arthrotec. NSAID may cause adherence of neutrophils to the vascular endothelium, probably through the release of cytokines and arachidonic acid metabolites. It may play a role in ischemic cell injury, and impaired repair of mucosa. Misoprostol, as a result of Arthrotec, effectively prevented Diclofenac-induced GM injury mediators production.

852 Selective COX-2 Inhibition: Its Relevance for NSAID-Gastrointestinal Toxicity
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Purpose: The main limitation in the use of NSAIDs is their gastrointestinal (GI) toxicity. The recent discovery of cyclooxygenase isoforms has resulted in further efforts to find new anti-inflammatory drugs. An inducible cyclooxygenase COX-2 produces mediators of inflammation, and a constitutive cyclooxygenase COX-1 has a cytoprotective effect on the gastric mucosa. Consequently NSAIDs that have a higher activity against COX-2 than COX-1 may prevent NSAID-related side effects. Meloxicam is a new NSAID derived from eicosanoid with a preferential COX-2 inhibitory capacity.

Methods: Meloxicam has been tested in controlled short- and long-term clinical trials in over 5000 patients, mainly in osteoarthritis (OA) and rheumatic arthritis (RA) to determine its clinical efficacy and GI-safety profile.

Results: In the treatment of OA and RA meloxicam 7.5 and 15 mg daily was as effective as standard doses of naproxen, piroxicam and diclofenac. Meloxicam, however, produced fewer GI-side effects. Compared to the comparator drugs significantly less upper GI perforation, ulceration and bleeding occurred with meloxicam (p < 0.05). Overall, there were significantly (p < 0.05) fewer discontinuations due to GI-side effects with meloxicam (meloxicam 7.5 mg and 15 mg, respectively, piroxicam: 6.7%, diclofenac: 10.5%, naproxen: 10.7%) as well as less dyspepsia and abdominal pain.

Conclusions: Meloxicam shows a favourable GI-tolerability profile. This seems to be directly related to its preferential inhibitory effect on COX-2 over COX-1. The main advantage of selective COX-2 inhibition is in producing an improved risk/benefit profile for the NSAIDs by maintaining efficacy, but improving GI-safety.

853 Combination Therapy of Reembapide, a Novel Antilucr, Agent, with Low Dose Metronidazole and Aomoxicillin Decreases Gastric Mucosal IL-8 and Heals Gastritis
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Objective: Reembapide is a novel antiulcer agent used in Japan. The exact mode of reembapide action is not known, but proposed mechanisms of this compound include its anti-oxidant and anti-inflammatory effects. Because gastric Helicobacter pylori infection is characterized by active persistent mucosal inflammation, we assessed the effect of reembapide on H pylori gastritis.

Methods: H. pylori status was confirmed by culture, histology, and rapid urease test at the end of 6 months. A total of 56 patients were enrolled in this clinical trial. Patients were randomly assigned into 2 groups and received either rebamipide 100 mg + amoxicillin 250 mg + metronidazole 250 mg t.i.d or rebamipide 100 mg alone. Rebamipide was continued for 4 weeks whereas amoxicillin and metronidazole were given for the first 2 weeks only. Four biopsies were taken each from antrum and gastric body. Three biopsies were processed for histology, culture, and rapid urease test respectively. Remaining one was homogenized and stored at −80°C for later measurement of mucosal interleukin (IL-8) content. IL-8 production mediated by EIA and Bio-Rad respectively. Reendoscopy was performed at least 4 weeks after completion of all medication.

Results: H. pylori eradication was achieved in 21 among 26 patients treated with rebamipide + amoxicillin + metronidazole. None of the patients treated with rebamipide alone showed eradication of H. pylori. Gastric mucosal IL-8 contents were significantly decreased after successful eradication, which was well correlated to the improvement of histologic gastritis, in rebamipide + amoxicillin + metronidazole group.

Conclusion: Reembapide with low dose metronidazole and amoxicillin normalizes gastric mucosal IL-8 and heals gastritis.

854 Decreased Levels of cGMP in Gastric Mucosa after Acute NSAID Administration. Relationship with Gastric Injury and Its Prevention by Phosphodiesterase Inhibition
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Purpose: NSAID-induced gastric injury is related with the decrease of mucosal protective mechanisms. As opposed to this, cGMP increases mucos protection and endothelial cells proliferation. Therefore, the decrease of synthetic prostaglandins produces a fall in gastric mucosal levels of cGMP. Then, it is possible that NSAID-induced gastric damage can be related with decreased levels of cGMP in gastric mucosa. In this sense, we have investigated the levels of cGMP in gastric mucosa after NSAID administration, their relationship with NSAID-induced gastric damage and its prevention by phosphodiesterase inhibition by 3-isobutyl-1-methyl-xantine (IBMX). Methods: We have used Wistar male rats (200-250 g). The NSAID tested have been: piroxicam (PIR) (5, 10 and 20 mg/kg), sodium diclofenac (DIC) (10, 25, 50 and 100 mg/kg) and acetylsalicylic acid (ASA) (100, 300 and 500 mg/kg), in all cases, the way of administration was p.o. Three hours after NSAID administration the animals were anesthetized with tiletobital, the stomach removed, the gastric injury (U) measured in mm² and the mucosa scraped and frozen until cGMP determination by immunassay. IBMX (10 mg/kg) was administered s.c., when necessary, 10 minutes before NSAID. Results: NSAID-induced gastric injury has been related with the fall of cGMP levels in gastric mucosa (p < 0.01). Similarly, both gastric injury and decreased levels of cGMP were dose related. On the contrary, IBMX administration prevents both, NSAID-induced gastric damage and cGMP fall in gastric mucosa. Levels of cGMP after ASA 100, 300 and 500 mg/kg and after IBMX (50 and 100 mg of IBMX 123.3 ± 7.5: 163.8 ± 7.5: 186.0 ± 8.4: 121.8 ± 6.6, PIR 5, 10, 20 mg/kg and after IBMX (10 and 20 mg/kg) (112.8 ± 34.8: 6.8 ± 11.1: 51.7 ± 16.9: 154 ± 5.5: 148.5 ± 4.9: 148.3 ± 4.8 and 148.3 ± 21.6). Ul after ASA 100, 300 and 500 mg/kg and after IBMX (0.45, 2.31: 5.15: 0.35: 0.48, 2.31: 0.33: 0.33: 0.39 and DIC 10, 50, 20 and 100 mg/kg and after IBMX (0.67: 2.35: 4.19: 7.96: 0.41: 0.50: 0.62: 2.21). Conclusions: cGMP plays an important role in NSAID-induced gastric injury and the maintenance of its levels at low concentrations prevents the production of gastric mucosal damage.

855 Effects of Ammonia Solution and Terpenone on Gastrointestinal Factors, Gastric Ulcus and System Gastrin in Acetic Acid-Induced Gastric Ulcers in Rats
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Objective: Ammonia produced by H. Pylori is considered to be responsible, in part, for the prolongation and recurrence of ulcer gastric in man. We induced prolonged acetic acid-induced gastric ulcer in rats by administering ammonia solution to the animals, and its effect was evaluated. Some previous studies showed that factors, gastric mucus quantity and serum gastrin level. In addition, anti-ulcer activity of terpenone, a mucosal protective agent, was evaluated after the coadministration with ammonia solution.

Materials and Methods: An acetic acid gastric ulcer was induced in male Wistar strain rats by the method of Okabe et al. and a prolonged gastric ulcer model was obtained by administering 0.1% ammonia solution to the animals. Rats given tap water were used as controls. Ulcers were observed at 24 hours after onset of ulcer induction. The rats were sacrificed at various time intervals after ulcer induction.
and the ulcer size was measured. The ulcer lesion was punched out as a tissue specimen for determination of b-FGF, TGF-β1, PDGF by ELISA. The quantity of surface cell mucus was calculated in computerized image of microscopic section after PAS staining. The serum gastrin level was determined by RIA method. The results were compared among the control, ammonia and ammonia + tetraprenylacetone group.

Results: The healing of ulcer was delayed in the ammonia group, compared to the control group, while administration of tetraprenylacetone tended to inhibit the delay of ulcer healing. The tissue level of b-FGF was increased with time, but was lower at all times in the ammonia group than in the control group. In the ammonia + tetraprenylacetone group, on the other hand, there was an improvement in the tissue levels of b-FGF. The tissue levels of TGF-β1 were lower in the ammonia group than in the control group at one time during the experiment, but was again improved with the administration of tetraprenylacetone. There was no difference in tissue level of PDGF between the ammonia and the control groups, whereas the tissue level of tetraprenylacetone and quantity of surface cell mucus and the serum gastrin level were lower in the ammonia group than in the control group, and were higher in the ammonia + tetraprenylacetone group than in the ammonia group.

Conclusion: The results of this study suggest that the presence of ammonia in the stomach causes the delay of ulcer healing and effects the tissue levels of growth factors, gastric mucus quantity, serum gastrin level and even the quality of ulcer healing.

856 Changes of Gastric Endocrine Cell Numbers in Rats by Long-Term Treatment with Ammonia
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Aim. This study investigated the changes of gastrin-immunoreactive cell (G-cell), somatostatin-immunoreactive cell (D-cell), and enterochromaffine-like cell (ECL-cell) numbers in stomachs of rats by 4 or 8 weeks treatment with ammonia.

Method. Wistar male rats (8 week old) were treated with distilled water (control), 0.001%, 0.01% or 0.1% ammonia solution (p.o.) for 4 weeks (A0.001%, A0.01%, A0.1%) or 8 weeks (A0.001%, A0.01%, A0.1%). G-cells, D-cells and ECL-cells were immunostained with labeled streptavidin-biotin-peroxidase complex method using antibodies to synthetic human gastrin-17, a commercially available somatostatin or histamine antibody. And the cell with viable nuclei was counted.

Results: The G-cell numbers in A0.001% and A0.01% group were not significantly different from those of the control group. The G-cell numbers were significantly increased in A0.1%, A0.01% and A0.001% group. However, the G-cell numbers in A0.1% group was significantly decreased compared with those of the control group. The D-cell numbers in A0.001%, A0.01%, A0.1% and A0.01% group were not significantly different from those of the control group. The D-cell numbers in A0.1% showed a tendency to decrease, and it was significantly decreased in A0.01% group. The ECL-cell numbers in A0.001% group was not significantly changed compared with the control group, but they significantly increased in A0.01%, A0.1% and A0.01% group. However, the ECL-cell numbers in A0.1% group was significantly decreased compared with those of the control group.

Conclusion: In this study, the G-cell and ECL-cell numbers were changed depending on ammonia concentration and its administrated period. The low dose of ammonia increased the G-cell and ECL-cell numbers, but the high dose decreased. It may be explanation for changes in gastric endocrine induced by H pylori infection.

857 Role of Free Radicals in Rat Experimental Model of Chronic Gastritis with Ammonia
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Helicobacter pylori (Hp) is known to be closely related to gastrudodenal mucosal lesions. The etiologic mechanisms in Hp induced gastric mucosal injury are presumed to be associated with ammonia produced by urease activity of Hp, monochloramine, and immunological cross reactions. In this study, we assessed the effects of ammonia on the gastric mucosa and whether free radicals and glutathione (GSH) are involved in the induction of gastric mucosal lesions. In addition, we evaluated the effect of novel anti-ulcer agent tetraprenylacetone (tetraprenyl) in the experimental model with ammonia.

Materials and methods: Male SD rats were used and sacrificed 6 weeks after the beginning of the study. Gastric mucosal injury was induced by giving 0.1% ammonia water ad libitum for 6 weeks. Group 4: Water was offered ad libitum. Group 5: EGF [human EGF (100 μg/kg/day)] was offered ad libitum for 6 weeks. Group 6: 0.1% ammonia water was offered ad libitum and 200 mg/kg/day of tetraprenylacetone was administrated orally for 6 weeks. The tissue sections of removed stomach were used to measure the thickness of body and antrum. Serum gastrin levels and tissue levels of myeloperoxidase (MPO), GSH and LPO (which is the index of lipid peroxidation) in the frozen gastric mucosa were determined.

859 Importance of Sensory Nerves and Nitric Oxide (NO) in Gastric Cytoprotection Induced by Epidermal Growth Factor (EGF)
Purpose: Capsaicin and NO have been shown to protect the gastric mucosa against various irritants but their relative importance in the cytoprotection afforded by EGF has not been determined.

Methods: In this study we examined the effects of intragastric (ig) capsaicin in small dose (0.5 mg/kg), to excite the sensory nerves or in a large systemic (sc) dose (100 mg/kg), to deplete these nerves, as well as EGF treatment plus EGF on ethanol-induced gastric damage. In addition, the influence of total salivary to remove endogenous source of EGF or suppression of endogenous NO synthase with Nω-nitro-L-arginine (L-NNA 40 mg/kg iv) on ethanol-induced gastric lesions was tested. Gastric lesions were measured planimetrically and gastric blood flow (GBF) was examined by laser Doppler technique.

Summary of results: Topical application of 100% ethanol produced widespread hemorrhagic mucosal lesions (area ~ 80 mm²) accompanied by about 60% reduction in GBF. Pretreatment with capsaicin (0.5 mg/kg ig), EGF (50 μg/kg sc) or their combination significantly reduced the area of ethanol lesions while restoring the GBF. These protective and hyperemic effects of capsaicin, EGF and their combination were almost completely eliminated by earlier deactivation of sensory nerves by pretreatment with large dose of capsaicin. Salivary, which by itself aggravated ethanol-induced lesions, failed to affect the protection and hyperemia afforded by EGF and capsaicin. The suppression of NO synthase with L-NNA reduced significantly the protection and hyperemia caused by EGF and capsaicin. The addition to L-NNA of L-arginine (300 mg/kg iv), the substrate of NO synthase, restored almost completely the protective and hyperemic effects of EGF and capsaicin. Application of CGRP-α3, an antagonist of calcitonin gene-related peptide (CGRP), decreased the hyperemia induced by topical capsaicin, EGF or both.

Conclusion: Cytoprotective and hyperemic effects of EGF involve the excitation of capsaicin-sensitive nerves and endogenous formation of NO and CGRP.

859 Interaction of Capsaicin-Sensitive Nerves with Epidermal Growth Factor (EGF) on Healing of Acute and Chronic Gastric Ulcerations in Rats
Purpose: Capsaicin (CAP) applied in a small dose protects gastric mucosa by stimulation of sensory nerves but administered in large neurototoxic dose aggravates the mucosal injury due to deactivation of these nerves. EGF accelerates healing of gastric ulcers but its interaction with sensory nerves on this healing has not been assessed.

Methods: We examined the effects of small (0.5 mg/kg po) and large dose (125 mg/kg sc) of CAP on healing of acute stress-induced lesions and chronic acetic acid-induced gastric ulcers. The rats were sacrificed at 0, 6, 12 and 24 h after restraint stress and 7 days after induction of chronic ulcers. The area of gastric ulcers was measured as the thickness of body and antrum of sections after dye impregnation with DNA dye. The DNA synthesis was assessed by laser Doppler flowmetry, the DNA synthesis by incorporation of TdR into DNA and the EGF in the oxyntic mucosa by RIA and RT-PCR.

Summary of results: Stress produced acute lesions with a marked fall of GBF (~50%) and DNA synthesis to ~50%. However, these lesions were reduced by 75%, the GBF and DNA synthesis were restored and mucosal GBF was markedly increased. Salicylate delayed significantly the healing of stress lesions and reduced further the synthesis of DNA and GBF. Stimulation by laser Doppler flowmetry, the DNA synthesis by incorporation of TdR into DNA and the EGF in the oxyntic mucosa by RIA and RT-PCR.

Conclusion: It was suggested that a significant elevation in MPO and LPO activity is associated with gastric mucosal atrophy induced by long-term administration of ammonia water, and that the anti-ulcer agent tetraprenylacetone inhibits the gastric mucosal atrophy without the elevation in MPO and LPO activity.
whereas CAP-denervation and salivary delayed healing and reduced the GFB and EGF expression in the ulcer area.

Conclusion: Sensory neurons interact with endogenous EGF in healing of both acute and chronic gastric ulcers.

**860 Synchronized Induction in Cyclin-Dependent Kinase Cdk2 and FGF Receptor during Gastric Ulcer Healing**

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The processes of gastric mucosal repair, characterized by massive cell migration, proliferation, differentiation and remodeling, are regulated by growth factors and cyclin-dependent cellular expression of their receptors. Cellular responses to growth factors and the cell passage through G1 phase of cell cycle are mediated by D-type cyclins and their specific cyclin-dependent kinases. In the study presented herein, we assessed the gastric mucosal expression of basic fibroblast growth factor receptor (bFGF-R) and cyclin-dependent kinase (Cdk2) p34 with ulcer healing. The chronic gastric ulcers were induced in rats with acetic acid. Following recovery, the animals were treated twice daily for 14 consecutive days either with a 100 mg/kg of ebrotidine or vehicle, sacrificed at different healing intervals, their stomachs dissected and subjected to bFGF-R and Cdk2p32 quantization. The ulcer area was measured by planimetry. In the FGF-R assays mucosal membrane bound 125I-bFGF was quantitated in a gamma counter, while Cdk2 was employed to Cdk2 p34, measurements. In the absence of ebrotidine the ulcer healing time was 14 days, while treatment with ebrotidine produced a 71% decrease in ulcer area by the 5th day and a complete healing by the 7th day. The results of parallel assays of bFGF-R and Cdk2 p34 revealed that expression of FGF-R reached a maximum of 2.2-fold increase by the 4th day of healing and remained elevated (1.4-fold) for up to 10 days. Accelerated ulcer healing with ebrotidine was also reflected in Cdk2, the expression of which showed the highest (2.1-fold) increase by the 4th day of treatment. This result suggests that the cell cycle regulatory kinase Cdk2 p34 during cellular proliferation associated with ulcer healing is controlled differentially by FGF-R, the induction of which determines the cell cycle progression through G1 and into S phase.

**861 Cell Cycle Progression with Ulcer Healing by Sulglycotide**

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The progression of the events associated with gastric mucosal repair following injury is controlled in an orderly manner by a plethora of extracellular bioactive factors exerting their effect on the cell cycle. The transitions between different cycle states are regulated by a family of cyclin proteins, cyclins and cyclin-dependent kinases, the expression of which vary through the cell cycle stages. The purpose of this investigation was to evaluate the expression of cyclin dependent kinase (CDK) and proliferating cell nuclear antigen (PCNA) with chronic ulcer healing by sulglycotide. The study was carried out on rats with acetic acid induced chronic gastric ulceration. Following postoperative recovery, the animals were given twice daily for 14 consecutive days either a 200 mg/kg dose of sulglycotide or vehicle. At different time interval of healing the animals were sacrificed, their stomachs dissected and the mucosa subjected to PCNA and CDK quantitation. The results of assays established that ulcer healing was accompanied by an increase in mucosal expression of PCNA and CDK. In the absence of sulglycotide treatment, the maximum expression achievement (4.7 fold) occurred on the second day of healing and remained elevated for up to six days, while CDK showed the highest intensity (17:4–19.7 fmoI/mI) at 4–6 days. Sulglycotide caused acceleration in the rate of ulcer healing and this process was reflected in a 2.2-fold enhancement in PCNA expression over that of controls on the second day of treatment and a 2.5-fold enhancement on the sixth day, whereas the CDK expression reached a maximum 2-fold enhancement (33.7 fmoI/mI) by the sixth day of treatment and remained elevated (32 fmoI/mI) for up to 10 days. The findings indicate that sulglycotide has the ability to modulate the processes associated with cell cycle progression.

**862 Role of Hepatocyte Growth Factor (HGF) and Trefoil Peptides in Experimental Gastric Ulcer Healing**

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Introduction: HGF and trefoil peptides are potent growth factors which are locally secreted during gastric ulcer healing. We assessed the role of HGF, its receptor c-met and trefoil peptides in an experimental gastric ulcer model.

Methods: The ulcers were induced by subcutaneous injection of 1 ml 10% HCl into the gastric fundic submucosa of rats for 3 and 15 days with either placebo, 1 x 40 μmol omeprazole or 2 x 100 μg/kg HGF. Ulcer healing was assessed by repeated videodensitometry, histology and in situ hybridization.

Results: HGF treated rats showed identical healing curves as placebo in contrast to omeprazole which accelerated ulcer healing. HGF treated rats showed a 80% increase of epithelial cell proliferation compared with placebo on day 15, but not in the early healing phase. HGF-receptor protein was decreased on days 3 and 8, but still overexpressed in the regenerated glands on day 15. HGF mRNA was detected in mesenchymal cells of the ulcer bed on day 15. Both trefoil peptides rSP (rat spasmolytic polypeptide) and ps2 (mouse one p-domain) mRNAs were significant increased in the regenerative epithelium on days 3 and 15. HGF did not influence the expression of trefoil peptides.

Conclusion: The expression of HGF in mesenchymal cells of the ulcer base and of HGF-receptor in regenerative glands on day 15, suggest a significant role. HGF in the glandular reconstruction in the late phase of ulcer healing. The strong expression of trefoil peptides in the early and late ulcer healing phases supports their relevant role in gastric ulcer healing.

**863 Chronological Changes of G-Cell and ECL-Cell Numbers After Long-Term Acid Suppression in Rats**

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Aim. This study investigated the chronological changes of gastrin-immunoactive cell (G-cell) and enterochromaffine-like cell (ECL-cell) numbers in stomachs of rats after 4-week treatment with histamine H2 receptor antagonist.

Method. Wistar male rats were treated with famotidine (15 mg/kg/day p.o.) for 4 weeks. After withdrawal of the drug, rats were divided into 8 groups: F0 (the group of cessation of famotidine administration), F2 (2 days after cessation of famotidine), F5 (5 days), F7 (7 days), F10 (10 days), F14 (14 days), F28 (28 days) and F56 (56 days) group and control group (n = 6). G-cells and ECL-cells were immunostained with labeled streptavidin-biotin-peroxidase complex method using antibodies to synthetic human gastrin-34, 56 or 60 nmol/kg-min), Norepinephrine, Insulin and Oxytocin. Results. The G-cell number significantly increased in F5, F7, F10 and F14 group compared with control group, but the numbers in F2, F14 and F56 returned to the control level. The ECL-cell number significantly increased in all famotidine-treated groups and they had not returned to the control level by 56 days after cessation of famotidine.

Conclusion. The long-term high-dose famotidine administration produced the increase of the G-cell and ECL-cell number in the rats. The G-cell number seemed to return to the control level in 14 days after cessation of the drug. However, the ECL-number did not return to the control level in this study.

**864 Nitric Oxide in the Regulation of Gastrin Release and Gastric Emrying in Humans**

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Nitric oxide (NO) has been shown to be formed from L-arginine (L-Arg) by constitutive NO synthase in enterochromaffine-like cells and motor nerves of the digestive tract. NO has been implicated in gastric hyperemia associated with gastric secretory stimulation by pentagastrin in anesthetized rats as noncholinergic and nonadrenergic mediator. Recently, it has been shown that NO is involved in the regulation of gastric emptying and acid secretion under physiological conditions in dogs and that those effects are partially mediated by the release of somatostatin. The aim of this study was to evaluate the role of NO in the control of gastric and somatostatin release in response to ordinary feeding. Gastric acid secretion was determined by means of continuous pH-monitoring (DigiTrapp, Synectics, Stockholm, Sweden) after feeding with 500 ml of caloric, semiliquid meal (Fresubin, Fresenius, Bad Homburg, Germany). Plasma levels of gastrin, somatostatin and insulin were measured using specific radioimmunoassays. The gastric emptying rate after feeding was determined using 13C-acetate breath test. In this double blind study gastric secretory activity and gastric emptying rate were determined in random order on three different days after pretreatment with 0.9% NaCl (control), Nω-nitro-L-arginine (L-NMMA 60 mmol/kg/min i.v.) or combination of L-NMMA and L-Arg (30 μmol/kg/min i.v.). Pretreatment with L-NMMA suppressed the postprandial increase in gastrin release and caused a small but significantly higher levels of plasma somatostatin when compared to control values. The gastric emptying half-time was reduced by about two fold and during the median two hours, postprandial intragastric pH showed tendency to increase above control values (L-NMMA: 3.6 ± 0.4 vs. control: 3.3 ± 0.5) but not significantly. Plasma insulin level reached significantly higher postprandial values in tests with L-NMMA compared to control tests probably due to enhanced gastric emptying of meal. Those effects of L-NMMA on the gastric secretory and motor activity as well as plasma hormones release were not observed in tests after pretreatment with the combination of L-NMMA and L-Arg. We conclude that: 1) endogenous NO is involved in the regulation of postprandial gastrin release and these effects appear to be mediated by plasma somatostatin, at least in part, by the release of somatostatin; 2) endogenous NO appears not involved in the regulation of gastric emptying presumably mainly through its excitatory action on the proximal stomach, and 3) inhibition of NO synthesis enhances plasma gastrin release probably due to increased gastric emptying of carbohydrate containing meal.
Effect of Capsaicin and Epidermal Growth Factor on Gastroprotection in the Rat: Influence of Sensory Ablation, Sialoadenectomy, and Close Arterial Infusion with a Calcitonin Gene-Related Peptide Antagonist

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We and others have shown that capsaicin and epidermal growth factor (EGF) protect against gastric mucosal injury in several experimental models. Both chilli, which contains capsaicin, and saliva, which contains EGF, have been proposed as possible protective factors in the pathogenesis of human peptic ulcer disease.

The present study aims to understand the mechanisms of gastroprotection afforded by capsaicin and EGF. We investigated the effect of capsaicin, EGF, and their combination on ethanol-induced gastric mucosal injury in intact rats, and in rats subjected to sensory ablation, sialoadenectomy, or both operations (n = 8 per group). The effect of sensory ablation and close arterial infusion of hCGRP8-37, an antagonist of calcitonin gene-related peptide (CGRP), on the gastric hyperaemic effect of capsaicin and EGF was evaluated in a gastric chamber preparation. Gastric mucosal damage was assessed by planimetry and light microscopy.

Capsaicin, EGF and their combination reduced ethanol-induced gastric mucosal damage in rats with increased damage. In contrast, they did not affect any protection in capsaicinsensitised rats. Sialoadenectomy had no effect. Administration of capsaicin, EGF or their combination increased gastric mucosal blood flow in rats with intact intestine but not after capsaicin desensitisation. In the rats with intact intestine, capsaicin (500 nmol/rat), EGF (20 ng/rat) and the combination of capsaicin and EGF exhibited a synergistic effect on gastric blood flow.

Our results suggest that capsaicin and capsaicin may exert their gastroprotective effects via stimulation of capsaicin-sensitive afferent neurones with release of CGRP.

Central Effect of Pilocarpine on Gastric Secretion and Gastric Mucosal Blood Flow in Anesthetized Rats

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Pilocarpine is a neuropeptide originally isolated from ovine hypothalamic tissue and has two amidated forms, PACAP38 and PACAP27. We examined the effects of centrally administered PACAP38 on gastric secretion and gastric mucosal blood flow (GMFB) in anesthetized rats.

Male Wistar rats were anesthetized with a urethane injection after 24 hr fast. A stainless steel cannula was implanted in the right lateral ventricle. The gastric secretion study was performed using Glusha-Lar’s rat preparation. PACAP38 or PACAP27 (2, 4, 8 nmol/rat) was administered ICV. Acute cervical vagotomy or atropine injection (10 mg/kg i.v.) was performed 15 min before ICV PACAP38 to examine the vascular pathway. PACAP antagonist PACAP38 (4 nmol/rat) was injected ICV to examine the role of PACAP receptor. The effect of ICV or IV bolus injection of PACAP38 on GMFB was examined by a laser doppler flowmeter.

ICV PACAP stimulated gastric secretion dose-dependently. PACAP38 was 1.5–2 times more potent than PACAP27 on gastric secretion. By contrast, IV bolus injection of PACAP38 had no effect on basal gastric secretion. PACAP38 by itself at higher doses (8, 16 nmol/rat) stimulated gastric secretion. IV PACAP38 (8 nmol/rat) that had no effect on gastric secretion, atropine or vagotomy pretreatment suppressed the stimulatory effect of PACAP38. IV PACAP38 increased GMFB continually, whereas IV bolus injection of PACAP38 increased GMFB transiently. These results suggest that centrally administered PACAP may have a regulatory role in gastric secretion through PACAP receptors and the vascular pathway and modulate GMFB.

Effect of Glicentin and Oxytomodulin on Isolated Smooth Muscle Cells from Antrum

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Glicentin (GL) and oxytomodulin (OXM), two peptides correlated from ileum and large intestine during digestion which are related to the enterochromaffin-like immunoreactants. Both hormones contain the same glucagon sequence and a C-terminal octapeptide. Moreover, GLIC has a 32-amino-acids N-terminal extension. GLIC and OXM activities differ from that of glucagon. They are directed to enhance digestive tract: inhibition of gastric acid secretion in vivo in rat and man, inhibition of gastric emptying and duodenal motility for OXM in man and inhibition of the antral motor activity at high doses for GLIC in dog.

The effect of GLIC or OXM on gut motility prompted us to analyse their action on the model of smooth muscle cells isolated from rabbit antrum after enzymatic digestion and mechanical stirring. The preparation contained 95% circular muscle cells. Human GLIC and OXM were obtained by chemical synthesis.

Glicentin or OXM induced a clear shortening of the cells, their maximal contraction corresponding to 13.9 ± 0.8% and 15.5 ± 0.9% of decrease in mean length. The contraction induced by GLIC and OXM was dose related, the observed IC50 were 5 and 83 ± 2.5 µM respectively. The effect of GLIC or OXM (19–37) was as potent as OXM (EC50 = 72 PM). By contrast, glucagon or IGLP exhibited no contractile effect.

In conclusion, it is the first time that a target cell is described for glicentin or oxytomodulin. These results point out the effect of these two orexins hormones on digestive motility in addition to their well established role on gastric acid secretion.

Effect of Epidermal Growth Factor, Capsaicin and Chilli Ingestion on Haemorrhagic Shock-Induced Gastric Mucosal Injury

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We, and others have shown that epidermal growth factor (EGF), chilli, and its pungent ingredient, capsaicin, are protective against ethanol- and aspirin-induced gastric mucosal injury in animals. In the present study, we further investigated the effect of EGF, capsaicin, and close oral ingestion of chilli, on haemorrhagic shock-induced gastric mucosal injury.

Fasted, anesthetised rats (n = 8 per group) were subjected to 60 minutes of haemorrhagic shock by withdrawing the blood, 1.7 ml/100 g body weight, followed by 45 minutes of reinfusion of shed blood. Using an in vivo gastric chamber preparation, superficial, white abnormal areas were observed on the gastric mucosa during haemorrhagic shock, and upon reinfusion of shed blood, bleeding occurred at these areas resulting in lesion formation. Gastric mucosal damage was assessed by planimetry and light microscopy.

Topical application of EGF (25 µg) to the gastric mucosa prior to haemorrhagic shock significantly reduced the gastric mucosal injury from 30% to 10% (p < 0.05). Similarly, administration of capsaicin (5 mg) prior to haemorrhagic shock reduced the damage to 7% (p < 0.05). The use of EGF and capsaicin after haemorrhagic shock, however, did not produce any beneficial effect. Chilli intake for four weeks (360 mg daily) reduced gastric mucosal injury from 21% to 11% (p< 0.05). Pre-treatment of rats with subcutaneous high dose capsaicin (125 mg/kg body weight) to achieve desensitisation of capsaicin-sensitive afferent neurones abolished the gastroprotection afforded by EGF, capsaicin and four-week chilli intake.

Epidermal growth factor, capsaicin, and long-term chilli intake protect against haemorrhagic shock-induced gastric mucosal injury and that this protection may be mediated by capsaicin-sensitive afferent neurones.

Short-Term Sucralfate Administration Alters Potassium Diclofenac Absorption in Healthy Volunteers

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The production of peptic ulcers is a clinically important side-effect of non-steroidal antiinflammatory drugs (NSAIDs). Sucralfate is a basic aluminium salt of sucrose sulfate that polymerizes in an acid medium to form a viscous substance capable of binding to the gastric and duodenal mucoses. This is thought to accelerate ulcer healing; however, the healing mechanism(s) remains to be fully defined. The objectives of the present work were to study the influence of sucralate on the pharmacokinetics of diclofenac in eighteen healthy male volunteers.

Methods: Potassium diclofenac suspension (Cataflam, Ciba-Geigy, 105 mg) was administered orally with or without a five-day pre-treatment with Sucralfate (2000 mg bid phases Suc+C and Suc−, respectively), and blood samples were collected before and 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, and 24h after diclofenac administration. The serum concentrations of diclofenac were quantified by reverse-phase HPLC with U.V. detection. The maximum plasma concentration (Cmax) of diclofenac was determined. The time taken to reach Cmax (Tmax), a first-order terminal elimination rate constant (Kt), the half-life (T½), the area under the time-concentration curves from 0–24 h (AUC 0–24) and the value AUC0–24/T½ as an index of diclofenac clearance, were determined.

Results: The peak serum concentration was increased and the amount of diclofenac absorbed (75% of the AUC during the Suc+ phase) of the Cmax (62%) with no significant effect on diclofenac elimination. Conclusion: Pre-treatment with sucralate significantly decreased the amount of diclofenac absorbed (75% of the AUC during the Suc+ phase) and the Cmax (62%) with no significant effect on diclofenac elimination. Financial support: CNPq, FAPESP
**Results:** Vasopressin induced a significant reduction in both GMBF and LGBAF, but the percent decrement was greater (p = 0.05) in LGBAF (47 ± 7%) than in GMBF (30 ± 4%). Isosomelic hemodilution was followed by an increase in both GMBF and LGBAF, the percent increment being significantly (p < 0.001) higher in GMBF (10 ± 14%) than in LGBAF (90 ± 14%). The percent increment in blood flow was significantly (p < 0.05) attenuated by L-NNAME in both the GMBF (78% attenuation) and the LGBAF (89% attenuation). In rats infused with pentagastrin, a significantly (p < 0.05) greater increment was observed in GMBF (39 ± 9%) than in LGBAF (90 ± 7%), both being partially being attenuated by L-NNAME. A similar gastric hyperemic response was seen in the GMBF and the LGBAF when gastric mucosa was challenged by HCl-taurocholate perfusion, an effect that was significantly attenuated by L-NNAME.

**Conclusions:** Gastric mucosal and left gastric artery blood flows changes may differ under certain pharmacological, pathological or physiological stimul. This illustrates the autoregulatory capability of the vascular tone at the mucosal-submucosal level. In non-acidotic animals, hyperemic responses to tagastrin, hemodilution, and HCl-taurocholate injury are modulated by nitric oxide inhibition in a similar manner in the left gastric artery and in the mucosal microcirculation.

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**Effect of Pyrillum on Secretions of Gastric Acid and Gastrin in Rats After Long-Term Acid Suppression**

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Aim—Long-term acid suppression is known to induce hypergastrinemia, but the underlying reasons why this is no increase in acid secretion, so-called acid rebound, after the treatment is widely debated. Acid secretion is known to be regulated by many factors, and long-term acid suppression may produce the change of other regulatory factors. Histamine H2 and H3 receptor subtypes are reported to be located on gastrin-immunoreactive cell (G-cell). This study investigates the effects of pyrillum (an H3 receptor antagonist) on gastric acid and gastrin secretions in rats after 4-week acid suppression. Methods—Pyrillum (H3 receptor antagonist, 15 mg/kg i.p.) was administered in drinking water for four weeks. On the 3rd, 5th, and 7th day after cessation of tamodine treatment, the gastric juice pH, acid output, and serum gastrin were measured in rats at 4 h after drug administration or with pretreatment of pyrillum (50 mg/kg, i.p.). If administered, pyrillum was given prior to 30 minutes before pylorus-ligation. Result—After the cessation of tamodine, the gastric juice pH, acid output and serum gastrin decreased significantly and remained significantly lower than the control group. However, pretreatment of pyrillum significantly increased the acid output and the serum gastrin level in the tamodine-treated group, but not in the control group.

Conclusion—These results suggest that gastric acid and gastrin secretions don’t decrease after long-term treatment with H3 receptor antagonist because they become inhibited via the H2 receptor.
fect of cetraxate was remarkably diminished by administration of L-NMMA. NO synthase activity increased significantly 30 min. after stress and decreased significantly 6 h. after stress. Cetraxate treatment increased NO synthase activity throughout the experiment in rats with or without stress treatment. Water immersion stress decreased all PGs detected, i.e., 6-keto-PGFα2, PGE2, and PGD2. Cetraxate prevented stress-induced decreases in PG synthesis. L-NMMA showed no significant effect on PG contents. Cetraxate increased gastric mucosal blood flow significantly and L-NMMA cancelled out cetraxate-induced increase in blood flow.

Conclusions. The pharmacological efficacy of anti-ulcer drugs such as cetraxate can be attributed to the enhancement of NO synthase activity resulting in an increase in gastric mucosal blood flow.

**876** Novel Evaluation Method for Drug Induced Gastropathy Using Endoscopic Sprayed Powder Drug Delivery System (IV)

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**Aim:** Previously, we have reported that administration of powdered drugs using an endoscopic compressed air drug delivery system technique was useful for the investigation of direct effects of drugs on the gastric mucosa, and demonstrated the direct irritant action of anti-inflammatory drugs. In this study, we aim to evaluate the direct irritant actions of ulcerogenic medicines in canine gastric mucosa using this technique.

**Methods:** 2.5 mg/kg of powder drugs were administered at target sites (about 10 mm) on the gastric mucosa of five dogs by endoscopically, followed by observation of changes in the character of the gastric mucosa after the experiment. Minocycline hydrochloride induced mucosal lesions were limited to the target site of gastric mucosa in all dogs. However, no lesions were observed at any other site. Aminocillin 25 mg (40%) induced superficial gastritis at the antrum, but did not appear to spray sites. Ethyrythromycin did not induce mucosal lesions. The control study of powdered NaCl produced gastric mucosal lesion at the site of administration in all dogs. No lesions were induced by lactose.

**Conclusions:** We could observe the experimental gastric mucosal lesion at the target site of the gastric mucosa by an administration of a small amount of powdered drugs via an endoscope. Minocycline hydrochloride induced direct irritant action on the gastric mucosa. Aminocillin and ethyrythromycin did not induce mucosal lesions.

**877** Gastroprotective Properties of Aminoosugar Glucosamine and Its Derivatives

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During the last 5–7 years aminoosugar glucosamine has been attracting the research workers close attention, as it is an integral element of biological membranes. Hence, glucosamine, studied in composition of mixed biopolymers and, being a natural metabolite of human organism, is absolutely harmless. In the field of gastroenterology there’s an opportunity of application for glucosamine, conditioned by existence of target-organs – stomach in the mucus of which its own mucosamine and neutral glycoproteides is contained, according to the data of the literature. In the course of experiments and clinical testing we proved the sudden lowering of endogenous glucosamine in target-organs in pathology of gastrointestinal tract. In the connection of above mentioned material the suggestion about the efficiency of glucosamine in gastric ulcer disease was brought up.

The experiments were held on white rats of Wistar line. Gastric ulcer disease was induced by combined intragastric putting of prednyzolon and 90% ethylic spiritus. This model gives the 100% development of gastric ulcer affections of stomach in control animals. The antilucier activity of the substances was valued at the following features: the ulcer area, the percentage of ulcer, ulcer index. Besides that the contents of endogenous glucosamine was studied in blood serum and gastric tissue. During the experiment, the following substances were studied: glucosamine hydrochloride, N-acetylglucosamine, glucosamine acid, glucosamine pentaacetate, glucosamine disulfate "SIGMA", USA, and the original substances, that are the oxalic acid derivates: oxoglucamine with one molecula of glucosamine and dioxoglucamine with two molecules of glucosamine. The studied substances were putting on before 1 hour of ulcer modeling and 3 hours after ulcer modeling.

Experiments that were made shows the gastroprotective properties of all studied substances. The highest antilucier activity had glucosamine hydrochloride and it syntetic derivates, that lowered the ulcer index in 10, 5 and 30 times, respectively, in comparison with the control group. The contents of endogenous glucosamine in blood serum and gastric mucosa restored to the level of intact rats under the influence of above mentioned substances. Received data makes it possible to propose glucosamine hydrochloride, oxoglucamine, dioxoglucamine for the further investigation on antilucier activity in order to clinical using.

**878** Involvement of Endogenous Nitric Oxide in the Gastroprotective Activity of Ebrotidine in Rats

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Ebrotidine is a novel H2-receptor antagonist with marked antiresecretory potency which affects the proliferation of smooth muscle cells, in a way that is different from cimetidine. In a previous study, we demonstrated that the administration of N-nitro-L-arginine methyl ester (L-NAME), inhibitor of nitric oxide synthase (NOS), antagonized significantly the gastroprotective activity of ebrotidine. The aim of this study was to investigate the influence of L-arginine and D-arginine on the antagonism exerted by L-NAME in the gastroprotective action of ebrotidine. Two groups of male SD rats received saline (i.v.) 10 min prior to ebrotidine (100 mg/kg i.v.) or the vehicle, while two other groups were given L-NAME (10 mg/kg i.v.) instead of saline under the same conditions. Then, other two groups of rats received L-arginine (200 mg/kg i.v.) or D-arginine (200 mg/kg i.v.) immediately prior to L-NAME and 10 min before ebrotidine. Thirty minutes after ebrotidine or the vehicle all the groups were administered with 100% ethanol (1 ml/kg i.v.) and after 60 min they were sacrificed. Results showed that mucosal damage in the control group in the absence and in the presence of L-NAME was 78.06 ± 4.28 mm and 143.71 ± 8.61 mm respectively. The lesion inhibition rate was 85% for ebrotidine in the absence of L-NAME. Pretreatment with L-NAME reduced the inhibition rate of ebrotidine to 24%. Finally, L-arginine, natural substrate for NOS, counteracted the reduction in the gastroprotective action of ebrotidine caused by L-NAME, the lesion inhibition rate being 69%, while D-arginine was ineffective and the inhibition and the lesion size was only 14%. Our findings indicate that nitric oxide plays a crucial role in the gastroprotective activity of ebrotidine.

**879** Neural Mechanisms and Gastroduodenal Resistances to Saline Flow Activated by Acute Blood Volume Expansion in Anaesthetized Rats


Acute blood volume expansion increases the gastroduodenal resistance to the flow of saline in rats (Xavier-Neto, J. et al. Gut, 34, 235, 1990). In this study, we searched out the possible gastroduodenal site(s) of resistance and neural mechanisms involved on the phenomenon. Four gut circuits were prepared (gastroduodenal, gastric, pyloric and duodenum) and used under barostatically controlled pressure (4 cm H2O) on male Wistar rats (n = 64, 200–300 g.). Perfusion flow rates did not change in time control euvalomnic animals. Blood volume expansion (i.v. injection of male heparin, 1 ml/min up to a 5% of body weight) reduced perfusion rate in gastroduodenal (10.3 ± 0.5 to 7.6 ± 0.6 ml/min < p < 0.05), pyloric (9.0 ± 0.6 to 5.6 ± 1.2 ml/min < p < 0.05), duodenal (10.6 ± 0.4 to 8.0 ± 0.6 ml/min < p < 0.05), but not in gastric circuit (11.9 ± 0.4 to 10.4 ± 0.6 ml/min < p > 0.05). The threshold for blood volume expansion to gastroduodenal flow was 4% of b.w., 2% for duodenal and 3% for pyloric flow reduction. Mean arterial pressure was not modified, but central venous pressure levels increased (p < 0.05). Yohimbine (3 mg/kg) and prazosin (1 mg/kg) blocked expansion effect on the pyloric and duodenal circulations, but not in the pyloric circuit. Atropine (0.5 mg/kg), was ineffective. The results show that blood volume expansion increases gastroduodenal resistance(s) to the flow of liquid in rat; pylorus and duodenum are two important sites of resistance and yohimbine probably blocks neural blood volume expansion, but not atrpine. Coupled to decreased intestinal absorption and increased secretion rates (Dufty, et al. Gastroenterology, 75: 413–8, 1979), these modifications on gastroduodenal flow may work as a mechanism to warrant liquid volume homeostasis.

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**880** Diet-Induced Changes of Rat Gastric Muscle Responses to Acetylcholine, Carbenul and Cholecytokinin. An In Vitro Study

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The influence of long-term modifications (i.e. adaptation) of diet on gastrointestinal motility is not well known. In rats, preliminary studies from our laboratory indicated that gastric emptying is delayed after 3 weeks of feeding with low protein diet. We hypothesized that this adaptation could result from changes in the smooth muscle responses to neuromediators. Consequently, we evaluated the effects of acute administration of CCK-8 (CCK) or the cholecystokinin subtype B agonist (CCK-B) on fundic and antral contractions of rats chronically adapted to high and low protein diets.

Methods. Wistar rats (n = 36, final weight: 300–350 g) were adapted during 21 days to two isocaloric diets. A group was fed with a high protein diet (56%), and the other one with a low protein diet (9%). All the rats were compared with control rats fed with standard diet containing 18% of protein (n = 12). Contracture of antrum and fundus from longitudinal muscle strips was performed in Krebs solution, by recording, for acid transducer in response to different doses of Ach (10−6 to 10−3 mol/L), carbenul (10−11 to 3.7 × 10−6 mol/L) and CCK (10−8 to 10−6 mol/L). Results were expressed as means ± SEM and compared to control by unpaired Student’s t-test.
Adaptive Cytoprotection and Adaptation to Topical Ammonia in Rat Stomach


Ammonia (NH₄OH) has been proposed to play a major role in the pathogenesis of the Helicobacter pylori (Hp)-associated gastric damage but the mechanism of this damage has not been fully explained. This study was designed to examine possible adaptive cytoprotection and the adaptation of rat gastric mucosa to the irritant action of ammonia (NH₄OH). Single application of ammonia alone in various concentrations (15–500 mM) caused a concentration-dependent mucosal damage starting at 30 mM and reaching a maximum at 250 mM, similar to that obtained with 100% ethanol and that was accompanied by the fall in the gastric blood flow (GBF) to about 30% of the normal value. When the mucosa was exposed first to the low, non-damaging concentration (15 mM) of NH₄OH and then insulted with 100% ethanol, the extent of ethanol damage was significantly attenuated as compared to that caused by ethanol alone. This "adaptive" cytoprotection was accompanied by the rise in the GBF and reperfusion, in part, by the pretreatment with indomethacin, an inhibitor of PG-cyclooxygenase, with L-NAME, a blocker of NO-synthesis or with capsaicin (selecting sensory nerves).

Damage concentrating of NH₄OH (125 mM) caused a widespread mucosal damage after first application but with repeated insults of 125 mM NH₄OH, a gradual reduction in the mucosal lesions accompanied by an enhanced mucosal cell proliferation and overexpression of epidermal growth factor (EGF) (using immunohistochemistry) and EGFmRNA (using RT-PCR) were noticed.

We conclude that: 1) NH₄OH alone damages gastric mucosa only at concentrations exceeding that found in Hp-infected stomach, while at lower concentration acts as "mild" irritant to induce adaptive cytoprotection, 2) this adaptive cytoprotection appears to be mediated, in part, by endogenous PG, sensory nerves and arginine-NO dependent pathway, and 3) repeated applications of NH₄OH induce gastric adaptation probably mediated by enhanced expression of EGF and its receptors and by an increased mucosal cell proliferation.

881 Adaptive Cytoprotection and Adaptation to Topical Ammonia in Rat Stomach

882 Tumour Necrosis Factor (TNF) Induces Expression of the Transcription Factor Nuclear Factor-B (NFkB) in a Human Gastric Epithelial Cell Line

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The transcription factor, NFkB, plays a major role in the regulation of inflammatory events such as secretion of cytokines, expression of adhesion molecules and potential cell proliferation. Regulation of expression of this transcription factor appears to occur through tissue-specific mechanisms. In these experiments, we have examined regulation of NFkB by tumour necrosis factor in the human gastric epithelial cell line, AGS, using an electrophoretic mobility shift assay. TNF produced detectable induction of NFkB in AGS cells at a dose of 10 ng/ml. This effect was maximal at 100 ng/ml. Time-course experiments revealed that the effect was maximal at 4 hrs with subsequent reduction at 24 hrs. The protein kinase C activation PMA produced low-level induction of NFkB. Lastly, hydrogen peroxide, a product of the acute inflammatory response did not produce NFkB induction.

These findings indicate that TNF can regulate induction of the transcription factor, NFkB, in gastric epithelial cells. As high levels of TNF are produced by macrophages in response to H pylori infection, this may represent a mechanism whereby the gastric immune response to H pylori may modulate cell function.

883 Overproduction of NO Retards Wound Healing by Inhibiting Cell Proliferation in a Cultured Rabbit Gastric Epithelial Cell Model

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Despite the wide knowledge of different physiological effects of NO in gastrointestinal tract, there are no reports on its direct effects in gastric epithelial cells.

This study investigates the role of NO in wound repair on a gastric epithelial cell monolayer culture. Methods: Isolated rabbit gastric epithelial cells (95% surface mucous cells) were cultured in F-12 round-shaped medium, forming a complete polarized monolayer cell sheet in 48 h. A round-shaped wound was created by mechanical denudation using rotating silicon tip. The restoration process was monitored by measuring and photographing the wound size every 12 h up to 72 h. The proliferative cells were detected by serial staining for BrdU. NO donor, sodium nitroprusside (SNP) (10⁻⁴, 3 x 10⁻⁴, 10⁻⁵ M) and NO-synthase inhibitor, N-nitro-L-arginine methyl ester (NAME) (10⁻⁴ x 10⁻¹, 10⁻⁴) were added to the serum-free media at the time of wounding.

Results: Quantitative analysis of wound repair is shown in the table (mm², mean ± SD, n = 5, * p < 0.01 compared to controls); SNP inhibited wound repair in a dose dependent manner. In controls, BrdU positive cells were detected mainly at 36 h after wounding. SNP inhibited this proliferation almost totally (BrdU-labeling index 1.5 vs. 0.02%, respectively, p < 0.01). This inhibition was partially reversed, if SNP was removed from the culture 24 h after wounding. Inhibition of endogenous NO synthesis by L-NAME had no significant effect. Conclusion: The data indicate that NO has no influence on the primary cell migration during wound restoration, but excess of NO retards wound healing by inhibiting cell proliferation.

884 The Behaviour of Bcl-2 Protein during Progression of Gastric Carcinoma

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The bcl-2 protooncogene, located on chromosome 18, codes for a 26 Kd protein involved in inhibiting programmed cell death (apoptosis). The role of this protein in human cancer progression remains to be defined.

The objective of the present study was to investigate the behaviour of bcl-2 protein during progression of gastric cancer.

Immunohistochemical staining for bcl-2 protein was performed in primary gastric carcinomas of different tumour stage, from early to advanced disease (n = 62), coexisting metastases (n = 57) and in a series obtained from recurrent tumours that had progressed to more advanced stages in the following 48–60 months (n = 5). The monoclonal bcl-2 antibody and paraffin material were used.

21% of gastric tumours showed positive bcl-2 staining with protein occurred already in early cancer. In most patients there was coordinate expression of bcl-2 in primary carcinomas, coexisting metastases and recurrent tumours. However, in 2 patients bcl-2 protein was subsequently detected in regional lymph node metastases.

The results suggest that the bcl-2 expression is an additional factor in the cascade of molecular alterations seen in gastric cancer and might contribute in some cases to the tumour promotion and in others to tumour progression.

885 Inhibition of Migration and Proliferation by 5-Fu, CDDP and Cepharanthin Using Cultured Human Gastric Cancer Cell Line


The mechanism of cancer cell metastasis involves cell migration which might be modulated by cytoketones, extracellular matrix and growth factors. However, the detail mechanism of metastasis is still unclear. We recently established a new, simple and convenient model to investigate the mechanism of metastasis in vitro using cultured human gastric cancer cell line, and also analysed directly the role of cytoketone. Using this model, we assessed the migration capacity of gastric cancer cell line (undifferentiated adenocarcinoma AGS, differentiated adenocarcinoma MNK28), and also assessed the inhibition of migration and proliferation by 5-Fu, CDDP and cepharanthin (CE). Methods: Human gastric cancer cell strain, AGS, MNK28 cells (3.5 x 10⁶ cells) were inoculated into the wound (1.5 x 10⁶ cells) in a plastic culture dish and cultured in each F12, RPMI 1640 medium with 10% FBS. Incubated cells formed round shaped cell sheet in 3 h and subsequently silicon fence was removed and the cancer cell migration was monitored under phase contrast microscope. The number of migrated cells in a unit area of free space was counted after 48 h. Antineoplastic agents 5-Fu, CDDP, and cepharanthin as alkaldoids, were added to the medium (1 to 10 μM) to investigate functional and morphological changes of the cells. The cell proliferation were detected by BrdU staining. Result: The number of cancer cells from the edge of the cell sheet at 48 h after the start of experiment was presented in a table.
tissue significantly through AGS, 5-FU10.gM and CDDP, CE10 ,uM 59 ± 34.6** MKN28.

cell expression penetration by node metastasis, Data: Fushida, S. Institute, Detroit, MI, K. Miwa, of School Materials and paraffin-embedded specimens was observed and demonstrated that increased expression of gp78-AMF receptor was performed in formalin-fixed, embedded tissue sections from 221 primary gastric cancers, which were diagnosed and treated at the Department of Surgery II, Kanazawa University, during 1986 to 1991. Immunohistochemical study was performed with the labelled streptavidin biotin method.

Results: One hundred twenty five out of 221 tumors (56.6%) expressed the AMF receptor gp78. There was not a significant association between gp78 expression and histological type or liver metastasis. Expression of gp78 was associated with macroscopic type, lymphatic invasion, venous invasion, lymph node metastasis, and peritoneal metastasis. In addition, positive rate of gp78 expression significantly raised according to increased grade of tumor penetration and pathological stage. Patients with gp78 expression had a significantly poor prognosis than those without gp78 expression in primary gastric cancer (p < 0.001). To be confined to stage I and II, only gp78 expression had a significant relationship to survival (p < 0.05).

Conclusion: The immunohistochemical study of gp78 expression is correlated with tumor invasion, metastasis, and poor prognosis in primary gastric cancer. This result indicates that AMF receptor plays an important role in progression of human gastric cancer.

Expression of bcl-2 Protein in Gastric Cancer and Its Relationship to Prognosis
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Introduction: The function of bcl-2 is known to prolong cell survival by preventing the onset of programmed cell death or apoptosis. Overexpression of bcl-2 gene has been found in variety of human malignancies. Here we examined the association of bcl-2 status and prognosis parameters in gastric cancer.

Materials and Methods: A total of 118 primary gastric cancer specimens embedded in paraffin were used in the present study. Using an anti bcl-2 monoclonal antibody we analyzed immunohistochemically its expression. Reactivity was detected in 21 cases (18%) and its tissue status was closely associated with tumor size and peritoneal dissemination. In addition, a positive bcl-2 immunoreaction was found to be significantly associated with shorter overall survival. Especially, in the group of patients without lymph node and liver metastasis, the prognosis of patients with bcl-2 positive tumors was significantly poorer than that of patients with bcl-2 negative tumors (p < 0.001).

Conclusion: These results suggest that immunohistochemical staining for bcl-2 may be useful in evaluating metastatic potential and prognosis in gastric cancer.

Open Access 13C-Urea Breath Tests (OAT3C-UBT): Comparisons with and Impact on Open Access Endoscopy

Introduction: We have recently introduced an OAT3C-UBT service to GPs. Patients < 40 years with dyspepsia were eligible and were given a 13C-UBT at the LGI. H pylori positive patients are given eradication therapy and a repeat 13C-UBT 2 months later. H pylori negative patients are referred back to their GP. We assessed patient satisfaction with this and its impact
on referral to open access endoscopy (OAE). Methods: Patients completed an anonymous questionnaire grading their satisfaction with the service on a 5 point Likert scale. Referral patterns to the OAIC-U and OAE services in patients < 40 years were evaluated retrospectively. Results: 251 patients < 40 years had attended the OAIC-U service; 88/251 (35%) were H pylori positive; patients attending the OAIC-U service were similar to those attending for OAE in terms of gender, smoking history and alcohol intake but had more severe dyspepsia scores (15.8 7.6 vs. 12.6 6.7 p < 0.001). 145 intestinal types of gastric cancer (ICGIC) was stated as the service was very good, 10% good and 3% found the service satisfactory. In Aug-94 to Apr-95 32/926 OAE were performed in patients < 40 years old. In Aug-95 to Apr-96 (after the introduction of the OAIC-U) this fell to 237/945. More OAE were performed (86% Cl = 30–39% reduction: p < 0.001) in endoscopies in patients < 40 years old. Only 6 patients referred for an OAIC-U have subsequently been referred for endoscopy (all H pylori negative). Conclusions: Patients are satisfied with the OAIC-U service and it has reduced endoscopy referral.

909 Overexpression of Mutant p53 and c-erbB-2 Proteins and Mutations of P15 and P16 Genes in Human Gastric Carcinoma: With Respect to Histologic Subtypes and Stages

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We investigate whether the genetic alteration of several oncogenes and tumor suppressor genes could be correlated with the two histologic subtype, the diffuse type of gastric carcinoma (GC).

In 60 patients with GC, the overexpression of mutant p53 and c-erbB-2 oncoproteins was studied using immunohistochromic stains. Mutations of p15 and p16 tumor suppressor genes were assessed by polymerase chain reaction, Southern blotting, and direct DNA sequencing.

Overexpression of c-erbB-2 and p53 was found in 21 (35.0%) and 27 (45.0%) patients, respectively. Overexpression of the c-erbB-2 oncoprotein was more common in the intestinal type (15/32) and the advanced stage (19/43) of GC. Similarly, p53 overexpression was more frequently found in the intestinal type (19/32) and the advanced stage (24/43) of GC. Homozygous deletions of p16 in exon 1 were found in 6 patients. Neither point mutations of p16 nor alterations of p15 were detected. The frequency of alterations of p53, c-erbB-2, and p16 was not related to sex and H. pylori infection. No correlation of genetic changes between any two genes was observed.

Alterations of p15 and p16 genes play a limited role in GC. Overexpression of c-erbB-2 and p53 is frequently encountered in the intestinal type advanced GC. The association between genetic alterations and histologic subtypes supports the notion that a distinct pathogenesis exists in different histologic subtypes.

910 Simultaneous Expression of Hepatocyte Growth Factor Receptor (C-MET), Autocrine Motility Factor Receptor (AMFR) and Urokinase-Type Plasminogen Activator (UPAR) in Gastric Adenocarcinoma. Especially in Borrmann 4 Type Carcinoma

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Background: The hepatocyte growth factor receptor (c-MET), autocrine motility factor receptor (AMFR) and urokinase-type plasminogen activator receptor (UPAR) are known to play an important role in tumor cell migration, invasion and metastasis. We have studied simultaneous overexpression of these genes in human gastric carcinoma.

Methods: we examined immunohistochemically the relationship between tissue status of c-MET, AMFR and UPAR and clinicopathological parameters of 103 gastric carcinomas using reacted primary tumor embedded in paraffin.

Results: Among 103 cases, 44 (46%) cases showed overexpression of c-MET, AMFR and UPAR immunoreactivity was observed in 38 (37%) and 46 (47%) cases. Carcinomas were classified according to Borrmann classification. The all three receptors were expressed in 23 (23%) cases of Borrmann 1, 12 (12%) of Borrmann 2, 26 (26%) of Borrmann 3, and 4 (4%) of Borrmann 4 cases. The incidence of overexpression of UPAR was significantly higher than other clinicopathological type (p < 0.01). The incidence of overexpression of two genes was also closely associated with lymph node metastasis and peritoneal dissemination. In addition, the overexpression of three or two genes were relevant to lymphatic invasion.

Conclusion: These results suggest that simultaneous overexpression of c-MET, AMFR and UPAR may be correlated with the progression and invasion of gastric carcinoma, especially biological nature of Borrmann 4 type carcinoma.

911 Immunohistochemical Investigation of Staining Development and Staining Intensity of sIa1-Tn Antigen in Human Gastric Cancer

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A cell surface sugar chain antigen, sIa1-Tn (STN), in gastric cancer lesions was immunohistochemically stained for measurement of staining development (positive area) and staining intensity (positive stain), to investigate its relationships to clinicopathological factors and assess its clinical significance as a tumor-related antigen. Materials and methods We studied 200 gastric cancer lesions, resected surgically in our department with preoperative STN data available. This set included 230 primary-embarrassed lesions fixed in 10% buffered formalin were immunohistochemically stained according to the streptavidin-biotin (SAB) method. The biological examination was measured in Otsuka Assay Laboratory by RIA. Positive areas and positive stains developed after immunohistochemical staining of STN were analyzed with a BECTON-DICKINSON CAS-200 image cytometer. Results Intestinal metaplasia in the non-carcinomatous gastric mucosa was positive in immunostaining for STN, while normal gastric mucosa was not stained at all. STN staining was predominantly apical or intracellular, with the cell surface facing the gland cavity and the extracellularly secreted substance stained. We also observed staining development of cytoplasmatic type with additional staining in the cytoplasm. The incidence of STN-staining-positive regions was significantly higher in well differentiated tumors, which was also the case with positive area and positive stain. Both positive area and positive stain increased significantly with increased degree of the depth of invasion and stage progression. These values increased in cases with liver, peritoneal invasion and lymph node metastasis. They also correlated well with serum STN. Conclusion We conclude that the positive area and positive stain for STN antigen in the gastric cancer tissue are closely correlated with clinicopathological factors and reflect the degree of clinical progression, suggestive of its clinical significance as a tumor-related antigen.

912 Cell Proliferation, Oncoprotein Expression (p53, c-erbB B-2, bcr2) and c-ki-ras Mutation in Juvenile Polyposis with Adenoma and Carcinoma of the Stomach

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Aims: Juvenile polyposis is recently being associated with malignancies. To clarify its neoplastic potential, we analyzed cell proliferation and oncogenetic abnormalities in three cases of juvenile polyposis limited to the stomach (JPs) including coexisting adenoma and adenocarcinoma.

Methods: A total of 155 slides of polyp, papillary adenoma (Pap-ad), papillary adenocarcinoma (Pap-ca) and signet ring cell carcinoma (Sig) in JPs were selected for Ki67 staining. For correlation study, the DNA ploidy pattern, cell surface polyoma (HP), tubular adenoma (TA), well differentiated adenocarcinoma (W-ca) and Sig were also analyzed. Immunohistochemistry for oncoproteins and DNA direct sequencing for c-ki-ras mutation were examined for tumors in JPs. Results: The KI67 labeling index (LI) for both HP, W-ca and Sig were lower than that for conventional TA, W-ca and Sig, respectively. PS3 was focally expressed in both Pap-ad and Pap-ca in JPs, bcr2 and c-ki-ras 2 expression, and c-ki-ras mutation were not detected in all tumors in JPs. Conclusions: Cell proliferation of polyps and tumors in JPs were lower than that of non-neoplastic diseases and conventional tumors, respectively. Oncogenetic alterations were not clearly demonstrated.

913 Flow Cytometric DNA Analysis, Clinicopathological Study and Prognostic Factors of MP Gastric Cancer (Multivariate Regression Analysis by Cox’s Proportional Hazards Model)

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Objectives: To study the relation between DNA ploidy patterns and prognosis as well as the involvement of other clinicopathological factors in patients undergoing resection of mp gastric carcinomas, analyzed by flow cytometry (FCM).

Subjects and methods: Seventy-two patients with mp gastric carcinomas who underwent resection at the Kitasato Department of Surgery between April 1980 and August 1988 were studied. Tumor specimens obtained at the time of surgery were embedded in paraffin, and DNA ploidy patterns were studied by FCM. In addition, clinicopathological factors were studied by a multivariate analysis to identify one or more significant variables.

Results: In univariate analysis (log rank and generalized Wilcoxon test) significant differences (p < 0.05) were obtained for four factors: ploidy pattern, tumor location, macroscopic type of primary tumor, and number of lymph node metastasis. A multivariate analysis using a Cox’s proportional hazards model identified only two factors, ploidy pattern and tumor location (in this order), as significant predictors of prognostic (p < 0.05).
Conclusion: We concluded that DNA ploidy pattern may be a very useful predictor of prognosis.

**1914 Blood Flow and Blood Flow Pattern Alteration in Adenocarcinoma of the Gastric-Pyloric Junction**  

Most fast growing malignant tumors maintain a sufficient nutrient supply by vascular proliferation. We recently demonstrated that blood flow in tumor bearing areas of gastric tumors coincides with an increased expression of CD31, a marker for neoangiogenetic endothelial cells. In this study we analyze blood flow (BF) and blood flow pattern in the gastric wall of patients with proximal gastric adenocarcinomas by laser doppler flowmetry (LDF). Methods: In 6 subsequent patients undergoing gastric and/or esophageal resection for adenocarcinoma of the gastroesophageal junction tumors blood flow assessed by LDF in normal as well as tumor bearing areas of the gastric wall. Blood flow was recorded for at least 30 seconds after a stable signal was obtained. Post sampling data processing included calculation of systolic and mean blood flow and pulse area analysis with integral under the curve calculations. Results: Blood flow in perfusion units

<table>
<thead>
<tr>
<th>Normal</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>183.2 (70.4)</td>
</tr>
<tr>
<td>Systolic</td>
<td>220 (66.0)</td>
</tr>
<tr>
<td>Integral</td>
<td>101 (19.0)</td>
</tr>
<tr>
<td>Pulsatile index</td>
<td>13.6 (2.5)</td>
</tr>
</tbody>
</table>

PU vs SE; *p < 0.05, **p = 0.01, ***p = 0.001 vs normal

Discussion: Adenocarcinomas of the gastroesophageal junction have and over twofold increase of tumor BF as indicated by an increase in mean and systolic blood flow on laser Doppler sonography. Not only was the total blood flow increase but also the flow curve pattern altered indicating an altered vascular reactivity of tumor microvessels as compared to normal gastric vessels.

**1915 Molecular Mechanisms of the Formation of Peritoneal Dissemination from Gastric Cancer**  
Y. Yonemura, K. Taniguchi, T. Kawamura, N. Nojima, T. Fujimura, I. Miyazaki, Y. Endo, T. Sasaki. Surgery II, School of Medicine, Kanazawa University, Kanazawa, Japan

Purpose: A new animal model by the i.p. inoculation of highly metastatic gastric cancer cell line MKN-45-P was developed, and the specific genes having a great role in the formation of peritoneal dissemination was identified.

Methods: MKN-45-P was established from a gastric cancer cell line of MKN-45 by the progressive growing of the intraperitoneal passages. By a specific detection method of metastasized human tumor cells in nude mice using PCR, a human β-globin-related sequence in the DNA from various parts of the peritoneum was specifically amplified and detected by gel electrophoresis by and a specific nucleotide probe. A novel ex vivo co-culture system using human gastric mucosa was developed. The differences of the expressions of metastasis related genes (MMP-2/9, uPA, uPAR, AMFR, met, erb-2, CD-44, Integrin subunits) between MKN-45 and MKN-45-P were examined by RT-PCR.

Results: Greater omentum showed a strong signal of human β-globin gene from the 1st day and the signals gradually increased. The signals in the gonadal fat, mesentery and ovariary could be weakly detected on the 1st day, transiently decreased on the 3rd day, and then increased from 7th day. In the diaphragm, and abdominal wall, signals could be detected from the 7th day. In contrast, small intestine and colon did not show any human β-globin signal. MKN-45-P cells were found to adhere on the naked areas of the submesothelial connective tissue. In ex vivo culture system, cancer cells adhered only to the naked area of the submesothelial basement membrane. The expressions of integrin α2 and α3 subunits in MKN-45-P were extremely elevated than those in MKN-45. Integrin β1 subunit expression did not change during the intraperitoneal passages. Anti-β1 integrin subunit antibody significantly inhibited the adherent number of MKN-45-P on the omentum. Other metastasis associated genes were not overexpressed in MKN-45-P. From these results, we conclude that the major metastatic route of the peritoneum may be through milky spots and by adhesion to the naked connective tissue exposed after shrinkage of the mesothelial cells. In this process, VLA 2 and VLA 3 have a great role in the formation of the peritoneal dissemination from gastric cancer.

**1916 The Change and Reflection of Curative Operation for Gastric Cancer Patients in every Decade**  
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Aim: The operative curative cases for gastric cancer patients past 34 years were divided into three groups by every decade. The clinical characteristics and the results of each group was retrospectively analyzed. We also examined whether extension of gastric cancer surgery could improve its prognosis.

Patients and method: The 1238 patients with primary gastric cancer except resection or multiple cancer were divided into the following three groups: the former era: 367 patients from April, 1961 to December, 1974 (the former); the mid era: 377 patients from January, 1975 to December, 1984 (the mid); the late era: 494 patients from January, 1985 to December, 1994 (the late). In the group of stage I or II, we focused on the following factors: curative or non-curative, relative curative or absolute curative resection. The Kaplan-Meyer method was used for calculation of the postoperative survival rate, and the Chi-square test and generalized Wilcoxon test were used to determine the statistical significance of differences.

Result: The change of each era in stage and curvature was that the rate of stage I and absolute curative resection increased, however, that of stage III or IV and relative non-curative resection was decrement. Ten (or five) year survival rate of the late era was better than in the former era. There was no significant difference between 'the late' and 'the mid' in 76.5 (78.6). although that of 'the former' was significantly low in 44.2 (65.5). When 10 (5) year survival rate by grade or number of lymph node metastasis was examined, there was a significant better prognosis in patients with n1 group than with n2 group of node metastasis (n0 and the n2 group positive between in 'the former' and in 'the mid' or 'the late' (p = 0.02). It means that in stage III there was a significant difference between them. There was no difference in survival time by the number of lymph node metastasis between 'the mid' and 'the late'. In the group of n0 lymphnode metastasis and of 4 to 9 lymph node metastasis positive, the survival rate in 'the former' was significantly worse than that in 'the mid' (p < 0.001) or that in 'the late' (p = 0.03). In the group of 10 lymphnode metastasis positive higher than 10, there was no significant difference between both eras.

Conclusion: There was a marked prolongation of the survival time in the curative surgery with R2-dissection after the 'mid' in comparison with R1 lymph node dissection in the former era. However, the gastric cancer patients in early stage has been relatively increasing. R3-dissection for the advanced gastric cancer patients was introduced into the operation after 1985 aiming at better prognosis in the curative surgery, however, there was no significant improvement of prognosis. Lymphnode metastasis of 10 or more was as the standard curative surgery for the gastric cancer patients prolonged the survival time rather than R1 level. Furthermore the curative operation for lymph node metastasis with n0 or at most 4 to 9 was in good prognosis.

**1917 Re-evaluation of Surgical Therapy for the Primary Gastric Malignant Lymphoma Patients**  
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Introduction and aim Gastric malignant lymphoma (ML) is different from the lesion of lymphomas origin and generally localized close to the primary lesion. Recently there are increasing more reports that even chemotherapy could cure gastric ML patients in early stage. The surgical treatment was a controversial, evaluated on the basis of prognosis and clinicopathologic findings of gastric ML removed surgically. The clinicopathological findings of ML depends on the Japanese general rules for the gastric malignancies.

Patients and results The 48 primary gastric ML patients by the end of 1995 from 1975 were analyzed. The ratio occurred in gastric malignancy of primary malignant lymphomas was 1.5%. Ten cases were histologically diagnosed as MALT lymphomas, however, 19 cases were available for the study (lymphoid hyperplasia). The ratio of sex was almost equal with 25 (M) to 23 (F). Mean age is 59-year-old. The survival time of giant rugae type, superficial type and protruded type were 100%, however, that of Bormann 2 type 82.5% and Bormann 3 type 44.4%. Significant difference was seen in the survival rate by macroscopic type. The correlation between lymph node metastases and prognosis was examined. Twenty one cases were alive in 24 cases with n0, and, three cases were dead and 8 alive in 11 cases with lymphnode metastases more than n2-group. But 3 cases were dead in 7 cases with n1-group positive. The 5 year survival rate was 90.9% in n0 group, 76.9% in the cases more than n2-group positive, however 64.3% in n1 group positive. The prognosis of resected ML was better than that of operated gastric cancer patients, but there was no correlation in the lymphnode metastasis. Histopathology of 29 cases was diffuse type and that of 5 follicular type. The six cases with diffuse large cell type were dead in 16. All of MALT lymphoma patients was alive, so this disease was in good prognosis and may present macroscopic superficial type. The 5 year survival rate of follicular type and MALT lymphoma was 100%, and that of diffuse type was 74.7. There were no dead cases with stage I and III. There were five patients dead in 9 cases with stage II, 4 dead in 5 with stage IV. The 5 year survival rate in stage I and III was 100%, and in stage II 66.7% in stage II and 33.3% in stage IV, but wasn’t correlated. When 5 year survival rate in surgical curvature according to the general rules of the gastric cancer study was examined, the ratio in curability C was 42.5%, 81.5% in B and 86.9% in A. Each survival curve by the curability was significantly graded.

Conclusion The overall 5 year survival rate of resected gastric ML was 76%. Operative curability and shallow invasion of ML to upper proper muscle (mp) were the deciding factors to regulate patients characters and 5 year survival rate. It is an important factors predicting prognosis. The patients in low grade ML such as follicular type or MALT lymphoma after operation was all alive in extremely good prognosis. As for MALT lymphoma and ML in early stage such as I or II of the Japanese classification for gastric cancer, surgical treatment should be first performed.
cancer and VN staining was performed, in 1 of 11 (9.1%) in invasive (-) group and 22 of 51 (43.1%) cases in invasive (+) group. VN positivity was significantly high in the cases with venous invasion. TN staining was observed in the cytoplasm of cancer cells. In differentiated type, the cytoplasmic positive staining was observed in 23 (73.9%) cases, while in undifferentiated type, positive staining was observed in only 12 of 33 (36.4%) cases. TN positivity was significantly high in the cases of differentiated type. Conclusion: This result suggested that positivity of LN and TN were related with histological differentiation of gastric cancer and VN staining was related with venous invasion.

921 Adenoseine Deaminase Activity in Patients with the Intestinal Type of Gastric Carcinoma
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Our previous study has shown that adenoseine deaminase activity is lower in the intestinal than diffuse type of gastric carcinoma (Cancer Lett, 1994). The proposed explanation for this was the stage tumor growth.

The aim of the present study was to analyse only those patients who had recognized the intestinal type of gastric carcinoma either in the non-operated or partially resected stomach.

46 objects were included in the study; 26 partially gastrectomized and 14 non-operated. Adenoseine deaminase activity was determined in the gastric cancer and surrounding unchanged gastric mucosa by means of ammonia liberated from the substrate during 10-min incubation.

We have found that the enzyme activity in the advanced gastric cancer (asites, metastases) of non-operated stomach as well as that developed in partially resected stomach due to duodenal ulcer was significantly lower than in recurrent cancer of the gastric remnant (no ascites and metastases) (36 ± 18.0 and 20.9 ± 17.5 vs. 75.8 ± 8.0 mmol NH₃/mg of protein/min, p < 0.05).

The other factors than histological type of the tumor are also involved in the regulation of adenoseine deaminase activity in the gastric cancer and surrounding unchanged gastric mucosa; one of them may be cancer progression.

922 Early Gastric Cancer: Relapse and Prognostic Outcome

Background: Patients with Early Gastric Cancer (EGC) are known to have a good prognosis with a low rate of relapse at five years. Aims: To prospectively evaluate prognostic variables in a group of patients in whom curative surgery was performed for EGC between 1983–1995. Patients and methods: 90 patients, 48 male and 42 female with a mean age of 58.3 ± 13.1 years were included in the present study. The staging (UICC) was based on the histopathological features of the tumor as well as survival curves and percentage of relapses. Results: From a histopathologic point of view, 58 patients (64.4%) had an adenocarcinoma and 32 of them (35.6%) presented as signet ring cell carcinoma. TNM staging (UICC) in the same patients was the following: T1N0M0 – 78 (86.7%), T1N1M0 – 10 (11.1%), T2N0M0 – 2 (2.2%). According to the Japanese classification 13 (14.4%) tumors were type I, 8 (8.9%) type IIa, 15 (17.7%) type IIb, 28 (31.1%) type IIIa, 16 (17.8%) type IIIb and 14 (15.6%) type IV. During a follow-up period of 52.6 + 42.9 months (1–154), 5 patients relapsed, two of them earlier than 6 months and the remaining three at 30, 43 and 59 months after surgery, respectively. Only one of these patients was re-operated. There were 18 deaths – 5 relapses, 4 peri-operative deaths and 9 patients for others causes. Rate of relapse (5.5%) was not related to histologic features although they were all NO (TNM). Nonetheless, all these relapses occurred in patients who were operated before 1988 when an extended lymphadenectomy was not routinely performed. In all these patients the number of resected lymph nodes was lower than 5. No metastasous tumors were observed. Conclusion: It is possible that limited lymph node resection performed in the eighties was the main responsible for relapses observed in the present series. Therapeutic possibilities of the relapses are limited and therefore, intensive surveillance is probably not advised.

923 Cag A Protein Seropositivity in Random Population and in Gastric Cancer Patients
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Purpose: To evaluate the presence of antibodies to CagA protein associated with the risk of developing gastric cancer (GC) in Estonian adult population with high prevalence (87%) of H. pylori (HP) infection and to compare it with presence of antibodies to CagA in GC patients.

Subjects and Methods: 196 subjects (86 M, 113 F, median age 41) as a representative sample of adult population (1461 persons) from the South
Estonian town of Karksi-Nuia and 45 patients (22 M, 23 F, median age 67) with gastric adenocarcinoma. (14 in antrum, 17 in corpus or cardia, 14 in antrum & corpus; types: 17 intestinal, 8 diffuse, 20 indeterminate) operated at the Oncological Clinic in Tartu were studied. HP status was determined using serological evaluation of IgG antibodies to glycan extracted proteins of HP (NCCT/11637) as previously (Eir, J. Gastroenterol & Hepatol. 1994, 6, 529–533). Anti-CagA IgG were determined by ELISA using a recombinant fragment of CagA antigen of HP CCUG strain (1.25 μg/ml). The absorbance value 0.300 OD of CagA fragment serum was taken as a cut-off level based on a study in 25 HP negatives (10% histology, serology).

Results. IgG antibodies to HP strain NCTC 11637 were revealed in 169/199 (85%) of the population, and in 41/45 (91%) of GC patients (p = 0.05). Anti-CagA IgG were seen in 126/199 (63%) of the population sample (in 120/199 of HP positive persons). In GC patients the prevalence of anti-CagA IgG was significantly higher, 39/45 (87%), than in the whole population (p = 0.002) in all age groups except 20–29 year old (76%; p = 0.25).

Conclusions. Seropositivity to HP strain NCTC 11637 was similarly high in Estonian adult population and in GC patients. The prevalence of anti-CagA IgG was significantly higher in GC patients than in the population studied. In population, persons aged 20–29 with the highest prevalence of anti-CagA IgG should be given further attention with respect to cancer development.

**Gastro-Intestinal Sarcomas: Prognostic Significance of the F.N.L.C.C. Histological Grading**


The FNCLCC (Fédération Nationale des centres de Lutte contre le Cancer) histological grading system has a well established prognostic significance which is used on smooth tissue sarcomas. Gastrestinal (GI) sarcomas are rare and of uncertain behaviour. Mietosis count is the only method for pathologists to evaluate the prognosis of such tumours.

The purpose of this work was to evaluate the FNCLCC grading system on a retrospective series of 19 GI sarcomas treated at the IGR Institute. There were 10 women and 9 men (mean age 51 years). The tumour was located in the stomach in 10 cases, in the small intestine in 8 cases and in the anal canal in 1 case. The treatment consisted of surgical removal of the tumour followed in 5 cases by radio or chemotherapy. Histologically, all cases were leiomyosarcomas. The average survival rate was 23 months, with a 5 year survival rate for 22%. All cases were reviewed by two pathologists and the 3 items of the FNCLCC grading system (differentiation, mitosis count, necrosis) were noted in each case.

The results show: the FNCLCC grading system has a significant prognostic value (p = 0.03) as well as the differentiation item and as the mitosis count item. The necrosis item has no significant value.

In conclusion, this preliminary study seems to demonstrate that: (1) the FNCLCC grading system is applicable to GI sarcomas, and (2) a new grading system with only two items (differentiation & mitosis count) could be used on such tumours.

**Gastric Smooth Muscle Tumours (SMT): Long Term Results of Surgery in 52 Patients.**

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SMT of the digestive tract are of 3 types: leiomyoma (LM), leiomyosarcoma (LMS) and leiomyoblastoma (LMB). They are characterized by their rarity, a difficult diagnosis, and a high incidence of recurrence, in the extreme extent of resection and the efficacy of chemo- and radiotherapy. We report here about the features and the results of surgery in a series of 52 gastric SMT.

From 1981 to 1996, among 105 mesenchymal tumours of the digestive tract operated on in two institutions, 83 (79%) were SMT. Of those, 52 (63%) were gastric and were divided in 14 LM, 26 LMS and 12 LMB.

There were 32 males and 20 females, 26 to 85 yr old (mean: 55). The mean delay between the first symptom and the diagnosis was 8 mos (0–60). The most frequent symptoms were: bleeding (41%), palpable mass (41%) and pain (38%), whereas 6 patients (pts) (12%) had no symptoms. The most frequent endoscopic findings were ulcerated (45%) and submucosal tumour (33%). The tumour could be demonstrated by ultrasound and CAT-scan of the abdomen in 27/30 and 22/22 cases, respectively. Its gastric origin was seen in 5 and 8 cases, respectively. Preoperative biopsies (n = 26) were contributive in 11 cases (42%). The mean size of the tumour was 11 cm (1–30) and was larger for LMS. The site of the tumour compared to the angulus did not differ between 3 types. In LMS, contiguous tumour spread of LMS was present in 12 pts (46%), and liver metastases and peritoneal carcinomatosis in 5 pts each. Lymp node metastases were not observed. Complete resection (elective: 45; urgent: 7) with curative intent was achieved in 44 pts (including 18 LMS). Sixteen of 17 gastrectomies were done for LMS. Extended resections for contiguous spread were done in 14 LMS pts. One patient had only exploration. After pathological examination of surgical specimens, there were: 16LM, 12LMB, and 24LMS divided in 24 malignant, 24 benign, and 4 intermediate prognosis SMT. Operative mortality was nil and the morbidity rate was 6%. One patient (LMS) was lost to follow-up. During a median follow-up of 6.2 years (n = 51), 11 cancer deaths (2LMS, 9LMB) were observed. All LMS patients died of their disease, whereas LMB patients survived. The mean survival after palliative resection of LMS was 55%, and 43% with a mean survival time of 38 mos. In 3 pts, despite an initial diagnosis of benign SMT, the appearance of distant metastases after 22, 24, and 101 mos switched the diagnosis to malignancy.

A prolonged follow-up is needed in cases of non resectable of so-called benign SMT since the outcome may contradict the initial diagnosis. The type of gastrectomy is to be adapted to the size and the site of the lesion. Extensive lymphadenectomy is not mandatory due to scarcity of nodal invasion. Resections extended to adjacent organs or of metastases with curative intent are worthwhile since no other efficient treatment is available.

**Surgical Treatment of Duodenal Adenomas in Familial Adenomatous Polyposis**


In familial adenomatous polyposis (FAP) duodenal adenomas are found in 80% of patients and duodenal cancer accounts for the majority of colorectal-related deaths after colectomy. Duodenal adenomas do not ameliorate (p > 0.05) or conventional endoscopic treatment. In case of multiple, large, villous and severely dysplastic adenomas (stage IV disease), prophylactic measures to prevent malignant change may become necessary.

The aim of this work was to assess the results of surgical treatment of stage IV duodenal polyposis in FAP.

Duodenectomy and closure of duodenal adenomatous polyposis was performed with 6 in GI tract (21 gastro-intestinal adenomas were removed, more than 9 times than that found at endoscopy. There was 2 duodenal leaks, one which necessitate reoperation. After a mean follow-up of 53 months (36–72) duodenal adenomas recurred in all patients and 4 had stage IV disease.

Pancreateoduodenectomy with pylorus preservation and pancreatico-gastro-anastomosis was performed in 7 patients. Histology of the specimens revealed 2 unsuspected duodenal carcinoma at an early stage. There was 1 pancreatic leak that was treated medically. After a mean follow-up of 33 months (9–108), 1 patient died of rectal cancer, there was no case of jejunal polyposis and the operation did not affect the bowel function.

In FAP, stage IV duodenal polyposis seems to carry a high risk of malignant change. Surgical polypectomy failed to guarantee a polyp-free duodenum and carried a risk of post-operative complications. Duodenopancreatectomy had a low morbidity, revealed cancers at early stages and did not affect bowel function.

In colectomized FAP patients, duodenopancreatectomy should be offered in some selected cases of stage IV duodenal polyposis.

**Role of Surgery in Localized Primary Gastric Lymphoma (PGL): Long Term Results of a Prospective Multicenter Study of 45 Patients.**


Aim: The role of surgery in the treatment of PGL is still controversial and must be discussed according to the grade of malignancy and the chemosensibility. Most series are retrospective and mix both high-grade (HG) and low-grade...
(LG) lymphomas. We aimed to study prospectively a therapeutic strategy based on follow-up of patients with gastoenteroid (CT) adapted to the histological subtype and the radicality of the resection in localized PGL.

Patients and Methods: As part of the multicenter study of the French cooperative group on gastrointestinal tract lymphomas, localized PGL, either LG (large cells) or LG (small cells), were studied. Primary surgical resection was recommended whenever possible for LG and when reasonable for LG. At this time, total gastrectomy was not systematically mandatory. Surgery was followed, or, when not performed replaced by CT: COP regimen in LG and AvnCP after radical (R) resection of M-BACOP after non radical (NR) resection in LG.

Results: From 1984 to 1990, among 54 PGL, we enrolled 45 localized PGL and 9 WMF; 27/18; median age 54.2 years; 16 LG and 27 HG; stages I2, n = 30) and II2, (n = 15). The median interval between the initial diagnosis and 4.6 mos. Endoscopic biopsies permitted final diagnosis in 70% of cases. Diagnosis was made at emergency laparotomy in 2 patients (pts). There were no differences between the 2 grades of malignancy concerning: site, size, depth of wall invasion, and nodal involvement. Primary laparotomy was undertaken in 40 pts (13LG, 27HG). Thirty five had tumour resection (11LG, 24 HG) either R (4LG, 19HG) or NR (7LG, 5HG). Exclusive CT was given to 10 pts (7LG, 5HG). One anastomotic leak and one jejunal perforation were observed during M-BACOP after NR surgery. The median follow-up was 7 yrs. Among 16 LG, 6 pts did not achieve complete remission (CR) after initial treatment (6 exclusive COP, 1 NR resection). For these pts, CR was achieved after secondary R resection (3), or radiotherapy (2), and second-line CT (1). Among the 12 LG who achieved CR after initial treatment, we observed 1 locoregional relapse (initially NR) after 9.7 yrs and unrelated death. Thus, 16 pts (30%) with LG are alive free of disease (of whom 2 exclusive COP, 6 R, 2 radiotherapy). In HG, 24 pts (89%) achieved CR after initial treatment and 3 pts undergoing laparotomy without resection died within 10 mos despite CT. The overall 5-yr survival (product-limit method) was 91.1% for LG, 94.1% for LG, and 89% for HG. R resection was associated with better survival rate either in the whole population (p = 0.04) or in HG (100% when R, p = 0.01).

Conclusion: In localized PGL, initial CR and long term disease-free survival were obtained each time primary or secondary radical surgery were performed in association with CT. Compared to surgery, the roles of radiotherapy in LG or exclusive CT in HG should be evaluated in larger randomized trials.

# 930 Prevalence of H. Pylori Infection in Subtotal Gastrectomy and Vagotomy

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Purpose: We investigated the prevalence of H. pylori infection in patients with gastrectomy plus pyloroplasty, for the treatment of peptic ulcer disease.

Methods: Fifty-five patients age: 48–72, mean: 60 yrs; 90% male) with subtotal gastrectomy and vagotomy were investigated: Billirho I (n = 28) Billirho II (n = 12) and vagotomy plus pyloroplasty (n = 11). At endoscopy biopsy specimens were taken from fundus and both sides of anastomosis (H&E stain, Gastroin and chromogranin A).

Results: The percentage of H. pylori infection was 48% in patients with Billirho I; Billirho II: 42%; and vagotomy + pyloroplasty: 92%. No differences were found between both reconstruction procedures. However, differences (p < 0.01) were obtained when comparing percentages of H. pylori infection between subtotal gastrectomy and vagotomy. In gastrectomized infected patients, H. pylori was detected in 76% of cases at gastric fundus, and in 96% of biopsies form the anastomotic region (p < 0.05).

In Conclusion: The prevalence of H. pylori infection was low (44%) in patients with subtotal gastrectomy and no differences were observed between both reconstruction procedures. H. pylori infection after vagotomy plus pyloroplasty was significantly higher (92%). In gastrectomized infected patients, H. pylori was detected with a higher frequency at anastomotic region, than in biopsies obtained from the gastric fundus.

# 931 Cathecolamines in Gastric Juice and Tissues before and after Vagotomy

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The purpose of the study was to reveal influence of vagotomy on local concentration of cathecolamines in gastric tissues and in nonstimulated basal juice.

Methods. The levels of epinephrine (E), norepinephrine (NE) dopa (DO) and dopamine (DE) were investigated in gastric juice of 10 patients with duodenal ulcer disease before and at 2nd, 14th and 30th days after combined posterior truncal with anterior seromuscular vagotomy by Taylor. The same substances were also investigated in gastric tissues of 50 white rats at 1st, 2nd, 7th and 14th days after the same operations. For identification of cathecolamines we used spectrophotometric method.

The results of the study of patients gastric juice are given below (in ng/ml).

<table>
<thead>
<tr>
<th>Before</th>
<th>After operation</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.39 ± 0.1</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2.5 ± 0.1</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Dopa</td>
<td>0.05 ± 0.02</td>
<td>0.02 ± 0.02</td>
</tr>
<tr>
<td>Dopamine</td>
<td>1.3 ± 0.4</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>2.4 ± 0.7</td>
<td>2.7 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>0.03 ± 0.03</td>
<td>0.07 ± 0.04</td>
<td></td>
</tr>
</tbody>
</table>
| Concentrations of EN and NE decreased by 0.8–3.9 times, especially at 2nd and 14th day after operation. On the contrary, levels of DO and DE were increased. The same pic-pure was revealed in gastric tissues of experimental rats.

Conclusion: Vagotomy leads to activation of sympathetic nerve system with local liberation of cathecolamines in gastric tissues and then into gastric juice. Low levels of EN and NE may be explained by negative feedback mechanism of their production. These changes may influence at gastric motility and regional hemodynamics after vagotomy.

# 932 Systemic Vascular Changes in Early Dumping Syndrome

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1 Dept. of Gastroenterology, University Hospital Leiden, The Netherlands; 2 Dept. of Nephrology, University Hospital Leiden, The Netherlands

Early dumping after gastric surgery has been attributed to systemic hypovolemia caused by redistribution of blood into the splanchnic vascular bed. The somatostatin analogue octreotide effectively prevents the occurrence of dumping symptoms. We have explored the systemic hemodynamic changes in early dumping that occur after provocation with glucose. Six patients with proven early dumping (partial gastrectomy n = 6, age 31–75 years) 6 patients, after gastric surgery (partial gastrectomy n = 6, age 35–70 years) without dumping (disease-controls) and 6 healthy volunteers (n = 6, age 25–64 yrs) were studied on two separate occasions. After a fast, 50 g glucose was given orally 15 min after s.c. administration of 25 µg octreotide or placebo in random order. Heart rate (HR) was measured and mean arterial blood pressure (MAP) was monitored by Dynamap; forearm blood flow (FFB) and forearm vascular resistance (FVR) were measured.

Results: are presented as peak increments after glucose provocation relative to basal values (* p < 0.05).
Baseline MAP was 92 ± 7, 91 ± 4 and 82 ± 2 mmHg resp.; MAP after glucose provocation was 89 ± 5, 86 ± 2 and 79 ± 2 mmHg resp. Octreotide prevented the increases in HR and FBF and decrease in FVR after provoking glucose. After glucose provocation patients with early dumping showed increases in HR and FBF, however without a drop in blood pressure, indicating aces peripheral vasodilatation. Conclusions: In patients with early dumping a glucose challenge does not induce a hypovolemic state as assumed previously but causes a peripheral vasodilatation and hyperdynamic state. Octreotide completely prevents these changes.

### Table 933

<table>
<thead>
<tr>
<th>L/M test</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>62%</td>
</tr>
<tr>
<td>Specificity</td>
<td>78%</td>
</tr>
<tr>
<td>PPV</td>
<td>87%</td>
</tr>
<tr>
<td>NPV</td>
<td>87%</td>
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</tbody>
</table>

No statistical significant difference was found between the two parameters. L/M test together with IA increased sensitivity to 85% and NPV to 94%.

### Table 934

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### Table 935

<table>
<thead>
<tr>
<th>Dumping</th>
<th>Disease controls</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHR (rpm)</td>
<td>17 ± 4*</td>
<td>1 ± 2</td>
</tr>
<tr>
<td>FBF (%)</td>
<td>141 ± 19*</td>
<td>107 ± 14</td>
</tr>
<tr>
<td>PVR (%)</td>
<td>75 ± 6*</td>
<td>85 ± 11</td>
</tr>
</tbody>
</table>

No statistical significant difference was found between the two parameters. L/M test together with IA increased sensitivity to 85% and NPV to 94%.

### Table 936

<table>
<thead>
<tr>
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<td>Sensitivity</td>
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<td>NPV</td>
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</tr>
</tbody>
</table>

No statistical significant difference was found between the two parameters. L/M test together with IA increased sensitivity to 85% and NPV to 94%.
937 Role of Ultrasound in the Detection of Post-Operative Recurrence of Crohn’s Disease (CD)

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Purpose: Ultrasound scanning (US) is a non-invasive method for the diagnosis and for monitoring the effects of therapy in CD. Aim of the study is to evaluate the overall accuracy of US versus clinical data, laboratory, radiology, endoscopy and surgical specimen in the detection of post-operative recurrence.

Methods: Patients and Methods: Starting from 1986, 208 US were performed in the follow-up of 92 patients operated because of Crohn’s disease complications. US was made at six months and then once a year after surgery or when clinically indicated. Clinical recurrence was defined following commonly accepted criteria. Surgical recurrence was confirmed by the specimen available for patients operated during the operation. The recurrence was defined by the presence of 1) bowel thickening (more than 5 mm) with or without 2) bowel stenosis 3) bowel dilatation.

Results: Accuracy of ultrasound scans was 81.6% (US+ only), 64.9% (US–) and 53.4% globally.

938 Association Studies in Crohns Disease: Approaches in Characterizing the Right Design

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Purpose: As the genetic basis of IBD is being uncovered, association studies are playing an important role in the fine mapping especially of minor risk loci. Accurate predictions of sensitivity and specificity of specific designs are of pivotal importance for the later interpretation of data. However, the theoretical basis of these studies in polygenic disorders is still incompletely understood. In order to provide guidelines for a robust and sensitive design, the properties of different association studies were evaluated using a computer simulation.

Methods: We developed a computer program “popsim” (C programming language), which allows for the simulation of genetic transmission in populations up to 3 million individuals under a polygenic model (prevalence: 0.05%, I(dia) = 20). Non-overlapping control samples were evaluated using a computer simulation.

Results: The population is propagated according to Mendelian laws, no further theoretical assumptions are made.

940 Impressive Histologic Improvement after TNF Antibody (cA2) Therapy in Active Crohn’s Disease

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TNF-a is an important mediator of inflammation in Crohn’s disease (CD). We studied the histologic effects of cA2 therapy in a detailed and systematic way. Biopsies of 13 patients with active CD before and 4 weeks after a single placebo or cA2 infusion (5, 10 or 20 mg/kg) were reviewed by one blinded pathologist. A minimum of six biopsies were taken per patient at every occasion in the most inflamed areas. If ulcers were present, biopsies were taken in the vicinity. Seven pts had colitis, four ileocolitis and two ileitis only. Assessment of the severity of inflammation was based on epithelial alterations (architecture and cytology), inflammatory changes (granulocyte, lymphocyte and plasma cell infiltration), the presence of granulomas and the number of biopsies affected. A score from 0–3 was given for each item according to severity. The minimal score was 0, the maximum score 16. In addition to classical H&E, immunohistochemical stainings for HLA – DR, CD68 (activated macrophages), I-AgM and LFA-1 were performed using an indirect immunoperoxidase method.

Results: The mean total activity score in the cA2 treated group dropped from 6.7 (2–12) to 3.0 (0–7) in ileitis and from 7.6 (2–12) to 3.0 (0–8) in colitis compared to 9.1 (6–16) to 4.0 (0–8) before and after placebo. The changes were most evident in the inflammatory components of the score were most pronounced. The enhanced epithelial HLA-DR and endothelial I-AgM and numbers of CD68+ monocytes and LFA-1+ lymphocytes observed at week 0 markedly decreased along with the class II components of inflammation in CD pts treated with cA2 but not in the placebo group.

Conclusion: Monoclonal TNF-α antibody therapy markedly improves histologic activity in active Crohn’s ileitis and colitis. The improvement is mainly due to a dramatic decrease of the inflammatory infiltrate, with no change in the number of HLA-DR expression and the number of CD68+ and LFA-1+ cells, whereas the architectural changes grossly remain unchanged 4 weeks after treatment.

941 Suppression of Bone Formation by Methyldיפיםosilinone But Not by Budesonide CIR in Active Ileocolonic Disease

G. D’Haens, A. Verstraete, F. Baert, M. Peeters, R. Bouillon, P. Rutgeerts. Dept of Gastroenterology and Endocrinology, University of Leuven, Belgium

One of the most severe long-term side effects of prolonged corticosteroid use is osteoporosis with an increased risk of fracture. Bone formation can be assessed by osteocalcin, a noncollagenous protein synthesized by osteoblasts, while bone resorption can be measured with urinary deoxypyridinolines (collagen cross-links). Aim: to compare the effect of conventional oral glucocorticosteroids and oral Budesonide CIR (Emcicitab, Astra) on bone metabolism in active ileocolonic Crohn’s disease (CD). Methods: 29 pts with active CD (CDAI > 200) were randomly assigned to either methylprednisolone (MP) 32 mg/day PO for 3 weeks and then tapered by 4 mg/week (total 13/29 pts), or budesonide CIR (BU) 9 mg/day PO for 10 weeks (15/29). Six pts with quiescent CD on S-ASA were used as controls for osteocalcin and bone resorption.

Results: Neither in the MP group (n = 13, 5 M/8 F, age 39.5 ± 3.3 yrs), nor in the BU group (n = 16, 4 M/12 F, age 39.3 ± 3.4 yrs), any changes in serum P or AP were observed. OC, however, decreased from 50.8 ± 22.1 ng/ml at w0 to 20.0 ± 1.8 ng/ml at w4 (p = 0.05) and 18.1 ± 1.9 ng/ml at w10 (p = 0.05) in the MP group versus from 20.2 ± 23.9 ng/ml at w0 to 29.6 ± 4.9 ng/ml at w4 and 37.9 ± 5.4 ng/ml at w10 in the BU group. OC in the control group (n = 6, 1 M/5 F, age 36.2 ± 4.5 yrs) was comparable to w0 in the MP group and w4, w5 and w10 in the BU group. Urinary (deoxypyridinolines) remained unchanged in all groups throughout the trial. Bone resorption (C-terminal cross-link) was suppressed with conventional steroids but not with budesonide CIR, while bone resorption appears unaffected. Topical steroids are probably safer for long-term use with regard to bone metabolism.
cancer, inclusion of FCM analyses of colorectal biopsies may therefore be a valuable complement to assessment of dysplasia in trying to identify high-risk CD-patients prone to develop CRC within the frame of colonscopic surveillance programs.

943 Use of Heparin in the Treatment of Chronically Active Crohn's Disease

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Department of Gastroenterology, University Hospital, Amiens, France

It has been suggested that the combination of hypercoagulable state and vasculitis may contribute to the pathogenesis of Crohn's disease (CD). Heparin, acting by its anticoagulant and immunomodulatory properties, may be effective in the treatment of inflammatory bowel diseases. Aim: To evaluate the effects of heparin in the treatment of patients with chronically active CD who failed to respond to corticosteroid and azathioprine.

Methods: 10 patients (6 F, 4 M; mean age 30 yrs; range 18-66) with chronically active CD were included in the study. The annual incidence of colitis increased from 0.2 in 1955-59 to 1.6 in 1970. A166 Crohn's disease who failed to respond to conventional treatments. The mean C-reactive protein decreased from 1.4/105 mg/dl before treatment to 0.35 mg/dl after 3 months follow up. Conclusions: These results suggest that heparin, which is an anticoagulant and antiplatelet agent, may have a role in the treatment of CD. The effect of heparin was not statistically significant. However, heparin may be useful in the treatment of patients with chronic active Crohn's disease who failed to respond to conventional treatments.

944 Crohn's Colitis in Stockholm County

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Background: The annual incidence of Crohn's disease (CD) in Stockholm County increased from 1.4/105 in 1955-59 to 4.6/105 as mean 1970-89. The proportion of colonic disease doubled during the study period from 14% to 32% as mean 1980-89.

Aims: To describe the natural history of Colitis' occurrence over time with regard to incidence, extent at diagnosis, initial treatment, age and gender.

Materials and Methods: Retrospectively, registers for in- and outpatients were investigated for possible cases of CD according to Lennard-Jones' criteria. All patients who got the diagnosis of Crohn's colitis in 1955-89 and were residents in Stockholm County at time for diagnosis were included in the study. Data of initial colitis at diagnosis, initial treatment, clinical course within the first year of diagnosis and time for surgery were registered.

Results: 512 cases of Crohn's colitis were included into the study. The annual incidence of colitis increased from 0.2 in 1955-59 to 1.6 in 1985-89 with an annual increase of this of distal colonic disease during the last study period (23% vs. 33% p < 0.05). Clinical remission was achieved within one year after diagnosis in 75% of the cases. 78% had at least one relapse. The risk for surgery within the first year of diagnosis decreased from 25% to 14% during the study period. The overall risk for surgery was 52%. The cumulative risk for surgery was higher among the patients with chronic continuous disease compared to those who achieved remission within the first year. Patients with distal colonic disease ran a lower risk for surgery compared to the other patients. Except for a higher propensity for distal disease among those aged > 60 years at diagnosis, there were no differences according to age or gender.

Conclusion: While the incidence of Crohn's disease remained stable during the last 20 years, the incidence of Crohn's colitis (particularly distal disease) increased. Half of the patients with colitis required surgery with highest risk for those who chronic continuous disease and lowest risk for those with distal disease.

945 Therapy of Refractory Crohn's Disease by 7S-Immunoglobulins

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About 10 to 20% of patients with inflammatory bowel disease are resistant to usual therapy. In immunomodulatory disturbances play an important role in pathophysiology we tried to improve the situation in therapy-resistant cases of Crohn's Disease by additional intravenous application of 7S-immunoglobulins. In an open controlled trial 20 patients with therapy-resistant Crohn's Disease received 10 g 7S-immunoglobulin (Venimunim®) per day for 10 days. Mean duration of illness was 10.3 ± 1.4 years and 9 patients had one or more operations in the past. Mean CDAAI was for more than 6 months higher than 200. Patients received prednisolone (16.4 ± 4.0 mg/die) and 5 ASA (2.2 ± 0.3 g/day). Before and after therapy CDAAI, laboratory data and immunoglobulins were checked.

Activity index (CDAAI) decreased during therapy from 201 ± 17.7 to 99 ± 8.6 (p < 0.0001). Frequency of diarrrhea was reduced from 4.5 ± 0.8 to 2.1 ± 0.3 per 24 h (p < 0.001). At the end of the therapy CDAAI was lower than 150. In 9 patients CDAAI decreased by more than 100 points. Follow up was done in 11 patients up to 6 months. 73% of patients were in remission even after a period of 6 months. BSR increased during therapy from 7.9 ± 5.5 to 7.6 ± 8.9 mm/h (p < 0.03). Lymphocytes increased (13.3 ± 3.0 vs. 23.3 ± 2.8; p < 0.008). Alpha-2-globulin decreased by 1.8% (p < 0.01). IgG, IgG2, IgG3, IgG4 and even IgG4 decreased significantly during therapy (p < 0.001). Flow cytometry of peripheral lymphocytes showed different results with increasing B-lymphocytes and decreasing CD4-cells.

Additional therapy of refractory Crohn's Disease by 7S-immunoglobulins was effective in our study. Immunoregulatory effects seem to be responsible for successful immunoglobulin therapy in Crohn's Disease. However mechanisms of acting of immunoglobulins are not identified. Further investigations are necessary.

946 A Prospective Randomized Trial in Active Crohn's Disease Comparing Prednisolone, a Polymeric Diet and a Polymeric Diet plus Heparin

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Polymeric diets may be useful in active Crohn's disease but their effects in conjunction with steroids have not been adequately studied. In this prospective trial, 35 patients were randomized to receive intravenous prednisolone (0.75 mg/kg body weight) (group I, N = 11), a polymeric diet (Nutrition High Energy, 1.5 l/day delivered via a nasoduodenal tube (group II, N = 11), or the previously described polymeric diet plus prednisolone (group III, N = 13). All patients received mesalazine (Salofalk 500 mg three times a day). The three treatment groups were similar with respect to sex, age, age at disease onset, anatomic site of disease, disease activity (Crohn's Disease Activity Index, CDAAI), nutritional status, and previous medical or surgical treatments. Seven patients (two in group II, three and three in group III) were undergoing the first attack of disease. Three patients have been treated once in group I, two in group II. A satisfactory response to treatment was defined by a fall of CDAAI by 100 points or below 150. After 4 weeks of treatment, there were 8 responders in group I (72.7%), 5 responders in group II (45.5%) and 10 responders (77%) in group III; differences were not significant. However, patients who received prednisolone (groups I and III) showed a better response than did patients who received only a polymeric diet whereas the combination therapy increased only marginally the effect of prednisolone. In addition, the time to response was significantly higher in patients receiving diet alone (19.8 ± 3.5 days versus 5.9 ± 2.1 days in group I and 5.2 ± 1.5 days in group III, p < 0.01). Polymeric diet did not increase body weight or other indices of inflammation. In general, patients undergoing the first attack of disease were responders. Of the six failures in group I, 4 patients responded to prednisolone. Thus, polymeric diets should not be considered as a substitute for steroids at least in patients presenting with a relapse of Crohn's disease.

947 Restricted T Cell Receptor V3 Regions in Crohn's Disease Patients Suffering from Joint Complications

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Little is known about the mechanisms triggering both the development and perpetuation of extraintestinal complications in Crohn's disease (CD). The aim of the present study was to test the hypothesis that the T-cell immune response in CD patients with extra-intestinal manifestations may be altered when comparing with patients without extra-intestinal manifestations. We used a semiquantitative polymerase chain reaction assay to analyse the T-cell antigen receptor repertoire in peripheral blood T cells from eight CD patients with extra-intestinal manifestations and four non-CD patients with ankylosing spondylitis. Twelve CD patients without extraintestinal manifestations, and from seven non-CD patients with ankylosing spondylitis showing typical changes on joint radiographs. Being concerned that different patterns may be seen in different phases of the inflammatory disease process we performed a careful to analyse sequential samples at various time points of the disease.

Expression of all Vα genes was found in each healthy control and in each CD patient without extra-intestinal manifestations and showed no major variation over time. Southern hybridization analysis of the Vα repertoire, revealed a highly restricted Vα repertoire in all CD patients suffering from peripheral arthritis and ankylosing spondylitis. In contrast, non-CD-patients with ankylosing spondylitis showed a repertoire without signs or symptoms of gastrointestinal problems demonstrated the presence of the entire Vα repertoire. Our longitudinal studies confirmed variable Vα usage over time, as certain transcripts were found only in distinct temporal phases of disease.

Our data are not directly suggestive of a common super-antigen model of
CD, but instead emphasize a specific decrease in signals throughout the TCR Vβ repertoire in CD patients suffering from joint complications.

948 Effect of Mild Exercise on Ileal Crohn's Disease (CD) in Remission
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We investigate the possible noxious effects of mild exercise in CD patients in remission by examining gastrointestinal transit time and permeability, lipid peroxidation and inflammatory cells function. Six male CD pts were evaluated before and after exercise (1 hr at 60% VO2 max), with both fasting and last meal (L/M) IL-6 test, malondialdehyde (MDA) levels, neutrophil activity and IL-6 production. Seven healthy volunteers served as controls. Sugars were measured by spectrophotometry, MDA by fluorimetry and neutrophil activity by chemiluminescence after PMA, FMLP and zymosan stimulations. Oro-saccal transit time and urinary IL-6 recovery were unchanged after exercise both in CD pts and in controls. MDA levels significantly increased in CD pts after exercise (1.77 ± 0.4) with respect to baseline (1.62 ± 0.4) (p < 0.05). Respiratory burst activity of isolated neutrophils was significantly increased after exercise in CD pts with FMLP (86 ± 20.2) and zymosan (238.9 ± 35.6) stimulations compared to controls (22.7 ± 4.3 and 133.88 ± 37.15 respectively, p < 0.05) while PMA did not affect neutrophil function in both groups. Exercise significantly decreased basal IL-6 production of isolated lymphocytes both in CD pts (2.7 ± 3.5 vs 0.7 ± 0.5) and controls (8.1 ± 7.1 vs 2.7 ± 4.2) while LPS response was similar in both groups. In conclusion, mild exercise may have detrimental effects in CD since it increases respiratory burst activity of neutrophils and IL-6 production of lymphocytes while it does not seem to affect gastrointestinal transit time and permeability.

949 Change from Ulcerative Colitis to Crohn's Disease: Two Features of the Same Disease?
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Anecdotal reports have raised the possibility that a change from Ulcerative Colitis (UC) to Crohn's Disease (CD) or vice versa may occur during the course of IBD.

Aim of this study was to assess the frequency of this change and the role of associated factors.

Methods: We reviewed the files of 1114 patients with IBD who attended the outpatients clinics of our Institution from 1979 to 1995. We defined the clinical, endoscopic and histological criteria for an "unequivocal" diagnosis, in order to exclude cases in which the diagnosis was indeterminate at the time of first assessment. For diagnosis of UC we used as endoscopic criteria the presence of aphthae, skip lesions and/or stenosis and histological criteria were the presence of follicles, granulomas and/or full thickness inflammation.

Results: we found only 5 cases where a "real" (i.e. endoscopy and histology confirmed) change in diagnosis occurred, all of whom had an initial diagnosis of UC. All were young males and the change took place within two to five years from the onset of disease in four of the patients and in three months in the fifth. Four were smokers or ex-smokers and 3 had been treated with several courses of high doses of steroids. None had familiar cases of UC.

We conclude that a change in diagnosis, always from UC to CD is rare (7.9/thousand cases of UC). It affects young males and takes place within few years after the initial diagnosis of disease. We could not demonstrate any causal relation with steroid intake.

950 Bone Mineral Density and Its Evolution in Patients with Crohn's Disease
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Low bone mineral density has been demonstrated in patients with Inflammatory Bowel Disease.

Aim of our study was to assess the prevalence of osteopenia and the rate of bone loss in patients with Crohn's Disease (CD).

Methods: We studied 32 patients (19 men and 13 women), mean age 37 years (range 18-69), 14 of whom had CD limited to the colon and 18 with ileocolonic involvement was measured by dual energy x-ray absorptiometry of the lumbar spine. In 21 patients (65.6%) the measurement was repeated after a mean of 23 months (range 9-48). During the follow-up period 8 patients (25%) received steroid therapy and 6 (18.7%) calcium and vitamin D supplements. Osteopenia was defined as z-score below −1.5. The fracture threshold was considered bone mineral density (BMD) of 0.8 g/cm². Results were related to site and extent of disease and type of medication.

Results: Osteopenia was present in 18 patients (56.2%) with values below the fracture change in t (15.6%). In the 21 patients in whom we measured BMD twice, no significant changes were observed, not even in those treated with steroids.

We conclude that osteopenia is frequent in patients with Crohn's disease but is a slow-evolving process and, at least in the short interval of our observation, independent of disease localization and of steroids intake.

951 Low Skinfold Thickness Predicts Osteoporosis in Crohn's Disease
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The aims of this study were to investigate the relation of skinfold thickness (SFT) to bone mineral density in Crohn's disease (CD), and to evaluate SFT as a screening test for osteoporosis in CD.

Methods: 117 patients with confirmed Crohn's disease were studied (Male = 49). Pregnancy, ankylosing spondilitis, medical conditions or medication affecting bone density were exclusion criteria. Bone mineral density was measured at lumbar spine (L2-L4) and left hip (femoral neck, trochanter, Ward's triangle) by dual energy x-ray absorptiometry (DEXA). SFT was measured at the observation, the thickness of a longitudinal skinfold over the 4th metacarpal was measured 3 times by a single observer and the mean calculated.

Results: Osteoporosis was present in 14 (12%) of the patients. Mean SFT was significantly lower in patients with osteoporosis than patients with normal bone density (Difference in means = 0.74 mm, 95% CI 0.33 to 1.15, p < 0.001).

There was a strong correlation between SFT and bone mineral density at all measured sites: Lumbar spine (r = 0.41, p < 0.0001, 95% CI 0.25 to 0.55), femoral neck (r = 0.38, p < 0.0001, 95% CI 0.21 to 0.53) and trochanter (r = 0.33, 0.16 to 0.48, p < 0.0001). SFT was associated with bone mineral density independent of age, BMI and lifetime steroid use (p < 0.05). If a significantly low SFT is taken as > ISD below the mean normal value (2.64 (0.71) mm), then subjects with an SFT less than 1.9 mm were at significantly greater risk of osteoporosis (p < 0.05, odds ratio 5.48, 95% CI 1.13 to 25.0). As a diagnostic test for osteoporosis, an SFT of 1.9 mm has 93% specificity and 29% sensitivity. Using 2.5 mm as the 'cut off', specificity falls to 54% and sensitivity increases to 93%.

Conclusions: In patients with CD there is a strong correlation between SFT and bone mineral density at the hip and lumbar spine. Measurement of hand skinfold thickness is a simple clinical marker of bone mineral density in CD, and will be a useful screening test in to determine which patients need DEXA.

952 Crohn's Disease – A Hyperreactivity of the Tight Junctions?
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Patients with Crohn's disease (CD) have a disturbed intestinal permeability. The epithelial tight junctions (TJ) regulate the mucosal barrier to hydrophilic molecules. The dynamics of TJ permeability during exposure of the mucosa to modulating substances has not been studied previously in CD.

Purpose: To study the permeability and electrical parameters in inflamed and non-inflamed ileal mucosa from patients with CD and controls during exposure to sodium caprate (C10), a fatty acid found in dairy products with effects on TJs in cell lines, and cyclohexalin B (CytB), a well established TJ modifier.

Methods: Five cm of the ileum was taken from 7 patients with CD and 8 patients operated for colonic cancer. The mucosa was dissected from the muscular layer and the specimens were mounted in Ussing chambers. Transepithelial potential difference (PD), electrical resistance (RER) and short circuit current (Isc) and permeation of 31Cr-EDTA and 14C-mannitol was studied for 90 min in control segments and in segments modulated with C10 or CytB with washout at 10 min and 45 min, respectively.

Results: Both CytB and C10 induced a partly reversible increase in tight junction permeability. Non-inflamed mucosa from CD patients showed a more pronounced decrease in PD, ER, Isc and a larger increase in 31Cr-EDTA permeability during modulation with C10 than did control mucosa. In inflamed CD mucosa permeability in unmodulated specimens was increased compared to controls, whereas the effect of modulators was less pronounced.

Conclusions: The results indicate a hyper-reactivity of the tight junctions in non-inflamed ileal mucosa in CD. This may be of importance for the pathogenesis in Crohn's disease.

953 Is ANCA Positivity in Crohn's Disease (CD) Associated with Particular Clinical Features?
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According to different studies, 10 to 20% of CD patients are ANCA+. The significance of this positivity is still unknown. The aim of our study was to compare ANCA+ and ANCA- CD patients on the basis of several clinical features.

Patients and methods: ANCA were searched, using an immunohistochemical method, in a sample of 180 CD patients. Twenty one of them (11.6%) were ANCA+. They were compared to a group of 41 ANCA- CD patients, matched...
for gender, smoking and duration of the disease. Comparisons of certainty of the diagnosis, type and location of the disease, systemic manifestations, age at onset, family history, and need for surgery and immuno-suppressive treatment, were made using either Fisher's exact test, or t test. Results: The frequency of gastro-duodenal location of CD was significantly higher in ANCA+ CD patients (33.3% vs 4%; p < 0.01). There was also a trend to an increased frequency of inflammatory disease and to a decreased frequency of non-inflamatory disease among ANCA+ CD. The need for surgery tended to be less frequent in ANCA+ CD, but the need for immuno-suppressive drug tended to be more frequent in the same population. Finally, the age at onset tended to be higher in ANCA+ patients (37.4 vs 28.5 years; p = 0.053). In conclusion, a minority of CD patients are ANCA+. This may represent a particular subset of CD, characterized by an increased frequency of gastro-duodenal location, and perhaps later onset, more inflammatory and less stenosing disease.

954 Familial Crohn's Disease: Study of 18 Families
The most recent data from epidemiology and molecular biology in Crohn's disease are consistent with a multifactorial, polygenic inheritance with a possible genetic heterogeneity. The aim of our study was, first to evaluate among families, the concordance rate for the type and location of the disease, and second, to compare familial and sporadic CD on the basis of the type and location of the disease, and age at diagnosis. Patients and methods: 16 families with 2 affected first degree relatives (n = 32), 2 families with 3 affected first degree relatives (n = 6), and 155 sporadic CD were studied. The concordance of the type of CD among families were calculated using the binomial law and compared to the observed numbers by a Chi2 test. Comparison between familial and sporadic CD was done by a Chi2 or a Kruassall-Wallis test. Results: 1) There was a significant increase in concordance rate of familial and sporadic for inflammatory disease, among the families. 2) Age at diagnosis was the same in sporadic and familial CD. There was an increased frequency of ileal (p < 0.022), and stenosing (p = 0.005) CD and a decreased frequency of colonic (p < 0.006) and inflammatory (p = 0.002) CD, in familial CD. In conclusion, 1) Among families, the concordance rate for stenosing CD was higher than expected, which may reveal the genetic inheritance of that feature. 2) Ileal and stenosing diseases were more frequent in familial than in sporadic CD, which may suggest some heterogeneity in CD.

955 Low Symptomatic Load and Crohn's Disease with Surgery and Medicine as Complementary Treatments
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Background: The treatment of Crohn's disease has changed due to the recognition of its chronicity. Maintenance medical treatment and limited resections has evolved into major concepts of management. Medical treatments are complementary, their indications being related, and both aim to reduce symptoms. The study aimed at to investigate how these treatment concepts influence the symptomatic load in Crohn's disease.
Patients and methods: An unselected population-based cohort of 202 patients from our primary catchment area and 119 referred patients were investigated. Symptoms were evaluated by a symptom-index, the physician's global assessment and the patient's perception of health by means of visual analog scale.
Results: Of catchment area patients 53% were on medication and the annual rate of abdominal surgery was 5.7%. Corresponding figures for the referred patients were 63% and 8.2% respectively. According to the symptom-index 76% were in clinical remission, 16% had mild, 8% moderate and 1% severe symptoms. Corresponding figures according to the physician's assessment were 63, 26, 10 and 1 percent. Patient's perception of health was 82% in normal health. Symptoms and perceived health were similar in referred patients.
Conclusions: The large majority of patients with Crohn's disease can live in remission or have only mild symptoms.

956 Osteoporosis in Crohn's Disease in a Danish Out-Patient Clinic: Bone Mineral Measurements and Biochemical Markers
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Methods: BMD was measured at the lumbar spine (L2-L4), the hip and of the forearm, using the Hologic 2000 DEXA-scanner. Biochemical markers of bone formation (osteocalcin) and bone resorption (urinary pyridinoline) were analyzed.
Patients: 56 unselected patients (33 females, 23 men) with Crohn's disease, mean age 41 years (SD 14.6), BMI 23.6 kg/squarem (SD 4.0 kg/squaremeter), half of whom had a bowel resection, were studied.
Results: Osteoporosis (defined as a T-score (mean BMD value for the young adult) less than −2.5 SD) was found in the lumbar spine, the hip (neck-region) or the forearm in 52%, 64% and 46% of patients, respectively.
Osteoporosis (defined as a T-score less than −2.5 SD) was observed in 14%, 16% and 16% of patients, measured in the same areas. In 25% of cases osteoporosis occurred at at least two sites. Increased urinary pyridinoline was found in 16% (mean value for the whole group: 46.6 nmol/mmol creatinine, SD 28.0, normal values 38.8 ± 10.8), elevated urinary deoxypyridinoline in 4% (mean: 11.1 nmol/mmol creatinine, SD 7.2, normal values 13.0 ± 4.6). Nine % of the patients had serum-osteocalcin above normal range (mean value for the group 9.0 ± 4.4).
Conclusion: In A Danish cross-sectional study of unselected patients with Crohn's disease, attending an out-patient clinic, osteoporosis is found in 25% (WHO definition). Biochemical markers of bone turnover indicates increased bone resorption.

957 Bone Metabolism and Remodelling in Crohn's Disease
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Purpose of the study was to evaluate bone metabolism and remodelling in Crohn's disease.
Methods. Thirty-five patients with Crohn's disease entered the study (17 men, 18 women, aged 17-64, mean 37, median 38). The diagnosis was based on typical endoscopic, radiological and histological findings (including 17 persons with previous history of bowel surgery). Bone metabolism was assessed by measuring serum osteocalcin (by ELISA), collagen-I carboxyterminal propopeptide [PICP] (by ELISA), parathyroid hormone (using immuno-chemiluminescence), 1,25-OH-vitamin D3 (by RIA), urine hydroxoprolin (using spectrophotometry) and urine free deoxypyridinoline (by EIA). Bone density was measured by peripheral broadband ultrasound attenuation (using CUBA, Mccue, UK). Data were statistically treated (t-test, Mann-Whitney, Spearman Correlation) using Jandel Scientific
Results. Peripheral bone density was decreased in 22/35 patients (63 per cent). Serum osteocalcin was increased (mean 6.66 ± std. dev. 3.15 µg/l) as well as the urine excretion of deoxypyridinoline (median 6.90, interquartile range 5.43-11.08 nmol/mL of creatinine). Serum PICP was in the upper part of reference values (mean 121.7 ± 47.53 µg/L). Serum 1,25-OH-vitamin D3 (mean 33.3 ± 14.4 ng/L) and parathyroid hormone (mean 24.6 ± 14.6 ng/L) were within normal range (except 3 patients). There was no significant correlation between bone density, biochemical markers of bone turnover, disease duration and cumulative dose of corticosteroids.
Conclusions. The bone metabolism is often heavily disturbed in Crohn's disease. The incidence of osteopenia and osteoporosis is high in these patients.

958 Low Body Fat and Risk for Osteoporosis in Crohn's Disease
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Reduced bone mineral density (BMD) has a reported prevalence of 13 to 31% in patients with Crohn's disease (CD). Several risk factors and risk conditions have been proposed. The aim of the study was to estimate whether body composition is correlated to bone mineral density (BMD) in patients with CD.
Methods. Fifty-seven out-patients with CD (17 M, 40 F, age 16-72, mean 43 yrs.) were investigated using total body dual x-ray absorptiometry (DXA). Total body BMD (TBMD), lumbar spine (LS) BMD and hip BMD (neck, Ward's triangle [WT], trochanter [Troc], and body fat percentage (% BF) were measured. BMD was expressed in T-Z and Z-score. Body mass index (BMI) was calculated. Serum 25-OH-vitamin D (vit D) levels were determined.
Results: The prevalence of osteopenia in this group of patients, defined as T-score ≤ −1 SD, was 54% (31/57). BMI was correlated with TBMD-T (r = 0.35, p < 0.01), and TrocBMD-T (r = 0.37, p < 0.05). There was a significant correlation between % BF and both TBMD-T (r = 0.59, p < 0.001), TBMD-Z (0.31, P < 0.05), TrocBMD-T (r = 0.32, p < 0.025) and WTBM-T (0.29, p < 0.05). There was a significant correlation between % BF and vit D levels (r = 0.43, p < 0.025).
Conclusion: Crohn's disease patients with low BMI and low body fat percentage are at higher risk for osteoporosis. Body mass index is a simple clinical parameter which can be helpful in selecting patients at risk for osteoporosis in Crohn's disease.

959 Prothrombin Fragment (F1+2) and Fibrin Degradation Products (FDP) in Peripheral and Splanchnic Circulation in Crohn's Disease (CD) Patients
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Coagulation and fibrinolysis is activated in patients with active inflammatory bowel disease. The granulomatous vasculitis demonstrated in CD is accompanied by intravascular fibrin deposition.
Aim: To study if the systemically demonstrated activation of coagulation and fibrinolysis is present locally in the gut of CD patients.

Methods: 10 females who underwent resection of CD affected gut (n 4 due to active inflammation, in 3 because of stricture, in 3 due to stricture and inflammation) participated. During surgery blood was drawn simultaneously from a cubital vein and a vein draining diseased area of the gut.

Results:

<table>
<thead>
<tr>
<th>Method</th>
<th>Median (range)</th>
<th>Plasma F1+2 (fmoI/l)</th>
<th>Plasma FDP (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubital vein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal vein</td>
<td>1.32 ± 1.6f</td>
<td>292.2*</td>
<td>292.2*</td>
</tr>
<tr>
<td>Cubital vein</td>
<td>0 (0-6.4-5.0)</td>
<td>(1.2-10.2-51)</td>
<td>(154.5-2872)</td>
</tr>
<tr>
<td>Cubital vein</td>
<td>1.60 ± 0.83</td>
<td>159 ± 0.83</td>
<td></td>
</tr>
<tr>
<td>Cubital vein</td>
<td>(0.82-2.41)</td>
<td>(93.3-675.9)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 vs. controls. Control: 0.58 vs. cubital vein.

Conclusion: Splanchnic and cubital plasmin FDP in CD patients were significantly higher compared to controls. Plasma F1+2 was marginally higher in splanchnic than in cubital blood, but F1+2 in cubital blood in CD patients was lower than in controls. Fibrinolysis is enhanced systemically and locally in the gut of CD patients. Activation of the coagulation cascade, as assessed by F1+2, is not evident in this group of patients with primarily stricturing disease although it may be more pronounced in close proximity to the inflammatory process.

**960 Change of Clinical, Laboratory Parameters and Clear ance-Alpha-1-Antitrypsin in the Chronically Active Patient’s with Crohn’s Disease**

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Practical value of clinical, laboratory and intestinal parameters for the estimation of the total activity, was analyzed in the group of chronically active patients with Crohn’s disease. Forty patients were tested, 16 with Crohn’s colitis, 15 patients with extensive small bowel disease and 12 patients with ileocolonic disease. Clinical parameters were measured by modified Best index (CDAI), laboratory parameters with acute phase reactants (CRP and orossomucoid) and intestinal activity with Clearance-alpha-1-Antitrypsin (CDAI=1-At). All parameters were determined at the beginning of testing and after 3, 6, 9 and 18 months. Initially, all patients were clinically active (CDAI > 200) as well as laboratory active (CRP, orossomucoid and CDAI=1-At were above the normal values). Every patient was tested, the results of CDAI in each quartile was statistically different. The area under the curve (AUC) of CDAI=1-At was 13.2% (p < 0.01). The area under the curve (AUC) of CDAI=1-At was 13.2% (p < 0.01). The area under the curve (AUC) of CDAI=1-At was 13.2% (p < 0.01). The area under the curve (AUC) of CDAI=1-At was 13.2% (p < 0.01).

Conclusion: Moderate increase of meal viscosity does not enhance the digestion or tolerance of lactose from a therapeutic milk in adults. The breath H2 excretion and intolerance signs were relatively low with the 3 milks, possibly owing to their high caloric and fat content. Other hypothesis should explain the good digestibility of fermented milks in hypolactasics subjects.

**963 Digestion and Tolerance of Lactose from Yoghurt and Semi-Solid Fermented Dairy Products – Is Bacterial Lactase Important?**


Lactase-deficient subjects digest lactose better from fermented dairy products than from milk. Three hypotheses which do not exclude each other have been proposed. Slower gastric emptying and intestinal transit (probably due to physical differences), stimulation of the endogenous residual lactase, and action of the bacterial lactase in vivo in the gastrointestinal tract. The specific role of each of these factors is debated. The aim of this study was to compare the digestibility and tolerance of three fermented dairy products with the same amount of lactose, and physical state (semi-solid), but different lactase and bacterial contents. Methods: 14 lactase-deficient healthy volunteers consumed, on 4 different days and in random order, after a 12-h fast, 3 semi-solid test meals containing 18 g of lactose, and 10 g of lactulose which allowed calculation of lactose malabsorption. The 3 meals were: yoghurt, a fermented milk containing Lactobacillus acidophilus and Bifidobacterium sp. (Ofilus®), and a similar product enriched with L. bulgaricus to increase the lactase content (Bulgofilus®). The lactase content (U/l product weight) was 0.19 for Ofilus®, 0.24 for Bulgofilus, and 0.86 for yoghurt. Breath hydrogen (H2) concentration and clinical symptoms were measured for 6 h after consumption of the test meals. Results: Symptoms scores were low, indicating a good tolerance of all products. Compared with lactulose, the sum of symptoms was significantly higher for Bulgolus (p = 0.05), and bloating was less severe for Ofilus® (p = 0.06). The area under the breath H2 curve was significantly higher for each fermented milk when compared to lactulose (p < 0.0001). There were no differences in symptoms between the fermented milks. The degree of maldigestion of lactose did not differ significantly between them and was 18 ± 3% (range 3–43) for yoghurt, 21 ± 3% (range 6–52) for Ofilus®, and 21 ± 3% (range 6–44) for Bulgolus.

Conclusion: Despite the differences in the lactase and bacterial contents, lactose was as well digested and tolerated from the 3 different fermented milks. This argues against a major role for lactase in the digestibility of semi-solid fermented dairy products.

No relationship was observed between the presence of ASCA and ANCA and any clinical parameters including UC or CD activity and location. Conclusion: ASCA and ANCA either used single or combined may help diagnosis of IBD. The remarkable PPV observed when combining both tests might be particularly useful in patients with unclassified colitis and should be confirmed in a prospective study.

964 Lactase and Sucrase-Isomaltase Expression in the Duodenum during Development in Children
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Purpose: A large number of diseases affect the integrity of the intestinal epithelium, which harbors a number of very important digestive enzymes. Particularly the brush border enzymes lactase and sucrase-isomaltase (SI) are essential for the digestion of milk-based lactose during early childhood and plant-based sucrose and starch later in life respectively. Clinical evaluation of the effects of epithelial damage on intestinal ability to digest carbohydrates is very important for diagnosis and therapy. Since the regulation of these brush border enzymes in health and disease is inherently very important for survival, we have studied the expression of both these enzymes at the mRNA and protein levels in children.
Methods: 85 Caucasian children (3mth-18y) were studied with normal or affected duodenal mucosa. Villus atrophy was scored in 3 classes. Endoscopic forces biopsies were taken in duplicate from both proximal and distal duodenum in each child. One of these duplicate biopsies was used in immunohistochemistry (IHC) with anti-lactase or anti-SI antibodies, and the staining of the brush border membrane of the villus enterocytes was measured semi-quantitatively. The duplicate biopsies were used to isolate RNA, and the lactase and SI mRNAs were quantified. Lactase and SI mRNA levels were expressed relative to Gapdh mRNA.

965 Reproducibility of a Combined Lactose-13C-Glycine Breath Test to Study Gastric Emptying, Orocecal Transit Time, and Lactose Digestion
Gastric emptying and orocecal transit time (OCTT) influence lactose digestion. Our aim was to set-up a combined test and assess its reproducibility to study gastric emptying, OCTT, and lactose digestion in lactase maldigesters.

Subjects & methods: After an overnight fast, 13 lactase maldigesters ingested 500g of milk containing 18 g lactose and supplemented with 13C-Glycine (99 AP). Breath gas samples were collected every 15 min for 6 h, and gastrointestinal symptoms were recorded using visual analogue scale. A second test was repeated for each subject after one week. Breath excretion of H2 and 13CO2 were measured using an electrochemical cell and an isotopic mass spectrometer respectively. The 13C-Glycine excretion curves were fitted using non-linear regression models to calculate the gastric emptying parameters: half-emptying time (t1/2), time of maximal gastric emptying (tmax), and gastric emptying coefficient (GEC) (Maes et al. 1994). The area under curve of breath H2 excretion (AUC H2) was calculated, and the OCTT was assessed by the appearance of H2 excretion in breath. Results were compared using the Wilcoxon test.

Results: (means ± SD)

<table>
<thead>
<tr>
<th></th>
<th>t1/2 (min)</th>
<th>tmax (min)</th>
<th>GEC</th>
<th>AUC H2 (ml)</th>
<th>OCTT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>87 ± 14</td>
<td>40 ± 12</td>
<td>2.6 ± 0.3</td>
<td>64 ± 30</td>
<td>122 ± 41</td>
</tr>
<tr>
<td>Test 2</td>
<td>84 ± 18</td>
<td>39 ± 12</td>
<td>2.6 ± 0.4</td>
<td>51 ± 35</td>
<td>180 ± 83</td>
</tr>
<tr>
<td>p</td>
<td>0.60</td>
<td>0.78</td>
<td>0.79</td>
<td>0.17</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Almost significant decrease was seen between the first and second test concerning abdominal pain (4.6 ± 7.5 vs 1.3 ± 3.9, p = 0.05), flatulence (6.0 ± 6.3 vs 3.8 ± 4.4, p = 0.07), and the sum of symptoms (24.6 ± 25.3 vs 12.9 ± 15.6, p = 0.07).

Conclusion: This new test allows simultaneous assessment of gastric emptying, intestinal transit time, and lactose digestion. Repeated measurements showed a good repeatability and the absence of a learning effect. Since there was a trend towards a period effect for the assessment of the intestinal transit time and intolerance signs, studies using repeated measurements of lactose digestion and tolerance in the same subject should always randomise treatment periods.

966 The Clinical Significance of Mucosal Lactase Deficiency: Correlation with Serum Glucose Levels and Symptoms during Lactose Tolerance Test
U. Nieminen1, M. Raatio1, M. Saxelin2, A. Sitonen1, T. Vesa1, H. Jousimies-Somer1, R. Korpeila2,4, M. Färkkilä1,1, Dept. of Medicine, Helsinki University Central Hospital, Helsinki, Finland; 2 Valio Research Center, Helsinki, Finland; 3 National Public Health Institute, Helsinki, Finland; 4 Foundation for Nutritional Research, Helsinki, Finland
Purpose: To study the correlation of duodenal mucosal lactase activity with the results of the lactose tolerance test and symptoms in patients with primary lactase deficiency.
Methods: The study group consisted of 30 patients with primary lactase deficiency; lactase concentration half of the normal determined by duodenal lactase measurement with normal histology. The exclusion criteria were: coeliac disease, inflammatory bowel diseases, active duodenal or ventricular ulcer disease, cholecystolithiasis, diabetes mellitus, and intense symptoms suggesting of an irritable bowel syndrome.
The standard lactose tolerance test was performed with 50 g of lactose liquid. The bowel transit time was determined using 1 g of carmine red to mark the lactose liquid. The symptom score during the lactose test and during the 6-hours follow-up was calculated using a questionnaire. The correlation of duodenal mucosal lactase activity with the results of the lactose tolerance test and with the symptoms in patients during the test were analyzed using the regression analysis test.

Results: The symptoms in the patients varied largely during the lactose tolerance test. No correlation of the duodenal mucosal lactase activity was found with patients' symptoms during the lactose test (r = -0.03), or with the rise of glucose in the test (r = 0.28). Moreover, there was no correlation of the mucosal lactase activity with the bowel transit time (r = -0.013). The symptoms in patients did neither correlate with the rise of blood glucose during the lactose test (r = -0.04).

Conclusions: The duodenal lactase activity was detected as an insignificant factor to define the result in the lactose tolerance test and the intensity of symptoms during the test.

967 Lactose Malabsorption Adult Type in Brazil
A. Sevd-Pereira, A.C. Sparvoli. Department of Medicine, State University of Campinas (UNICAMP), Campinas and Department of Medicine, University of Rio Grande, Rio Grande, Brazil
Lactose malabsorption adult type (LMA) has different prevalences in distinct ethnic groups. Brazil has 150 million people distributed in 5 regions of different ethnic and genetic admixture. Indians and the Asian descendent mixed centurie has occurred with other races. Whites came from Europe as settlers. Negros came from Africa since 1538 as slaves. Later on many immigrants arrived: Europeans and Orientals.
The Southeast (SE) has 64 million people of an intermediate mix of Portuguese, Spanish, Italians, Syrians and Japanese. The Northeast (NE) has 43 million people of intense interracial genetic admixture, mainly Indigenous, Negroids and Portuguese, then they are considered hybrids. The South (S) has 23 million people with poor genetic admixture and the strongest European influence, specially German, Italian and Portuguese. The other 2 regions, North and Middle West, are less populated, only 13%. Our investigation was undertaken to clarify the LMA prevalence in the different Brazilian regions, thus establishing a complete picture of our country.
A lactose tolerance test consisting of the administration of 50 g lactose as a 1L aqueous solution was applied to healthy adults, noncassuxaurgous, with no secondary lactase deficiency (40 Caucasians and 20 Negroids and 20 mongoloids of Japanese ancestry) born in SE; 70 (48 Caucasians and 22 Negroids) from S and 37 (trihybrids) from NE.
The results of prevalence of LMA are summarised in the table:

<table>
<thead>
<tr>
<th>Brazilian region</th>
<th>Population</th>
<th>Caucasoids (%)</th>
<th>Negroids (%)</th>
<th>Japanese (%)</th>
<th>Trihybrid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE</td>
<td>64,000,000</td>
<td>45</td>
<td>55</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>NE</td>
<td>43,000,000</td>
<td>76</td>
<td>24</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>S</td>
<td>23,000,000</td>
<td>37.5</td>
<td>62.5</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Total</td>
<td>130,000,000</td>
<td>41</td>
<td>59</td>
<td>100</td>
<td>76</td>
</tr>
</tbody>
</table>

We conclude that Brazilian Caucasoids have an intermediate prevalence of LMA, whereas Negroid, Japanese and trihybrid Brazilians have a high prevalence of LMA.

968 Lactose Intolerance: Role of the Colon and of Changes in Motor Activity in the Occurrence of Symptoms
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In lactose intolerance, symptoms are attributed to the colonic fermentation of unabsorbed lactose. In the small bowel unabsorbed lactose could also produce symptoms via its osmotic load. Mechanisms of colonic symptoms are unsettled. They could be related to the occurrence of motor events induced in the small intestine by the osmotic load and/or in the colon by the bacterial fermentation of unabsorbed lactose. We compared in healthy volunteers the effects of lactulose, a nonabsorbable sugar biochemically similar to lactose,
taken orally or directly infused into the colon in order to bypass its possible effects on the small bowel. Methods: During two periods separated by one month, 8 healthy volunteers swallowed a multilumen tube consisting of 9 ports for delivery of test solution. After migration of the infusion catheter was in the cecum, at least 3 perfused catheters were in the jejunum, and 3 in the colon. After an overnight fast, subjects ingested a 500 kcal liquid meal containing either 40 g lactulose or 40 g saccharose; in this last case, the 40 g lactulose was infused directly into the colon 45 min after the beginning of the meal for 4 hrs at flow rates pre-established in 2 ileostomized patients. Motor activity was recorded for 5 hours. Symptoms were also recorded and graded hourly for 10 hrs and their occurrence was marked on the motility record.

Results: Neither the score for each symptom, nor the overall score (29 ± 6 vs 30 ± 4; p = 0.7; mean ± SEM) was significantly different between the 2 periods. Out of the 48 reported symptoms, only 18, i.e. 38%, (1/22) borborygmus, 3/28 abdominal pain (2/27) and 3/28 flatulence were coincided directly in time with the particular colonic motor event; propagated contractions were associated with borborygmus (8), abdominal pain (3) and flatus (3). waves of localized contractions were associated with borborygmus (2), whereas prolonged waves of contractions that occurred simultaneously on several catheters were associated with borborygmus (1) and pain (1). No symptom coincided with a particular small bowel motor event.

Conclusion: In healthy subjects, symptoms induced by a nonabsorbable sugar are similar when this sugar is ingested orally and when it is infused directly into the colon. This shows that symptoms originate from the colon. However, symptoms were not clearly correlated with particular motor events. This suggests that nonrecorded motor events (for example tonic variations) or other factors could be involved in the occurrence of symptoms.

969 Intestinal Mucosal Permeability to Lactulose, L-Rhamnose in Adult Patients with Chronic Diarrhoea
Mohamed A. Nafef 1, Ahlam M. Ahmed 1, Soaad M. Abdel-Ghany 2, Nabilah M. Rashwan, Abdel-Ghany A. Soliman 1, 3. Department of Tropical Medicine, Assiut University; 2, Department of Biochemistry, Faculty of Medicine, Assiut University. Intestinal permeability to lactulose (La) and rhamnose (rhm) was studied to show integrity of the small intestine in chronic diarrhea. Thirty-six patients with chronic diarrhea as well as 14 healthy controls were studied. The aetiological diagnosis of diarrhea was settled through a set up for management of chronic diarrhea. The study was prepared from Tropical Medicine Department, University of Assiut.

According to the histopathological changes in the proximal intestine, patients were classified into 2 groups. A group with normal histological appearance (9 patients), showed a significant increase in La/rhm ratio in comparison to controls (0.07 ± 0.02 vs. 0.04 ± 0.02). On the other hand, those with histopathological changes in the proximal intestine (27 patients), showed significant increase in the mean La/rhm (23.3 ± 9.9 vs. 11. ± 7.8) and highly significant decrease in rhamn/rhm (23.6 ± 12.9 vs. 51. ± 14.5) compared with controls. All patients had higher La/rhm ratios without overlap with the normal range and the mean ratio was statistically highly significant (0.25 ± 0.17 vs. 0.044 ± 0.022 for controls).

Conclude: that the lactulose permeability test – in addition to being non-invasive technique – is a sensitive index of small intestinal integrity. We hope that it may replace the endoscopic biopsy and histopathologic study or at least decreases the need for such invasive procedures.

970 Longitudinal Mapping of Sodium-Glucose Transport and Disaccharidase Activity in Human Small Intestine
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Purpose: We have used vesicles prepared from resection specimens to map the profile and properties of some brush border membrane proteins along the length of human small intestine Methods: Sodium-dependent glucose uptake and disaccharidase activity were determined in intestinal brush border membrane vesicles (BBMVs) prepared from duodenum, jejunum, mid and terminal ileum by differential centrifugation and Mg precipitation. A potential role of ras in regulating non receptor-mediated transport of glucose was investigated by measuring ras expression in intestinal brush border membrane vesicles from healthy subjects. Results: BBMVs prepared from all 4 regions had comparable diameter (142±60 to 9 mm) and a similar appearance on EM examination. Purity was confirmed by the 7–12 fold enrichment in alkaline phosphatase and 3–4 fold enrichment in basolateral membrane marker enzymes. Recovery and enrichment of sucrose ranged between 17–29 fold and 27–47 fold respectively. Vesicles from all four regions of small bowel supported sodium-dependent transport of 3H-labeled D-glucose as revealed by a substantial overshoot in the presence of NaCl. Diffusional uptake of D-glucose was not influenced by KSCN. Peak rates of D-glucose uptake in the duodenum, jejunum, mid and terminal ileum were 188, 829, 352, and 169 pmol/mm protein respectively. Corresponding values for the specific activity of sucrose were 0.3, 1.6, 3.6 and 1.4 µmol/mg protein/min. Vesicles prepared in the presence of an excess of neurotransmitters displayed rates of glucose uptake similar to control.

Conclusions: These data reveal the regional differences along the human small intestine with respect to membrane-bound disaccharidase and transmembrane monosaccharide transport. Sucrose activity was maximal in the mid ileum but substantial activity was still present in the terminal ileum. Sodium-dependent glucose uptake was maximal in the jejunum (initial rate 126 ± 9 pmol/mg protein/sec) and was unaffected by inhibition of ras.

971 Celiac Disease and Autoimmune Thyroid Disease
M.T. Passaleva, G. Macri, G. Romano, M. Orsini, A. Calabro. G1 Unit, Dept. of Clin. Pathophysiology, Univ. of Florence, Italy

The association of Celiac Disease (CD) and Thyroid Disease (TD) has previously been described. However, based on the published data based on retrospective studies or case note review, the exact frequency of thyroid disorders in CD is yet unclear. We prospectively examined a cohort of adult CD patients drawn from a defined geographical area in Central Italy. Patients and methods: the study group comprised 92 CD patients diagnosed between April 1992 and March 1996 (26 M, 69 F; mean age at diagnosis 38.3 yr, range 15–78). The diagnosis of CD was based on the clinical history, laboratory and histological findings, and a good clinical response to a gluten free diet. Age and sex matched controls were selected from among outpatients with HCV-related chronic hepatitis, consecutively referred to our center for interferon therapy. Total and free T3 and T4, and TSH were measured by standard RIA s as thyroid function; thyroid microsomal (TM) and thyroglobulin (TG) antibodies were determined by indirect immunofluorescence and agglutination techniques. Results: an associated thyroid disorder was found in 15.2% of patients and 2.3% of controls (Chi square, p < 0.001); 7 patients (7.6%) were hypothyroid, 3 (3.3%) were hyperthyroid, and 3 (4.3%) had TG and/or TM antibodies with a normal thyroid function. The mean age of patients with both CD and TD was significantly higher than that of those with just CD (49.1 vs. 29.5 yr; Student’s t test, p < 0.001). In 6 of the 14 patients with both diseases the TD had presented first: 2 patients with Grave’s disease and 3 with hypothyroidism had received adequate treatment and were euthyroid at the time of examination; in a further hypothyroid patient chronic diarrhea was thought to be a complication of thyroxine supplementation. Moreover, in 3 patients a prior diagnosis of CD delayed the recognition of the symptoms of hypothyroidism (2 cases) or hyperthyroidism (1 case). All the others were found to have overt TD or TG and TM autoantibodies at the time their CD was diagnosed. Conclusions: we have shown that the association of CD and TD is clinically important and more frequent than previously recognized. Since both diseases can present with similar clinical manifestations, we believe that thyroid function and autoantibodies should be checked routinely in all celiac patients at presentation.

972 Gluten Free Diet (GFD) Induces Regression of T-Cell Activation not Only in Duodenum but also in Rectum of Adult Patients with Coeliac Disease (CD)
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An increase in the number of intraepithelial lymphocytes (IEL) has been described in rectal mucosa of patients treated with GFD. However, it is not clear whether GFD reduces CD T-cell activation in rectal mucosa of patients treated in CD. Patients and Methods: Duodenal and rectal frozen biopsies were available in 4 adult coeliac patients (1 M, 3 F, mean age = 39 years) before and after 7 to 24 months of GFD. Monoclonal antibodies directed against CD3, CD25 and HLA-DR were used for each biopsy. Numbers of labelled IEL were counted by using the peroxidase stained cells per 100 epithelial cells. Four normal duodenal and rectal biopsies were used as controls. Results: Results of immunostaining

Aim: To assess the effect of a GFD on the number of IEL and local signs of T-cell activation in rectal mucosa of CD patients. Results: Duodenal and rectal frozen biopsies were available in 4 adult coeliac patients (1 M, 3 F, mean age = 39 years) before and after 7 to 24 months of GFD. Monoclonal antibodies directed against CD3, CD25 and HLA-DR were used for each biopsy. Numbers of labelled IEL were counted by using the peroxidase stained cells per 100 epithelial cells. Four normal duodenal and rectal biopsies were used as controls. Results: Results of immunostaining

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973 Immunoglobulin Deficiency in Coeliac Disease: A Single Institution 25 Year Experience

M.A. Heneghan, E. Cryan, R. Warner, F.M. Stevens, C.F. McCarthy, Department of Medicine, Clinical Science Institute, University College Hospital, Galway, Ireland

Immunoglobulin deficiency, especially deficiency of IgA has been described in coeliac patients. Between 1971 and 1996, over 700 coeliac patients have been treated at this institution. Immunoglobulins have been measured on at least one occasion in 604 of these. Case notes of these patients were reviewed to determine the prevalence of Immunoglobulin deficiency states in this population.

Aims: To examine the clinical characteristics of coeliac patients found to be deficient in IgA, and to compare them with a group of age and sex matched coeliac patients with normal IgA levels.

Results: 14 cases (8 women and 6 men) were identified as being selectively deficient in IgA. One man had common variable immunodeficiency. Mean age at diagnosis was lower in the IgA deficient group (17.52 versus 26.12 yrs). These patients present in 8/14 IgA deficient patients compared with 3/14 controls, p = 0.121.

Abdominal pain was more prevalent among coeliac controls, (5/14) versus (1/14) IgA deficient coeliac patients, (p = 0.167). Recurrent infection and an increased prevalence of autoimmune conditions was noted in the IgA deficient group, but the difference was not significant. Response to gluten free diet was similar in both groups. No difference was found in the prevalence of HLA B8 and DR3 among the two groups. No IgA deficient coeliac was deficient in any IgG subclass.

Conclusions: The prevalence of IgA deficiency in west of Ireland coeliac is 2.31/100. This is similar to other coeliac groups and 13–18 times greater than the general population. These are a distinct group of coeliac patients with unique features and should be followed closely. We also suggest that all coeliaics be monitored for this state.

976 Gastric intraepithelial lymphocytes (GIELs) and Lymphocytic Gastritis (LG) in Adult Cellic Patients


Background and aims: LG has been associated with H. pylori infection and with celiac disease. The prevalence of LG in adult cellic patients from the Mediterranean area is still unknown. The aims were to correlate GIEL concentration and the prevalence of LG and H. pylori infection in adult cellic patients.

Patients and methods: Two or more antral gastric biopsies were taken prospectively in a consecutive series of 49 cellic patients (37 on free diet, 12 on gluten free diet for 6 months at least) and compared with those from 22 control non-celiac patients comparable for sex and age. Biopsies were examined separately by 2 observers and assessed for the presence of gastritis and H. pylori infection. LG was diagnosed if 25% GIELs were counted in at least 300 surface epithelial cells per biopsy. GIELs were also identified by antibody anti-CDS and anti-CD20.

Results. LG was not diagnosed in any patient or control. Mean (range) GIEL concentration was 3 (1–20%) in celiac patients on free diet, 2 (1–10%) in those on gluten free diet, and 0–6% in controls (P < 0.001). H. pylori infection was observed in 25% patients and 32% controls.

Conclusions. LG may be rare in adult cellic patients from the Mediterranean area. Genetic factors may affect the immunological status of these cellic patients. Whether patients with and without increased GIELs differ in response to gluten free diet and in risk of intestinal lymphomas should be investigated.

977 Eating Habits of Children with Down Syndrome

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Children with Down syndrome (DS) frequently have feeding problems which can predispose to an inadequate dietary intake. Aims: 1. To study the eating habits and nutrient intake of 44 children with DS (0–4 year). 2. Compare them to those of 373 children, matched for age and sex. 3. Investigate whether the Recommended Dietary Allowances (RDA) [1] are appropriate for these children. Methods: The food intake was assessed by the dietary history method. Data from patients and controls were compared using the ANOVA analysis. The data from the children with DS were compared to the RDA by means of the Student-t test. Results: The mean weight of the children with DS was 9.7 ± 2.7 kg (P25) versus 11.7 ± 3.6 kg (P50) in the controls. The mean height of the children with DS was 92 ± 13.4 cm (P25) in the controls (p < 0.001). The median age at introduction of bread, of hard pieces of fruit and of warm meals was significantly older among the children with DS (12, 30 and 24 months respectively) than in the controls (8, 12 and 12 months respectively). No significant differences were found in the energy intake from macronutrients. The daily intake of vitamins B2, B6 and calcium of the children with DS was significantly lower than in the controls, but in agreement with the RDA. The energy intake per kg body weight of the children with DS reaches the upper limit of the RDA. No significant difference in the eating habits of children with DS versus controls is the age at introduction of solid food. The fact that the energy intake per kg body weight of the children with DS reaches the RDA can be explained by the significant lower body weight of the children with DS compared to the controls (p < 0.01). Dietetic advise to DS children should be based on the body weight and on the developmental age of the child and not on their chronological age.


978 Cow's Milk Allergy and Down Syndrome

G.G.D.S. Ceizmadia, G.D. Hopman, E.A.B. de Graaf, J. Hermans, M.L. Mearin, Dept. of Paediatric; Dept. of Dietetics and Nutrition, Dept. of Medical Statistics, Leiden University Hospital, The Netherlands; Dutch Down Syndrome Foundation, The Netherlands

The board of the Dutch Down Syndrome Foundation (DDF) suspected children with trisomy 21 (DS) to have cow's milk allergy (CMA) more often than children in the general population (1.7–2.8%) [1]. Aim. The DDF asked us to establish the frequency of CMA. Design. Experimental, prospective, double-blind, food intervention study. Patients. All 109 families living in the western part of the Netherlands were invited. Inclusion criteria: having a child with DS age 0–4, home-reared, not diagnosed as having CMA, not taking any breast-feed. Methods. The prevalence of CMA was based on the gold standard of double blind food intervention: improvement of symptoms on cow’s milk protein (CMP) elimination and worsening of the same symptoms on CMP reintroduction. A positive elimination-introduction test was considered diagnostic. During the whole study the children followed a CMP-free diet based on an adapted hypo-allergic whey hydrolysate milk formula (Nutrigen Pepti Plus, Nutricia Nederland BV). CMP was double-blind introduced by adding 1.5 g CMP per 100 ml CMP-free formula. Before and after each food intervention the symptoms compatible with CMA (respiratory, dermatological, gastrointestinal) were scored. Results. Data on CMA before the study were available in 92 children: in 3 of them CMA had already been diagnosed, but not according to the elimination-introduction elimination principle. 49 children participated in our study (41%, 22 boys. Mean age: 21 ± 11 months).

The main reason to participate (63%) was to exclude CMA. Reasons for not participating were too great a burden on the family (13%), no suspicion of CMA (12%), a critical clinical condition (7%) and unknown reasons (27%). CMA was proven in 1 child (2.8%. 95% CI: 0.1%–15.4%). Conclusion. In a selected group of children with DS (nearby parents suspecting their child to have CMA participated) we found CMA only in 1 of 109 children (1%, 95% CI: 0%–5.1%). The frequency of CMA in children with DS seems to be similar to that reported in the general Dutch child population.


979 Acute Diarrhoea in France Probably Due to Rotavirus during Winter: A Case-Control Approach


Background—The surveillance data gathered from the Sentinelles Network at a national level indicates that acute diarrhoea (AD) occurs with an endemic pattern usually including an epidemic winter outbreak [1]. We estimate that 670,000 cases of AD were diagnosed in general practice in January 1996. However the determinants of AD during the winter period are not well established in France. The aim of this study was to ascertain risk factors of AD: mode of transmission (consumption of shellfish, of soft water; recent contact with a case of diarrhoea) and facilitating factors (drug consumption; association with influenza or ear infection; underlying chronic disease).

Methods—A case-control study was conducted with incident cases matched to controls for age class; 588 cases and 568 controls were included among the patients of sentinel practitioners between December 24, 1995 and January 31, 1996. Conditional logistic regression was used for statistical analyses.

Results—There was no association between AD and any shellfish consumption – e.g. raw oysters (OR = 0.9 [0.9; 1.0]) – or soft water drinking (OR = 0.7 [0.5; 1.0]). Factors significantly associated with AD were: an intra-familial contact with a case of diarrhoea within the last ten days (OR = 4.4 [3.0; 6.3]); an estimated delay inferior to 3 days between the time of contact and the date of consultation (OR = 10.8 [4.9; 23.6]); and cohabitation with a child under two (OR = 1.9 [1.3; 2.7]).

Conclusion—These results stress the major role of person-to-person transmission in the occurrence of winter acute diarrhoea epidemics. The nature of the risk factors significantly associated with the case of suspected rotavirus infection. Rotavirus, because of its infective epidemiology and its incubation period usually inferior to 3 days, is one of the most plausible causes of winter diarrhoea.

A French Survey on Epidemiology and Management of Acute Diarrhoea

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Although acute diarrhoea is a common problem, little is known about its epidemiology, management and socio-economic impact.

Method: 6-month survey, using 2 previously validated questionnaires (Q) via internet: the system allows real-time follow-up and validation of data. 176 of 277 practitioners (Gps) who initially agreed on participating throughout France, completed 1 over 6 months: phase-1 in all patients (pts) (> 15 yrs) presenting with acute diarrhoea (> 3 stools per day, max 72 hrs) and during 2 consecutive (max 2) O to outcome of diarrhoea in 5 consecutive pts (4 ± 3 days after phase 1).

Results. Information was generated in 4200 patients by 176 GPs (age 42–75 yrs, ratio M:F 42/58, 48.4% had profession). Seasonal variations were not observed. The main associated symptom was abdominal pain (90%). Vomiting was reported in 39, fever in 33%, mucus in stools in 9% and dehydration in 3%. The cause was thought to be viral in 51%, alimentary 23%, drug-induced 8%, bacterial 6.5% and parasitic 0.7%. The duration of episode was shorter in acute (ACE), an antibiotic without effects on gut peristalsis and thought to give less constipation than loperamide.

Comparison of Loperamide-Oxide and Atorphan in Acute Diarrhoea

J. Frerixos1, J.-R. Sallenne2,1 Hospital Rangueil, Toulouse, France; Janssen-Cilag and GPs Cooperative Group, France

Loperamide-oxide (LOX), a new loperamide derivative with higher mucosal (antisecretory) than myenteric (mobility-inhibiting) properties, was compared with loperamide (LOX-A237), an antibiotic without effects on gut peristalsis and thought to give less constipation than loperamide.

Method. Randomized, double-dummy placebo (PLA)-blinded study in 574 adult outpatients (pts) with acute diarrhoea, > 12 hrs ± 72 hrs, ± 3 (semi-)liquid stools/day). Pts received LOX, 2 tabs of 1 mg at start and 1 tab after each unformed stool (max 8 tabs/day), plus PLA caps identical to ACE, or ACE 100 mg tid, plus LOX-identical PLA tabs. Hospitalization, blood in stools, fever (> 38.5°C), severe infection, chronic diarrhoea, IBD, and intolerance of antibiotics or other anti-diarrhoeals were excluded. Treatment lasted until the end of diarrhoea or max 96 hrs.

Results. diarrhoea was resolved in 53% LOX pts, vs 48% ACE pts within 24 hrs. However, ACE were symptoms) lead to absenteeism at work in 1 of 5 pts, usually of short duration (> 3 days). Direct cost of management were the lowest in case of imodium prescription, but indirect costs (days of sick-leave) appeared not to be affected by the type of medication prescribed.

Bacterial Overgrowth of the Small Bowel (BOSB) and Malabsorption of Low Weight Sugars in Isolated IGA Deficiency

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In isolated deficiency of IgA patients BOGB is frequent, leading to chronic diarrhoea. The reference method for BOGB was the demonstration of a large number of microbial colonies (≥ 2 × 10^5/cm^2) in cultures of jejunal fluid. Recently, H2-breath test (HBT) was found useful: a good correlation between jejunal fluid carbohydrate consumption and H2 in expired breath (1 ppm) was reported. Relevant lactate malabsorption was demonstrated by our group in chronic achlorhydria, frequently affected by diarrhoea and impairment of IgA function. In this study, a series of patients affected by primary IgA deficiency (p-IGAD) was studied to confirm fasting basal overproduction of H2 and BOGB, and to assess the frequency of low weight sugars (LWS) malabsorption. Materials and methods. A series (A) of 27 patients (14 male, 0.13 female, age 33–46 yr, m ± SD = 39.9 ± 17.16) affected by primary IgA deficiency, without any resectable parasite in the gut were investigated. Controls (C) were 38 healthy people, matched for age, sex and dietary habits. All the subjects were taken at a low-fiber diet for two days before the test. Body weight and height were measured. HBT was performed in the morning (starting about at 9 a.m.) after a 12-hour fasting. Basal H2-level in expired air was assayed; lactose (20 g/H2O 100 ml) was administered; samples of expired air were taken each 30 min for 4 hours. The diagnosis of lactose malabsorption was established in case of fasting baseline H2-levels were > 20 ppm higher than basal levels. Statistical evaluation was performed by x2-test and Tau-C Kendall's test, for Area Under Curve (AUC) evaluation, by Mann-Witney's test. Results. Basal H2-level was 8.5 ± 9.0 ppm [confidence interval (ci) 3.9 – 7.9 ± 5.2 ppm (ci = 4.99 ± 12.06) in group A and 5.6 ± 5.2 ppm (ci = 4.99 ± 12.06) in group C. The frequency of malabsorption was 78.6% in group A and 41.0% in group C: H2-ACE was 12.741 ± 11.497 (ci = 0.833.30 ± 17.199,58) in group A and 3.185.77 ± 3.617.92 (ci = 2.012 .7 ± 4.358.56) in group C. Body Mass Index (BMI, body weight/m^2) in group A and 3.17 ± (ci = 2.713 ± 2.419) in group A, 24.18 ± 3.26 (ci = 23.12 ± 25.25) in group C. Conclusions. According to our data, basal H2-levels are increased in IGA deficiency respect to controls, suggesting BOSB (p < 0.001). Also the frequency of malabsorption is increased in IGA deficiency, as confirmed by AUC values (p < 0.001). LWS malabsorption leads to lowered BMI in IGA deficiency, suggesting impaired LWS utilization. These clinical findings may be related to: 1) modifications of intestinal microenvironment, specific for IGA deficiency (both congenital and acquired), leading to H2-conserving decrease and to saccharolytic bacteria increase, producing the increased H2-levels in the colon; 2) small bowel mucosa impairment, frequent in IGA deficiency patients, leading to reduced activity of brush border enzymes, producing increased frequency of malabsorption; 3) increased osmolality of stool and increased production of volatile fatty acids (with cathartic activity) in the colon, leading to increased frequency of diarrhoea, promoting the BMI decrease (p < 0.001) observed in IGA deficiency patients.

Efficacy of Two Antibiotics and a Probiotic in the Treatment of Small Intestinal Bacterial Overgrowth

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Although antibiotics are widely used in the treatment of small intestinal bacterial overgrowth (SIBO), no controlled trial has been performed to test their efficacy. In this study we compared 3 treatments: 1) amoxicillin-clavulanic acid (Am-c) which is in vitro the most efficient antibiotic against aerobic and anaerobic bacteria isolated from jejunal aspirates; 2) norfloxacin (Nor) which is only efficient against aerobic bacteria; 3) Saccharomyces boulardii (Sb) a probiotic agent whose efficacy has been reported in children with SIBO. Methods: Ten patients suspected to have SIBO (predisposing conditions, conditional diarrhoea, malabsorption syndrome) and a positive H2 breath test (H2BT) were enrolled and received for five 7 days periods no treatment (basal period), a placebo (Pla) and then, in a random order and double blinded fashion, Nor (800 mg/d), Am-c (1500 mg/d) and Sb (1500 mg/d). The main criteria of efficacy was the mean daily number of stools reported on the last 3 days of each period. When the treatment was considered efficient, patients were followed until complete resolution of diarrhoea (> 12 hrs ± 72 hrs). There were no significative differences in mean duration of diarrhoea (26.8 hrs for LOX, vs 28.9 hrs for ACE) or daily number of unformed stools. The number of unformed stools, however, was lower with LOX than with ACE during the total study period. The last day of each period, was 00.00) and in the responding pts (< 0.01). Overall response was in favour of LOX when rated by physicians (< 0.01), a difference not found among the pts' assessments. Both drugs were well tolerated, but less aggravation of bloating occurred with LOX. The quality of life was comparable in both groups during the 1st and 2nd day, but in favour of LOX during the 3rd day (less pts with incapacitating symptoms or interrupting work, < 0.05).

The Ursodeoxycholic Acid–p-Aminobenzoic Acid Loading Test, a New Diagnostic Tool in the Bacterial Overgrowth Syndrome

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Introduction: Contaminated small bowel syndrome (CBSB) is frequently associated with different clinical symptoms, among which meteorism and diarrhoea are the most common. Meteorism is an excess of gas and flatus, and not a result of bacterial toxins and pathological fermentative processes. These mechanisms include abnormal splitting of carbohydrates, and deconjugation and dehydroxylation of bile salts. Some bacteria capable of metabolizing bile salts have been shown to release p-aminobenzoic acid (PABA) from...
an ursodeoxycholic acid (UDCA)–PABA conjugate. The present aim was to determine the possible complementary role of the UDCA–PABA test in the diagnosis of intestinal bacterial overgrowth. Patients and methods: The H2 breath and UDCA–PABA tests were performed simultaneously in 68 patients with suspected C. difficile colitis, and in 5 healthy control subjects. The H2 breath test involved was performed by oral loading of 25 g lactose and 10 g lactulose. The UDCA–PABA test was carried out by the oral loading of 250 mg UDCA and 295 mg PABA. The results of both tests were pathological if the amount of urinary excreted PABA was less than 20% of the administered dose. The diagnosis of bacterial overgrowth was considered to be established when either the H2 breath test or the UDCA–PABA test yielded positive results. Results: 35 of the 68 patients (51%) proved pathological. 13 of 35, only the enhanced urinary PABA excretion (11.7 ± 1.42 mg vs. 3.6 ± 0.68 mg) indicated the bacterial overgrowth. 15 of the 35 gave only a positive H2 breath test, and in the remaining 7 cases the results of both tests were pathological. 8 CSS cases, the urinary excretion of PABA decreased significantly following a 10-day Tindalize treatment (5.5 ± 1.29 mg vs. 13.1 ± 2.07 mg). Conclusion: The UDCA–PABA test is to be a valuable clinical adjunct to the H2 breath test for the detection of intestinal bacterial overgrowth: the H2 production alone failed to reveal bacterial overgrowth in 37% of the cases.

985 Bacterial Colonisation of the Upper Gastrointestinal Tract is Related to Severity of Illness

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The upper gastrointestinal tract is usually regarded as being sterile. The occurrence of bacterial colonisation in the upper gastrointestinal tract may predispose to septic morbidity. It has been suggested that this occurs more frequently in critically ill or immunocompromised patients. The aim of this study was to assess changes in gastric flora and to attempt to relate these to severity of illness.

We have prospectively evaluated proximal gut microflora in 279 surgical patients by culturing aspirates obtained aseptically from indwelling nasogastric suction tubes. Severity of illness was assessed using the “POSSUM” physiological scoring system.

Eighty five (31%) aspirates yielded no growth, eighty four (30%) patients grew one organism type and 110 (39%) grew multiple organisms types. Candida albicans was the most abundant organism cultured and was present in 104 (37%) of aspirates. This was followed by E. coli 38 (11%), Staph Sp. 39 (12%), Lactobacillus 27 (10%) and Strep. Faecalis 28 (8%). Forty eight percent (175) of bacteria isolated could not be commonly associated with intestinal colonisation. Multiple organism colonisation occurred in significantly fewer patients with low (<20) POSSUM scores than those with high (>30) scores (35% vs 67%, p < 0.02, χ2 = 7.09) and was associated with an increase in septic morbidity.

We conclude that upper gastrointestinal tract bacterial colonisation is common in surgical patients and that bacterial overgrowth is related to the degree of physiological stress and may predispose to septic morbidity.

986 Prophylaxis of Mucosal Damage with Sucralfate During Cancer Therapy

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Purpose. Radiotherapy and chemotherapy of different malignancies may be complicated by a variety of side effects, some of which may be related to mucosal damage. The value of sucralfate in the prevention of radiation induced symptoms was suggested by the results of two open studies one with prostate and urinary carcinomas and the second with gynaecological cancer treated with radiotherapy.

Methods. A double-blind randomised placebo-controlled study in patients treated with curative intent for prostate and urinary bladder cancer with external radiotherapy and the study included 70 patients. The other study also double-blind, placebo-controlled included 50 patients receiving irradiation against the head and neck with curative intent.

Summary of the results. For the head and neck patients the mucosal reactions were significantly worse for the placebo group at week 1, 2 and 3, but at other observation times the differences did not reach statistical significance. The results of the pelvic treated patients showed that the frequency of diarrhoea, stool consistency and the number of patients requiring symptomatic therapy with loperamide were significantly in favour of sucralfate group.

Conclusions. The data demonstrated that sucralfate can be of value in reducing radiation induced bowel and oral symptoms during and following radiotherapy of the head and neck and pelvic region.

987 H2 Starch Breath Test in the Study of Functional Gastrointestinal Disorders

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Many patients with irritable gut experience gastrointestinal distress after starch ingestion. We studied the orococcal transit and absorption of starch by means of a H2 breath test in 121 H2 producers: 106 patients with functional gastrointestinal disorders (72 with dyspepsia, 17 with constipation, and 17 with diarrhoea) and 15 healthy volunteers. Breath samples were taken every 30 min for 9 hours after ingestion of 100 g of starch in the form of white bread. H2 breath tests were performed with 10 (20) mg of starch carried out in 34, 76 and 67 subjects, respectively. Results are expressed as medians and interquartile ranges (25–75%). Results: Incomplete absorption of starch peaked in 10 patients (10 ppm) was present in 11/15 healthy controls (73%) and in 76/106 patients (72%). Starch ingestion caused gastrointestinal symptoms in only 11 patients of whom 7 showed starch malabsorption. The 9 hour H2 excretion (area under the curve) after starch ingestion was significantly lower (p < 0.05) in patients (42 ppm·h, 26–82) than in controls (80 ppm·h, 36–126). The orococcal transit time of starch did not significantly differ between the two groups (300 min, 270–390 in patients and 300 min, 180–300 in controls), but was significantly lower (p < 0.01) in patients with diarrhea (240 min, 180–330) when compared with patients without diarrhea (360 min, 270–405). An inverse relationship was found between H2 output and transit time in patients (r = 0.65), but not in controls (r = 0.22). No relationship was found between the H2 excretion or transit time measured after starch and those after lactulose. The H2 excretion after starch was not significantly different between the 36 patients with lactose malabsorption (43 ppm·h, 29–92) and the 40 patients with normal lactose response (35 ppm·h, 15–78). In the 33 patients with fructose malabsorption in the H2 excretion after starch was higher (55 ppm·h, 29–96; p = 0.06) than in the 34 with a normal fructose breath test (36 ppm·h, 17–75). Conclusions: The H2 starch breath test needs further investigation before it can be used for the diagnosis of functional gut disorders. According to our results gastrointestinal distress after starch ingestion in patients with irritable gut cannot be attributed to excessive H2 intestinal production.

988 Treatment with Lidocaine Gel Enema for Ulcerative Colitis

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Purpose: Neuropeptides liberated from enteric neurons have been suggested to contribute to the inflammatory response at the site of mucosal injury. We examined the inhibitory effects of lidocaine on the responses elicited by neuropeptides were also studied. We studied the efficacy of lidocaine gel enema (LG), reported in 1989 by Bjork, for UC. Methods: The subjects of this study were 10 patients who underwent LG at our department. Eight patients were male, and two were female. The conditions before the start of LG were the followings. Seven patients had poorly controlled on sulfasalazine. One became in worse condition during progressive reduction of steroid dosage. One could not reduce the dose level of steroid. One had to stop the steroid therapy because of the side effect. LG was performed as follows. 40 ml (10 ml in the morning, 10 ml in the daytime and 20 ml at night) of 2% lidocaine gel was administered into the rectum. Endoscopy was carried out immediately before and 1 week after the start of LG. Tissue samples were collected for histochemical localization and the tissue was examined histologically. Results: In all cases, rectal discomfort disappeared within 5 days, and viscous bloody feces disappeared within 2 weeks after the start of LG. Endoscopically, the disappearance of rectal ulceration and a reduction in rectal erosion were observed after 2 weeks of LG. The numbers of crypts and goblet cells were increased, and the inflammation was reduced after 2 weeks of LG. Substance P immunoreactive for nerve fibres slightly increased after 2 weeks of LG. None of the patients complained about any side-effects of LG. Conclusion: LG is easy to do and is expected to reduce inflammation, probably through suppressing the release of neuropeptides. LG will be a promising new therapy for UC.

989 Interleukin-8 Induced Neutrophil Activation is Suppressed by the Thiol Modulating Anti-Collitis Agent OR-1384

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The extensive infiltration of neutrophils into the inflamed mucosa plays a major role in the pathogenesis of inflammatory bowel disease. One of the most powerful inflammatory mediators responsible for the attraction and activation of neutrophils is interleukin-8 (IL-8). OR-1384 is 3-[4-(methylsulfonyl)phenyl]methylenemalononitrile, a 4-pancreatinase isolated by the Bio-Pharm Ltd. company from oral fluid of various animal colitis models at doses of 0.3 – 10 mg/kg. OR-1384 forms reversible adducts with free thiols, which are essential for the proper function of the specific IL-8 receptor on the surface of neutrophils. The aim of the study was to evaluate how the reversible thiol scavenger OR-1384 can affect IL-8 binding and subsequent neutrophil activation.

Methods: Human neutrophils were isolated from buffy coats. The neutrophils (2 x 10⁶ cells) were treated with different doses of OR-1384 and reference compounds and incubated with 125I-IL-8. The free and bound 125I-IL-8 were separated and the specific binding of 125I-IL-8 to the neutrophils was measured. The nature of OR-1384 binding to the IL-8 receptor (IL-8R) was evaluated by adding glutathione to the incubation mixture containing OR-1384. Elastase
release from the neutrophils (20 x 10^6 cells) was used as an IL-8-induced functional assay.

Results: OR-1384 dose-dependently prevented IL-8 binding to the neutrophil (IC50 = 70 μM) while the analogue of OR-1384 without thiol modulating properties was ineffective. The reversible nature of OR-1384 binding to the IL-8 receptor was confirmed by the addition of glutathione. The neutrophil functional assay showed that elastase release was effectively inhibited by OR-1384 (IC50 = 18.9 μM), 5-ASA did not inhibit IL-8 binding but showed some effect on elastase release at high mM concentrations.

Conclusions: The thiol modulating compound OR-1384 was shown to prevent IL-8 binding to neutrophils and interfere with the neutrophil activation process determined as inhibition of elastase release. The effects were clearly dependent on the thiol modulating properties of OR-1384. However, unlike other thiol reactive compounds the effect was reversible. In addition to the previously reported mechanisms of cytokine formation in inflammatory cells, OR-1384 is likely to exert its effect by inhibiting IL-8 induced neutrophil-mediated deleterious effects in the inflamed gut.

990 A Pair of Twins with Myo-Neuro-Gastrointestinal Encephalopathy (MNGIE) Syndrome
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MNGIE syndrome is a rare multisystem mitochondrial disorder affecting the nervous system and Gastrointestinal (GI) tract. Here we report a pair of male twins, 45 years old, suffering from this syndrome. Both were short, thin, almost cachectic (35-40 kg) and stated intermittent diarrhoea since childhood, leading to malabsorption, which deteriorated recently.

The one of them had been treated for coeliac disease, without success, until we considered his neurological findings, which had gradually become prominent and consisted in bilateral eyelid ptosis, neurosensory hearing loss, nasal speech and mild limb weakness.

Laboratory investigation did not reveal specific pathological findings, except malabsorption. However brain MRI showed severe leuencephalopathy. Muscle biopsy showed scattered ragged red fibres and denervation. Mitochondrial enzyme analysis showed significant deficiency of cytochrome-c-oxidase.

Southern blot analysis and PCR showed no deletion of mitochondrial DNA. Investigation of the second patient revealed similar findings.

Both patients died recently, within 3 months the one from the other. Their parents, two older brothers and one sister are alive in good health.

MNGIE syndrome seems to be a separate nosological entity in the spectrum of mitochondrial encephalomyopathies affecting also the GI tract. However, although gastrointestinal symptoms are firstly presented and lastly in this syndrome, this has been reported only in the neurological literature, in four cases only, and never in twins.

991 Vasoactive Intestinal Peptide Is Involved in the Interleukin-1β Inhibitory Action on the Acute Jejunal Contraction
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We have previously shown that interleukin-1β (IL-1β) decreased the acetylcholine (ACh)-induced intestinal contractility through an action on the enteric nervous system. However, the neuromediators potentially involved are poorly known.

The aim of the present study was to determine the possible involvement of the three main cholinomimetic, nonadrenergic relaxant mediators: nitric oxide (NO), vasoactive intestinal peptide (VIP) and adenosine triphosphate (ATP) in the inhibitory effect of IL-1β on the ACh-induced intestinal contractility.

Methods. Isometric contraction of rat jejunum longitudinal muscle-myenteric plexus (LM-MP) preparations, bathed in Krebs solution was recorded by a force transducer, IL-1β (10 ng/ml) was added to the bath for 90 minutes. The effect of potentially inhibitory agents on the LM-MP jejunal motor response to ACh (10-5 M) was investigated before and after exposure to IL-1β. The following drugs were used: N0-nitro-L-arginine methyl ester (LNAME); N0-nitro-L-arginine (L-NAME); N0-nitro-L-arginine-L-NAME; N0-nitro-L-arginine active intestinal peptide (VIP) 10-28; [4-Cys-DPh-Ph, Leu1]VIP and suramin to inhibit NO synthesis, VIP and ATP effect respectively.

Results: L-NAME (3 x 10-4 M), L-NAME (3 x 10-4 M) and L-NAME (3 x 10-4 M + IL-1β) produced significant jejunal contractions, which were reduced by IL-1β, but increased the ACh response of smooth muscle when administered alone. Moreover, suramin (3 x 10-4 M) failed to inhibit the inhibition induced by IL-1β. On the contrary, addition of VIP (10-28 M) (6 x 10-5 M) [4-Cys-DPh-Ph, Leu1]VIP and VIP to inhibit the inhibitory effect of IL-1β on the jejunal contractions. The effect of IL-1β was fully abolished by VIP (10-6 M).

Conclusions. In LM-MP jejunal preparation, neither NO nor ATP are involved in the inhibitory effect of IL-1β on ACh-induced contractility. This inhibitory effect seems to be mediated by VIP.

992 Is Small Bowel Motility Induced by Duodenal Enteral Nutrition Dependent on Osmolality?
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Background: Aim: Recently, we have demonstrated that upper small intestinal motility induced by duodenal enteral nutrition solution is not dependent on the amount of calories administered (Gastroenterology, May 1996: abstract). The aim of the present study was to investigate, whether the intestinal fed pattern induced by duodenal enteral nutrition is dependent on osmolality.

Methods: Duodenal infusion (5ml/min) of an enteral nutrition (2.64 kcal/ml; 17% proteins, 59% carbohydrates, 24% lipids) at 3 different osmolalities (190, 300, and 600 mmosm/kg obtained by the addition of sodium chloride) on one consecutive days in a randomized order in 8 healthy volunteers. Duodenal infusion started 10 min after a phase III activity and was continued for 90 min. Motility was recorded with a digital data logger and 6 catheter-mounted miniature pressure transducers located around the duodenojejunal flexure. Results: Water content and computer-aided analysis (Scand J Gastroenterol 1994; 29: 1076–82).

Results (means ± SEM):

<table>
<thead>
<tr>
<th>Osmolality (mosm/kg)</th>
<th>190</th>
<th>300</th>
<th>600</th>
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<tbody>
<tr>
<td>Contraction frequency [min⁻¹]</td>
<td>1.95 ± 0.21</td>
<td>1.94 ± 0.28</td>
<td>1.92 ± 0.27</td>
</tr>
<tr>
<td>Contraction amplitude [mm Hg]</td>
<td>20.7 ± 0.3</td>
<td>21.3 ± 0.9</td>
<td>20.6 ± 0.6</td>
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<tr>
<td>Propagated contractions [%]</td>
<td>36.5 ± 1.0</td>
<td>32.7 ± 4.1</td>
<td>32.5 ± 4.5</td>
</tr>
<tr>
<td>Propagation distance [cm]</td>
<td>4.1 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>4.1 ± 0.2</td>
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</table>

Conclusion: Small intestinal motility induced by duodenal enteral nutrition is not influenced by osmolalities ranging from 160 to 600 mmosm/kg.

993 Enteric Dysmotility Revealed by Computer Analysis of Prolonged Small Bowel Manometry
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Prolonged ambulant small bowel manometry (PSBM) has been shown to discriminate groups of patients (Chagas’ disease, HIV) from groups of normal controls, and the precision of PSBM is increased by computer analysis. However, its value in the diagnosis of individual patients remains to be determined. We analyzed PSBM data from 37 patients with neurological or gastrointestinal disorders. The commonest cause of referral was suspected chronic idiopathic intestinal pseudo-obstruction (CIPI), with differential diagnoses of CIIP, mechanical obstruction, irritable bowel syndrome, or chronic intractable abdominal pain. Three patients with intractable post-vagotomy diarrhoea and 4 diabetic patients with diarrhoea and abdominal pain were included in the cohort. After intubation with a multi-channel pressure-sensitive catheter under fluoroscopic control, recording on a portable datalogger continued for 17–24 hours with the patient freely ambulant at home or in hostel accommodation. In 5 patients, all with CIIP, endoscopic assistance was required to position the catheter; recording was unsuccessful in 2 patients with disabling CIIP because the recording catheter was not retained in the proximal small bowel. The fasting data recorded from each patient was characterised by computer analysis, and the values obtained were compared with control values derived from 47 comparable recordings in healthy volunteers.

Abnormal motility activity was found in 13/28 patients with suspected CIIP, in 44 diabetics and in 3/3 vagotomised patients. The commonest abnormality was increased nocturnal contractile activity. There was a significant (p = 0.005) excess of prolongation and/or diminished migration velocity of Phase 3 of the migrating motor complex (MMC) in CIIP, suggesting myenteric plexus damage: this was not seen in the other groups where there was, however, a significant (p = 0.05) excess incidence of accelerated Phase 3 migration velocity. We conclude that systematic analysis of prolonged small bowel manometry promises to be an important clinical tool in the diagnosis of enteric neuropathy.

994 Computer Programmes Disagree in Measurement of Small Bowel Contractions Recorded by Ambulatory Manometry
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Introduction: Computer analysis of small bowel manometry has been shown to give discordant results for different programmes with regard to quantitative recognition of contractions events [1]. It is unclear to what extent different programmes agree with regard to quantitative measurement of contractions.

Methods: Six ambulatory test records with normal intestinal motility patterns including fasting and postprandial motility were analysed by three computer programmes: SBMA 1.41, (Krankenhaus München-Bogenhausen), Motan 3.3 (Gatehouse ApS), Multigram 6.31 (Synectics Medical AB). The method of comparison has previously been described [1]. Amplitude, area under the curve (AUC) and duration of contractions, that were recognized by all programmes,
were subjected to analysis. Correlation coefficient (r) and slope of linear regression with confidence intervals (CI) were calculated for each pair of programmes.

Results: 2285 contractions were recognized by all programmes, and thus subjected to analysis, out of a total of 4827 contractions recognized by at least one of the programmes.

Programmes

<table>
<thead>
<tr>
<th>SBMA vs Matot*</th>
<th>Matot vs Multigram*</th>
<th>Multigram vs SBMA*</th>
</tr>
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<tbody>
<tr>
<td>r slope LCI UCI</td>
<td>r slope LCI UCI</td>
<td>r slope LCI UCI</td>
</tr>
<tr>
<td>0.81 0.55 0.54 0.56 0.62 1.51 1.49 1.53 0.64 1.09 1.08 1.09</td>
<td>0.66 0.36 0.36 0.37 0.63 3.25 3.15 3.35 0.88 0.55 0.54 0.56</td>
<td>0.29 0.90 0.99 0.91 0.28 1.78 1.75 1.81 0.21 0.52 0.51 0.53</td>
</tr>
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</table>

*first programme y, second programme x for regression; L. and U. CI: lower and upper 95% confidence limits

Conclusion: The degree of agreement between different computer programmes in measuring contractions is unexpectedly low, showing that the outcome depends critically on the algorithm applied. Difficulties are encountered particularly in the analysis of duration of contractions.


995 The Importance of Immune Genetic Test in the Study of the Pathogenesis of Chronic Pancreatitis

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Aim. To deepen knowledge on the pathogenesis of chronic pancreatitis (CP), its use in the diagnosis and treatment of the disease.

Task. To study the immune genetic predisposition to CP in connection with the specialty of its manifestation.

Material. The frequency of occurrence of erythrocyte antigens (ABO-system and rhesus-factors – CcDee) and leucocyte antigens (HLA-system) with a calculation of the risk of the disease was studied on 52 patients of CP and 56 non-patients.

Results. The risk of the development of CP was high in those belonging to blood group A0 by 3.23 times. Antigens of the HLA-system A1, B8, B4, B28, the risk of rise in the development of the disease in 2.79, 3.51, 3.52 and 3.44 times correspondingly. These antigens were associated with regression between the T- and B-branches of the immune system with a deficit of T-suppressor cells and a marked cell autosensibilisation to pancreas tissue. In the presence of the phenotype B40 the risk of developing CP rose by 6.47 times which was connected to a rise in the blood concentration of natural killers. Antigen B40 was associated with a fall in the debit part of lipase and B7 with a rise in the echogram of pancreas in sonography with i.e. with fibrosis of the tissue of the organ. The risk of developing CP in patients having the phenotype of the antigens rose correspondingly by 3.17 and 3.38 times. Antigen protectors were A3, B4, Cw4.

Conclusion. In part of the patients with CP immune genetic predisposition to the development of the disease has a place, and separate antigens were associated with its pathogenetic branches. This information in perspective can be used in the diagnosis and treatment of CP.

996 Comparison of the Preventive Effects of Somatostatin and SMS 201-955 in ERCP-Induced Hyperamylasemia

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The aim of this study was to compare the preventive effects of SMS 201-955 and somatostatin in ERCP-induced hyperamylasemia.

Materials and Methods: 120 patients who underwent ERCP were included in our study and were divided in to 3 equal groups. After an overnight fast, the patients were sedated with 10 mg midazolam and duodenal relaxation was achieved with 40 mg hyoscine-n-butylbromide, intravenously (iv). Group I was treated with SMS 201-955 (3 × 100 μg/day sc on the ERCP day) and the second group was treated with somatostatin (3.5 μg/kg iv bolus with the start of ERCP, and then 250 μg iv infusion for 4 hours). The control group received only iv saline. Contrast material was same in all groups. Serial blood samples were withdrawn pre-ERCP and at timed intervals after ERCP (4th hour, 24th hour, 48th hour). Serum amylase and isoenzyme levels were determined.

The results are shown in the table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-ERCP</th>
<th>ERCP</th>
<th>Post-ERCP</th>
<th>Post-ERCP</th>
<th>Post-ERCP</th>
<th>Post-ERCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ERCP amylose at 4th</td>
<td>Pre-ERCP amylose at 24th</td>
<td>Pre-ERCP amylose at 48th</td>
<td>Pre-ERCP isoamylose at 4th</td>
<td>Pre-ERCP isoamylose at 24th</td>
<td>Pre-ERCP isoamylose at 48th</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>116 ± 44</td>
<td>186 ± 44</td>
<td>220 ± 28</td>
<td>202 ± 36</td>
<td>69 ± 11</td>
<td>107 ± 12</td>
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<tr>
<td>2</td>
<td>94 ± 37</td>
<td>147 ± 42</td>
<td>116 ± 17</td>
<td>149 ± 28</td>
<td>55 ± 19</td>
<td>81 ± 2</td>
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<td>152 ± 49</td>
<td>236 ± 98</td>
<td>238 ± 86</td>
<td>237 ± 86</td>
<td>80 ± 15</td>
<td>136 ± 74</td>
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</tbody>
</table>

Conclusion: According to this study, somatostatin was more potent than SMS 201-955 for inhibiting ERCP-induced hyperamylasemia.

998 Prognostic Factors in the Therapeutic Approach to Pseudocysts of the Pancreas

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Purpose: This study was performed to test the prognostic value of etiology, location and the amount of liquid in the pancreatic pseudocyst (PC), as well as the concentration of biochemical parameters (LDH, glucose, proteins, sodium, potassium, bilirubin and lipase) of the PC contents and the serum of the patients regarding the efficiency of ultrasound (US)-guided percutaneous evacuation (PE) as a possible method of therapeutic approach.

Methods: After obtaining informed consent, a total of 43 patients with histories of acute pancreatitis and PCs persisting for more than 6 weeks were included in the study. The diagnosis was made by US examination and CT scan. The PC content samples were obtained using a Chiba needle of 21-gauge under US control. Biochemical parameters were determined by standard laboratory methods.

Results: Concerning the various etiologic factors, no differences were noted in the outcome of PE. PE was a successful method of treatment for the PCs located in the tail of the pancreas, while those located in the head of the pancreas had a significantly lower healing rate. The amount of liquid taken during the PE was significantly lower in patients successfully treated by PE (median 96.5 mL) compared to the PC liquid amount in the patients with the failed treatment (median 222 mL). Concerning the biochemical parameters, unlike the serum data, significantly lower values of proteins, potassium and lipase in the PC liquid were found successively treated patients.

Conclusion: It can be concluded that the analysis of the mentioned parameters (location, the amount of liquid, proteins, potassium and lipase concentrations in the evacuated material) can allow an early decision concerning the therapeutic approach to patients with PC.

999 Long-Term Effects of ONO-3403, A New Oral Protease Inhibitor, on Experimental Chronic Pancreatitis in Rats

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Purpose: ONO-3403 is a potent newly developed oral protease inhibitor. In rats, long-term administration of ONO-3403 has a pancreatotoxic effect. We therefore evaluated the protective effect of chronically administered ONO-3403 against the development of pancreatic fibrosis in a rat model of chronic pancreatitis.

Methods: Rats were injected intraduodenally with zineoleic acid solution. After three days in the acute phase, there was progressive pancreatic atrophy, leading to diffuse fibrosis by day 28. Some of the rats were fed a diet containing 0.1% ONO-3403 from day 2 or 4 until day 28. Histologic findings and pancreatic enzyme contents of ONO-3403-treated rats were compared with untreated controls.

Results: On day 2 there was no acinar cell loss and the fibroblasts appearing in the interstitium were immature. On day 4 acinar cell loss and proliferation of stromal fibroblasts were evident. ONO-3403 given from day 4 did not significantly prevent pancreatic fibrosis by day 28. However, in the group given ONO-3403 from day 2, acinar cells showed regeneration and interfascial fibrosis was almost absent, indicating a marked protective effect of ONO-3403.

Conclusion: To prevent pancreatic fibrosis, chronic treatment with ONO-3403 should be started from the early stage of acute pancreatitis when there is no acinar cell loss, CKC receptors on acinar membranes are well preserved, and stromal fibroblasts are immature. Institution of long-term ONO-3403 therapy immediately after the attack of abdominal pain may prevent the progression of pancreatic fibrosis and consequent impairment of exocrine pancreatic function.

1001 Micronutrient Status in Tropical Pancreatitis

Paul Labio 1, K.T. Shenoy 2, C. Jayakumar 1, 1 Dept. of Medicine, Medical College, Trivandrum, India; 2 Dept. of Gastroenterology, Medical College, Trivandrum, India

Objective: To study micronutrient status in Tropical pancreatitis (TP). Study design: Case control study.

Subjects: 25 cases of TP with either pancreatic calcici or diabetes mellitus with exocrine pancreatic insufficiency and 25 age matched controls with no pancreatic disease.

Study variables: Clinical evaluation, biochemical parameters (albumin, alkaline phosphatase, transaminases, blood glucose and glycated haemoglobin) and nutritional assessment (BMI and WBC).

Outcome measures: Serum levels of zinc, copper and iron estimated by atomic absorption spectrophotometry.

Data analysis: Odds's ratio (OR) and 95% confidence interval (CI) using cut off differences in the means by independent 't' test and regression analysis using micronutrient level as dependent and age as independent variable.

Results: 12 males and 13 females were recruited. Age ranged from 21 to 41 years. Baseline characteristics were similar among cases and controls.
### 1002 A Randomised Controlled Trial of Antioxidants (Antioxid) in Tropical Pancreatitis*

K.B. Leena, K.T. Shenoy. Dept. of Gastroenterology, Medical College, Trivandrum, India

Objective: To test the hypothesis that a combination of antioxidants is effective in reducing lipid peroxides and pain relief in tropical pancreatitis.

**Design:** Randomised double blind cross over trial using either Antioxid or placebo. Each capsule of Antioxid contains Beta carotene 50 mg, Vitamin A 2500 i.u., Vitamin E 10 i.u., Vitamin C 50 mg and Zinc sulphate monohydrate 27.45 mg and was given thrice daily for 30 days followed by placebo capsule or vice versa. A washout period of 2 weeks was given.

**Sample size:** 15 patients with tropical pancreatitis.

**Intervention:** Treatment of diabetes mellitus with soluble insulin; pancreatic enzyme preparation and analgesics for relief of pain.

**Measurements:** Clinical and biochemical (lipid peroxides, red cell enzymes, vitamin C and blood glucose) at the baseline and during each treatment period. Pain and global improvement were scored by visual analogue scale.

**Outcome measures:** Improvement in blood glucose and reduction in lipid peroxides and other red cell enzyme changes; subjective improvement in pain and global improvement.

**Compliance to treatment:** Consumption of more than 80% of capsules was assessed as good and more than 90% as excellent.

**Data analysis:** Descriptive and independent ‘t’ test and Mann Whitney U test to detect difference between the two groups in the basal state. Wilcoxon matched pair signed rank test to detect the treatment effect (α = 0.05).

**Results:** 8 received Antioxid and 7 received placebo as the first drug. Compliance was 100%. Baseline characteristics were similar. Significant reduction in lipid peroxides (P = 0.001), red cell glutathione (P = 0.005) and scores (P = <0.001) were noted with Antioxid. Surgery could be avoided in 70%. Global improvement was marked with Antioxid.

**Conclusion:** Antioxid is a promising drug for pain relief of tropical pancreatitis and surgery could be avoided in majority of TP.

* Study funded by American Remedies Ltd, Madras.

### 1003 Computed Tomography in Tropical Pancreatitis

K.B. Leena, K.T. Shenoy. Dept. of Gastroenterology, Medical College, Trivandrum, India

Objective: To determine the morphology of pancreas and other organs by computed tomography (CT) in tropical pancreatitis (TP).

**Methods:** 102 patients with TP had CT performed. Calcification, ductal dimension and distribution, atrophy, fluid collection, focal and diffuse enlargement of pancreas, peripancreatic tissue planes, hepatobiliary and vascular involvement, renal changes were studied.

**Results:** Calcific: Calcification was seen in 54 patients in the whole pancreas, 5 in the body and 5 in the tail. Ductal dilatation was seen in 14 patients and main ductal diameter was 5–18 mm (mean 8.8 mm). Margins of the pancreas were smooth in 38 patients and irregular in 26. Pancreas was atrophic in 20 patients and lipomatosus atrophy was noted in 16. Fluid collection was noted in 18 patients, localised in 12; peripancreatic in 4 and remote in 2. Gait stones were noted in 9, choleodochal cyst in 1, renal calculi in 3, horseshoe kidney in 1 and hepatic haemangiomata in 1. Non calcific: Of the 18, 4 had calculi and 9 had ductal dilatation and lipomatosus atrophy and 4 had pancreatic fluid collection as pancreatic ascites. Pancreatic malignancy with TP: Mass lesion with calcification and obstructed duct located in the head in 18 and dilatation in 12. Involvement of the peripancreatic planes was noted. Hepatic metastasis was noted in 50%.

**Conclusion:** CT is useful in studying the morphology of pancreatic pathology in tropical pancreatitis. Even in non calcific cases, pancreatic calcification could be noted by CT and malignant division of calcific and non calcific by radiology may not reflect actual pathology.

### 1004 Elements Influencing the Evolution of the Pancreatic Pseudocysts

A. Tudora, C. Duta, F. Miculit, R. Sarandar. University of Medicine and Pharmacy-Timisoara, Romania

To assess the elements which influence the evolution of the pancreatic pseudocysts we have followed 40 patients between 1991–1995: 14 with chronic pancreatitis (CP) and 26 with acute pancreatitis (AP). The evolution possibilities in the patients with CP were as follows: spontaneous resolution in 2 cases (14%), persistence of the pseudocysts with clinical symptoms (1 case) and disappearance of complications (4 cases)–obstruction of the biliary or biliary tree (2 of these cases associated the abcesses formation). The acute pancreatic pseudocysts resolve spontaneously in 9 cases (35%), the rest presented complications that required intervention: 2 (8%) intraductal hemorrhage, 11 (42%) obstruction of the main duct, 3 (11%) abcesses formation and 1 case-the portal vein thrombosis.

The pseudocysts in the cephalic area were associated with a spontaneously resolution (65% in the cases with AP respectively 69% for CP).

The size under 3 cm (for the acute pseudocysts), respectively 4.5 cm was significantly correlated with the resolution.

The number of the pseudocysts (single or multiple) has no influence over the evolution.

**Conclusion:** The predictive factors which indicates the resolution evolution in the pseudocysts during the acute and chronic pancreatitis are the size (under 3 cm respectively 4.5 cm) and the localisation in the cephalic area. In these cases the pseudocysts resolved either spontaneously or persisted asymptomatic or paucisymptomatic requiring only a follow-up.

### 1005 Can Gastroprocted Pancreatic Extracts (GPPE) Improve Undernutrition Criteria in Elderly People? A Double Blind Anthropometric and Biochemical Study

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**Involution of pancreatic enzime and bicarbonate secrections have been demonstrated among people over 60 and particularly when malnutrition was present. Clinical consequences of these findings are unknown and the potential benefit of pancreatic enzime supplementation had never been assessed in this population.**

The aims of this study was thus to evaluate the effect of GPPE on anthropometric and biochemical data among undernourished elderly during a 3 month follow-up period.

**Methods:** 52 patients (46 women) with a mean age of 87 ± 6 years were included. Their caloric intake calculated by a dietitian on three consecutive days by using Euronut program (on average 1,082 kcal/d) was 30% lower than RDA. Main inclusion criteria were BMI (kg/m²) <23 ± 1 and low serum albumin (32 ± 3 g/l). GPPE 2 capsules tid or placebo were administered in a double blind and double dummy fashion. Patients were examined at D15, D30, D60, D90 for dietary intakes, anthropometric and biochemical assessment.

**Results:** At inclusion, the two groups were similar for age, sex, BMI, albumin and other biological variables. Evolution of caloric intakes and body weight were not different between the two groups. Conversely, serum prealbumin level at D90 was higher in the GPPE group compared to placebo (0.23 ± 0.06 g/l vs 0.19 ± 0.06 g/l, respectively: p = 0.05). In addition, there was a trend in favour of the GPPE for retinol binding protein (0.043 ± 0.0013 g/l vs 0.038 ± 0.011 g/l, respectively: p = 0.09).

**Conclusion:** These data suggest that the administration of pancreatic extracts may improve several nutritional parameters in undernourished elderly subjects. Further studies are needed to confirm these results on a large scale.

### 1006 Impact of Continuing Alcohol Addiction on the Outcomes of Resective Surgery for Chronic Pancreatitis

B. Charleton, M. Foglia, O. Gérard, C. Sastik, G. Spiliopoulos, J.P. Campion, B. Launois. Department of Digestive Surgery and Transplant Unit, CHR Pontchaillou, Rue Henri Le Guilloux, 35033 Rennes, France

**Materials and methods:** Between 1972 and 1991, 149 patients underwent resective surgery for chronic pancreatitis. Surgical procedures included 87 pancreatoduodenectomies and 62 distal splenopancreactomies. Excluded from the study were patients lost to follow-up and 10 patients having died in the post-operative period.

**Results:** 46 patients had continuing alcohol addiction (OH+) and 88 patients had been weaned for alcohol (OH–). Post-operative comfort was poor in 3.5% of OH– versus 30.4% of OH+ patients, medium in 26.7% of OH– patients versus 30.4% of OH+ patients and good in 69.8% of OH– versus 39.2% of OH+ patients. Pain was present in 8% of OH– versus 57% of OH+ patients. Body weight was stable or increased in 100% of OH– versus 47% of OH+ patients. 53% of OH+ patients lost weight. Persistent pain activity was 85% in OH– versus 50% in OH+ patients. 5, 10 and 20 year survival for OH– and OH+ patients was 90% vs 75%, 85% vs 60% and 70% vs 50% respectively. Following 5, 10 and 20 years survival for OH– and OH+ patients was 95% vs 70%, 90% vs 50% and 60% vs 50% respectively. Following distal splenopancreatectomy 5, 10 and 20 year survival for OH– and OH+ patients was 90% vs 90%, 70% vs 70% and 70% vs 50% respectively. Late deaths occurred in 21 of 46 patients in the OH+ group: 5 oropharyngeal/oesophageal tumors, 2 cardiovascular conditions, 9 acute alcohol related complications, 5 "other" causes. Late deaths occurred in 17 OH– patients: 5 opharyngeal/oesophageal tumors, 6 cardiovascular conditions, 9 acute alcohol related complications, 6 "other" causes.

_**Gut:** first published as 10.1136/gut.39.Suppl_3.A121 on 1 January 1996._ Downloaded from http://gut.bmj.com/ by guest. Protected by copyright.
Conclusions: The best results of pancreatic resection for chronic pancreatitis are obtained in those patients who can be weaned from alcohol. Comfort, return to normal activities and survival are improved.

1007 Resection in Chronic Pancreatitis. A Retrospective Study with 154 Patients with Special Reference to 20 Years and 10 Years Survival
We retrospectively studied results in 154 patients who underwent pancreatic resection. Methods: Between September 1972 and December 1994, we performed 67 cephalic pancreaticoduodenectomy (30 with pylorus conservation), 65 splenopancreatectomy (SPC) and 4 total pancreatectomy for chronic pancreatitis. Patients with simultaneous neoplasia at histological control were not included. Mean age was 44 years (range 20–70 years). The most common reason for surgery was severe pancreatic duodenal compression, segmental portal hypertension, suspicion of pancreatic neoplasia. 140 (90%) patients were male. Chronic ethiology was the most common aetiology. We could establish a score confirm based on pain, diabetes, diarrhea and weight increase in 60% of patients. Median follow up was 10 years. Cause of death was determined in all patients. Results: Perioperative mortality was 4.5% in Whipple procedure, 9.6% in splenopancreatectomy and 50% in total pancreatectomy. Survival after duodenopancreatectomy at 10 and 20 years was 59% and 54%. Survival after splenopancreatectomy at 10 and 20 years was 68 and 38%. In both group 20 years survival was significantly higher among patients who stop alcohol intake (62 vs 52% for Whipple and 72 vs 16% for SPC). Low contour score was clearly associated with alcohol intake. Conclusion: Postoperative operative comfort score was higher with pylorus conservation than in patients without pylorus conservation but this difference desappeared when patients who didn't stop alcohol consumption were excluded. None of the patients in which we carried out Whipple operation needed another surgical procedure for pancreatic pathology while 9% of the patients splenopancreatectomy group were operated again. ENT neoplasia (10 cases) and cardiovascular accidents (8 cases) were the major cause of long term mortality. Conclusion: However pancreaticoduodenectomy in chronic pancreatitis seems an heavy procedure its operative morbidity and mortality are low. A good and long term comfort is obtained in most of the patients. As for any ethnic patient screening for ENT neoplasia should be the rule...

1008 The Risk of Occurrence of Diabetes Mellitus is Influenced by the Type of Elective Pancreatic Surgery in Patients with Chronic Pancreatitis
D. Malik, P. Hammel, P. Lévy, A. Sauvanet, J. Belghiti, P. Ruszniewski, P. Bernades. Fédération Médico-Chirurgicale d'Hépato-Gastro-Entérologie, Hôpital Beaujon, Clichy, France
Whether elective pancreatic surgery (EPS) in patients with chronic pancreatitis (CP) influenced the occurrence of diabetes mellitus is unclear.
Aim: To assess if patients with CP who underwent EPS had an increased risk of diabetes as compared to those who did not.
Methods: 482 patients with CP (mean: 85.3%; alcoholics: 84.6%) followed 8.0 years (1–32) were studied. Among those EPP were compared to 224 who did not. Thirty-six patients who underwent a non-elective pancreatic surgery were excluded.
Results: Prevalence of diabetes was 40.7% (insulin-dependent: 19.9%) in the whole group of 446 patients and increased time of follow-up (48.4% (26.8%) and 60.1% (37.2%) at 5 and 10 years, respectively). The actuarial rate of diabetes: a) was not influenced by EPS (35.6% vs 43.3% at 15 years); b) was higher in patients who underwent pancreatic resection (n = 95 (distal pancreatectomy: n = 56)) than those treated by derivation (n = 126) (31.9% (distal pancreatectomy: 64.3%) vs 37.4% at 15 years, p < 0.01 (p < 0.001) and in those not operated on (p < 0.05); c) was lower in patients treated by pancreatic drainage (n = 42) than in those not operated on (20.9% vs 32.8% at 10 years, p < 0.05).
Conclusions: Distal pancreatic drainage is the only procedure of EPS which increases the risk of diabetes in patients with CP. By contrast, pancreatic drainage seems to delay the onset of diabetes.

1009 Spatial Blood Flow Distribution in the Normal and Chronically Inflamed Human Pancreas
In experimental models many pancreatic diseases namely acute and chronic pancreatitis are accompanied by, caused or aggravated by microcirculatory changes. In this study we assessed blood flow as well as the flow curve pattern in 13 patients of patients undergoing laparotomy for non-pancreatic diseases as well as patients undergoing pancreatic head resection for chronic pancreatitis by laser doppler flowmetry (LDF). Methods: In 13 patients undergoing laparotomy, EBF was assessed by LDF on the normal pancreas as well as in 9 patients with chronic pancreatitis. Blood flow was recorded for at least 30 seconds after a stable signal was obtained. Post sampling data processing included calculation of systolic and mean blood flow and pulse curve analysis with pulsatile index and integral under the curve calculations. Results: Results (for the normal pancreas) in perfusion units (upper row: systolic/diastolic flow, middle row: mean flow ± SD, lower row: pulsatile index).

Discussion: A typical spatial distribution of pancreatic blood flow was found, correlating with the anatomic vascular supply and lowest flow on the mesenteric vein, the water shed area between pancreaticoduodenal supr/inf splenic arterial blood supply. Furthermore blood flow and blood flow pattern was significantly decreased in chronic pancreatitis, most pronounced in the pancreatic head.

1011 Transforming Growth Factor Beta Mediates Both Fibrogenesis and Hyperglycemia in Patients with Chronic Pancreatitis
P. Fogar, A. Floriani, D. Basso, C. Passuqui, M. De Paoli, C. Sperti, M.G. Piva, A. Melis, M. Piebani. Dipartimenti di Medicina di Laboratorio, Università degli Studi di Padova, Italy; Gastroenterologia, Università degli Studi di Padova, Italy; Seminario Chirurgica, Università degli Studi di Padova, Italy
Transforming growth factor beta (TGFβ) has suggested to mediate liver fibrosis which can be monitored by the serum determination of the N-terminal peptide of type III procollagen (PIIIP) and laminin. Fibrogenesis is also an important phenomenon found in patients with chronic pancreatitis (CP), for which no data are available on TGFβ or PIIIP and laminin patterns. The aims of our study were to compare the serum patterns of PIIIP, laminin and TGFβ in patients with CP and to verify if there is any correlation between these indices. We studied 81 subjects; 20 were controls (CS), 23 patients had CP, 17 viral cirrhosis (VC), 11 alcoholic cirrhosis (AC) and 10 primary biliary cirrhosis (PBC). In the sera of all subjects we measured PIIIP and laminin (IRMA and ELISA, ELISA, Boehringer Mannheim, Germany). PIIIP and laminin increased in VC and AC in comparison with CS, CP and PBC (Anova one-way; F = 8.86, p < 0.001 and F = 11.57, p < 0.001 respectively). In CP high levels of PIIIP and laminin were found in 72/3 and 5/5 patients. TGFβ significantly decreased in patients with VC (43 ± 3 ng/ml, mean ± SEM), AC (54 ± 9) as compared to CS (101 ± 6) (F = 11.29, p < 0.001). High levels of TGFβ were found in 62/3 patients with CP. In patients with CP, PIIIP varied independently from laminin (r = 0.568, p < 0.05), but correlated with TGFβ (r = 0.24, p = 0.816). On the contrary in LC patients PIIIP and laminin varied consensualy (r = 0.709, p < 0.001) and the variations of PIIIP were inversely correlated with those of TGFβ (r = −0.337, p < 0.05). In CP, a reduced exocrine function (PABA test) was associated with an increment of laminin values (r = −0.519, p < 0.05). Fasting serum glucose was correlated with TGFβ (r = 0.884, p < 0.001), while HbA1c was correlated with C-peptide values (r = −0.570, p < 0.01). 18 patients with CP were followed up for a medium period of 7.5 yrs (4–12 yrs range). TGFβ significantly decreased during follow-up (Student’s t test: t = 3.09, p < 0.01). A trend towards a decrement was found also for PIIIP. Conclusions: 1. biochemical markers of liver fibrosis can be considered of limited value in assessing pancreatic fibrosis; 2. in LC, the existence of a feed-back regulation of TGFβ mediated by the fibrinogen process may be hypothesized; 3. this feed-back does not seem to be present in CP, where TGFβ seems to be involved in favouring fibrosis on the one hand and the development of hyperglycemia on the other; 4. pancreatic fibrotic phenomena, more marked when exocrine function is severely impaired, seem to go towards quiescence in long term follow-up.

1012 Is the Pancreas Able to Adapt to Repeated Caerulein-Induced Pancreatitis?
Z. Warzocha, A. Dembinski, P. Canarowicz, J. Jaworek, J. Bliski, S.J. Konturek. Institute of Physiology, Collegium Medicum of Jagiellonian University, Krakow, Poland
Acute pancreatitis with tissue damage and acinar cells loss is followed by recovery. We studied biochemical, histological and functional regeneration of pancreatic tissue after repeated caerulein-induced pancreatitis. Caerulein-induced pancreatitis was evoked in rats by s.c. infusion of caerulein (10 µg/kg/hr) for 8 h. After infusion, rats were divided into three groups. First group was infused with caerulein one time, in the second group infusion of caerulein...
was repeated 10 days later. The third group was infused with caerulein 3rd time 10 days after the 2nd infusion. Rats were sacrificed at time sequence of 0, 12, 24, 48, 72 hours and at 5th, and 10th day after last infusion. Pancreatic blood flow was measured using laser Doppler flowmeter. Plasma and supernatant amylase activity as well as DNA and RNA content, as well as histological changes in 1st group were showing progression of regeneration after 3 days. Regeneration after caerulein-induced pancreatitis was almost completed within 10 days and amylase content in the tissue and plasma amylase level returned close to normal values. Repeated infusion of caerulein caused significantly less pronounced destruction of the pancreas as compared to the group with chronic pancreatitis (28.5% ± 15.5) and those with elevated amylase levels (30.3% ± 14.7). Eleven of the 18 sera with macroamylase and 15 of the 61 without macroamylase were also tested with a precipitation technique using another chromogenic method for amylase assay (Phadebas, Pharmacia); the results were similar to those obtained using the automated method. All the sera but one with macroamylase showed an elevation in pancreatic isoamylase using the immunoinhibition test; this enzyme was found to be the predominant fraction (> 50% of the total amylase activity) in 11 of these sera. Conclusion: The results demonstrate that PEG precipitation procedure is a simple and reliable technique for quick detection of macroamylase. This test can be easily applied to automated assays for amylase and should be carried out whenever dealing with hyperamylasemia of uncertain origin.

1015 Pancreatic Ascpatic And Gastroinestinal Disease in Response to Intraluminal Ammonia

J. Bitki, J. Jaworek, A. Dębnińska, Z. Warzocha, M. Cieszkowski, W. Bilasinski, S.J. Konturek, Institute of Physiology, Collegium Medicum, Jagiellonian University, Krakow, Poland

Recent studies have suggested that Helicobacter pylori caused persistent elevations in the ammonia content in stomach leading to the development of G-cell hyperfunction and enhanced level of plasma gastrin. In patients with Helicobacter pylori infection, interdigestive pancreatic enzyme secretion was increased. The aim of this study was to evaluate the effect of ammonia on plasma gastrin and exocrine pancreatic secretion in conscious dogs equipped with pancreatic fistulas and in vitro on secretory activity of isolated pancreatic acini. Ammonia given intraduodenally (0.5, 1.0, 2.0, 4.0, 8.0 mM/L) resulted in increased pancreatic protein output, reaching respectively 9%, 10%, 16% and 25% of 17 and maximum in 11 of strong increase in gastrin plasma level. Ammonia (8 mM/L, 1d) given during intravenous infusion of secretin (50 pmol/kg/h) and cholecystokinin (50 pmol/kg/h) reduced the protein and bicarbonate output by 37% and 35% respectively, as compared to control response obtained with those peptides alone. When pancreatic secretion was stimulated by oral feeding the same load of ammonia decreased the protein and bicarbonate responses by 47% and 78% respectively and has no significant effect on plasma gastrin. In isolated pancreatic acini, increasing concentrations of ammonia (10\(^{-7}\) M to 10\(^{-5}\)M) produced a dose-dependent stimulation of amylase release reaching about 45% of caerulein induced maximum. When ammonia was given together with submaximal dose of caerulein (10\(^{-12}\) M) enzyme secretion was reduced by 30%. Conclusions: 1. Ammonia affects pancreatic enzyme secretion; 2. Rise in gastrin plasma level may be responsible for stimulation of basal pancreatic secretion in conscious animals; 3. Effects of ammonia on pancreatic secretion may be mediated in part by its direct action on pancreatic acini.

1016 Effect of Dose Escalation of Pancreatic Enzymes on Steatorrhea in Patients with Pancreatic Insufficiency

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In patients with cystic fibrosis increasing the dose of pancreatic enzymes will further and significantly reduce steatorrhea. However, it is not known whether this is also true for patients with pancreatic insufficiency due to chronic pancreatitis. Therefore we have studied the effect of two different regimens of pancreatic enzyme supplementation (Pancrease\(^\text{®}\), lipase 3 x 10,000 U daily versus lipase 3 x 20,000 U daily) each dose for 2 weeks combined with omeprazole 40 mg/day, in a double blind, randomized cross-over study. Results were compared with those obtained during control period. Sixteen patients (13 male, 3 female; age 22-75 yr) with chronic pancreatitis (alcoholic n = 4; idiopathic n = 7) and exocrine insufficiency (fat + 10 g/day) participated in the study. Food intake, fecal parameters (weight, fat, stool frequency) were measured and subjective abdominal symptoms were scored.

Results:

<table>
<thead>
<tr>
<th>Control</th>
<th>3 x 10,000 lipase</th>
<th>3 x 20,000 lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal fat (g/24 h)</td>
<td>38 ± 7</td>
<td>18 ± 5*</td>
</tr>
<tr>
<td>Fecal weight (g/24 h)</td>
<td>56 ± 7</td>
<td>49 ± 14 *</td>
</tr>
<tr>
<td>Fat absorption (%)</td>
<td>30.3 ± 14</td>
<td>26.7 ± 12*</td>
</tr>
</tbody>
</table>

*p < 0.05 versus control

Enzyme supplementation significantly (p < 0.05) reduced abdominal symptoms: pain score from 3.2 ± 0.6 (control) to 1.3 ± 0.4 and 1.3 ± 0.4 during low and high doses lipase respectively; abdominal distention significantly from 4.8 ± 4.0 (control) to 6.1 ± 0.4 and 6.2 ± 0.4 during low and high doses lipase.

It is concluded that dose escalation from 30,000 U to 60,000 U lipase daily does not further improve fat absorption or abdominal symptoms in patients with pancreatic insufficiency due to chronic pancreatitis.

1013 Studies of Exocrine Pancreatic Function in Patients with Sjögren’s Syndrome

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Sjögren’s syndrome (SJS) is a chronic, slowly progressive autoimmune disease, involving primarily the salivary and lachrymal glands and occasionally other exocrine glands as well as gastrointestinal and pancreatic glands. The special aim of this study was to elucidate the relation between salivary gland destruction and the incidence of macroamylasemia. We performed a double-blind, randomized cross-over study. Results: A. In 25 consecutive patients (2 M, 23 F, age 55.8 ± 2.2 yrs, M ± SD) with SJS (15 primary SJS/10 secondary SJS) patients had xerostomia and xerophthalmia. Diagnostic evaluation of the salivary and lachrymal glands with sialography and indirect lachrymal duct imaging showed the following findings: was abnormal in 11 patients. In 1 patient, no abnormalities were noted. Interestingly, the maximal bicarbonate output by 37% and 35% (50 0.4) of 10 patients was reduced to 50% of the normal value. B. The maximal bicarbonate output by 37% and 35% (50 0.4) of 10 patients was reduced to 50% of the normal value. C. The results demonstrate that the PEG precipitation procedure is a simple and reliable technique for quick detection of macroamylasemia. This test can be easily applied to automated assays for amylase and should be carried out whenever dealing with hyperamylasemia of uncertain origin.

1014 Detection of Macroamylase in Serum by a Rapid Assay

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Simple procedures are currently available for the determination of amylase isoenzymes in serum which are based on the specific inhibition of salivary isoamylase. Unfortunately, they are not able to detect macroamylasemia and in the majority of these cases they erroneously indicate an increase of pancreatic amylase. In 1992 a new test was developed which readily distinguishes macroamylase by means of a PEG precipitation technique. In the present study we combined this technique with a widely used automated assay for amylase and isoamylase determination in order to establish the clinical utility of the two combined methods. We studied 18 sera from 4 patients with normal macroamylase and 61 negative for macroamylase using gel filtration chromatography (Sephadex G-100); of the latter, 32 had normal and 29 elevated amylase activity. Total amylase concentration was estimated using a colorimetric method (Amyl, Boehringer Mannheim). Pancreatic isoamylase was determined after inhibition of the salivary fraction by two monoclonal antibodies (Amyl, Boehringer Mannheim). The precipitation of macroamylase was obtained by adding PEG
Non-Alcoholic Chronic Califying Pancreatitis (NA-CCP) Is it Less Severe Than Alcoholic CCP?

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Non-alcoholic chronic califying pancreatitis (NA-CCP) represents in our experience 11% of chronic califying pancreatitis (CCP) cases. Some authors claim that NA-CCP have a more benign course than alcoholic CCP (ACCP). The aim of this study is to report on the behavior of NA-CCP as observed in our service. Material: From 1996 to 1996 we have cared for 528 cases of CCP: 473 (89%) were alcoholic, 42 (8%) idiopathic, 10 (1.9%) nutritional, and 3 (0.6%) were cases of hereditary CCP. The mean age of the 55 cases of NA-CCP at the moment of the diagnosis was 26 ± 17.3 years (range 1-75), with 34 males (61.8%) and 21 females (38.2%). From which were 32 white (58.2%), 19 (34.5%) colored and 4 (7.3%) negroes. Pancreatic calcifications were noticed in 38 cases (70.9%). Age at the beginning of the symptoms was 20.8 ± 16.1 years (range 1-74). The main symptoms were weight loss in 49 patients (89%), pain in 38 (69%), diabetes in 18 (33%), obstructive jaundice in 14 (26%), steatorrhea in 14 (26%), cysts and pseudocysts in 7 (13%), and other pancreatitis complications in 17 cases (31%). Surgery was undertaken in 26 cases at patients' mean age of 32.3 ± 18.5 years (range 1-75). The main indications were clinically uncontrollable pain in 12 cases (43%) and pain associated to pancreatitis complications in 16 patients (29%). Nine patients were inoperable (4%) due to occurrence of pain (4 cases) or pain pluoric complications (5 cases). Results: From the 28 initially operated on patients 12 are dead (57%), with a mean survival of 15 months. The other 9 cases were doing well (mean follow-up of 12 years). Pancreatic carcinoma (PCC) was diagnosed in 7 patients with idiopathic CCP* (17%) and in 1.7% of ACCP cases. Conclusion: NACC is a severe disease, showing morbidity and mortality comparable to ACCP. All deceased.

Postprandial Release of Glucagon-Like Peptide-1 (GLP-1) with and without Pancreatic Enzyme Substitution in Pancreatic Insufficiency

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Secretion of glucagon-like peptide 1 (GLP-1), a gastrointestinal hormone with insulinotropic action and inhibitory action on gastrointestinal secretion and motility is stimulated by ingestion of a meal. Both metabolizable and non metabolizable sugars may stimulate secretion, but it is unknown how pancreatic enzyme substitution affects GLP-1 release in pancreatic insufficiency.

Methods: Eight patients with pancreatic insufficiency (meal-stimulated intraduodenal lipase and amylase < 5% of normal mean concentrations) ingested a mixed meal containing 2100 kJ with 50 g carbohydrate. Each participant were studied twice at random without or with pancreatic enzyme substitution (50 KU lipase and 45 KU amylase). Plasma GLP-1 (7-36) determined by RIA, C-peptide (ELISA) and blood glucose were measured over 300 min.

Results: (Means ± SE). No significant differences were found in meal stimulated blood glucose, C-peptide and GLP-1 responses (area under curve) with and without pancreatic enzyme supplementation. Peak GLP-1 levels were observed after 146 ± 37 min and 73 ± 21 min with and without enzyme supplementation, respectively (not significant). Peak glucose was observed after 69 ± 12 min and 68 ± 9 min and C-peptide after 116 ± 9 min and 112 ± 11 min with and without enzyme supplementation, respectively.

NBT-PABA Chromatographic-Pass Function Test Using a Novel Dual Isotope Technique and Gas Chromatography-Mass Spectrometry

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We present a tubular test of exocrine pancreatic function based on a new dual isotope technique using NBT-PABA (N-benzoyl-tyrosyl-p-aminobenzoinic acid) as substrate for intestinal chymotrypsin activity and the stable isotope 13C-PABA (p-aminobenzoinic acid) as pharmacokinetic marker.

We have developed a gas chromatography-mass spectrometry (GC-MS) method for analysis of PABA and 13C-PABA in serum. Ten healthy volunteers and 10 patients with exocrine pancreatic insufficiency were orally administered 500 mg NBT-PABA and 50 mg 13C-PABA together with a standard meal after an overnight fast. The test dose contained 1003 mmol PABA and 0.349 mmol 13C-PABA. Blood samples were drawn at specified intervals. Serum concentrations of PABA and 13C-PABA were measured and the ratio PABA/13C-PABA was calculated.

The analytical procedure showed good precision with a CV% 6.3 for the ratio. Best separation between the two groups was found 1.5 hour after administration of the test mixture. The average ratios were 2.64 ± 0.15 (mean ± SEM) and 1.26 ± 0.22, respectively, the cut off limit of normal was calculated to 1.72 (mean ± 2SD), giving sensitivity 0.90 and specificity 1.00 in this material.

Introducing a stable isotope and GC-MS in the NBT-PABA test, allows a